ASPECTS OF BIOMEDICAL ENGINEERING IN DENMARK

The Danish Society

for Biomedical Engineering

1973 - 1998

Edited by

The Danish Society

for Biomedical Engineering

ASPECTS OF BIOMEDICAL ENGINEERING IN DENMARK

The Danish Society for Biomedical Engineering

1973 - 1998

DENMARK

Edited by

The Danish Society for Biomedical Engineering

Edited by

The Danish Society for Biomedical Engineering

Reviewed and prepared for printing by

Gert Kokholm, Annelise Rosenfalck and

Peder M. Holmkjær

ISBN 87-987005-0-2

Printed and bound in Denmark 1998 by

Hertz Bogtrykkergården, Copenhagen

PREFACE

The Danish Biomedical Society has been in existence for 25 years. During this time, the Society has been a forum where engineering colleges and technical universities, companies and institutions of the Danish Health Services have had the opportunity to present activities and discuss biomedical developments. The diverse background of the Society's members has perpetuated profitable dialogue on optimization and integration of biomedical solutions.

Biomedical engineering has been part of the Health Services' treatment regimes for many years. Growth in this field has practically been exponential due to the introduction of microprocessor based control units and communication systems. The majority of the large hospitals have seen an advantage in starting biomedical departments. In addition, medical engineering departments have been expanded in universities. New educational specialities such as clinical engineering and structured academic biomedical education have been established, which has opened up for new fields of employment for biomedical engineers such as management and research.

Danish biomedical companies have succeeded in including major parts of new technology in the development and promotion of innovative products. In comparison with other countries, Denmark's rate of turnover and export of biomedical products is relatively high.

In recent years, biomedical engineering has been rapidly changing. Whereas the biomedical engineer of the past was responsible for detailed services and design projects, his/her tasks are now directed towards changing whole modules and diagnosing instrument errors by remote coupling. New management responsibilities have also been added. Thus, the importance of universities taking into consideration this development is evident. At the same time, companies must be aware of the users' new demands, e.g. better integration of individual types of instruments.

This book presents numerous aspects of biomedical activities within universities and companies as well as in the Health Services. It is hoped that the reader will find it exciting to follow the activities and the technical and biological issues which have characterized the Danish Biomedical Society during the past 25 years.

The articles presented here have been edited only with regard to language and layout. They do not necessarily represent the views of the Society. However, the Society is very grateful for the contributions and for the financial support from the many companies listed in the *tabula gratulatoria.*

Hans Stødkilde-Jørgensen
Chairman

TABULA GRATULATORIA

ARTEMA MONITORING AND EMERGENCY CARE A/S

B-K MEDICAL

CARL BRO a/s

DEMKO

FORCE INSTITUTE

JUDEX DATASYSTEMER A/S

MOGENS BALSLEV CONSULTING ENGINEERS A/S

RADIOMETER MEDICAL A/S

S&W FONDET

SANTAX A/S

CONTENTS

The history of the Danish Society for Biomedical Engineering*

ANNELISE ROSENFALCK

Department of Medical Informatics and Image Analysis, Aalborg University, Denmark

In 1998 the Danish Society for Biomedical Engineering has been active in 25 years. The aim of this paper is to describe the background for founding the society, and to shed light on some of the society's work during the first 25 years.

Key words: History of science; The Danish Society for Biomedical Engineering; The International Federation for Medical and Biological Engineering.

Professor Annelise Rosenfalck, Annasvej 4A, 4th, DK-2900 Hellerup, Denmark.

INTRODUCTION

The first general assembly in the Danish Society for Biomedical Engineering was held on 27th November 1973. It was prepared by a group from universities, industry and engineering societies. They had a common goal, and found it important that the society should be a forum for collaboration between these groups and that the first president should come from medicine.

The Nordic collaboration in this area has always been large. Two Nordic guides to keypersons and companies in biomedical engineering were published in 1969 and in 1975 [1,2]. British-Danish collaboration was great; a large group (about 50) came to Denmark for a common seminar in 1972 and the sixth Nordic meeting of medical and biological engineering was held in Aberdeen in 1984. The first Nordic meeting on medical and biological engineering was held in Finland in January 1970 (200 participants) and the second Nordic meeting in Oslo in June 1971 with 300 participants and a large commercial exhibition. At this meeting the initiator Øivind Lorentsen saluted with a "Lur", which has been blown at later Nordic meetings. The third meeting was in Finland 1975. The new Danish Society hosted the IV Nordic meeting in 1977. This meeting was held at The Technical University of Denmark with professor Georg Bruun as president (250 partici-

* In Danish: Dansk MedikoTeknisk Selskab (DMTS).

pants). Since then the meetings have been held every three years. In 1990 it was held at Aalborg University (150 participants). By now there are often two or three conferences on biomedical engineering each year. It is thus excellent that Finland was able to collect about 400 participants to a conference in Tampere in 1997. The next conference is planned to be held in Estonia in year 2000.

The International Federation of Medical and Biological Engineering (IFMBE) held its first international meeting in 1958 and the second in Paris in 1959 [3]. About 6 Danes participated in this meeting, four came from the Institute of Neurophysiology in Copenhagen.

The other Nordic countries joined the Federation in the late 1960s and Denmark in 1976. However, there were about 10 individual Danish members of the Federation since 1959.

The Federation published its history in 1997 [4].

THE PRECESSOR OF THE SOCIETY

In the 1960s the Danish Biomedical Engineering Committee (DBMEC) was extremely active. The committee was established in 1966, connected with the Danish Academy of Sciences and supported by the Medical Research Council and the Danish Council for Scientific and Technical Research. The aim was to promote cooperation between the medical, biological and engineering disciplines. The Committee was headed by professor Tybjerg Hansen and had an academic secretary, Lone Dybkjær [5].

The members of the Danish Biomedical Engineering Committee were elected among the most active groups at universities and hospitals. In 1968 DBMEC established three sub-committees: a contact committee, an education committee and an industrial committee. The members of DBMEC and its subcommittees are listed in Appendix I.

The Contact Committee

The contact committee arranged meetings, symposia and lectures, established contacts to the Nordic countries and the international world and maintained a database on active persons in the field.

The meeting activity in the first years was extremely high and excellent meetings with up to 200 participants were held 8-10 times each year. The list of subjects for the meetings in 1969 is quite impressive:

Biomedicine and intensive care. The meeting was held at Gentofte hospital and it included a commercial exhibition (200 participants),
Small portable data instruments was held at the Institute of Neurophysiology (100 participants),
Computers for on-line signal analysis; seminar at RISØ,
Ultra sound,
Recent developments in radioisotope scanning and image processing (40 participants),
Plastic in biomedicine,
Electro-sleep and electro-anesthesia,
Thermography (lectures with demonstration of equipment),
Engineering and biomathematical techniques to facilitate bedside management of the critical ill.

The Education Committee

The education committee encouraged biomedical engineering education on the academic as well as the non-academic level. The main result was that The Technical Highschool of Denmark (DTH), later the Technical University of Denmark (DTU) and Aalborg University Center (AUC), later

Aalborg University (AAU), increased their activities [A02, A03]. When the education committee began its activity there already existed two formal courses in medical electronics: a half year course at the Technical University for Master students in their last year of the study and a course for Bachelor students at the Technical Engineering School in Copenhagen. The universities had previously held a rather large course in physiology for engineers working in hospitals and medical institutes, a half-year course in mathematics, physics and physical chemistry as well as shorter courses in statistics, programming, biochemistry and chromatography for physicians. In addition some scientific medical societies had arranged 1-2 days' courses in specific subjects, for instance electrodes.

The Industrial Committee

The industrial committee had 15 active members in 1969 and 22 members in 1970. They discussed themes of mutual interest, attended the seminars and meetings, and contributed financially to DBMEC.

The Patient Safety Committee

In addition to these three main committees DBMEC organized a patient safety committee. This topic was extremely urgent because mains driven invasive instruments had just been introduced in the study of critical ill patients. Two of the members of DBMEC, Georg Bruun and Christian Guld, collaborated on screening of instrumentation and mains supply. They developed methods for measuring magnetic and electrical interference and developed excellent rules that are still used in hospitals, universities and industry [6].

Since 1940 there has been a tradition in most countries that physicists worked in hospitals in the radiotherapy departments and chemical engineers in the clinical chemistry departments. Around 1960 a few engineers came into biomedical engineering. In 1969, about 12 with a technical education worked at the University Hospital in Copenhagen, only two at Aarhus University but about 20 at the Copenhagen County hospital. Most of the engineers were attached to a single department, but a new idea of collecting the engineers in biomedical departments was on its way. The development is described in [A01].

THE FOUNDATION OF THE DANISH SOCIETY FOR BIOMEDICAL ENGINEERING

In 1969, the Danish Biomedical Engineering Committee suggested to start a biomedical society and the three subcommittees and active persons in the field received a questionnaire. The majority preferred the existing organization and expressed great admiration for the excellent work done by the chairman of DBMEC, professor Tybjerg Hansen and by Lone Dybkjær. The hesitant attitude was also due to the fact that the active group in Denmark was larger than the societies in the other Nordic countries. In addition a large number (app. 30%) of the active group were physicians, dentists or scientists. Some preferred a society with the aim to join the International Federation for Medical and Biological Engineering. At that time only few were individual members of the Federation.

However, the support from the research councils to DBMEC was not continued after May 1972 and in January 1973 the head of the Danish Academy of Sciences, Bjerre Lavesen, took the initiative for planning a biomedical society. He asked professor Georg Bruun to arrange a meeting in his office at the Electronics Institute at DTU. Lone Dybkjær and Annelise Rosenfalck

were asked to participate and this group agreed on the importance of establishing a biomedical society. They were also eager to continue the biomedical activities of the two engineering societies in Denmark (The society for M.Sc. engineers and for B.Sc. engineers), where Sven Erik Jensen, Torben Jørgensen and Peder Holmkjær were very active. They negotiated with their societies and the societies helped to write laws for the biomedical society and promised financial support for the first years. However, in the last negotiations it became clear that the president for the society should be M.Sc. in engineering and that engineers, who were not members of one of the engineering societies could not join the society. The group could not agree on these restrictions and decided to start an independent society.

The first general assembly of the Danish Society for Biomedical Engineering was held on 27th November 1973. Georg Bruun had asked professor H. Hertz from Lund's Technical University to speak about: "New methods for image-recording in biology and medicine".

About 100 participated in the meeting. After a short welcome by Annelise Rosenfalck it was suggested to ask Sven Erik Jensen to be conveyor of the meeting. Annelise Rosenfalck made a short speech, describing the previous history and the future goal for a society. Torben Jørgensen presented the laws and suggested voting on them. However, that was a problem as one of the participants claimed, that the group, who had arranged the meeting, had done it on their own initiative – the society did not exist and thus, had no members who could vote on the laws or elect a board. This came as a surprise, especially since this participant had previously turned down an offer of becoming the first president of the society.

After several hours of discussion, a preliminary law, which should be valid up to 1st April 1974 was accepted and a non-permanent board elected.

Professor Erik Skinhøj became the first president.

It was a very tired professor Hertz from Lund who gave an excellent lecture. Most interesting was his message on the new ink-writer, the Mingograph.

THE AIM OF THE DANISH SOCIETY FOR BIOMEDICAL ENGINEERING

The aim of the Danish Society for Biomedical Engineering is to promote the scientific and technical development of biomedical engineering.

To reach this goal the society should make an effort:

1. to create contact between groups of different education and occupation interested in biomedical engineering,
2. to promote mutual education between these groups by arranging meetings, seminars and study-groups,
3. to collaborate with the Scandinavian and international societies in biomedical engineering,
4. to provide information on biomedical engineering.

In the law it is also stated that when electing the board, the goal is to obtain a wide representation from all groups occupied in biomedical engineering. As can be seen from the list of board members over the 25 years (Appendix II) this goal has been reached.

The first president professor Erik Skinhøj was chief physician in neurophysiology in Copenhagen, professor dr.med. Jørgen Fabricius, chief physician in cardiology in Odense, took over in 1975, Annelise Rosenfalck, electronic engineer and professor of biomedical engineering in Aalborg followed in 1981, professor, dr.med. Ole Siggaard-Andersen, head of the Clinical

Chemistry Department at Herlev University Hospital, followed in 1992 and the present president associate professor, dr.med. Hans Stødkilde-Jørgensen, The MR Centre of Aarhus University Hospital, took over in 1995.

It has been important that members from the industry have been very active. The first secretary of the society was Armand Schlägel; he came from industry (Simonsen and Weel), the second Sven Erik Jensen came from the hospital sector and the third Gert Kokholm come from industry (Radiometer). They have had the main responsibility for the society and all activities have depended on them.

SOME ACTIVITIES OF THE DANISH SOCIETY FOR BIOMEDICAL ENGINEERING

The main activity has been to arrange 5-6 meetings each year. This has been done pretty much in the same line as done by DBMEC's contact committee. At all meetings new subjects have been presented from the medical and the technical aspect. In the first years, only few courses were held, but several of the meetings acted as courses and were free of charge. It was attempted to plan meetings in all parts of the country. The meetings usually have taken place at universities and in hospitals. Meetings have generally been well attended (40-100 participants).

Some of the most successful meetings were arranged by industry. The timing has usually been in December. Industry invites the members to come to their plants. The industry plans the meeting, the speakers are half physicians and half engineers. The clue is a nice meal, where the participants can continue the discussion. These meetings usually have at least 100 participants.

Many meetings have been planned together with other medical societies, and WHO's European headquarter in Copenhagen has several times invited the society to meetings on technology assessment.

Several times it has been possible to arrange meetings with international speakers, when EEC seminars were held in Denmark. It was always attempted to inform about the EEC projects and to keep members of the society updated.

Biomedical engineering has been an integral part of the EEC biomedical and health research program since the first concerted actions was initiated in 1978. The physician Steen Dawids was one of the first three project leaders. In the first years the activity was planned by a group of two participants from each of the EEC countries. Steen Dawids and Annelise Rosenfalck were elected by the medical research council to represent Denmark. In the first years about 1 million ECU was spent on three concerted actions mainly for travelling of the 100 teams, who participated in the activity. The BIOMED I program (1990-94) had available 133 million ECU, which supported 362 concerted actions and 41 shared cost projects with a total of 7300 participants. A shared cost project grants money for labor, instrumentation and travel. In the running program BIOMED II 336 million ECU will be awarded. There is only limited information on the number of participants from Denmark but just to mention some examples it can be said that AAU at present participates in at least 4 shared cost projects and that DTU has an even greater activity. Many researchers have also participated in the Advanced Informatics in Medicine program AIM, and in several programs for handicap engineering. It is interesting to notice that Nordic collaboration within research has been increased by EEC collaboration. The Nordic countries in the first years participated in the activities as guests,

later they became affiliated members and finally in 1994 as full members and project leaders.

INTERNATIONAL COLLABORATION

The society joined the International Federation of Medical and Biological Engineering in 1976.

The Federation was founded in 1958 and held the first international conference in Paris in 1959 [3]. About 6 Danes participated in this meeting, four came from the Institute of Neurophysiology in Copenhagen. At present a conference is held each third year. The 18th conference was held in Nice in 1997. The other Nordic countries joined the Federation in the late 1960s and Denmark in 1976. However, there were about 10 individual members of the Federation since 1959. At present the Federation has 44 member countries. The history of the international federation was published in 1997 [4].

The Federation publishes the Journal of Medical Electronics and Biological Engineering, which individual members of the Danish Society can obtain for a very low subscription rate. In recent years they also publish a newsletter, which is distributed to all members.

The board of the DMTS has attended the meetings of the secretaries and the general assembly at most of the international conferences. Peder Holmkjær has been member of the clinical engineering working group. Annelise Rosenfalck has served on the IFMBE European Working group and several times at the nomination committee. Recently, she was appointed Founding Fellow of the International Academy for Medical and Biological Engineering.

The Danish Society for Biomedical Engineering sponsored and participated in the arrangement of the IMIA (the International Medical Informatics Association) and the IFMBE Working Conference on "Biosignal Interpretation" in 25th-27th August 1993. It was the first meeting where IMIA and IFMBE arranged a joint meeting on "Biosignal Interpretation". The organizers were professor Jan van Bemmel, The Netherlands, professor Niilo Saranummi, Finland, and Annelise Rosenfalck, Denmark.

The meeting was held in Rebild Bakker near Aalborg. The main sponsor for the meeting was the Commission of the European Communities-DG XII.

The main topics were: Detection and parameter estimation, Monitoring and real time interpretation, and Model based biosignal interpretation. The scientific program included 47 papers of which 30 papers were selected to be published in a special issue of *Methods of Information in Medicine*, January 1994 [9]. The meeting was extraordinary in that most time was left for discussion. The participants (about 70) came from Europe, USA and Japan.

The usual excursion at the meeting became a surprise for the participants. There was no bus! We were in the midst of nature and walked with guidance in Rebild Bakker.

The second meeting on biosignal interpretation was held in Japan in 1996.

NORDIC COLLABORATION

The Nordic activities started in 1969 mainly on Finnish initiative. Two Nordic guides were published in 1969 and 1977 [1,2], Fig. 1. Planning meetings have been held regularly. Planning of Scandinavian meetings was the main goal and the first Nordic meeting was held in Helsinki in 1970 under the auspices of IFMBE.

The Danish Society for Biomedical Engineering has sponsored and arranged two Scandinavian meetings in 1977 in Copenhagen and in 1990 in Aalborg.

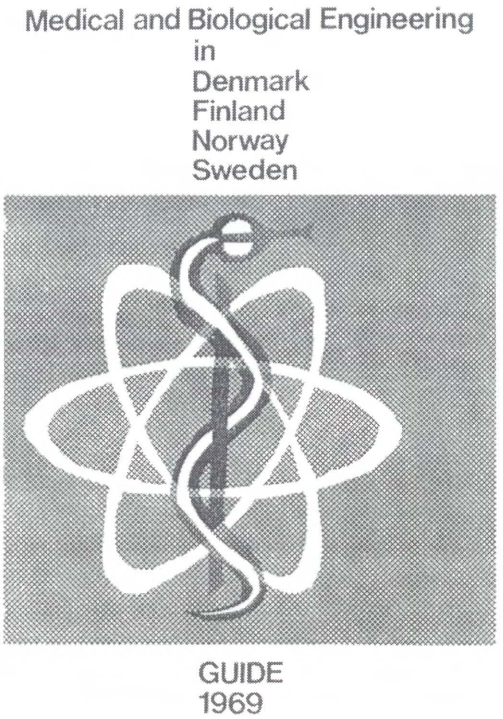


FIG. 1. Front page of the Medical and Biological Engineering Guide, 1969.

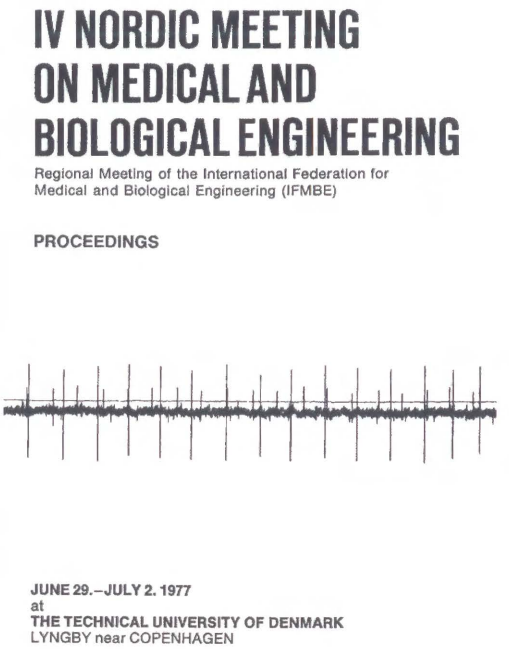


FIG. 2. Front page of the Proceedings booklet from the IV Nordic Meeting on Medical and Biological Engineering, 1977.

The IV Nordic Meeting was held at the Technical University of Denmark, 28th June-2nd July 1977, near Copenhagen. Professor Georg Bruun was president. The 67 papers were presented in two parallel sessions and in poster sessions [7]. The meeting was held in English, Fig. 2.

The subjects were grouped around nine main themes: The organization of clinical engineering; Symposium on ion sensitive and metal electrodes; Interaction between tissue and implanted materials; Electrodes; Clinical information systems; Technical aids for the handicapped; Transducers, measurements and methods in clinical physiology; Symposium on ultrasound and Signal processing in biomedical engineering. One afternoon excursions to hospitals, scientific institutes and factories were arranged. The City Council of Copenhagen invited the members of the meeting to a reception at the Copenhagen City Hall, where the "Lur" was blown. The meeting was supported by NORDFORSK and from the Danish foundation Thomas B. Thrige's Fond.

The 8th Nordic meeting was held at Aalborg University 10th-13th June 1990. Five themes were selected: Diagnosis and care for the cancer patient; Monitoring and care of the critically ill patient; Diagnosis and care of the patient with neurological disorders; Quality and technological assessment in health care; and Knowledge based systems.

The themes were selected because Danish

industry and research are active within these areas. In the mornings invited speakers presented lectures and a few free communications were given. Most free communications were presented in the afternoons as posters, where the invited speakers from the morning sessions conducted the discussions. It was possible to invite speakers because EEC's biomedical program, Danish funds and Danish industry gave financial support. The advance selection of themes limited the number of participants to 150, but most were active, 102 papers were presented [8].

Before the conference dinner the municipality of Aalborg had invited the participants to a reception at Aalborg art museum. The "Lur" was blown.

It has often been attempted to publish a Nordic Journal, which could be distributed among members. The problem has always been whether a high scientific level can be obtained, if the journal is published in a Scandinavian language. Another problem is finances; biomedical industry has often hesitated to buy expensive advertising. Over a span of years we had a Swedish publication *Medicinsk Teknik*, which was sent to Danish members. The level of the papers decreased, however, considerably. For about two years a high quality journal *Medicinsk Teknologi* was published in Denmark and distributed free of charge to the medical profession but not to engineers.

In recent years the contact at the society level is less frequent, however, at the scientific level it has increased due to EEC sponsored projects.

FUTURE OF THE DANISH SOCIETY FOR BIOMEDICAL ENGINEERING

At present the Society has 206 individual members (2 live abroad and 5 are honorary members) and 22 industrial members. The meetings are advertised in the weekly medical publication, *Ugeskrift for Læger*, and in the weekly engineering publication, *Ingeniøren*. The meetings are open for everybody interested in biomedical engineering. A new trend is to arrange 2 days-courses, with a course fee, because it is at present possible to obtain support for postgraduate education. The first evening is combined with a meeting of the society.

The society has got a web page: www.ouh.dk/dmts, where information on upcoming meetings, members list, etc., can be retrieved. The last contribution is a discussion group.

The society wants to interfere in planning of education and to further develop its activities. New goals will be discussed at a seminar 27th November 1998. There will be a paper contest and a seminar with speakers from industry, universities and hospitals.

REFERENCES

1. Medical and Biological Engineering in Denmark, Finland, Norway, Sweden. Guide 1969.
2. Medical and Biological Engineering in Denmark, Finland, Norway, Sweden. Guide 1977.
3. Smyth, ed. Medical Electronics. Proceedings of the second international conference on medical electronics. London: Iliffe and Sons Ltd., 1959.
4. Hopps JA, Saito M, Richter N, eds. Meeting challenges in medicine and health care through biomedical engineering. A history of the IFMBE. Kurashiki: Co. Ltd., Japan, 1997.
5. Dybkjær L. Medikoteknikudvalget. In: Dybkjær et Hägerby, eds. Medicinsk Teknik, Medicoteknik 1966; 2: 3-5.
6. Bramslev GR, Bruun G, Buchthal F, Guld C, Steen Petersen H. Reduction of electrical interference in measurements of bioelectric potentials in hospital. Acta Polytechnica Scand, Electrical engineering series 1967; 15: 1-37.

7. IV Nordic Meeting on Medical and Biological Engineering. Proceedings. 1977.
8. 8th Nordic Meeting on Medical and Biological Engineering. Proceedings. 1990.
9. Special Issue on Biosignal Interpretation. Methods of Information in Medicine. 1994.

References referring to articles in this booklet:

A01. Holmkjær PM, Jarløv A. The development of biomedical engineering into a hospital activity: 27-41.
A02. Arendt-Nielsen L, SinkjærT, Rosenfalck A. 20 years of biomedical engineering at Aalborg University – education and research: 43-50.
A03. Jensen JA, Andersen OT, Wilhjelm JE, Kofoed B, Hansen LK. Biomedical engineering at the Technical University of Denmark: 51-60.

Reference: Rosenfalck A. The history of the Danish Society for Biomedical Engineering. In: The Danish Society for Biomedical Engineering, ed. Aspects of biomedical engineering in Denmark. Copenhagen, 1998: 7-18.

APPENDIX I

Members of the Danish Biomedical Engineering Committee (DBMEC) in 1969:

Georg Bruun, professor of Electronics, The Technical Highschool of Denmark (DTH)
Christian Guld, biomedical engineer, lecturer, Institute of Neurophysiology. University of Copenhagen (UNI)
Anders Tybjerg Hansen, professor dr.med., Rigshospitalet Copenhagen University (chairman)
Lars Anton Hyldgård-Jensen, professor of electrical engineering, (DTH) (vice-chairman)
Knud Jansen, chief physician, dr.med., Hospital of Orthopaedics
Vagn Aage Jeppesen, professor of mechanical technology, (DTH)
Per Lous, chief physician, dr.med., Bispebjerg Hospital, Copenhagen
Johannes Moustgaard, prof., dr.med.vet., The Royal Veterinary University
Jens Gregersen Nørby, M.Sc., lecturer at Aarhus University
Søren Rasmussen, M.Sc., free lance engineer
Ove Steen-Knudsen, prof. in Biophysics, dr.med., University of Copenhagen.

Members of the Contact Committee of DBMEC 1969:

Bent Ebskov, chief physician, Copenhagen
Christian Guld, biomedical engineer, lecturer, (UNI)
Ole Siggaard-Andersen, professor, dr.med., Herlev University Hospital
Anders Jarløv, Chief engineer.

Members of the Education Committee of DBMEC 1969:

Georg Bruun, professor of Electronics, (DTH)
Christian Guld, biomedical engineer, lecturer, (UNI)
Edmund Kaiser, director for Kaiser's Laboratory Ltd, Copenhagen
Ole Munck, dr.med., chief physician, Herlev University Hospital
Ove Steen-Knudsen, professor in Biophysics, dr.med., University of Copenhagen.

Members of the Patient Safety Committee of DBMEC 1969:

Georg Bruun, professor of Electronics, (DTH)
Christian Guld, biomedical engineer, lecturer, (UNI)
Peder Holmkjær, chief-engineer, Herlev University Hospital.
A. Kirkeby, M.Sc., Birch and Krogboe
Arne Mose-Christensen, director for DEMKO
Asger Pedersen, dr.med., chief physician, Glostrup Hospital
Leif Rystrøm, electronic engineer M.Sc., Chr. Rovsing Ltd.
Erik Sandøe, dr.med., chief physician, Rigshospitalet, Copenhagen University.

Members of the Industrial Committee of DBMEC 1969:

The Danish Center for Datahandling
The Danish Sugar Corporation Ltd. (now Danisco).
DISA Electronics (now Dantec)
N. Foss Electric
Hellesens
HETO Hfg, Co.
Kaiser's Laboratory Ltd.
LK. NES, Ltd.
Oticon Ltd.
Philips Ltd.
Chr. Rovsing Ltd.
Radiometer Ltd.
Svend Schrøder
Simonsen and Weel's successors (now Artema Monitoring and Emergency Care Ltd.)
Torben Søderberg Ltd.

APPENDIX II

The Danish Society for Biomedical Engineering, board of directors: 1973 – 1998:

1973	**ES**[1]	**AR**[2]	**PH**	**SEJ**[5]	**AS**	**PZO**	**SSS**	**GB**	**JP**[5,3,4]	**SH**[R]	**TJ**[RS]	
1974	**ES**[1]	**AR**[2]	**PH**[3]	**SEJ**[5]	**AS**[4]	**PZO**	**SSS**	**GB**[5]	**JP**[5] **NL**	**SH**[R]	**TJ**[RS]	
1975	**JF**[1]	AR[2]	PH[3]	**SEJ**	**AS**[4]	PZO	**SSS**[5]	**BR**[5]	NL	SH[R]	TJ[RS]	
1976	JF[1]	**AR**[2]	**PH**[3]	SEJ	AS[4]	**PZO**	**ORR**	BR[5]	**BBL**[5]	**SH**[R]	**TJ**[RS]	
1977	**JF**[1]	AR[2]	PH[3]	**SEJ**	**AS**[4]	PZO	ORR	**BR**[5]	BBL[5]	**SH**[R]	TJ[RS]	
1978	JF[1]	**AR**[2]	**PH**[3]	SEJ	AS[4]	**PZO**	**PHo**	BR[5]	**JM**[5]	SH[R]	**TJ**[RS]	
1979	**JF**[1]	AR[2]	PH[3]	**SEJ**	**AS**[4]	PZO	PHo	**BR**[5]	JM[5]	**LJ**[R]	TJ[RS]	
1980	JF[1]	**AR**[2]	**PH**[3]	SEJ	AS[4]	**PZO**	**PHo**	BR[5]	**JM**[5]	LJ[R]	**TJ**[RS]	
1981	**AH**[5]	AR[1]	PH[3]	**SEJ**[4]	**AS**	PZO	PHo[2]	**HRA**[5]	**JM**[5]	**LJ**[R]	TJ[RS]	
1982	**AH**	**AR**[1]	**PH**[3]	SEJ[4]	AS	HRA[5]	**PHo**[2]	**NR**[5]	JM	LJ[R]	**TJ**[RS]	
1983	AH	AR[1]	PH[3]	**SEJ**[4]	**GKO**[5]	**HRA**	PHo[2]	**NR**[5]	**JM**	**LJ**[R]	TJ[RS]	
1984	**AH**[2]	**AR**[1]	**PH**[3]	SEJ[4]	GKO[5]	HRA	**JCD**[5]	**NR**[5]	JM	LJ[R]	**TJ**[RS]	
1985	AH[2]	AR[1]	PH[3]	**SEJ**[4]	**GKO**[5]	**HRA**	**JCD**	NR	**JM**[5]	**LK**[RS]	**TJ**[R]	
1986	**AH**[2]	**AR**[1]	**PH**[3]	SEJ	**GKO**[4]	HRA	JCD	**NR**[5]	JM[5]	LK[RS]	TJ[R]	
1987	AH[2]	AR[1]	PH[3]	**SEJ**	GKO[4]	**HRA**	**JCD**	NR[5]	**SD**[5]	**LK**[RS]	**TJ**[R]	
1988	**OH**	**AR**[1]	**PH**[3]	SEJ	**GKO**[4]	HRA	JCD[2]	**NR**[5]	SD[5]	LK[RS]	TJ[R]	
1989a	OH	AR[1]	PH[3]	**SEJ**	GKO[4]	**HRA**	**JCD**[2]	**OSA**[5]	**SD**[5]	**TS**[RS]	**TJ**[R]	
1989b	OH	AR[1]	PH[3]	SEJ	GKO[4]	-	JCD[2]	**OSA**	SD[5]	TS[RS]	TJ[R]	
1990	**OH**	**AR**[1]	**PH**[3]	SEJ	**GKO**[4]	**POR**[5]	JCD[2]	OSA	SD[5]	TS[RS]	TJ[R]	
1991	**JJK**	AR[1]	PH[3]	**LAN**[RS]	GKO[4]	**POR**	**JCD**[2]	**OSA**	**SA**[5]	**TS**[5]	**TJ**[R]	
1992	JJK[3]	**PL**[5]	**HO**	LAN[RS]	**GKO**[4]	POR	**HSJ**	OSA[1]	**SA**[2]	TS[5]	TJ[R]	AR[6],PH[6]
1993	**JJK**[3]	PL[5]	HO	**LAN**[RS]	GKO[4]	**POR**	HSJ	**OSA**[1]	SA[2]	**TS**[5]	**TJ**[R]	AR[6],PH[6]
1994	JJK[3]	**PL**[5]	**HO**	LAN[RS]	**GKO**[4]	POR	**HSJ**	OSA[1]	**SA**[2]	TS[5]	TJ[R]	AR[6],PH[6]
1995	**NFA**[3]	PL[5]	HO	**LAN**[RS]	GKO[4]	**POR**	HSJ[1]	**OSA**	SA[2]	**TS**[5]	**TJ**[R]	AR[6],PH[6]
1996	NFA[3]	**PL**	**CT**[RS]	**LAN**[5]	**GKO**[4]	POR	**HSJ**[1]	OSA	**SA**[2]	TS[5]	TJ[R]	AR[6],PH[6]
1997	**NFA**[3]	PL	**CT**	LAN[5]	GKO[4]	**POR**	HSJ[1]	**HG**[RS]	SA[2]	**TS**[5]	**TJ**[R]	AR[6],PH[6],OSA[6]
1998	NFA	**PL**	CT	**JAJ**[RS]	**GKO**[4]	POR	**HSJ**[1]	**HG**[5]	**SA**[2]	TS[5]	TJ[R]	AR[6],PH[6],OSA[6]

See next page for explanation of the abbreviations.

Initials marked in bold:
Elected in the year.

x^1:	Chairman
x^2:	Vice chairman
x^3:	Treasurer
x^4:	Secretary
x^5:	Substitute to the board
x^6:	Consultant for the board
x^R:	Accountant
x^{RS}:	Substitute for the accountant.
AH:	Chief physician Anders Hjort Hald
AR:	Professor Annelise Rosenfalck, M.Sc.
AS:	Armand Schlägel, B.Sc.
BBL:	Chief physician Birgit Blatt-Lyon
BR:	Bjørn Runge, M.Sc.
CT:	Chief Medical Engineer Calle Thøgersen
ES:	Professor, Chief physician, dr.med. Erik Skinhøj
GB:	Professor Georg Bruun, M.Sc.
GKO:	Gert Kokholm, M.Sc.
HG:	Dr.med. Hans Gregersen
HO:	Chief physician, dr.med. Henrik Oxhøj
HRA:	R&D Manager Henrik Rask (Andersen)
HSJ:	Associate professor, dr.med. Hans Stødkilde-Jørgensen
JAJ:	Professor, dr.techn. Jørgen Arendt Jensen, Ph.D.
JCD:	Professor, dr.med. Jens C. Djurhuus
JF:	Professor, dr. med. Jørgen Fabricius
JJK:	Chief physician Jens Jacob Krintel
JM:	Dr. med. Jørgen Meibom
JP:	Lic.tech. Jørgen Pontoppidan
LAN:	Professor, lic.techn, dr.med. Lars Arendt-Nielsen
LJ:	Leif Jønsson, M.Sc.
LK:	Physician Lasse Kjær
NFA:	Chief physician, dr.med. Niels Fogh-Andersen
NL:	Professor, dr.med. Niels A. Lassen
NR:	Chief physician, dr.med. Niels Rossing
OH:	Professor, dr.med. Ole Henriksen
ORR:	Chief physician Ole Rydén Rømer
OSA:	Professor, dr.med. Ole Siggaard-Andersen
PH:	Director, Biomed. Eng. Peder M. Holmkjær
PL:	Manager of Medicotechnical Dept. Per Loubjerg
POR:	After sales service manager Per Overgaard Rasmussen
PZO:	Chief physician, dr.med. Poul Zander Olsen
SA:	Docent, lic. scient Steen Andreassen
SD:	Chieh physician Steen Dawids
SEJ:	Manager Sven Erik Jensen
SH:	Steen Hasselriis, M.Sc.
SSS:	Chief physician S. Sølvsten Sørensen
TJ:	Torben Jørgensen, B.Sc., HD
TS:	Professor, lic.techn., dr.med. Thomas Sinkjær

Early work in Danish biomedical engineering

ANNELISE ROSENFALCK[1], GERT KOKHOLM[2] & PER OVERGAARD RASMUSSEN[3]

[1]Department of Medical Informatics and Image Analysis, Aalborg University, [2]Skovbrynet 31, Bagsværd, [3]Artema Monitoring and Emergency Care A/S, Albertslund, Denmark

The aim of this paper is to describe the early research in basic science, which became the background for biomedical engineering in Denmark. The paper focuses on three areas: clinical chemistry, cardiology, and clinical neurophysiology. The current Danish activities in some of these areas are described elsewhere in this book.

Key words: Cardiology; clinical chemistry; clinical neurophysiology: history of science.

Professor Annelise Rosenfalck, Annasvej 4A, 4th, DK-2900 Hellerup, Denmark.

INTRODUCTION

Basic research in the ninetieth and twentieth century within medicine, physiology, physics and chemistry has been the basis for biomedical research.

Excellent researchers in these early days did most of their experiments with a minimum of technical support and had to rely on their own skill for creating their experimental set-up. In the first part of this century this changed somewhat and many institutes at the universities had a good workshop, where very skilled technicians built the equipment. Recent years dynamic evolution, where university institutes and hospitals occupy physicists and engineers with the highest level of education shows that there was a need for biomedical engineers.

A great part of the research at universities and hospitals has been used by the industry or probably more optimistically forms the basis for the Danish biomedical industry.

Papers on some of these successful collaborations within clinical chemistry, cardiology, clinical neurophysiology, hearing aids and ultrasound can be found in this booklet [A02-A08].

It will be attempted to report on some of the rewarding collaborations in this century within clinical chemistry and cardiology which are of great importance for care of all patients including the critical ill. A report on neurophysiology is also included. The reason for including these subjects is that they are early activities, they show a good collaboration between industry and research and because many of the initiators were ac-

tive in the Biomedical Engineering Committee and in the Society of Biomedical Engineering.

Clinical chemistry

The development of the clinical chemistry discipline has been enormously in the course of the last century.

A great part of all analyses was beforehand made by manual laboratory work but is now performed by automated analyzers producing almost millions of data.

This change has only been possible due to an intensive cooperation between the researchers within the field and the industry.

One example is the development within the pH, acid-base and oxygen field.

Many internationally known Danish researchers have contributed to this development – below just a few will be mentioned:

S.P.L. Sørensen, head of the chemistry department of the Carlsberg Laboratory in Copenhagen, introduced the electrometric method for determination of the hydrogen-ion concentration and defined the pH concept.

Karl A. Hasselbalch, head of the Finsen Laboratory in Copenhagen, and Christen Lundsgaard described the first electronic measurements of blood pH at body temperature (in 1912) using Sørensen's method.

One of Sørensen's assistants, Gotfred Haugaard, produced his own glass electrodes for pH measurements and got the Danish company, Radiometer A/S, to produce a high-impedance voltmeter (a pH meter) and later pH electrodes designed more or less for measurements on blood samples, Fig. 1.

Poul Astrup, professor of the clinical chemistry laboratory at Rigshospitalet, the main University Hospital in Copenhagen, performed very important work within the pH and acid-base area during and after the polio epidemic in Denmark in 1952-53. It resulted in a better understanding of acid-base disturbances of the blood and apparatuses for determining the necessary parameters. This work was to a great extent performed in direct cooperation with Radiometer A/S.

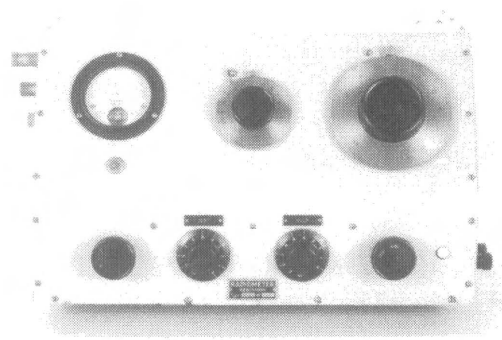


FIG. 1. The first pH meter from Radiometer A/S introduced in 1937.

Ole Siggaard-Andersen, one of Astrup's coworkers during the development of the acid-base technique, now professor of clinical chemistry at the University Hospital of Herlev, developed several acid-base nomograms and described the hemoglobin-oxygen-dissociation curve in a mathematical form. He later developed a very complex set of algorithms describing the relationship between acid-base and oxygen parameters of the blood – today used in most automated pH/blood gas analyzers, among others the analyzers from Radiometer Medical A/S [A07].

Cardiology

Electromedical instrumentation was slowly coming into use for research at the university hospitals in 1920-30. The first instrument was an ECG amplifier connected to an external cathode-ray oscilloscope. This instrument was produced by "The Electronic Workshop" in Aarhus, which had just been bought by Simonsen and Weel's successor

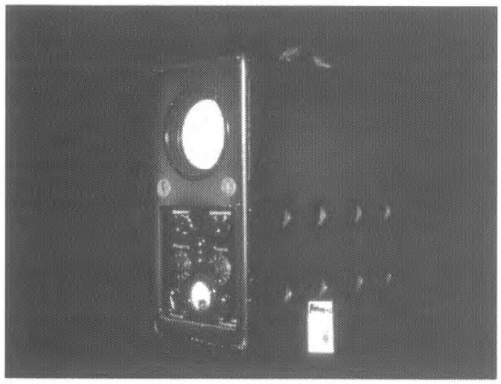


FIG. 2. The first ECG amplifier produced by "The Electronic Workshop" in Aarhus in 1936.

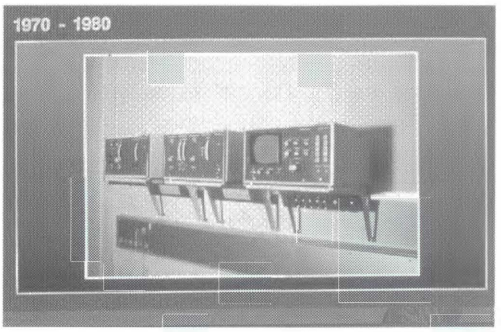


FIG. 3. The first real modular monitoring system in the world. Delivered to the University Hospital in Copenhagen, Rigshospitalet, in 1970. The system was at that time called: "Compose your own system".

(S&W). The equipment is mentioned in Ugeskrift for Læger 1936, Fig. 2.

The director and owner of S&W Ole Lippman had before the war got experience in anesthesia because he worked at a hospital with his new equipment, from McKesson, USA (1939).

After the war USA wanted to send animals and man into space and to monitor electrical activity from heart, brain and muscle. The generally applied sensors were too large and NASA started the development of small robust sensors for astronauts. This more or less became the *go* for to-days intensive care.

The first coronary and intensive care departments started in the early 1960s. S&W was ready with instrumentation and the first 4-channel scope was marketed in 1959. It included facilities for recording of ECG and EEG.

The invasive measurement of blood pressure was developed at Warburg's department at Rigshospitalet by professor Tybjerg Hansen, the chairman of the Biomedical Engineering Committee. His main contribution was the construction of the transducer and the theory behind the function of the system [1]. The transducer was constructed by Ole Dich, who had his own plant, Factory for Mechanical, Electrical Laboratory Apparatus and Scientific Equipment. Different Danish industries tried to develop the detection and recording instrumentation with limited success.

The first modular systems where the users could choose the monitors they needed for ECG, EEG, temperature, respiration, pulse or invasive measurement of venous and arterial pressure was produced in 1970, Fig. 3. Central facilities based on analogue and later on digital networks followed. The number of parameters has expanded over the years and adapted to the need of the clinicians. Microprocessors have provided extra functionality with small size and user-friendly graphic interface.

In the beginning the users were very much focused on the equipment. Today they consider it to be a technical aid, which some times take up too much room, and which must provide both raw data and derived data, with graphs and tables.

Defibrillators for revival were first brought to the market in USA in the late 1950s and S&W sold their first AC-defibrillator in 1961 (Fig. 4) and the DC defibrillator in 1964.

The instruments were first used in hospi-

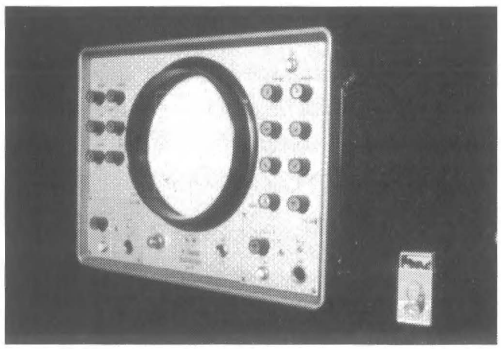


FIG. 4. AC-defibrillator marketed by S&W in 1961.

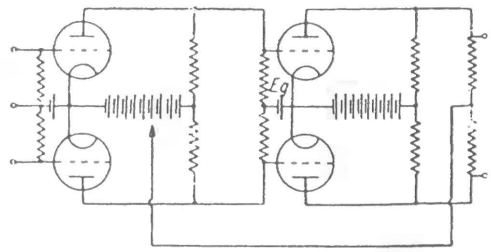


FIG. 5. DC amplifier designed for electrophysiological recordings at DTH in 1936 [2].

tals but there was a demand for better portability of the equipment. The first portable defibrillator with a built-in ECG amplifier and display was marketed in 1973. It was heavy then, but later development has made it useful in ambulances, helicopters, airplanes or wherever many people are gathered. Even defibrillators of today are very easy to use but some development still needs to be done on guidance and education of the users.

External pacing of the heart has its own story. S&W marketed the first pacemaker developed by the company in 1964. It had limitations as the patients had to be anesthetized to endure the stimulus. First in 1982 S&W as the first company in Europe marketed a well functioning external pacemaker for temporary use. At present, the pacemaker and the defibrillator are housed in the same instrument and the user can select the relevant treatment.

Clinical neurophysiology

Clinical neurophysiology has developed within this century. It has its roots in the early observation by Galvani (1737-1798) who demonstrated electrical current and showed that it is related to muscular motion.

In the years from 1933, the Danish contribution to clinical neurophysiology started at the University of Copenhagen where Erling Asmussen and Fritz Buchthal worked at the Laboratory for the Theory of Gymnastics.

In the 1930s Buchthal worked on electrical and mechanical properties of single muscle and nerve cells and at the same time started to record brain and muscle activity (EEG and EMG). Buchthal came to Copenhagen in 1933 with great experience in electrophysiology; he brought an amplifier and a stimulator. Further development was needed, particularly of the amplifier. This was done in collaboration with professor Jens Oscar Nielsen at the Technical Highschool of Denmark where he in 1936 constructed a differential amplifier, Fig. 5, [2]. Just before the war researchers started to use EEG and EMG clinically and the first department for clinical neurophysiology was established in 1940 by Grey Walter in UK. During the war it was not possible to buy equipment in Denmark and Buchthal and Kaiser developed a Danish EEG system, Fig. 6. [3] The amplifiers were remarkable. The input amplifier had a common mode rejection of 100 and the ink-writer used for recording was linear from 0-50 Hz. Buchthal's first recordings of clinical EMG used electrostatic oscillographs and it was not until 1948 that cathode ray tubes were used in DISA's first EMG system [A08].

Buchthal, who became professor in 1955, collected in his laboratory a multidisciplin-

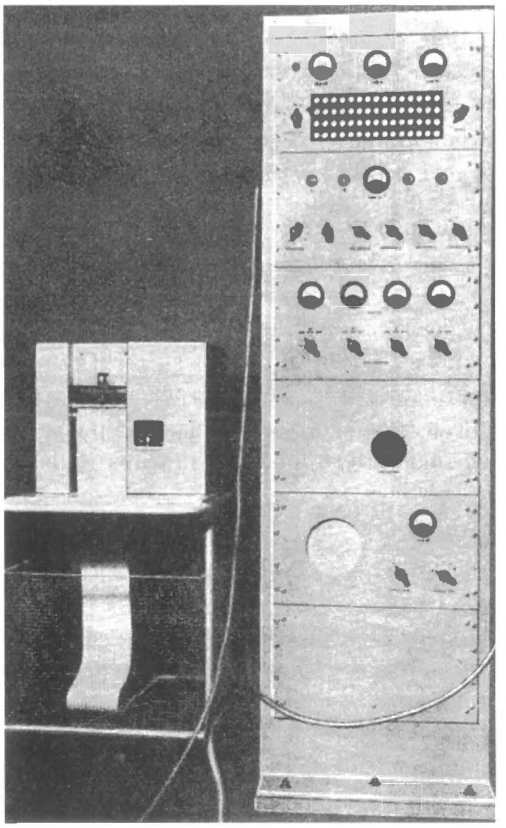


FIG. 6. Buchthal and Kaiser's first three channel EEG system (1943) [3].

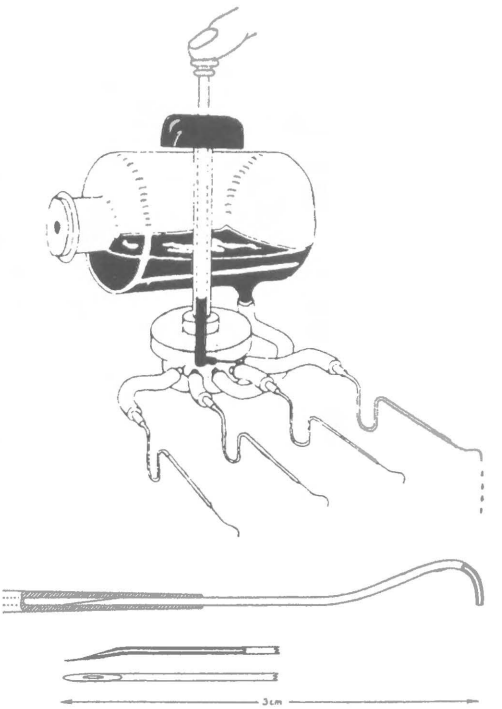


FIG. 7. Above: Kaisers ink-recorder that could reproduce the signal linearly from 0-50 Hz. The ink supply had a pressure pump. Below: The light-weight writing pen and its attachment to the writing lever (1943) [3].

ary team, a group that probably was close to what you today hope to find in a biomedical research team. Researchers of all fields of education participated in experiments in the laboratory and in the clinic.

Edmund Kaiser was one of the most gifted among Buchthal's first collaborators. He worked on very basic subjects such as mechanical properties of single muscle fibers. In 1941 he established his own company, where he produced the EEG system and EMG amplifiers, Fig. 6-7. After the war, Kaiser had a large export of EEG-equipment to Scandinavia, UK, Russia and even China. His later contributions were an electro-manometer, an EEG analyzer, a small portable tape recorder for EEG, a X-ray photometer, implantable amplifiers for steering of prosthesis and miniature electronics for physiological investigations under extreme conditions, e.g., in jet-aircrafts.

The first international conference on electroencephalography and clinical neurophysiology was held in London in 1947 with Lord Adrian as president. The third conference was in Boston in 1953. The main subjects were new methods for automatic analysis of electrophysiological signals. Grey Walter presented a toposcope, to demonstrate how brain potentials spread over the brain. Dawson reported on auto- and cross-correlation of EEG by optical and

mechanical methods and on his averaging technique based on charging electrons into capacitors, which were selected by the commutator of a motor. Norbert Wiener participated in the discussion and pointed out the importance of signal processing. DISA's first electromyograph was exhibited [A08].

Two members of the Danish Biomedical Engineering Committee, Christian Guld and Ove Sten-Knudsen, came from the Institute of Neurophysiology. Since 1946 Christian Guld worked on the differential amplifier and improved it considerably. This development and several later findings, e.g., a specially shielded stimulator to avoid stimulus artifact, were handed over to DISA [4].

Action potentials from sensory nerve were first recorded in man by R.G. Willison and R.W. Gilliatt, UK. Willison demonstrated the technique at a course on EMG in Copenhagen in 1959. The technique was further developed by Buchthal and Rosenfalck such that action potentials from few nerve fibers could be recorded (0.02 μV), Fig. 8, [5]. They developed a near nerve electrode, an input transformer and used a small portable Nicolet CAT computer for averaging. V.O. Andersen later constructed a special low noise amplifier and a double shielded stimulator [6]. This technique has also been used by DISA.

Guld, Willison and Rosenfalck worked for a number of years on a committee set up by the International Society for Electroencephalography and Clinical Neurophysiology on the harmonization of EMG instrumentation [7]. This could be done in collaboration with industry because Willison was consultant for the English manufacturer of EMG systems MEDELEC and Rosenfalck worked together with DISA. The collaboration with Willison was continued in Aalborg in an ESPRIT project [A01, A02].

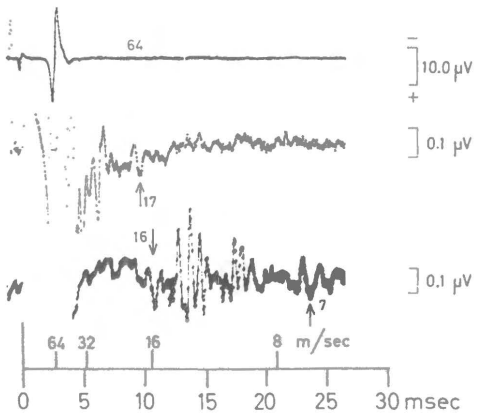


FIG. 8. Recording of sensory action potentials from the median nerve at wrist in a normal nerve and in two patients with pressure lesions at the wrist.
Above: normal; middle: moderate lesion; below: serious lesion (only few fibers were left). The numbers above the trace indicate the maximum velocity of the fibers.

Werner Trojaborg, and many Danish and international clinical neurophysiologists worked at the University Hospital in Copenhagen (Rigshospitalet) and at the Institute of Neurophysiology (Buchthal, Guld and Poul Rosenfalck) with the expansion of EMG. Some of the most important results were new methods and databases of reference values.

The development of electrodes was important for EMG studies. The first concentric needle electrode was made by Person in the workshop of the Laboratory for the Theory of Gymnastics. The insulation was a glass-capillary and lacquer. The concentric electrode was later made by DISA, Fig. 9. They used an epoxy glue for insulation and contributed much to the development of multi-electrodes with up to 24 leading off areas of different dimensions, Fig. 10 [8, A08].

Up to the 1960s all model and statistical

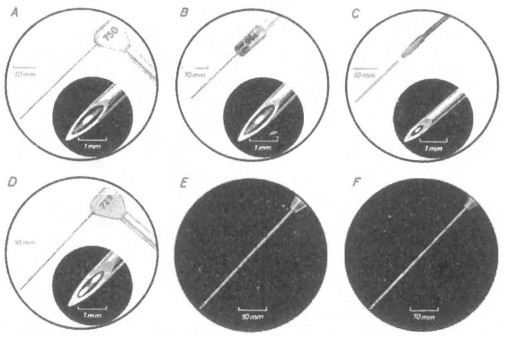


FIG. 9. Concentric electrodes for EMG recording (A, B, C). Bipolar electrode (D) and some of the first multielectrodes (EF).

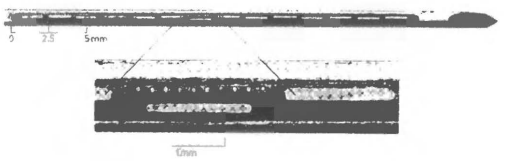


FIG. 10. Multielectrode with 24 recording areas.

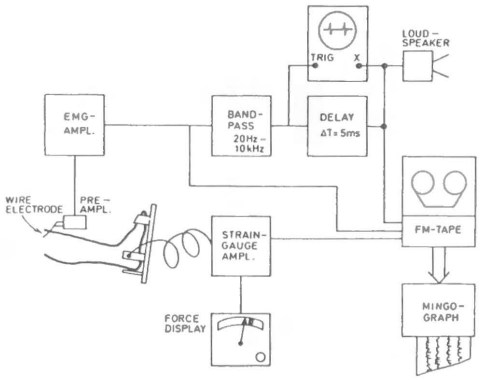


FIG. 11. Set-up for studying of single motor units in the anterior tibial muscle. EMG and force were recorded on FM-tape for later analysis. A pre-amplifier (input impedance about 100 MΩ) was placed close to the electrode. Single motor unit potentials could be recorded at 60% of maximal effort.

calculations were performed by hand. An advanced mechanical Olivetti calculator became the first help (1963) and at the same time, off-line calculations could be carried out at the university computer centers. The first digital computer for on-line data-collection and signal-processing a PDP 8 was bought by the University of Copenhagen in 1968. It had a very limited memory and the cost was at the same level as an electronmicroscope. A large tape recorder and a hard disc later became available but the computer room had to be large and air-conditioned. Ten years later a Ph.D. student from Georg Bruun's laboratory at DTU, Steen Andreassen developed a wire electrode to record from single muscle fibers at high effort, Fig. 11. He also developed the first microcomputer system based on the Intel chip 8080 [9]. The system was transferred to Aalborg University, where the research was continued and some of the results transferred to JUDEX Datasystemer A/S [A01, A02].

DISCUSSION

In this paper some examples of collaboration between research, industry and hospitals have been presented. Most collaborations have been positive for the partners: industry received new ideas and researchers at universities and hospitals obtained equipment, which they could not produce in their laboratories and often not afford. However, for several years around 1970 to 1990 the students opposed against this collaboration. Today it is a necessity and supported by the EEC and national resources.

Biomedical industry in Denmark has in common, that 95% of all products are exported. If this should be maintained with the fast development of microcomputers and

miniature components it is necessary that large groups work together.

Probably the Danish Society for Biomedical Engineering has contributed to and maybe even strengthened this collaboration.

REFERENCES

1. Tybjerg Hansen A. Pressure measurement in the human organism. 1949.
2. Buchthal F, Nielsen JO. Ein neuer Gegentakt-Gleichstromverstärker zum Kathodenstrahloscillographen zur verwendung in der elektrophysiologie. Skand Arch Physiol 1936: 202-38.
3. Buchthal F, Kaiser E. On the clinical application on electroencephalography with a description of a new electroencephalograph. Acta Psych et Neurol 1943; 18: 389-409.
4. Guld C. Use of screened power transformers and output transformers to reduce stimulus artifacts. Medical Electronics. Proceedings of the second international conference on medical electronics. Paris, 24-27 June 1959: 28-32.
5. Buchthal F Rosenfalck A. Evoked action potentials and conduction velocity in human sensory nerves. Brain Res 1966; 3: 1-122.
6. Andersen VO, Buchthal F. Low noise alternating current amplifier and compensator to reduce stimulus artifact. Med Biol Eng 1970; 8: 501-08.
7. Guld C, Rosenfalck A, Willison RG. Technical factors in recording electrical activity of muscle and nerve in man. Report of the Committee on EMG Instrumentation. Electroench Clin Neurophysiol 1970; 28: 399-413.
8. Buchthal F Rosenfalck P. On the structure of motor units. In: Desmedt JE, ed. New developments in Electromyography and clinical neurophysiology, Vol 1. Basel: Karger, 1973: 71-86.
9. Andreassen S, Rosenfalck A. Recording from a single motor unit during strong effort. IEEE Trans Biomed Eng, Vol. BME-25, 1978; 6: 501-08.

References referring to articles in this booklet:

A01. Arendt-Nielsen L, SinkjærT, Rosenfalck A. 20 years of biomedical engineering at Aalborg University – education and research: 43-50.
A02. Gade J, Andreassen S, Henningsen E. The Vikings are coming!: 93-102.
A03. Laursen P, Sams T, Eskelinen L. The Cognitive Function Scanner®. Research and development: 103-09.
A04. Northeved A, Langkjær C, Sevel T. Development and quality documentation of miniature ultrasonic hydrophony: 111-16.
A05. Morrison P. The Madsen Story: 117-24.
A06. Zinck JP, Jensen HJ, Rasmussen JK, Fabricius PE, Dalgaard T, Rasmussen KM, Schilkowski G. Bang &Olufsen a/s – A new partner in disease management: 125-31.
A07. Holbek CC. 25 years of RADIOMETER™ blood gas analyzers: 133-41.
A08. Boelt P. The electromyograph, a success in Danish industry: 143-46.

Reference: Rosenfalck A, Kokholm G, Rasmussen PO. Early work in Danish biomedical engineering. In: The Danish Society for Biomedical Engineering, ed. Aspects of biomedical engineering in Denmark. Copenhagen, 1998: 19-26.

The development of biomedical engineering into a hospital activity

PEDER M. HOLMKJÆR[1] & ANDERS JARLØV[2]

[1]Biomedical Engineering Department, Herlev University Hospital, Copenhagen,
[2]Munkerisparken 68, DK-3460 Birkerød, Denmark

Examples of the use of technology in the treatment of diseases can be traced back to prehistoric times. Up through the historic times including the renaissance and the following century the medical profession evolved mainly on the basis of the classical Greek tradition. The rapid development of the natural sciences in the last two centuries and the subsequent technological development has revolutionized the medical profession and thus led to public hospital systems hitherto unseen. Biomedical engineering has become a hospital activity and the staff involved is generally responsible for the budgeting, the purchase and the maintenance of equipment and instruments.

Key words: Health care; history of medicine; medical physics; patient monitoring; patient safety; technology assessment; The Danish Hospital Institute; The Danish National Board of Health; The Danish Society for Biomedical Engineering; The International Federation for Medical and Biological Engineering.

Peder M. Holmkjær, Department of Biomedical Engineering, Herlev University Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark.

INTRODUCTION

Biomedical engineering is often defined as a professional line including development and application of apparatus and technical aids in the treatment and prevention of diseases. The biomedical engineer has an engineering or scientific education and is supposed to posses the necessary knowledge on theoretical and practical subjects within medicine.

This definition may appear rather natural to some – others may disagree. In the present context the expressions "Medical and Biological Engineering" and "Biomedical Engineering" are used synonymously. The question as to how biomedical engineering is to be defined has been discussed since 1950 and probably also before that time, however, often under the designation "Electromedicine", "Medical Physics" or "Medical Electronics".

A shorter definition such as "The applica-

tion of technical aids in the treatment of diseases" would lead to the conclusion that biomedical engineering has existed as long time as human beings have dealt with diseases and injuries.

However, the term "Medical and Biological Engineering" suggests of course that professional fields as medicine, biology and engineering precedingly must have developed to some professional level thus limiting the existence of biological engineering to a few centuries.

In an attempt to state the time of emergence of biomedical engineering in the sense generally used by the profession some of its effects on the development of hospitals and of remedies for disabled are being dated in time. Some events in the history of science and medicine will be elucidated – if only by short glimpses – by calling to mind some of the persons who have contributed to the development of the medical sciences by remarkable discoveries.

In continuation to the above a few episodes of the contemporary history of biomedical engineering in Denmark will be laid out and its present definition is reevaluated.

Prehistoric time

Technical methods have at all times been applied in the treatment of the diseased and the injured. Trepanation, which is supposed to be one of the oldest operations, was carried out by scraping with a sharp chip of flint. Anthropologists believe from experiments on corpses that the encroachment could be done in about a little more than half an hour.

Ancient Egyptian papyruses show evidence of surgical treatment carried out by the use of knives and branding irons. The Egyptians did not use trepanation. Pregnancy was detected by testing the sprouting of corn moistened by the diluted urine from the women.

The Chinese used acupuncture and developed a complicated pulse diagnose several thousand years before the Roman Empire expanded over Europe. Today acupuncture is still widely used in China and the method has gained considerable access in western medicine during the last 25 years.

In Indian literature from the fourth to the fifth century A.D. one may read about the application of magnets for the removal of iron splints and find detailed descriptions of surgical instruments such as pincers, scissors, saws, knives, etc.

It may seem a little far fetched to characterize acupuncture needles, magnets, knives and scissors as medical technology. However, the instruments mentioned were in many cases designed specifically for medical use and were generally not tools for every day use.

The Greeks

The antique art of medicine in Greece had its prime in the period 400 years before to 200 years after Christ. The medical profession was influenced by oriental medicine, but was methodically developed by the Greek doctors into an independent line of profession freed from witchcraft and magic.

Hippocrates, who lived from 460 to 377 B.C. has, besides many well known and important contributions to the medical profession, also described an extension table which in principle functions in the same way as a modern operating table.

Hippocrates was borne on the island of Kos, which was the domicile for one of the medical schools belonging to the Asklepiades family, and Hippocrates, who was a member of the family, was educated here.

The Hippocrates knew the auscultation of the lungs and the associated sounds were characterized by sounds, which could be produced by means of materials from everyday life. The well-known auscultatory fric-

tion sounds were, e.g., described as "squeaking leather".

The Romans

The roman culture was extended over domains where Greek culture previously had dominated and thus the art of medicine flourished in the Roman Empire. In the contemporary literature *Asklepiades* from Prusa is mentioned as the first Greek doctor who secured himself a footing in Rome. But he had many opponents. *Plinius* and *Cato* despised him because he was a Greek and moreover impecunious.

In order to improve the circumstances and esteem of the roman medical profession emperor *Augustus* allocated in the year of 10 B.C. certain privileges to the doctors.

The roman military doctor *Pedamios Dioskorides* undertook at the time when *Nero* was emperor (54-68) extensive travels studying products of foreign countries and his work on drugs, "De Materia Medica", is an outstanding source of knowledge about pharmacology of the antique era. He also applied electrotherapy, which was carried out by placing an electric ray on the head of patients suffering from protracted headache. The species of ray used has presumably been "Torpedinidae hebetans", which can grow to a length of 2 m and can yield 150 electric shocks pr. sec.

The fall of the Roman Empire started about 500 A.D. and simultaneously the art of medicine started to degenerate.

Arabia

The Arabian countries expanded during that period and also Persia was conquered. The Arabs found in Gundeshapur a large and vigorous medical school, founded by Christians, who were expelled from Syria. The school honored the classical Greek art of medicine. In the year 765 A.D., the head of the school, *Georgios*, was sent for by the caliph *Al Mansur* in Baghdad. Georgios son was appointed physician in ordinary to Harun al Raschid.

The Arabs adapted the Greek tradition of medicine and transcribed the Greek medical writings. Thus the Arabian doctors collected and worked on the heritage of the medical tradition from the classical time.

Amar, who practiced in Cairo at about 1000 A.D. described a new method for the couching for cataract. He applied a cannula with a triangular square area and a side-hole. After the entering of the needle into the eye the lens was put downwards, what was usual practice, but was then brought into contact with the side-hole where upon an external vacuum produced by the assistant of the doctor made it possible to remove the opaque lens.

The Middle Age

During medieval times the church of Rome dominated culture and society by means of religiously motivated rules. Hospitals were founded by clergymen of high rank. "Hotel Dieu" in Lyon from about 500 A.D. is an example. Hospitals were also established in Danish convents which excavations in Øm and Æbelholt monasteries have unveiled. In those days almost all medical and scientific literature were in the possession of the church which did not approve of the monks exercising medicine.

However, in Salerno, a little south of Naples, a significant secular medical school existed, which flourished at about 1100 A.D. The education was of high standard and subject to detailed statutory provisions.

Among the clergymen in Denmark were also medically skilled persons as, e.g., *Asser*, dean and canon in Lund (since 1658 belonging to Sweden), who by his death 1137 left his books, many of which were medical, to the cathedral. The most famous Danish doctor of that time was *Henrik Har-*

pestreng, who died in 1244. He was canon in Roskilde and was described as "Magister" (Master of Arts) rendering probable that he studied abroad. He is specifically known for his book about medical herbs written in Danish.

Universities arose in Paris and other places in Europe and from 1100-1200 the classification in faculties is known. The medical faculty was designated "Facultas in Physica" and the practitioners were addressed by the title of "Physicus". This indicates that the basis of the profession was physics. The designation "Medical Faculty" dates back to 1300 and shows that the medical profession now was met with increasing respect and was regarded as a separate line of science. At the same time the vast spread epidemics of the plague, which extirpated about $^1/_3$ of the European population, were contributing to the reduction of the authority of the church.

The Renaissance

During the renaissance the medical faculties assumed a considerable influence on public health issues and on forensic medicine.

Surgery, however, did not receive great respect nor did it develop to any remarkable stage. But the doctor and teacher of medicine, *Paracelsus* (1493-1541) is the great rebel having as little respect for the Greeks as for the Arabs. His motto was: "Learn both surgery and medicine or neither!". Also *Ambroise Pare* (1510-1590) fought in order to improve surgery. As a military surgeon he reintroduced the legation of arteries and designed a pair of forceps called "Bec de Corbin" (beak of raven) to lay out arteries. In spite of initial low professional status and lack of knowledge of foreign languages he eventually ended up in 1562 as "Premier Chirurgien du Roi". He devoted much time and effort in the study of all kinds of protheses from opturators to ingeniously designed leg- and arm-protheses. Pare experienced a number of attacks from the established medical faculty and from envious colleagues.

The university of Copenhagen was founded in 1479 by *King Christian I.* It comprised four faculties: theology, law, medicine and philosophy.

In England *William Harvey* (1578-1657) demonstrated the circulation of the blood and *Thomas Bartholin* (1616-1680) and his pupil *Niels Steensen* (1638-1686) published their famous works about anatomy and physiology.

Galilei (1564-1642), Italian physicist and astronomer, developed the first usable microscope in 1612. His motto was: "Measure what ever can be measured and make measurable which is not!".

Sanctorius Sanctorinus (1561-1636) in Padua complied to this motto and developed four instruments: a pulse-meter, a thermometer, a hygrometer and a balance for the determination of the amount of perspiration. The pulse-meter consisted of a lead ball suspended in a string. The length of the string was adjusted until the period of the pendulum was synchronous with the patient's pulse.

Isaac Newton (1642-1727), English physicist and mathematician, pioneered many scientific works, which became turning points for future science and mathematics and thus for the art of medicine and its development into a science.

After having traveled speedily through five eras it must be realized that medical technology during that period played a modest part with regard to the treatment of diseases and injuries. The reason is of course that medicine and technology in the modern sense was in no way developed. The revolutionary discoveries within science and mathematics dominate the historical picture.

The Age of Enlightenment

The chemist *Antoine Laurent Lavoisier* (1743-1794) demonstrated in a treatise from 1777, that during respiration oxygen is absorbed and carbon dioxide is removed from the body, and in 1780 he shows in collaboration with the mathematician Pierre Simon Laplace (1749-1827) that body-heat is generated by metabolism in the body. The mathematician *Joseph Louis Lagrange* (1736-1813) claims in a work from 1791 that metabolism takes place in the blood.

In the last part of the 18th century the Italian doctor *Luigi Galvani* (1737-1798) discovered that cut off limbs of frogs contracted by electrical stimulation. Galvani believed that living cells produced electricity. But his compatriot *Alessandro Volta* (1745-1827) had the opinion that body fluids conducted electrical current. Later it turned out that they were both right.

In 1744 *King Christian VI* (1699-1746) entertained himself and his family by performing experiments with electricity. The voltage was produced by means of an electrical machine, possibly manufactured by the royal art turner *Lorenz Spengler* (1720-1807).

The king was enthusiastic when the sparks emerged from the tip of his rapier and from the Queens jewelry.

In 1745 the German doctor and scientist *Christian Gottlieb Kratzenstein* (1723-1795) published a treatise about the utilization of electricity in medicine. In 1753 he became a professor of medicine and experimental physics at the University of Copenhagen. According to order from *King Frederik V* (1723-1763) Kratzenstein carried out experimental electrotherapy on patients suffering from rheumatism, gout, cataract, etc. His extensive collection of books and instruments was destroyed during the great fire of Copenhagen in 1795.

The royal "Frederiks Hospital" in Copenhagen, which had about 90,000 citizens, was founded by *Frederik V* in 1757. The hospital, placed between Amaliegade and Bredgade, had a capacity of 300 beds but was in the beginning equipped with only 150 beds. The public aid authorities erected in 1769 "Almindeligt Hospital" located in Amaliegade being the first municipal hospital in Copenhagen. It was in use until 1863, Fig. 1.

FIG.1. Tin pot dated 1854 from "Frederiks Hospital" in Copenhagen.

The members of the medical faculty of the University of Copenhagen fought with the surgeons who demanded better education and equal status to the university doctors. As a consequence the "Academia Chirurgorum Regia" was inaugurated the 25th of October 1787 in Bredgade 62 close to Frederiks Hospital. The professors here ranked with the professors of the university.

The epoch of liberalism

Distinctive practical and scientific discoveries were being done during this epoch and some examples are enumerated in the following.

R. Laennec (1781-1826) constructed the stethoscope in 1816, the same year he was appointed senior physician at "Hospital Necker". The idea came to him when he

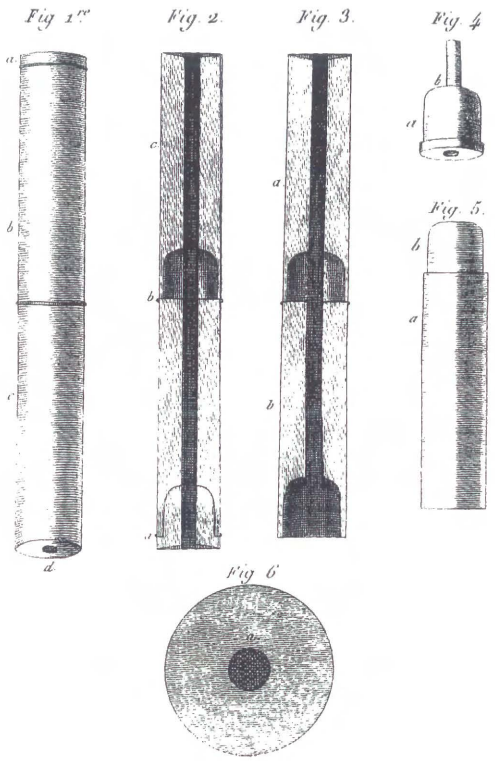


FIG. 2. Original drawings from Laennec's work on auscultation (1826).

saw some children keep one end of a wooden cane to the ear in order to hear the sound produced by scratching the other end of the cane, Fig. 2.

H.C. Ørsted (1777-1851), Danish physicist, demonstrated in 1820 the magnetic effect of the electrical current and contributed thus to the tremendous development within the electro-technical professions. It was Ørsted's initiative that the Technical University of Copenhagen was erected in 1829.

The English physicist *Michael Faraday* (1791-1867) demonstrated the electrical induction and formulated the laws of electrolysis in 1883. He contributed thus considerably to the development of electrochemistry. His compatriot *James Clerk Maxwell* (1831-1879) formulated a mathematical description comprising both electrical and magnetic fundamental rules, hereby predicting the existence of electromagnetic waves.

Charles Darwin (1809-1892) published in 1852 after twenty years of study his work "On the Origin of Species by Natural Selection". The work created a stir especially on the account of the postulate that the human species had animal ancestors, which led to a permanent break with the contemporary prevailing religious opinion.

The French chemist *Louis Pasteur* (1822-1895) and the German physician *Robert Koch* (1843-1910) performed the basic research within bacteriology.

But prior to that an epidemic of cholera broke out in Copenhagen in 1853. 7,219 were contaminated and 4,737 of these died. The town had 130,000 citizens and the supply of drinking water and the sewerage were in a terrible state. The health authorities and the public aid authorities were severely criticized due to lack of effectiveness. However, six prominent physicians intervened and organized - mainly supported by voluntary labor - an effort against the epidemic. *P.L. Panum* (1820-1885) had already in 1850 defeated a minor cholera epidemic in the town Banholm on the island of Lolland in the southern part of the country by using quarantine and isolation. But his effort was not appreciated. The spirit of liberalism was turned against every sort of limitation and one of the above mentioned enterprising six physicians, *C.E. Fenger* (1814-1884), being a national liberal politician, abolished quarantine against yellow fever and cholera.

When the epidemic was at its worst Fenger organized the fight against the disease and participated actively himself. It was the chemist *Julius Thomsen* (1826-1909) and the engineer and physicist *August Colding* (1815-1888) who pointed out that the chol-

era afflicted areas were mainly those with the most unhealthy soil. But no one believed in cholera contagium as none of the bearer nor of the gravediggers died. It was not until 1883 that Robert Koch demonstrated the cholera bacteria.

After the failure of the authorities, which appeared to be in great contrast to the initiative of the Danish medical association in fighting the epidemic and building new houses for the workers in Copenhagen, the government was urged to build a large scale hospital. It was the second municipal hospital ("Kommunehospitalet"), which opened in 1863 ten years after the worst cholera epidemic ever experienced in Denmark.

Later Fenger devoted his life to politics and consequently left his position as a professor in clinical medicine. On his instance Øresundshospitalet and Blegdamshospitalet were erected in 1875 and 1879, respectively.

The English physician *Joseph Lister* (1827-1912) – after having read Pasteur's treatise from 1863 on putrefaction – applied as the first in March 1865 the principle of antiseptics using carbolic acid.

Samuel von Basch (1837-1905), professor of experimental pathology in Vienna, invented the sphygmomanometer in 1883, which was improved by *Scipione Riva Rocci* (1863-1936) but still only systolic pressure could be measured. *N.S. Korotkov* (1876-1920) utilized the so-called "Korotkov-sounds" from the stethoscope placed above an artery in fossa cubiti as a criterium for the onset of diastolic pressure during the slow decompression of the blood-pressure-cuff.

The German physicist *W.C. Røntgen* (1845-1932) demonstrated the X-rays in November 1895 and received as a result of his research in this field the Nobel price in 1901.

The first diagnostic X-ray-picture in Denmark was taken on the Technical University in February 1896 as the only usable X-ray tube in the country was to be found in the Technical University's collection of physical instruments.

The Danish physician *N.R. Finsen* (1860-1904) demonstrated in 1896 that ultraviolet radiation cured skin-areas attacked by lupus (tuberculosis of the skin).

Radioactivity was first explained in 1896 by *A.H. Becquerel* (1852-1908) who discovered the radioactive radiation from uranium.

Pierre (1859-1906) and *Marie Curie* (1867-1934), both physicists, produced radium in 1898.

The four above-mentioned scientists received the Nobel price in 1903.

X-rays and atomic theory

In February 1897 Professor *Oscar Bloch* (1847-1926) applied for a X-ray apparatus to be installed in Frederiks Hospital. The expenses were preliminarily calculated to be 558 kroner and 50 øre, but before the application was granted the amount raised to 1000 kroner. Already in 1901 the medical counsel asked for an improved installation. There was no dark room and the "Glass-plates" were developed by an external dealer and returned 8-14 days later. Frederiks Hospital was in 1910 replaced by "Rigshospitalet" (the new university hospital) having 974 beds.

Radium was for the first time used therapeutically about 1900 for the treatment of skin-cancer. In 1912 the radium foundation was inaugurated with the purpose that a greater number of patients could receive radiation therapy.

In 1913 the English physicist *F. Soddy* (1877-1955) formulated the theory on isotopes and *Irene Curie* (1897-1956) and *Frederic Joliot* (1900-1958) discovered in 1938 the artificial radioactivity which

among other things was used in the research on amino acids and fat metabolism.

The pioneering works of *Albert Einstein* (1879-1955) and *Niels Bohr* (1885-1962) brought the understanding of the many aspects of atomic theory thus also leading to its application in medicine.

The application of radiology and isotope theory for the measuring of physiological phenomena was precipitated by the development within physics and electronics. The invention of the radio-tube in 1913, which was based on the work on electron-emission by *Langmuir* (1881-1957), became the basis for the later application of electronic amplifiers in physiology and for the construction of the electron-microscope.

The invention of the transistor in 1945 and its wide spread application in almost all electronic equipment during the decades following 1960 brought considerable improvements in the specifications of hospital apparatus. The implantable heart-pacemaker is an example. The electronic technology was mainly developed during and after the World War II for military purposes and was afterwards offered for civil application.

Miniaturization of electronic components and the establishing of their mutual connections by means of sophisticated microphotographic methods lead to the production of "Integrated Circuits". Hereby the manufacturing of computers was improved to such an extent, that large and fast electronic memories could be mass-produced at decreasing prices from about 1970. Such systems are widely used in equipment such as digital X-ray, CT- and MR-scanners, ultrasound- and isotope-cameras, etc.

The beginning of biomedical engineering in Denmark

In 1903 *W. Einthofen* (1860-1927), physiologist in Leiden, demonstrated his first electrocardiograph. ECG has since gained an enormous importance in cardiology and the cardiograph has continually been subject to technical improvements.

From 1920 the interest for the clinical measurement of the pH of the blood was increasing and the electronic tube became a component of major importance in the clinically usable pH-meters.

In 1939 a "McKesson" anaesthetic apparatus was imported from USA and put into use during a lung-surgery on the "Finsen Institute" in Copenhagen for the first time. Danish production on a small scale of diathermic-apparatus and cardio-scopes had been going on for some years, Fig. 3-5.

In 1943 the development of an electronic manometer for the dynamic measurement of blood pressure was initiated on Rigshospitalet and neurophysiological instruments were developed on the Institute for Neurophysiology in a cooperation between the institute and the industry.

Biomedical engineering can now be identified as an activity with a great development-potential. About 1950 far-sighted Danish corporation managers saw the necessity to develop and supply up to date technical equipment to the Danish hospitals. The anaesthetic departments were extremely interested in monitoring pulse- and respiration-rate, temperature, electrocardiograms, blood pressure, oxygen and carbondioxide-tension in the blood and a variety of gases in the respiration-air. These demands were highly motivating for the Danish industry and one of the first patient-monitoring systems on a recovery-department was consequently developed by a Danish firm in cooperation with physicians from at home and abroad.

The International Federation for Medical Electronics and Biological Engineering was founded at the concluding session of the second international conference on Medical Electronics in 1959. The Federation was the

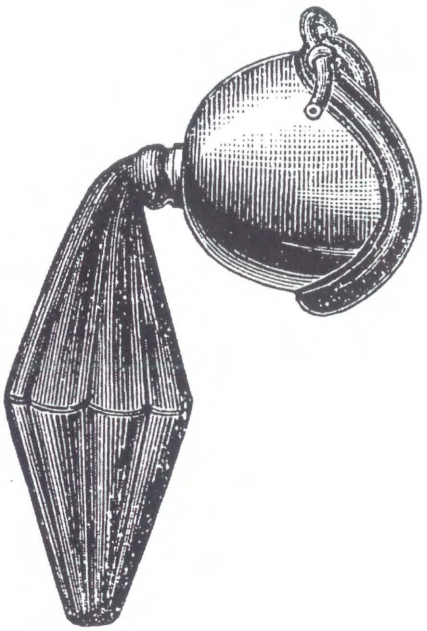


FIG. 3. Wanchers bag for anesthesia from about 1883 (O. Secher: "From ether inhalation to anesthesiology" 1965, Copenhagen).

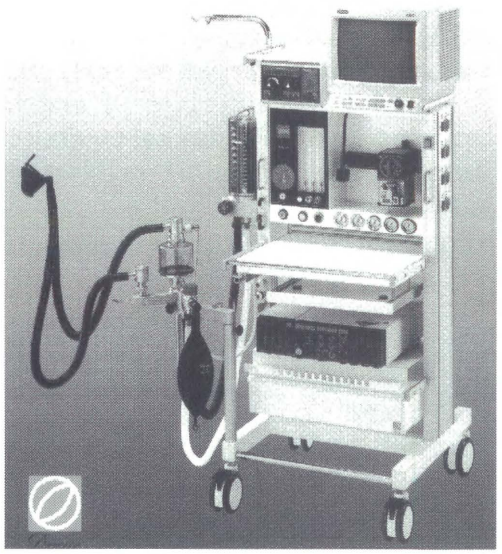


FIG. 4. Anesthesia apparatus and patient monitoring system put together in one unit.

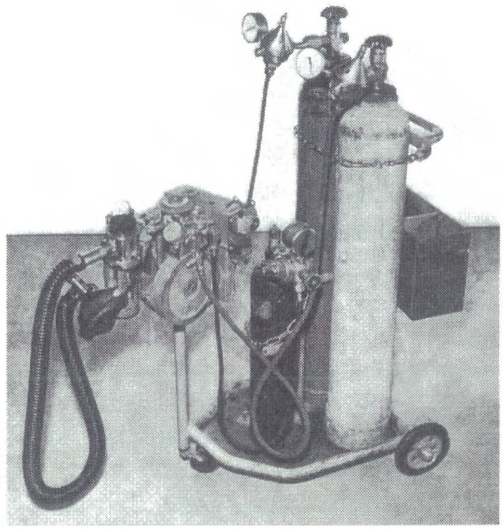


FIG. 5. McKesson anesthesia apparatus from 1939 taken into use for the first lung operation in Denmark (Simonsen and Weel Inc., Denmark).

first European initiative in establishing an international organization in this profession and thereby contributing immensely to the understanding of the importance of Medical Engineering as a profession. In the mid-sixties the organization adopted the name "International Federation for Medical and Biological Engineering" using the initials IFMBE.

The association of Danish Anesthesiologists took the initiative at the annual meeting in 1962 to teach physicians basic electronics. At that time the hospitals had a demand for technical assistance in taking into use new equipment on a growing scale. Enthusiastic doctors and nurses made a great effort to be acquainted with the new and expanding technology. Numerous courses and a lot of textbooks appeared as a result of an optimistic faith on the possibilities of the new hospital-technology.

The first hospital-employment's in Denmark

However, it became soon evident that the medical staff could benefit from leaving the electronic equipment to the engineers and technicians who from about 1965 gradually was employed in the major hospitals. During this period the counties and the municipality of Copenhagen made large investments in new hospitals and in the improvement of existing hospitals. Many hospitals were thus in the course of a few years time supplied with medical instrumentation of the highest standard. On account of this an increasing demand for technical advice and equipment-maintenance arose. This kind of service was in some cases rendered from the firms but often under the supervision of the technical staff of the hospital.

These problems were dealt with years before on a smaller scale on the radiation-therapy-departments. Radioactive sources and high voltage accelerators must be operated by engineers and physicists, but the term "Biomedical Engineer" was not used for this category of personnel who generally is called "Radiation Physicists".

The basis for the improvement and expansion of the hospitals can be ascribed to the capability of society to raise the economical means as well as to the level of education and professional standard of doctors, nurses and other employees. As the technology was available and even favored by the media the hospital-departments proposed a variety of technology in order to improve diagnosis and treatment. The necessary political decisions were thus supported by optimism and great expectations.

Biomedical engineering as a hospital activity

In the late sixties the municipality hospitals of Copenhagen, the major county hospitals and the university hospital "Rigshospitalet" employed an increasing amount of engineers and technicians to work in departments for radiology and ultrasound, clinical chemistry, isotope-diagnostics, cardiology and audiology. Hospital engineers and technicians were gradually organized in a separate department, now frequently called "Technical Department" or tentatively "Biomedical Department". Such changes in the hospital organization sometimes, as might be expected, raised conflicts in relation to the existing technical maintenance departments. Hospital departments could dispose full time over individual engineers if the arguments for biomedical engineering assistance were sufficiently qualified.

Biomedical Engineering developed from this level into a hospital activity at present called Clinical Engineering which is a necessary service for the successful running of a hospital utilizing high technology.

Between 1970 and 1980 large expansions of the hospitals in the Copenhagen area took place and the increasing demand for hospital equipment of all kinds led to a somewhat overheated market supply. This situation was some times the reason for faulty purchase and wrong application of medical equipment. Technical errors and insufficient instruction-manuals resulted in cases of malfunctioning or even accidents especially when safety-regulations were violated. To improve the quality level and the patient-safety the biomedical departments were involved in the purchase, the functional- and safety-test and the maintenance of most electronic and electrical apparatus.

In some major hospitals an "Apparatus Committee" was established representing medical end technical expertness. In general the objective of the committee was to make decisions concerning budgets, resource-consuming Biomedical Engineering projects and concerning applications for the intro-

duction of new hospital-technology of importance.

Some of the apparatus committees were under political management and had a secretariat at disposal.

In the 1970's several of the larger hospital projects were subject to public criticism. The public expenses were generally running high and recessions of public hospital budgets were unavoidable, however, also very difficult to manage as most of the projects were already advanced or contracted.

In the Copenhagen area the hospital planning lacked coordination on a superior level. On an operational level numerous examples of severe budget excesses were experienced in spite of a well-grown bureaucracy. Political decisions did not correspond well with revised planning which in an importunate way unveiled that to obtain economical recessions many advantages of the hospital projects in being were to be sacrificed.

One of the political reactions was to tighten up budget control and improve project management. Numerous control procedures were initiated in order to avoid inappropriate purchases and excess of delivery time. The biomedical departments introduced safety- and quality control of electrical and electronic apparatus. In order to get sufficient influence on the quality and efficiency of equipment and installations the biomedical engineering departments were involved in the hospital planning at an early stage. Standard rules for the tests of equipment and individual rules for the proper use of apparatus were introduced. This work led naturally to a cooperation with the national board of health and other public organizations with the purpose of issuing national standards and recommendations.

An important and generally very attractive activity for the biomedical engineer has been research and development-projects. There are numerous examples of projects carried out in a cooperation between the medical and technical personal and the industry. Examples are the development of diagnostic ultrasound scanners, therapeutic ultra sound, measuring apparatus for the use in audiology, cardiac flowmeters and radiological auxiliary equipment.

The involved parties contributed with money and resources, and sometimes agreements concerning royalties turned out to be profitable with earnings far exceeding the total expenses of the project. Thus the economical basis for future projects could be founded.

The education in biomedical engineering

During the sixties biomedical engineering seemed a promising profession both in industry and the public health sector. Education in such topics as might support doctors, nurses and technical personal to be acquainted with what ever technology that were offered for hospital use was needed. Later on also other categories of hospital staff members were involved and a specific cast of roles were gradually established so that everybody knew how the technology was to be used and by whom.

Formal as well as informal mutual education in technical and medical subjects became quite common. This kind of education "on location" is often disregarded but has in many ways been a necessary provision for the integration of biomedical engineering in hospital activities.

At present the Technical University of Denmark (DTU) and the Aalborg University (AAU) offers courses of lectures in biomedical engineering related topics and numerous candidates have graduated having carried out examination papers on medical and technical questions of current interest. The Aalborg University erected in 1978 a professorship in biomedical engineering thus promoting education and research in

the topics mentioned. In 1997 a professorship was also instituted at the DTU.

Recently a paper called "Proposal for the education in biomedical engineering" issued by the "Institute for Information Technology" on the Technical University of Denmark is being discussed. The content is based on a broad cooperation with everybody concerned and contains a specific professional profile of a biomedical engineer.

The motivation for the improvement of the education is that Denmark has a noticeable net-export of biomedical engineering products and at the same time there is easy access to the public hospital sector for the establishing of an indispensable cooperation between equipment designers and the hospital staff. In the development and design phase this cooperation is of utmost importance in reaching the highest possible quality of the final product which necessarily must be offered on the international market, as the home market is often too small.

During the last decades information technology has had an enormous impact on medical instrumentation and forms a natural transition between biomedical engineering and topics as statistics, medical informatics, medical image processing, the electronic patient record, etc.

Trade policy and biomedical engineering

The Danish ministry of health has in a strategic paper from 1996, "Activity plans concerning electronic patient records", supported the initiatives already taken in Denmark in utilizing the information technology for the creation of an electronic patient record.

The ministry of trade has in an effort to formulate the trade policy of the Danish government carried on a dialogue with the drug industry, the biomedical engineering industries and the public health sector. The results are based on comparative studies in Sweden, Holland, USA and UK and are titled "Dialogue with the medico and health sector".

Hospital technology in the Copenhagen area

In the mid seventies the reduction of public expenditures in general lead to a recession of public hospital budgets. The retrenchments could only be arrived at by intensive rationalization and reduction of services and activities.

In this period representatives from the biomedical engineering departments from five hospital administrations in the Copenhagen area had on their own initiative formed a working group the objectives of which was to exchange experience about practical problems, apparatus maintenance and about patient safety and to find solutions to the repetitive reductions of budgets. The hospital administrations had given their consent to the objectives and activities of the group.

In 1988 there were 12 larger or smaller hospitals within 30 km from each other in the Copenhagen area with a total bed-capacity of 8,082 beds. The population to be served amounted to 1.4 million citizens and 294,000 patients were discharged each year not to mention the ambulatory activity. However, in spite of this seemingly great capacity the politicians often met with the voters' criticism of long waiting lists even in hospitals equipped with expensive technology.

The total of yearly hospital expenses in the area was about 8.5 milliard (billion) Danish kroner or 1 milliard ECU. The value of hospital equipment amounted to 2 milliard kroner. The applications for new equipment amounted to 240 million kroner but only 72 million kroner was granted. The users looked upon this amount as far too little and

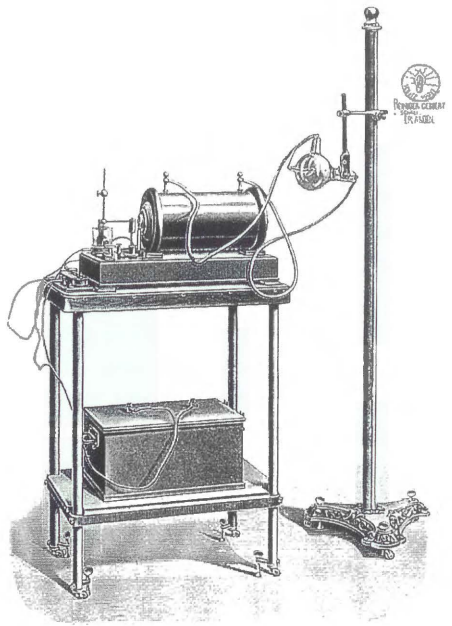


Fig. 6. Reiniger, Gebbert and Schall X-ray equipment from 1896 (From:"100 years of X-ray" published by Siemens Inc).

somber prophecies of equipment failure were often conveyed to the authorities. But failures and accidents were extremely rare due to both the vendors and the hospital engineers' common interest in servicing the equipment in order to extend its functional lifetime, Fig. 6 and 7.

In 1988 the hospitals in the area employed 103 engineers and 32 radio-physicists.

The Danish National Board of Health and the Danish Hospital Institute

The Danish Hospital Institute is an independent freeholding institution erected in 1975 by the Danish government, the association of county councils and city councils of Copenhagen and Frederiksberg. The objective of the institute is by research and development, counseling and information to improve working plans for the hospitals. The institute has published a great number of reports, some of which deal with biomedical engineering by treating topics as, e.g., safety precautions against electricity accidents, equipment inspection, and systems for the analysis of technical services. Information technology is dealt with in papers concerning the electronic patient record, the electronic data communication in the hospital sector and medical informatics in Denmark and Europe.

Medical technology assessment or health technology assessment (HTA) has also been dealt with. HTA comprises an all round analysis of the application of a particular technology, its effectiveness, the patients view of it, the implicated risks and an analysis of economical, educational and environmental consequences. The general interest in HTA was increased during the eighties because of recessions of the public expenses. These raised the demand for detailed analysis of the argumentation used in the applications to be discussed with the management. Here HTA proved to be an efficient method for arriving at a decision.

The Danish National Board of Health has issued recommendations to be used when purchasing hospital equipment. Further more the board has put forward notices on active implantable medical devices, on equipment purchase and on HTA. In the publications mentioned use has been made of the broad experience of the application of biomedical engineering in the last two to three decades as all the issues have been discussed prior to their being published in working groups with ample representation of hospital staff members.

Analysis using the HTA-concept also, as mentioned, took place locally on the hospitals in an effort to state criteria for the introduction of new technology and initiate it in an appropriate manner. Both the Danish National Board of Health and the Danish Hospital Institute have understood to profit from these initiatives. The National Board

FIG. 7. CT-scanner (Philips Medical Systems Inc.).

of Health has in 1997 erected an institute for HTA in order to contribute to the improvement of the services of the public health sector.

In January 1995 new rules in the European community concerning events and accidents when using hospital technology came into force. The topic has always been of great importance to the biomedical engineer because one of the main reasons for the employment of a biomedical staff is to ensure that the use of hospital equipment does not present any danger neither to the patients nor to the medical staff. The National Board of Health is monitoring the safety level by means of a compulsory accident reporting system introduced into all Danish hospitals.

The Danish Society for Biomedical Engineering

The above accounts on historical and present-time events give some contributions to the understanding of the background for the idea of founding a national biomedical society. The founding itself took place on the 27th of November 1973 the first chairman being Professor, M.D., *E. Skinhøj* (1918-1983), who was a specialist in neurology and from 1979 also rector of the University of Copenhagen.

The objectives of the Danish Society for Biomedical Engineering are to promote the scientific and technical development of the biomedical engineering profession. To fulfill these goals contacts between persons being interested in biomedical engineering and having different education and employment are being established on a national as well as an international level.

In earlier periods one became automatically a specialist due to ones special capabilities within a certain field of profession. To day the biomedical engineer finds himself in a turbulent development and is daily overwhelmed by so much new literature that it is impossible to attend to it all on a sufficient detailed level. Experience shows that there are no other ways to solve the problem than to divide the work on as many persons as possible and organize a national as well as an international cooperation. By these means it can be avoided that the role as a specialist does not lead to stagnation but rather opens up for a profound professionalism together with a broad general view.

The demand for a national society for biomedical engineering has accordingly shown to be great and the idea of founding it has proved to be correct. The society has undoubtedly been of benefit to the members, the private enterprises and the public organizations that al together constitute the health sector in a broader sense.

The Danish Society for Biomedical Engineering, maintains relations to international societies and organizations and of course especially with the International Federation for Medical and Biological Engineering (IFMBE) and being an affiliate member, represents the federation in Denmark and is represented in its Clinical Engineering Division.

Reevaluating the definition of Biomedical Engineering

Most definitions concerning human activities can be subject to different interpreta-

tions depending on background and opinion. The more detailed and specific a definition the greater is the probability of it being the cause of conflicts in connection with job-descriptions, responsibility assignments, etc., since the freedom of its appropriate interpretation will be reduced.

The present definition seems to be appropriate not only to the members of the profession but equally important, also to other groups of professionals employed in hospitals and industry.

Future fields of knowledge and technology, which may prove useful to the biomedical profession, can be included in the definition by mere interpretation without violation of its principal meaning.

For the sake of argument one could imagine that subjects like X-rays and electronics and other important technological innovations from our century were left out from the context of the definition. This would still be applicable provided we go about 10 decades back in time. However, some flexibility of mind is required to do such an experiment of thought and the more so the further back in time we travel.

For practical purposes one could perhaps claim that medical and biological engineering has existed for about a 100 years thus giving the profession an opportunity to celebrate its 100 years anniversary in the year 2000.

ESSENTIAL SOURCES OF LITERATURE

1. Gotfredsen E. Medicinens historie. Copenhagen: Arnold Busck Inc., Copenhagen, Denmark, 1973. ISBN 87 17 01661 4.
2. Gotfredsen E. Det kongelige Frederiks Hospital. 30. marts 1957. Novo Terapeutisk Laboratorium Inc., Denmark.
3. Pakkenberg H. De første røntgeninstallationer i Danmark. Dansk Røntgenteknik Inc., 1960.
4. Møller PF. Radiologiens historie i Danmark. Bibliotek for Læger, 1960.
5. Bergmark M. Lægekunst, tro og overtro. Politikens forlag, 1968.
6. Jarløv A, Bojsen J. Report on the status of clinical engineering in five hospitalsystems in the Copenhagen area. Med Biol Eng Comput 1989; 27: 623-27.
7. Secher O. Fra ætherindånding til anæsthesiologi. Copenhagen: Simonsen & Weel A/S (Inc.), Denmark, 1965.

Reference: Holmkjær PM, Jarløv A. The development of biomedical engineering into a hospital activity. In: The Danish Society for Biomedical Engineering, ed. Aspects of biomedical engineering in Denmark. Copenhagen, 1998: 27-41.

20 years of biomedical engineering at Aalborg University – education and research

LARS ARENDT-NIELSEN, THOMAS SINKJÆR & ANNELISE ROSENFALCK

Center for Sensory-Motor Interaction, Aalborg University, Aalborg, Denmark.

Key words: Center of Excellence; Doctoral School; history; master of science; research funding.

Prof. Lars Arendt-Nielsen, Center for Sensory-Motor Interaction, Aalborg University, Fredrik Bajers Vej 7, D-3, DK-9220 Aalborg, Denmark.

HISTORY AND CURRENT STATUS

Research and education within Biomedical Engineering were active in Aalborg from the start of the 1970s. Thus, when the University Center was established in 1974 and even during the planning phase in 1970 it was suggested to establish this multidisciplinary area. In 1972 a planning group of head physicians at Aalborg Hospital and engineers from the engineering schools in Aalborg published a report which recommended to establish a strong biomedical engineering research group at Aalborg University Center which later slowly should take up the education.

In 1978 Annelise Rosenfalck was appointed professor in Biomedical Engineering at the Institute of Electronic Systems. A major problem in the first years was the fact that the Ministry of Education did not allocate research time to professors at university centers, as university centers were not considered as real universities. This slowly changed in the 1980s when the university was recognized as Aalborg University (AAU).

In 1979 Steen Andreassen joined the group, and about one year later he obtained a 3-year senior research fellowship from the Danish Technical Research Council and the Danish Medical Research Council to develop a microprocessor system to analyze electromyographic action potentials. Annelise Rosenfalck and Steen Andreassen both came from the Institute of Neurophysiology, University of Copenhagen, where professor Fritz Buchthal had created a strong tradition for interdisciplinary research.

During the first years the main activities were related to those disciplines already implemented at the Institute. These activities were related to cardiology, ultrasound, speech recognition, and audiometry, but the

new group had a great interest in electrophysiology and biomechanics and slowly changed the research interests accordingly.

In the early years grants from the Government and from the Danish Technical Research Council allowed invitations of guest scientists, one came from Lithuania and another from Israel.

In 1983 the research was expanded to include image processing and pattern recognition applied to automatic analysis and classification of human chromosomes. Erik Granum came from the Danish Technical University and had worked for three years at MRC in Edinburgh. In 1984 he obtained a 3-year senior fellowship from the Research Planning Committee of the Ministry of education. Over the years several projects in biomedical research have been carried out by the medical staff at Aalborg Hospital and by Henning Nielsen. Erik Granum was appointed full professor in Image Analysis and Computer Vision in 1989.

The interest in medical knowledge based systems began in 1984, when the department participated in an ESPRIT EU project "A Knowledge Based Assistant for Electromyography" together with University of London and software houses in Denmark and United Kingdom. This interest in medical informatics developed over the years and several international decision support research projects took place within the EU VALUE, BIOMED and TELEMATICS programs. In 1996 Stig Kjær Andersen established a Virtual Center for Health Informatics as a cooperation between Aalborg University, Århus University, the health care sector and the health care industry in Denmark. The Center aimed at establishing a network of supporting research, development and consulting as well as developing competence and expertise within information technology in health care. Furthermore, the group took a cross-disciplinary initiative to formulate a 2-year education (open university) in Health Informatics. The first year, 1994, 35 attended the education. Recently, a master program in Health Informatics has been approved, and 40 students were enrolled for a degree in 1998.

The department of Medical Informatics and Image Analysis was formed in 1986, when the Institute of Electronic Systems was divided into four departments. Image Analysis was extended to include computer vision through support from the Danish Technical Research Council and participation in ESPRIT Basic Research.

Annelise Rosenfalck retired in 1992, and in 1993 Lars Arendt-Nielsen was appointed full professor in Biomedical Engineering.

In 1993 the Department vas evaluated for the first time by an international committee consisting of three specialists in biomedical engineering [1].

In 1993 the Danish Technical Research Council and private foundations provided funding to Thomas Sinkjær for a research council professorship. This was converted into an ordinary professorship in 1997.

The real kick off for the biomedical engineering research came in 1993 when very large grants were awarded to the Department from the Danish National Research Foundation, the Danish Cancer Society and the Research councils. The award from the Danish National Research Foundation was the most prestigious. The research in biomedical engineering with focus on sensory-motor interaction was selected as one of the 23 research centers after international review of more than 350 applications. At the same time, the Danish Cancer Society selected Center for Sensory-Motor Interaction to host a center for cancer pain research. Among 74 applications three were selected after international review.

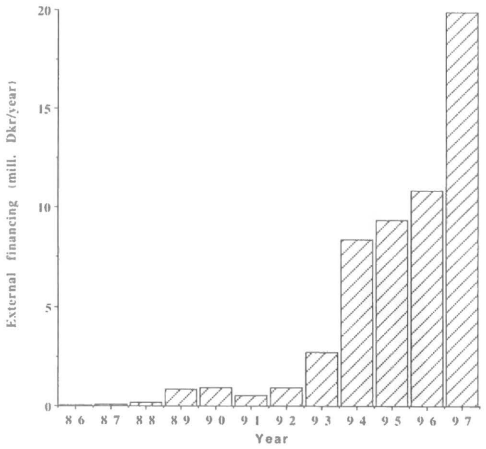


FIG. 1. The external funding for the biomedical engineering group at Department of Medical Informatics and Image Analysis, Aalborg University. In 1993 the Center for Sensory-Motor Interaction was established.

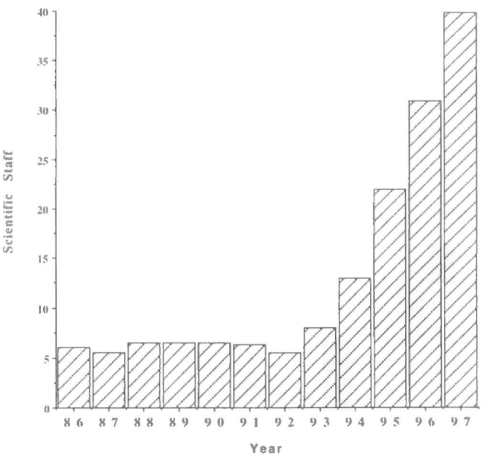


FIG. 2. The development in number of scientific biomedical engineering staff employed in the biomedical engineering group at Department of Medical Informatics, Aalborg University (up to 1993) and at Center for Sensory-Motor Interaction (after 1993).

These grants allowed Thomas Sinkjær and Lars Arendt-Nielsen to establish Center for Sensory-Motor Interaction (SMI), and Thomas Sinkjær was appointed as director of the Center.

The Center was situated in new, modern buildings. The laboratories were all equipped with new and up-to-date equipment.

A substantial network of national and international collaboration ensures a direct coupling between the basic experimental studies performed at SMI and the clinical as well as industrial applications.

The economical situation for SMI developed well, and in 1997 the annual external funding exceeded DKK 20 mill (Fig. 1). The stable economical situation allowed the Center to organize a secretariat with an academic administrator. The staff increased in the same period to include a total of 40 employees in 1997 (Fig. 2).

In 1998 a large program on interaction between the biomedical industry in Denmark and biomedical engineering research institutions are headed by SMI. The program is supported by the Research Council by DKK 20 mill over four years. The program is the first of its kind, and hopefully it will facilitate exchange of ideas and personnel between industry and universities and visa versa. In the annual report from the University [2] you can read more about medical engineering education and research at Aalborg University.

CENTER FOR SENSORY-MOTOR INTERACTION

The interpretations of biomedical engineering are very different. At some institutions, the biological aspects are highlighted whereas others concentrate on theoretical/applied engineering aspects. However, the experience is that research institutions combining and integrating the two aspects by bridging the gab from basic science to clinical application obtain substantial synergism and facilitation of research.

The Center for Sensory-Motor Interaction

(SMI) is a biomedical engineering research center within the field of neuroscience. The Center is mainly involved in bioengineering combined with somato-sensory research. The research activities are concentrated on motor control, experimental pain research and rehabilitation technology (neural prostheses). The studies involve electrophysiological recordings from nerves, muscles and brain.

The activities in motor control and pain research have been consolidated over 10 to 15 years, whereas the activities in neural prostheses have been developed over the last five years. All activities are characterized as multi-disciplinary fields of research involving a wide range of biomedical engineering aspects and experimental neuroscience disciplines.

SMI benefits from its participation in a number of institutional networks within biomedical engineering, neuroscience and clinical disciplines. A substantial resource is present in the established research cooperation and partnerships with a number of Danish, European and North American research centers, hospitals and companies. Currently, the cooperation includes some 25 organizations in 12 different countries.

SMI has access to 10 well-equipped laboratories for quantitative analysis of the human motor system, and one laboratory for the development of implantable electrodes used in functional electrical stimulation systems in the restoration of paralyzed persons.

At the Institute of Pathology, Aalborg Hospital very good facilities for animal experiments have been established and five to seven researchers from SMI are working at these facilities.

Motor Control: The objective is to study the principles governing human movement. The research comprises theoretical and experimental analyses of the segmental interaction between motor and sensory control mechanisms in the central nervous system and the biomechanical structures of lower extremities in healthy and motor impaired persons. This includes a description of the neural networks in the spinal cord which constitute the movement pattern and reflexes, the interaction with the electrophysiological and biomechanical properties in the muscles, and the interaction between muscle pain and motor function under static and work-related conditions.

Pain Research: The aims of pain research are to develop and apply quantitative techniques to induce pain in human skin, muscles and viscera and to develop and apply electrophysiological and psychophysical techniques to assess the induced pain-related responses under normal and pathophysiological conditions. Human experimental pain research is a way of gaining quantitative insight into the mechanisms involved in transduction, transmission and processing of pain. As the pain system can change its response characteristics to various stimuli, methods are needed to assess the reactions to different natural sensory stimuli such as mechanical, thermal and chemical stimuli in order to characterize changes in sensory processing. Better knowledge of pain mechanisms can lead to better management.

Neural Prostheses: Every year thousands of people are paralyzed due to illness (e.g. stroke) or accidents. Our approach is to exploit the information and functionalities retained in the natural sensory-motor systems – even with paralyzed and seriously ill people, i.e., to re-establish the communication between the sensory system and the muscular system that has been disrupted in paralyzed people. The methods are based on

the neural coding in the human sensory-motor system and on new technologies for stimulation, registration and processing of electrical signals from muscles and nerve tissue. These technologies are not yet fully developed. One major problem is how to record and process the extremely weak electrical signals coming from the nerves (a few microvolts).

UNDERGRADUATE EDUCATION

Aalborg University has a unique educational philosophy that emphasizes project-oriented education. There is an excellent match between research projects interfacing medicine with technology and the innovative educational philosophy of the university.

Many M.Sc. projects have been carried out in collaboration with the health sector and industry, and the trend is that many students spend the last semester abroad.

There are no statistics showing the number of students who graduated as biomedical engineers over the years. We have estimated that in the years since 1976 there have been about 15/year adding up to more than 300. Of these 5-10% is now working in hospitals, about 10% in biomedical industry and 10-15% in research at Danish and international universities. The remaining group is primarily working in the electronic and IT industry.

Over the years the education in biomedical engineering has changed slightly. During the first years (late 1970s, early 1980s) the biomedical engineering education was developed and all master students followed courses in biomedical engineering at the 9th semester. These courses dealt with basic aspects of biomedical instrumentation, physiology and terminology. Specific focus was on recording of bioelectrical signals and volume conduction of bioelectrical fields. All students visited different hospital departments in Aalborg, Århus and Copenhagen. Medical personnel from the local hospital were affiliated as external teachers.

Later a specialization in biomedical engineering was established. Course and projects were mainly related to the 9th semester and the 10th semester was spent on the final thesis work.

From 1st January 1998, an international master education in biomedical engineering was established. Students with a bachelor degree or 8th semester or a M.Sc. education can enter this international program and receive a M.Sc. degree in biomedical engineering. All courses are taught in English.

PH.D. EDUCATION AND GRADUATE SCHOOL

Due to the size of the department and to the relatively small number of grants available from the faculty, the production of "licentiater" (later Ph.D.) from the department was low during the1980s.

In 1984 and 1985 the university awarded five Ph.D. grants to the basic electrophysiological research. The projects were concentrated on EEG during sleep and anesthesia, EMG and muscle fatigue, modulation of stretch reflexes and quantitative assessment of pain.

In 1985 Hans Harding finished an industry-related (erhvervsforsker) Ph.D. thesis (licentiat) from the department. In 1987 Lars Arendt-Nielsen defended his Ph.D. (licentiat) thesis on quantitative assessment of pain and in 1988 Thomas Sinkjær defended his thesis on modulation of the human stretch reflex.

In 1993 a new law on research education was passed by the Danish Parliament. The law has advantages and disadvantages. The major disadvantages are that the time for research is reduced, and the status of candidates changed from university employee to

student. The major advantage is that the system strongly encourages the students to finish their thesis within three years. Furthermore, it has strengthened the supervision and there has been focus on collaboration with other institutions (mainly international institutions). Together with the new Danish Ph.D. law, the total number of government Ph.D. scholarships increased dramatically. Although students are obliged to visit an international laboratory, this does not automatically mean an internationalization of the Danish research environment, and the number of visiting scientists has not necessarily increased.

At the Faculty of Technology and Science, Aalborg University, a graduate school was established in 1993, and the students affiliated with biomedical research were enrolled in the program on Electrical and Electronic Engineering.

After the establishment of SMI and the Graduate School at the Faculty the production of Ph.D. students within biomedical engineering increased (Fig. 3).

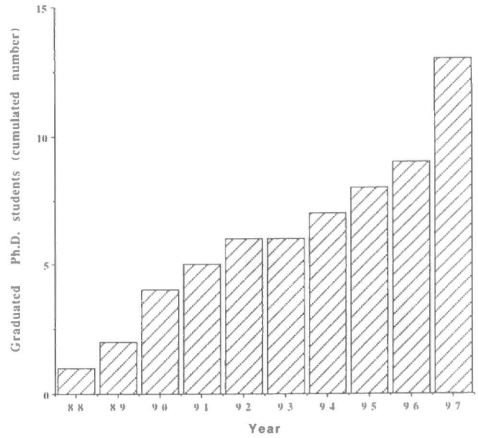


FIG. 3. The cumulated number of graduated Ph.D. students (or "licentiater" up to 1996) with a degree in biomedical engineering.

In 1996 SMI was asked by the Danish National Research Foundation to formulate an application for a doctoral school in biomedical engineering. The idea was to have a specific Ph.D. program within biomedical engineering. The submitted application was evaluated by an international panel and approved to start 1st January 1997. The School was opened by the Minister of Research Jytte Hilden, and Lars Arendt-Nielsen was appointed as director.

The reasons for the Danish National Research Foundation to establish the doctoral school at SMI were to:

- meet the increasing demand from national and international enterprises for candidates with a Ph.D. degree in biomedical science and engineering
- establish an internationally recognized and efficient Ph.D. training comparable to the best in the world
- act as a model for efficient Ph.D. training in Denmark
- recruit highly qualified Ph.D. students from abroad and internationally recognized scientists within biomedical science and engineering
- maintain and further develop a well-organized and efficiently managed inter-disciplinary Ph.D. program.

One of the requirements from the Danish National Research Foundation was to have 50% foreign students. The foundation awarded 15 Ph.D. grants and six senior scientist grants. SMI was obliged to raise 15 additional grants. The course and research program should try to broaden the scope of SMI by including new research areas. The first new area to be included was microneurography.

The post graduate education program which combines biomedical science and engineering involves:

- a combination of inter-related life science and engineering disciplines

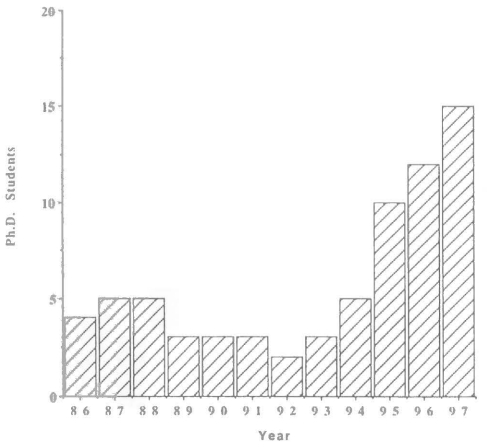


FIG. 4. The number of Ph.D. students within biomedical engineering. As can be seen a substantial increase was obtained after the establishment of Center for Sensory-Motor Interaction in 1993.

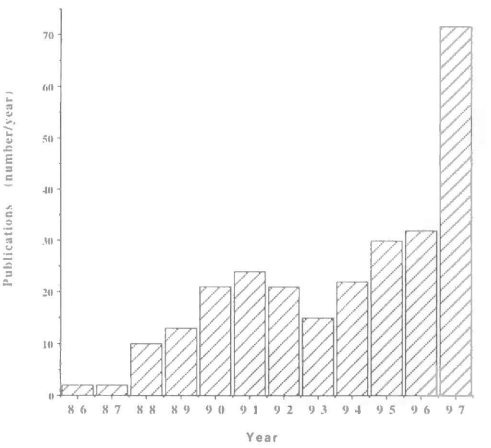


FIG. 5. The development in number of papers published in international journals with peer-review. Only papers from the biomedical engineering group at the department are included.

- scientists with different and hybrid, educational backgrounds
- close contacts with clinical and theoretical departments and to the industry.

The multi-disciplinary nature of the program provides a firm foundation for careers in many areas in public and private health care institutions, research and industry.

During 1997 a Ph.D. course program was formulated involving a total of eight different courses equal to 124 hours. At the end of 1997 15 students were enrolled in the program – six from Denmark and nine from abroad (Japan, Ukraine, Slovenia, Spain, France, Holland, United Kingdom and Norway) (Fig. 4).

DISSEMINATION

From 1988 the number of scientific publications within the biomedical field began to increase dramatically from a couple a year to up to 20 (Fig. 5).

This increase in the scientific production was partly due to support from the Faculty for Technology and Science as they awarded several grants to additional research time and traveling.

After the establishment of SMI the number of publications increased even further and reached a level of around 70 international publications each year (Fig. 5). An interesting observation is that approximately 90% of all publications is produced in collaboration with national or international collaborators whereas most of these are from clinical departments.

A total of three Doctoral Degrees in Medical Sciences (dr.med.) have been awarded to researchers from the department. One was defended at Århus University, Faulty of Medical Sciences, in 1994 [3] and two were defended at Aalborg University under auspices of University of Copenhagen, Faculty of Medical Sciences [4-5].

Besides the scientific production the Center participates in many research and research policy related activities. Furthermore, a substantial number of newspaper reports have been written over the years together with programs on radio and television in Denmark and abroad.

FUTURE PERSPECTIVES

It took 20 years to establish a strong international research environment in biomedical engineering at Aalborg University. Today the field has its own international master education, international Ph.D. education and center of excellence.

The research environment concentrated around SMI seems to have good perspectives concerning future consolidations. The major problem is how to anchor the research environment at the university as only four faculty positions are affiliated with SMI currently.

Hopefully, the Danish biomedical industry will continuously utilize the research at SMI and participate in programs aiming at educating more industry-related Ph.D. candidates in the future. The Danish biomedical industry allocates a substantial amount of its money to research and development, and qualified Ph.D. candidates from the Doctoral School in Biomedical Science and Engineering are a valuable resource for this industry.

The substantial internationalization of the research at SMI is expected to continue in the future as Ph.D. students graduating from the SMI Doctoral School hopefully will return to their respective countries and advocate for the research environment and for the School.

The key words at SMI will in future remain: internationalization, interdisciplinarity, networks and efficient research management.

REFERENCES

1. Evaluation of research activities at Department of Medical Informatics and Image Analysis 1986-1992. Department of Medical Informatics and Image Analysis, Institute of Electronic Systems, Aalborg University, Denmark, 1994: 1-124.
2. Aalborg Universitet, Forskningsberetning 1995 & 96, Aalborg Universitet: 1-356.
3. Arendt-Nielsen L. Characteristics, detection and modulation of laser-evoked vertexpotentials. Acta Anaesthesiol Scand 1994; 38, Suppl 101: 1-44.
4. Toft E. Mechanical and electromyographic stretch responses in spastic and healthy subjects. Acta Neurol Scand 1995; 92, Suppl 163: 1-24.
5. Sinkjær T. Muscle, reflex and central components in the control of the ankle joint in healthy and spastic man. Acta Neurol Scand 1997; 96, Suppl 170: 1-28.

Reference: Arendt-Nielsen L, Sinkjær T, Rosenfalck A. 20 years of biomedical engineering at Aalborg University – education and research. In: The Danish Society for Biomedical Engineering, ed. Aspects of biomedical engineering in Denmark. Copenhagen, 1998: 43-50.

Biomedical engineering at the Technical University of Denmark

JØRGEN ARENDT JENSEN[1], OLE TRIER ANDERSEN[1], JENS E. WILHJELM[1], BENT KOFOED[2] & LARS KAI HANSEN[3]

[1]Department of Information Technology, [2]Department of Physics, [3]Department of Mathematical Modelling, Technical University of Denmark, Lyngby, Denmark

The paper gives a brief overview of the biomedical engineering research and education at the Technical University of Denmark. An account of the research activities since the 1950s is given, and examples of major efforts within ultrasound, biomagnetism, and neuroimaging are described. The evolution of the teaching activities since the late 1960s along with an account of the recent initiatives to make a biomedical engineering profile at the university is described.

Key words: Biomagnetism; neuroimaging; research; teaching; ultrasound.

Jørgen Arendt Jensen, Department of Information Technology, Build. 344, Technical University of Denmark, DK-2800 Lyngby

1. INTRODUCTION

Biomedical engineering has a long tradition at the Technical University of Denmark (DTU). A large range of projects in very diverse areas has been carried out and it is our aim to give some examples of the research from the last 25 years. A general overview of the development of Biomedical Engineering (BME) is given in Section 2, and some specific projects made over the years are described in more detail in subsequent sections. The processing of medical ultrasound data for resolution enhancement and for detecting atherosclerotic plaque is described in Section 3 and 4, respectively. Application of non-linear signal processing in neuroimaging is illustrated in Section 5, and finally, the measurement of faint biomagnetic fields using superconducting techniques is described in Section 6.

Biomedical engineering has been taught at DTU for more than 25 years. The first introductory course dates back to the late 1960s and was given by Dr. Saul Aronow from Massachusetts General Hospital. The history of this and other teaching activities is given in Section 7, which also gives a description of the many recent initiatives within the biomedical engineering education at DTU.

2. EVOLUTION OF BIOMEDICAL ENGINEERING RESEARCH AT DTU

A dating of 'first appearance' of BME at the Technical University of Denmark will depend on how this concept is defined. People who claim that the first biomedical engineers were the chemists might argue that BME was there almost from the beginning. But if chemistry is left out of account the 1950s should be appointed the decade of the first 'visible' research projects at the Technical University of Denmark within the field of BME. One of the projects from this period, which received public attention, was an investigation of explosion risks in anesthesia equipment carried out by professor R.E.H. Rasmussen and his group at the Department of Technical Physics.

During the 1960s BME projects were emerging in many places at the university, and more than ten departments have contributed within BME, thus reflecting the breadth of this field. However, most of the departments were involved with BME projects only occasionally, while continuous BME research took place at two departments, Electronics Laboratory and Department of Mechanical Technology. At the Electronics Laboratory, founded in 1961 and headed by professor Georg Bruun, BME played an important part almost from the beginning. One of the first guest researchers was Victor Pollak who made studies on the characterization of bioelectrodes and amplifiers for myography, and report *number one* from the laboratory was a survey of BME education in the United States and other foreign countries. It was written by Ph.D. student Hans Kunov, who is now professor of BME at University of Toronto. The subject of Hans Kunov's Ph.D. study was 'Nonlinear Transmission Lines Simulating Nerve Axons' (1966). The second Ph.D. study, 'Power Supply for Heart Pacemakers' (1969) was done by Jørgen Pontoppidan. Studies on amplifiers for bioelectric recording, and impedances of skin, body, and electrodes were also made in the 1960s by Leif Otterstrøm, and equipment for bladder stimulation was developed by Ole Trier Andersen and Peter Speldt in cooperation with M.D. Tage Hald, Herlev Hospital.

Examples of BME projects at other university departments during the 1960s are:

- Development of blood pumps, membrane support, and control systems for dialysis equipment at the Department of Mechanical Technology
- Measuring equipment for the diagnosis of hearing impairment at the Acoustics Laboratory
- Numerical processing of radio renography at the Department of Numerical Analysis
- Studies on bioelectrodes and blood flow measurements at the Applied Electronics Laboratory
- Water transport in synthetic membranes at the Department of Physical Chemistry.

During the 1970s much research and engineering design work was devoted to the development of aids for the handicapped, probably most intensively at the Electronics Laboratory where 15 master thesis projects and 4 Ph.D. studies were carried through within this area. In one of the Ph.D. studies, 'A TV-display based interactive writing aid for the severely motor handicapped' (Ib M. Tolstrup 1976) a communication system for almost totally paralyzed persons was developed. On the TV screen letters and other signs were displayed to be selected one by one by means of some transducer device, designed according to the abilities of different patient groups: One patient might con-

trol the selection with a slight movement of the head or a toe, another with eye blinking, and so on. This communication system, called VIDIALOG, was put into production by the Danish company ELMI A/S.

A series of projects were made with the goal of designing aids for the blind, e.g., to help them move around, use a computer terminal, or read a text. Possibilities of improving the white cane by means of ultrasound were investigated, and vocoders were developed to serve as an acoustic link between the blind person and the computer. Different attempts were made to use the blind person's other senses for perceiving the shape of a letter or a figure by electronic scanning and subsequent transformation into a tactile or acoustic signal. In two Ph.D. projects, 'Reading Aid for the Blind – Automatic Input System' (Peder H. Krabbe 1981) and 'On the Automatic Recognition of Characters in a Reading Machine for the Blind' (John E. Aasted Sørensen 1982) a system was developed for text scanning and conversion to ASCII data.

At the Department of Mechanical Technology an electric drawing machine was developed in cooperation with Geelsgaard Kostskole. Also this system could be controlled by people with reduced hand function or by people who can use a pointer mounted at the forehead or a mouth stick. Other projects at the same department concerned investigation and improvement of artificial hip joints. This work was done in cooperation with Gentofte Hospital. The Acoustics Laboratory made investigations and design of suitable sound signals as aids for the blind in the traffic, signaling 'red' and 'green', and developed electronic systems for automatic amplification control in hearing aids.

Within the area of Functional Electrical Stimulation a series of projects have been carried through at the Electronics Laboratory and from 1997 the Department of Mathematical Modeling supervised by associate professors Steffen Duus Hansen and Ole Trier Andersen. In 1984 a master thesis project was made with the goal of improving the gate of a person with partly paralyzed muscles in the legs. This was done with carefully designed sequences of stimulation pulses delivered to skin electrodes. In the 1990s three Ph.D. studies were made in cooperation with M.D. Fin Bjering Sørensen from the University Hospital's Hornbæk department for spinal cord injured. The goal of these projects (Ernst-Ulrik Haxthausen 1992, Søren Sennels 1996, Rune Thorsen 1997) was to develop a device for stimulation of certain muscles in the forearm in order to enable patients with partial paralysis to perform a simple movement, called the key grib. In this project stimulation is done exclusively via skin electrodes, and the muscle stimulation is controlled by myoelectric signals created by the same muscle. This signal requires advanced signal processing to prevent positive feedback, which might generate serious spasms in the stimulated muscle.

3. MEDICAL ULTRASOUND

The use of medical ultrasound has increased tremendously since its introduction into the market in the 1970s. This is due to the easy application of the method and the use of non-ionizing radiation, which makes the investigation painless and risk-free for the patient. The images, however, look quite different from X-rays or other image modalities used in the hospitals; most notable the contrast and resolution is often low and the speckle pattern is very pronounced. A project was therefore initiated in 1987 at the Electronics Laboratory for increasing the contrast and resolution of ultrasound images. The project was a collaboration be-

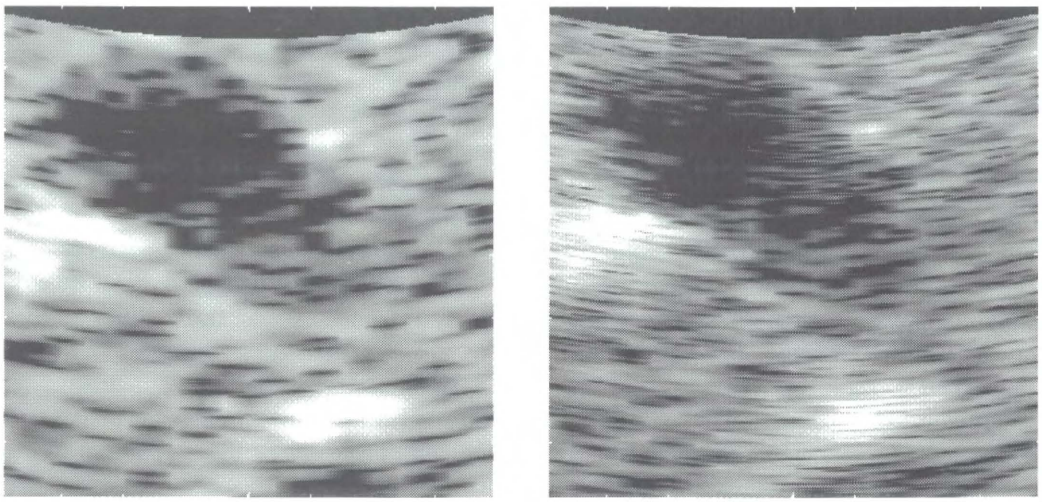


FIG. 1: Normal (left) and deconvolved (right) image from the liver of a 28 years old male. The dark area is the hepatic vein and the brighter surroundings are the liver tissues. The images cover an area of 2×2 cm. An increase in axial resolution of a factor of 2.4 was obtained (from [1]).

tween the Laboratory, Herlev University Hospital's department for ultrasound, and the commercial manufacturer Brüel & Kjær in Nærum. The funding was provided by the Danish Science Foundation, which made it possible to establish an ultrasound laboratory with the necessary measurement equipment and computers to obtain and process digital ultrasound images. The equipment was constructed over a two-year period and moved to Herlev University Hospital for clinical trials. Here over 280 clinical images where acquired in digital form and subsequently processed using an adaptive signal processing algorithm developed during the project. The algorithm takes into account and corrects for the actual transducer pulse used, the attenuation of the ultrasound by the tissue, and the noise in the acquired data making the approach self-calibrating. A result of this processing is shown in Fig. 1. The image shows part of a liver from a healthy 28 years old male subject. The conventional image is on the left with the hepatic vein being the dark area, and the processed image is on the right. An increase in axial resolution of a factor of 2.4 was obtained from the processing without introducing significant new noise into the image.

The efforts in medical ultrasound have been continued and have generated a number of papers within ultrasound signal processing and acoustics. The group has also been responsible for developing a simulation program for ultrasound images in which fairly realistic images of computer phantoms can be made. The program has been posted on the Internet and is used by a number of universities and ultrasound manufacturers around the world in the design of new ultrasound scanners. Another topic for the group has been the use of ultrasound for estimating blood velocity. This work resulted in a book and doctoral dissertation (dr.techn.) on ultrasound systems for blood velocity estimation [2].

The efforts within medical ultrasound are continued and expanded in the newly established Center for Fast Ultrasound Imaging, which was started on January 1, 1998 at the Department of Information Technology. The

center is a collaboration between the Department of Information Technology at the Technical University of Denmark, Herlev University Hospital, Gentofte University Hospital, and the manufacturer B-K Medical A/S. The purpose is to investigate methods for making fast ultrasound images using parallel beam forming and coded signals and using these techniques for creating better flow images using adaptive signal processing. This includes the development of algorithms capable of finding the flow transverse to the ultrasound beam, and the development of real-time three-dimensional imaging. The various techniques will be tested clinically during the center's four years of existence from January 1, 1998 to December 31, 2001. The funds for the center are provided by the Danish Science Foundation (10 mill. DKK) and the company B-K Medical A/S (4 mill. DKK). The director of the center is Professor, Dr.Techn. Jørgen Arendt Jensen.

4. CAROTID PLAQUE VISUALIZATION WITH ULTRASOUND

Another important application of ultrasound is diagnosis of vascular diseases. An important area is detection of atherosclerosis of the carotid arteries, which is a common cause of stroke, the leading cause of disabling disease and the third most common cause of death.

Center for Arteriosclerosis Detection with Ultrasound (CADUS) was formed in 1993 by MD Henrik Sillesen and Ph.D. Jens E. Wilhjelm with the specific purpose of improving and developing ultrasound methods and equipment for quantitative diagnosis of atherosclerosis. The center is partly supported by the Danish Medical and Technical Research Councils. The participants are: Department of Information Technology, DTU; Rigshospitalet, University of Copenhagen; the University Hospital in Gentofte; B-K Medical A/S; Skejby University Hospital and Worcester Polytechnic Institute, Massachusetts, USA.

Atherosclerosis arises from the formation of material deposits (plaque) on the inside of the artery wall. The plaque slowly builds up over a number of years. The pathogenetic mechanism is believed to be embolic in the large majority of cases, with either fragments of the atherosclerotic lesion or thrombotic elements of the plaque surface braking off and moving with the blood into the brain. Once a major brain artery is occluded by such an embolus and brain damage has resulted, no specific therapy exists today. Therefore, prophylactic measures are of great importance, and recently, multicenter studies have shown that surgical removal of the atherosclerotic plaque decreases the risk of strokes.

Ultrasound Doppler techniques have been shown to be accurate in the diagnosis and quantification of the *size* of carotid stenosis and today this modality is the screening method of choice and has in many institutions supplanted arteriography, also as the preoperative diagnostic test. Recent investigations suggest, however, that the composition, rather than the size is an important factor governing the risk of stroke. The composition can be assessed from the appearance of the ultrasound image, but the quality of current ultrasound imaging does not allow for determination of the condition for the individual patient.

For the purpose of improving ultrasound imaging of plaque, CADUS has engaged in developing technologies and equipment for *multi-angle spatial compound imaging* (MACI). With this technique, images are recorded from different angles and combined to an image which is less angle-sensitive and contains less speckle noise, [5]. The multi-angle ultrasound data also

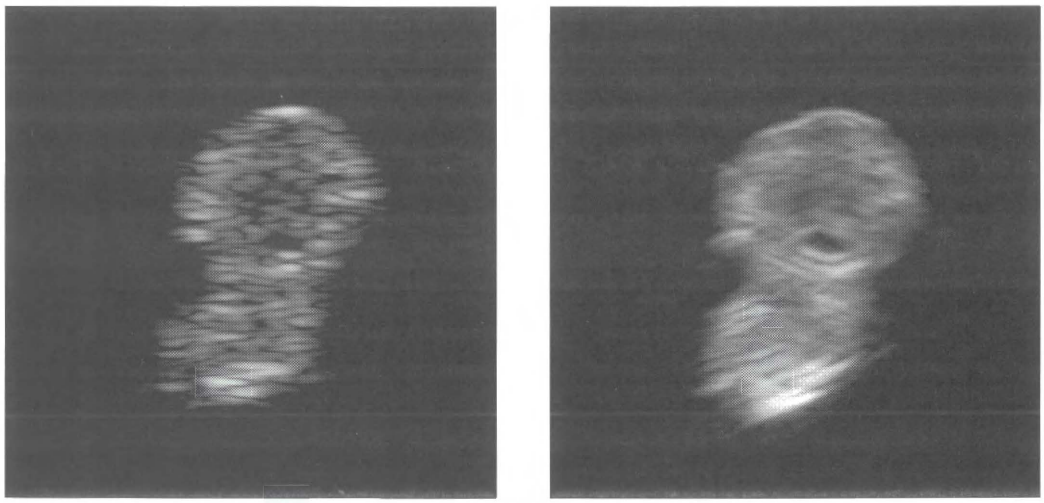


FIG. 2: 7.5 MHz conventional (left) and spatial compound (right) images of atherosclerotic plaque removed form the carotid artery by surgery. The images show cross-sectional views perpendicular to the axis of the internal carotid artery and the smaller external carotid artery. The image to the right contains less speckle noise and provides a better outline of the plaque. Notice how the residual lumen is clearly visible in the image at the right. The image covers an area of 20 by 20 mm. (from [4]).

have the potential for plaque *materials differentiation*, i.e., distinguishing soft plaque materials (which are considered the most dangerous) from hard. An entire computer controlled off-line ultrasound scanner capable of recording B-mode images from arbitrary angles and combining these to compound images has been designed and build by Ph.D. student Søren Kragh Jespersen. *In vitro* scanning of a series of formalin fixed plaques (removed during surgery) has shown that the compound images provide much better visualization of the plaque (Fig. 2) and that the angle-dependent ultrasound data have potentials in material classification.

CADUS is involved with many other clinical projects and examples include investigation of the influence of formalin fixation of fresh tissue, [6], and estimation of first and second order features from conventional clinical ultrasound images for the purpose of investigating the correlation with histological analysis.

On the technical side, a complete simulation program for calculating the received electrical signal in a pulse-echo system, due to an arbitrarily curved smooth surface, has been developed and implemented in collaboration with Prof. Peder C. Pedersen at Worcester Polytechnic Institute, Massachusetts, USA. The simulation model has been compared with other models as well as experimental data, and very good agreement has been found, [7]. The advantages of the model are large flexibility and very fast calculation speed for a given precision.

5. NEUROIMAGING

The field of neuroimaging, "brain mapping", is an important and rapidly expanding area in current neuroscience. The main brain map techniques are Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI). Furthermore, electroencephalography (EEG) and magnetoencephalography (MEG) are used to map the electric and magnetic activity of the brain. PET and MRI provide high-resolution vol-

ume data while EEG and MEG provide high temporal resolution. Combining neuropsychology, 3D brain scan techniques, and spatio-temporal statistics, neuroimaging offers a unique *in vivo* window to the function of the human brain. Experiments typically involve neuropsychological formulation of stimuli (e.g., simple motor exercises or visual tasks), definition of scanning protocols (volunteer subjects, repetitions) and finally data analysis and visualization of patterns of focal activation.

PET offers high sensitivity and biochemical specificity, and the physical and chemical mechanisms are quite well understood. Traditionally MRI has been used mainly to study neuroanatomy and neuropathology. Recent developments have permitted the extension of MRI techniques to visualization of human brain *function* (fMRI). Compared to PET, fMRI has better spatial resolution and its temporal resolution is orders of magnitude better. Today whole brain scans can be obtained at second intervals. In addition, since fMRI is totally non-invasive, scan sessions can involve many repetitions on a given individual. The main drawback of fMRI relative to PET is the lack of a detailed neuro-biological theory of the contrast and the inevitable audible noise from magnetic gradient switching during scan sessions.

The main objectives of functional neuroimaging research are to formulate statistical models of macroscopic brain function, to extract the salient image features, to organize image and activation protocol data sets, and to visualize activation patterns. The global dissemination of data, software and results on the World Wide Web (WWW) is an important practical issue in functional neuroimaging. Functional neuroimaging using fMRI scanning protocols now faces a situation where massive amounts of data are routinely collected, creating an urgent need for new efficient processing techniques. At present only quite primitive linear signal processing techniques have been applied, so it is evident that there is significant potential for breakthrough engineering innovations in this area. In particular, adaptive non-linear signal processing techniques can lead to efficient exploration of the new spatio-temporal phenomena present in fMRI data sets.

Following President Bush's and the US Congress' declaration of the 1990s as the Decade of the Brain, 1997 was celebrated as the "Year of the Brain" in Denmark. In Denmark the Research Councils launched the "Interdisciplinary Neuroscience Programme" and in the US the "Human Brain Project" was founded by a number of governmental funding agencies, now under the leadership of the National Institutes of Health. In the formulation of the American Human Brain Project significant emphasis is put on visualization and neuroinformatics. A main objective of that program has been to support the innovation and dissemination of advanced data analysis tools and databases, and also Web tools for global interactivity.

The neuroimaging activities at the Department of Mathematical Modelling (IMM), DTU, are conducted by Associate Professor Lars Kai Hansen and take place within an international consortium funded by the American Human Brain Project, the European Community, and by the Danish Research Councils. The activities involves neuroscientists, neuropsychologists, physicists, mathematicians, statisticians, computer scientists and health informatics specialists in the US and in Japan: Minneapolis VA Medical Center; University of Minnesota; Florida State University; Massachusetts General Hospital, Boston; Department of Psychiatry, Harvard Medical School; Akita Research Institute of Brain and Blood

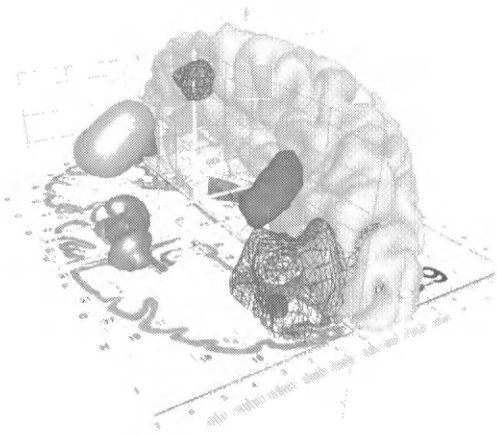


FIG. 3: A virtual environment on the World Wide Web for presentation of neuroimaging experiments. The environment is based on a standard geometric frame of reference that allows comparison of different experiments. The so-called Virtual Reality Modeling Language (VRML) allows the user to navigate in the environment and the objects are hyperlinked to other Web sites creating a very rich platform for communication of neuroinformatics. The VRML models, software and on-line papers related to the neuroimaging research at IMM are available from http://hendrix.imm.dtu.dk.

Vessels, Japan. The national collaborators are at the National University Hospital, Rigshospitalet; the Niels Bohr Institute, University of Copenhagen; Psychological Laboratory, University of Copenhagen; Clinical-Physiology/Nuclear Medicine, Rigshospitalet, University of Copenhagen; and the Danish Center for Magnetic Resonance, Hvidovre Hospital.

The work at IMM is focused on design, evaluation, and visualization of adaptive non-linear signal processing models. A generic tool for visualization of high dimensional non-linear statistical models, the so-called Saliency Map, has been developed and used in a number of functional studies. A new scheme for fast, automatic, volume "warping" for intersubject co-registration has been developed and used in PET group studies assisting in the finding of new activated areas under saccadic eye movements. A comprehensive software toolbox for spatio-temporal analysis of fMRI is to be released.

An important aspect of the group's work concerns "neuroinformatics" combining visualization and WWW interactivity in virtual environments. The group has pioneered the use of the Web virtual reality standard VRML (Virtual Reality Modeling Language) in the context of neuroimaging.

6. BIOMAGNETISM

It has since the 1970s been possible to record magnetic fields generated from electric currents in human nerves and muscles. The activity of the brain and heart can be measured using advanced superconducting techniques like SQUIDs (Superconducting Quantum Interference Device). From this the research topic of Biomagnetisme has evolved, which is a multi-disciplinary research area encompassing physics on one side and biology and medicine on the other. The area has undergone a tremendous development during its 25 years of existence.

The biomagnetic group at the Department of Physics, DTU was established in 1979 through the acquisition of a one-channel SQUID system. A seven-channel system acquired in 1987 is the only one in Denmark capable of measuring magnetic fields from electric currents in biological tissues (see Fig. 4). The Department performs measurements on human volunteers and neurologic and cardiologic patients as well. The measurements cover both fundamental scientific experiments and experiments with the purpose of developing new diagnostic methods for the clinic.

The purpose of the first type of measurements is the localization of areas of the brain that is activated by either different

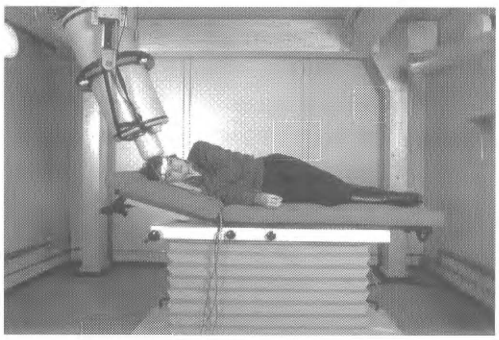


FIG. 4: SQUID system used for measuring biomagnetic signals at the Department of Physics.

sensory stimuli or by decision processes, that involves finger movements. The fundamental scientific experiments also include studies of spontaneous brain oscillations. The diagnostic experiments investigate spontaneous activities (brain waves) of patients suffering from epilepsy or tinnitus. The magnetic fields measured from cardiologic patients are generated from the muscle activity in the heart and the sources of pathogenic signals are sought localized.

7. EDUCATION

The first BME course at the university, entitled Medical Electronics, was given in 1969 by Ph.D. Saul Aronow from Massachusetts General Hospital, Boston, USA, who was guest professor at the Electronics Laboratory. During his one-year visit, sponsored by the Fulbright Foundation, professor Aronow also supervised a series of BME thesis projects and gave invaluable inspiration to the teachers at the laboratory. The course in Medical Electronics was continued by associate professor Ole Trier Andersen. Guest lecturers from hospitals, mainly Rigshospitalet and Gentofte and Glostrup Hospitals, and from industrial BME companies have contributed with inspiring lectures in special topics such as cardiology, clinical laboratory instrumentation, nuclear medicine, medical technology assessment *etc.* About 1500 students and many guests from industrial companies have until now attended this course, and about 160 students have made thesis projects in BME at the Electronics Laboratory, mostly in collaboration with hospital departments or industrial companies.

In 1971 the Electronics Laboratory proposed that a professorship of bioelectronics at the Technical University be established. The university senate appointed a BME committee, which was asked to give proposals concerning the placement and future of BME at the university. The committee, headed by professor Georg Bruun, proposed in a report January 1973 that good facilities for biomedical experiments should be established at a single department, and that BME projects primarily should be created on contacts to institutions and companies outside the university. A further result of the work in the BME committee was the establishment of an introductory course in human physiology for electrical and mechanical engineering students. This course which has been given by M.D. Steen Dawids at the Department of Control and Engineering Design has served as a prerequisite for the Medical Electronics course. A similar introductory course in physiology was established later especially for chemical engineering students.

In 1995 the university selected 12 focus areas of which biomedical engineering was one. This created the momentum to expand the biomedical area with more staff and thereby the possibility of a larger range of courses. A professorship in biomedical signal processing was filled by Jørgen Arendt Jensen in May 1997 and an associate professorship in biomedical engineering by Jens E. Wilhjelm in December 1997. A further associate professorship will be filled in 1998. A workgroup headed by Jørgen

Arendt Jensen was formed in 1996 and made a proposal for a biomedical engineering education at DTU [3]. A series of seven new courses was suggested to supplement the regular courses given at DTU and a plan for a biomedical engineering degree was given. The proposal was presented at a symposium for biomedical companies and the public sector in December 1996, and was very well received. Currently three of the new courses are given and others are being planned for the next years. The course Medical Imaging Systems was given in the autumn of 1997, and the students here made ultrasound and CT images from clinical data. The hands-on experience was further expanded in the course Hospital Tuition in which the students spend 3 weeks at different hospital departments. The course was given in collaboration with all major hospitals in the greater Copenhagen area. It is the goal to have a formal biomedical engineering education in place around the end of the century.

REFERENCES

1. Jensen JA, Mathorne J, Gravesen T, Stage B: Deconvolution of *in-vivo* ultrasound B-mode images. Ultrasonic Imaging 1993; 15: 122-33.
2. Jensen JA: Estimation of blood velocities using ultrasound. A signal orocessing approach. Cambridge University Press, 1996.
3. Jensen JA., Andersen OT, Christensen MS, Conrad F, Grunkin M, Korsbech U, Sjøntoft E, Søndergaard I. Proposal for biomedical engineering education at DTU (in Danish). Department of Information Technology, DTU, 1996.
4. Jespersen SK. Tools for improving the diagnosis of atherosclerotic plaque using ultrasound. Ph.D. thesis. CADUS. Department of Information Technology, DTU. November 1997.
5. Jespersen SK, Wilhjelm JE, Sillesen H. Multi-angle compound imaging. Accepted for publication in Ultrasonic Imaging.
6. Wilhjelm JE, Vogt K, Jespersen S K, Sillesen H. Influence of tissue preservation methods on arterial geometry and echogenicity. Ultrasound Med Biol 1997; 23, No. 7: 1071 -82.
7. Jespersen SK, Pedersen PC, Wilhjelm JE. Modeling of received signals from interfaces of arbitrary geometry. Submitted for publication in IEEE Transactions on Ultrasonics, Ferroelectrics and Frequency Control, 1997.

Reference: Jensen JA, Andersen OT, Wilhjelm JE, Kofoed B, Hansen LK. Biomedical engineering at the Technical University of Denmark. In: The Danish Society for Biomedical Engineering, ed. Aspects of biomedical engineering in Denmark. Copenhagen, 1998: 51-60.

Scanning acoustic microscopy in biomedical research

CLAUS SCHIØTT JØRGENSEN[1] & HANS GREGERSEN[2]

[1]SAM Laboratory and [2]Biomechanics Laboratory, Institute of Experimental Clinical Research, University of Aarhus, Skejby University Hospital, Aarhus N, Denmark

Scanning acoustic microscopy (SAM) is new in Danish biomedical research. Acoustic lenses holding ultrasonic transducers operating in the range of 60 to 2000 MHz comprise the heart of the SAM microscope. The technique can be used for imaging and quantification properties like sound wave velocity, acoustic impedance, attenuation and density of biological cells and tissues, implants and grafts. The resolution of SAM is in the micrometer range. Several diseases are currently studied with SAM, including atherosclerosis and osteoporosis.

Key words: Scanning acoustic microscopy; sound wave velocity; cells; implants; atherosclerosis.

Claus Schiøtt Jørgensen, MD, PhD, SAM Laboratory, Skejby University Hospital, DK-8200 Aarhus N, Denmark.

INTRODUCTION

Scanning acoustic microscopy (SAM) is new in Denmark where the first SAM laboratory started implementation of a high-frequency (up to 2000 MHz) microscope into Danish biomedical research in 1995. The idea of using sound for studying material structure and properties was first suggested by the Soviet scientist S.Y. Sokolov in 1949. At that time, the technologies for generating such acoustic waves and processing the signals were not available. The first SAM microscope was developed in 1975 [1]. Since then, work done primarily at Stanford University in the USA, University of Oxford in the United Kingdom and Tohoku University in Japan, has refined the SAM technique by increasing the resolution and implementing methods for quantification of acoustic properties.

Today, SAM is mainly being used for 'Non-Destructive Evaluation' (NDE) of materials and in quality control, but its use in biomedicine is increasing. In NDE, corrosion, cracks, voids, fractures and delaminations are detectable with SAM. A typical example is delaminations in semiconductors

[2]. In material science, SAM is used to study ceramics and composites and in geology it is used to study rocks, e.g. granodiorite, which is a typical candidate for disposal of nuclear waste [3].

It is the utilization of low-energy high-frequency acoustic waves in SAM that makes it an interesting technique in biomedicine. That not only ensures that the object of study remains intact and can be studied repeatedly, but living objects like human cells in culture can be studied microscopically during drug manipulation [4]. Also, it allows for examination of even small cell inclusions and tissue constituents since the resolution of SAM normally is in the micrometer range. The best resolution ever recorded with SAM is 15 nm at 15,300 MHz [5].

The most important property of SAM is its ability to measure acoustic properties with great accuracy. This property resides in the simple fact that acoustic waves are mechanical by nature and thus interacts mechanically with the object under investigation: the object responds to insonification from the microscope lens in accordance with its own mechanical properties (below), and it is that response which is recorded by the microscope.

MICROSCOPE DESIGN

Different types of SAM microscopes exist. The most common one is the *reflection mode SAM microscope*. This microscope has a single acoustic lens which is used both for transmitting and receiving reflected acoustic waves. With typical microscopes lenses capable of generating waves in the frequency range of 50 – 2000 MHz can be used. The resolution (w) of such lenses depends on wave velocity in the object of study (v), the numerical aperture of the lens (NA) and the wave frequency (f) in the following manner [6]:

Eq. 1 $$w = \frac{0.51v}{NAf}$$

Using a 2000 MHz lens with NA of 0.6 and assuming v is 1540 $m \times s^{-1}$ in the object of study (which is reasonable for soft biological tissue), the resolution would be approximately 0.65 μm. A lens is shown in Fig. 1. It has a transducer made of an epitaxially grown layer of zinc oxide between two gold electrodes at the top. Plane acoustic waves are emitted and travel through a sapphire rod with a hemispherical cavity for focusing at the tip. As the waves pass from the cavity to the couplant and the object of study, they become spherical and travel towards a focus on the axis of the lens. A typical wave path is shown schematically in Fig. 1. Because the acoustic wave velocity is much greater in sapphire than in water, which is usually used as a couplant between

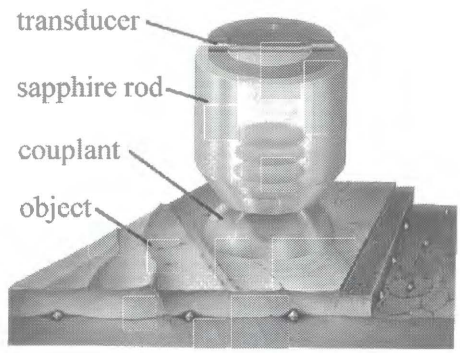


FIG. 1. Drawing of an acoustic lens for a typical *reflection mode scanning acoustic microscope*. The gold coated zinc oxide ultrasound transducer generates the sound waves that are transmitted to the object and detects the waves reflected from it. Focusing, and thus an increase of resolution is achieved with a small cavity at the tip of the short sapphire rod. The pathway is then: transducer, sapphire rod, couplant, object, sapphire rod, transducer.

the lens and the object of study, there is almost no spherical aberration even though the lens has only one spherical surface.

Acoustic microscopes may have two oppositely located lenses: one for transmitting and one for receiving. However, in these *transmission mode SAM microscopes*, the lenses are difficult to align and this technique is not commercially available. Another type of acoustic microscope is the *scanning electron acoustic microscope*, where it is the excitation of the acoustic waves that is focused. Yet, another type is the *scanning laser acoustic microscope*, called SLAM, where the waves are transmitted through the object of study and detected by a focused optical probe that measures local surface tilt on the surface of the object. The SLAM has the advantage of live images, but high-frequency waves cannot be used. The following technical descriptions in this paper refer to the reflection mode SAM microscope.

A complete description of the electronics in a SAM microscope is beyond the scope of this paper, but Fig. 2 is included to show the radio-frequency chain of a reflection mode microscope. It is a fact that most SAM microscopes truly working in the high-frequency range are built in dedicated laboratories by the investigators themselves. Some are equipped for transmitting short acoustic pulses, others for transmitting several pulses of different frequencies, and others again for measurement of the phase of the reflected signal.

Before discussing what acoustic microscopes can actually do, a brief presentation of some of the similarities and differences between SAM and optical microscopes is given. The resolution offered by a SAM microscope is normally comparable to that of the optical counterpart. However, it is possible to achieve a much better resolution with an acoustic microscope than with an optical, but very special techniques must be applied. By use of superfluid liquid helium which has a very low acoustic attenuation due to its low temperature, it is possible to use far higher wave frequencies than those described in this paper. That enables resolution in the nanometer range [7]. The magnification offered by conventional acoustic microscopes is of the same magnitude as that of optical microscopes. The resolution sets the limit of the highest usable magnification. In theory, the only factor that limits the magnification of an acoustic microscope is the smallest area of the object that the microscope can scan. The greatest advantages using SAM, is in the field of subsurface imaging. First, many materials are opaque to light but transparent to sound. Second, it is possible to separate subsurface acoustic echoes due to their relatively low travel velocity compared to the velocity of light. Third, an acoustic lens in the reflection mode acoustic microscope is confocal, resulting in a greater depth discrimination when compared to a traditional optical microscope. Those differences are indeed the properties that give rise to the use of SAM in NDE.

MICROGRAPHS AND ACOUSTIC PROPERTIES

The SAM functions can arbitrarily be divided into making micrographs and measuring acoustic and elastic properties of the object. Micrographs of small to large objects, or regions of interest, are made by scanning the lens across the object because of the very limited spatial size of the lens focal zone. The scanning is done in a raster fashion, i.e., a scan in a series of lines. Either the lens or the object is scanned. The latter can be achived by use of a stage stepper- or DC-motor, and this method usually offers the largest scanfield. An acoustic mi-

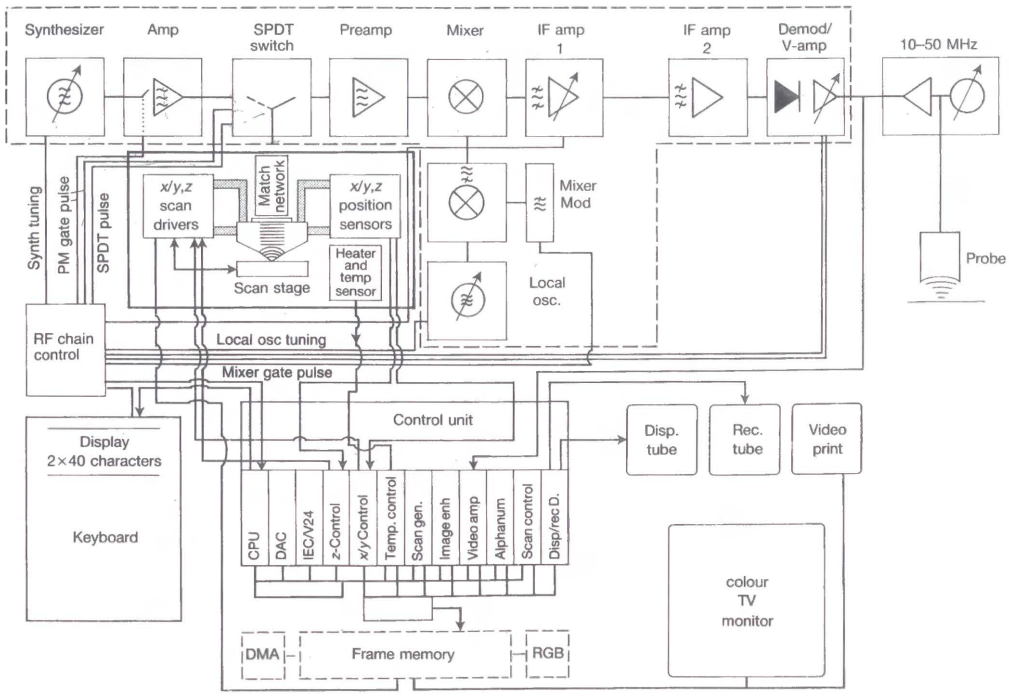


FIG. 2. Schematic diagram of the electronic circuitry of a *reflection mode scanning acoustic microscope* (Courtesy of Leica, Wetzlar, Germany).

crograph with a scanfield of 1 by 1 mm taken at 400 MHz is shown in Fig. 3. In imaging mode, most acoustic microscopes aquire the envelope-detected video signal in each 'point' along the lines of scanning for modulation of the micrograph brightness. Thus, in that mode usually no individual and particular acoustic property gives rise to the pixel brightness [8]. The brightness is, so to speak, modulated by the interaction of several different properties at various magnitudes. Consequently, a conventional micrograph cannot be used for quantitative analysis of acoustic properties. However, several SAM techniques exist for such analysis, and that is exactly what gives SAM a leading position in the field of bioacoustics and microelastic analysis.

Two quantitative techniques are the *plane*

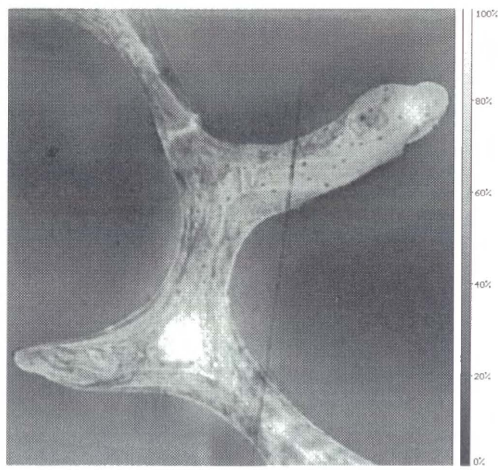


FIG. 3. Micrograph of bone taken at 400 MHz. The field is 1 by 1 mm. The bone was embedding in plastic, cut and grinded to a thickness of 20 micrometer before scanning.

wave interference contrast method and the *focused interference contrast* method. Both are being used in biomedicine and they are thoroughly described elsewhere [9,10]. Briefly, both techniques rely on certain assumptions of one or the other acoustic properties and their constancy across a field of highly anisotropic biological tissue. Yet another two methods are available that make no presumptions of the properties of the object of study. One is based om measurements of both the amplitude and the phase of the reflected signal and their associated frequency characteristics [11]. The other is the *time-resolved SAM technique*. In biomedicine this technique was first applied to study single living human cell placed on a glass slide under the acoustic microscope [12] and later to the walls of healthy porcine coronary artery branches [13]. As an example of the interdisciplinary use of SAM in characterizing artificial implants, it was recently applied to ePTFE (teflon) prostheses for implantation and substitution of atherosclerotic human arteries [14].

Several acoustic and elastic properties are of interest in biomedicine. Among the most important ones are the velocity of sound (v) which is the velocity of propagation of the acoustic waves, the acoustic impedance (Z) which represents the ratio of sound pressure to particle velocity, the acoustic attenuation coefficient (α) which expresses the natural logarithm of the ratio of the amplitudes of the sound pressures at two points at different distances from the transducer in the propagation direction, and the tissue density (ρ). Basically, the time-resolved technique consists of analysis of the timing (t) of interface echo amplitudes (A) reflected from the object of study placed on a substrate with known acoustic properties. There are 2 such interfaces:

1. the couplant/top surface of object interface (t_1;A_1)
2. the bottom surface sample/top surface of object interface (t_2;A_2)

Also the couplant/top surface of object interface (t_0;A_0), which is referred to as the reference signal must be analyzed. Furthermore, the technique requires knowledge of the substrate v and ρ (v_s and ρ_s) and the couplant v, α and ρ (v_{cp}, α_{cp} and ρ_{cp}). The known and measured values are inserted into the formulas Eq. 2-5:

Eq. 2 $$v = v_{cp}\frac{t_0 - t_1}{t_2 - t_1}(ms^{-1})$$

Eq. 3 $$Z = v_{cp}\rho_{cp}\frac{1+A_1}{1-A_1}(kgm^{-2}s^{-1})$$

Eq. 4
$$\alpha = \left(\alpha_{cp} + \frac{1}{(t_0 - t_1)v_{cp}}\log_e\left\{\frac{A_0}{A_2}\frac{(v_s\rho_s) - Z}{(v_s\rho_s) + Z}\frac{4Zv_{cp}\rho_{cp}}{\left(Z + v_{cp}\rho_{cp}\right)^2}\frac{v_s\rho_s + v_{cp}\rho_{cp}}{v_s\rho_s - v_{cp}\rho_{cp}}\right\}\right)8.686(dBm^{-1})$$

Eq. 5 $$\rho = \frac{Z}{v}(kgm^{-3})$$

There are several strict requirements of the equipment and the circumstances during which such measurements are made, but is is beyond the scope of this paper to describe those. An example of a reference and an

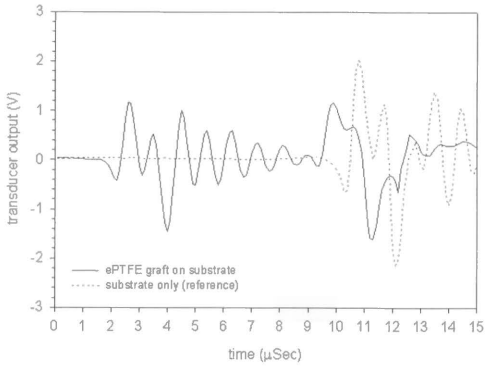


FIG. 4. Acoustic signals recorded from a section of a ePTFE vascular graft on a substrate and from the substrate alone. By analyzing the timing and amplitudes of the interfaces echoes, graft properties can be calculated (see text).

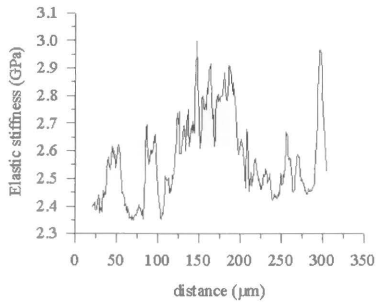


FIG. 5. Curve showing the elastic stiffness (E) calculated on the basis of the *time-resolved SAM* method. It was made by scanning the transducer in a line across the wall of a porcine artery which was approximately 275 micrometer wide.

object signal taken under a study of ePTFE vascular prosthesis acoustic properties using a 10 MHz transducer [14] is shown in Fig. 4. On the basis of the calculated v and ρ, the elastic stiffness (E) can be calculated from Eq. 6.

Eq. 6 $$E = v^2 \rho (Nm^{-2})$$

E can be compared to Young's modulus. In the study of porcine coronaries [13], we first made a micrograph of a coronary and then scanned the transducer along a line while recording the reflected signals along that line, subsequently analyzing them for the abovementioned properties. The calculated E as a function of distance is shown in Fig. 5.

TISSUE PREPARATION FOR SAM

Because high-frequency acoustic waves are highly attenuated, their penetration range is limited. At 2000 MHz the waves may not penetrate more than a few micrometers into biological tissue. This implicates that most SAM investigations can only be done on tissue sections; analogously to what is done in optical microscopy. There is a need for tissue preparation before micrographs and measurements can be done. Little scientific proof exist as to what method is the best. In choosing one, one must consider that most fixatives alter the elastic properties of the tissue, but it seems that until now no systematic investigation of such alterations has been performed. A qualitative study of transmission mode SAM micrographs showed that the embedding medium, which must be used prior to sectioning, influences the micrograph contrast to some extent [15], but some doubt exist to whether the authors actually removed the embedding medium prior to imaging. Staining is not needed, in fact staining seems to alter tissue properties as well [unpublished observations]. But the acoustic and elastic heterogeneity among the constituents of most biological tissue ensures that contrast is always present in acoustic micrographs.

SELECTED SAM STUDIES

Several organ systems have been studied with SAM over the recent years. One example is the cardiovascular system. Thus

far, only few studies in that field have used wave frequencies above 200 MHz for high resolution; one such study is the abovementioned [13] where normal porcine coronary arteries were quantified for acoustic and elastic properties at 350 MHz. Among studies in the vascular field is a study of normal human coronary arteries [16], where the purpose was to quantify the wall thickness and the thickness of the individual layers of the wall. That was done at 50 MHz to assess the layer thickness, with a good resolution, and compare it to that measured by means of clinical intravascular ultrasound (up to 30 MHz). Another study measured the acoustic backscatter, i.e., the reflection from a diffuse collection of very small scatterers that comprise the tissue itself [17], of simple atherosclerotic lesions in the arteries of cholesterol-fed rabbits [18]. They used 50 MHz SAM and found that this measure could actually discriminate fibrous lesions from fatty lesions. Both studies are good examples that SAM studies contribute to our understanding of disease and can accelerate better methods of clinical diagnosis. Other studies using the SLAM technique at 100 MHz have shown that it is possible to differentiate normal myocardium from ischaemic myocardium and infarcted myocardium [19]. SAM studies using higher frequencies are mainly morphological of nature. One example is a study at 200 to 1000 MHz of myocardial inflammation and fibrosis [20]. Another organ system for which SAM shows great promise is bones. Recent studies have described semi-quantitatively some properties of normal bone and bone-prosthesis interfaces [21,22]. Another study has concentrated on osteoporosis, which is a disease of low bone mass and decreased bone quality [23]. A low acoustic velocity was found in bone from osteoporotic individuals when compared to bone from healthy age-matched individuals, inferring that osteoporosis involves altered tissue elasticity. Methods of measuring bone elasticity at the macrolevel could have shown the very same, but not with a resolution in the micrometer range. Because of the good resolution offered by SAM, even single cell acoustic and elastic properties can be measured. Some studies doing so were mentioned above [9,10,12]. Another study described various distinct motility domains in cells *in vitro* [24]. Although mainly quantitative, that study showed a new application for SAM: imaging of movement and how the individual cell *in vitro* prepare and carry out the complex procedure of movement. Even gastric ulcers can be identified and differentiated with SAM *in vitro*. One study examined experimentally induced gastric ulcers in rats and was able to differentiate two distinct types of ulcer healing [25].

CURRENT AND FUTURE ASPECTS OF SAM

SAM can contribute to biomedical research in several fields. Two fields are basic biomechanics and diagnostic ultrasound. One example of ongoing research in our laboratory has its roots in the former field, but eventually extends its branches into the latter. That is the SAM study of atherosclerotic plaques. According to the predominant constituent of plaques, 'soft' and 'hard' plaques exist. The soft plaque is the dangerous one because its content of lipids, when exposed to the blood stream after rupture of its fibrous cap, will clot the blood and induce tissue infarction. The underlying mechanism of cap rupture is unknown, but it is believed that mechanical forces of the streaming blood play a role. In mapping the distribution of elastic properties across the cap and the adjacent artery wall, SAM could aid the understanding the cap rupture

process. Much effort is currently aimed at improving diagnostic ultrasound to enable early diagnosis of 'soft' plaques *in vivo* to intervene surgically and remove the plaque [26]. SAM quantification of acoustic properties such as the wave *velocity* and *impedance* in both types of plaques could lead to improved diagnosis *in vivo*. That is because the velocity determines the size of an object in a diagnostic image which, in this instance, corresponds to the spread of the plaque. The impedance partly determines the reflectivity and echogenicity of the plaque. If the ultrasound equipment does not use the correct velocity for image construction, the size of the plaque on the image will be faulty. Knowledge of the impedance would help interpretation of diagnostic images for 'soft' or 'hard' plaques based on its echogenicity on the image. Another study in our laboratory concerns newly formed bone tissue adjacent to mature bone tissue in bones that have been elongated by use of osteotomy and application of Ilizarov's method for bone elongation. The treatment is time-consuming due to the relatively slow growth of bone tissue, and it may be optimized and shortened by a better knowledge of the properties of the newly formed bone tissue.

In our laboratory future work will be directed at developing methods for simultaneous SAM quantification and object stressing by means of external forces. That would enable us to measure plaque cap and bone properties under different stress loads and thus measure under circumstances closer to those *in vivo*.

ACKNOWLEDGEMENT

The Karen Elise Jensen Foundation is kindly thanked for its support of our SAM Laboratory.

REFERENCES

1. Maugh TH. Acoustic Microscopy: A new window to the world of the small. (Editorial). Science 1978; 201: 1110-14.
2. Burton NJ, Thaker DM, Tsukamoto S. Recent developments in the practical and industrial applications of scanning acoustic microscopy. Ultrasonics Int 1985; 85: 334-38.
3. Rodriguez-Rey A, Briggs GAD, Field TA, Montoto M. Acoustic microscopy of rocks. J Microscopy 1990; 160: 21-29.
4. Lüers H, Hillmann K, Litniewski J, Bereiter-Hahn J. Acoustic Microscopy of cultured cells. Distribution of forces and cytoskeletal elements. Cell Biophysics 1992; 3: 279-93.
5. Muha MS, Moulthrop AA, Kozlowski GC, Hadimioglu B Acoustic microscopy at 15.3 GHz in pressurized superfluid helium. Appl Phys Lett 1990; 56: 1019-21.
6. Kino GS. Acoustic Waves: Devices, imaging and analog signal processing. Prentice Hall, New Jersey, N.J., 1987.
7. Foster JS, Rugar D. Low-temperature acoustic microscopy. IEEE Trans 1985; SU-32: 139-51.
8. Daft CMW, Briggs GAD, O'Brien WD. Frequency dependence of tissue attenuation measured by acoustic microscopy. J Acoust Soc Am 1989; 85: 416-22.
9. Bereiter-Hahn J. Scanning acoustic microscopy visualizes cytomechanical responses to cytochalasin D. J Microscopy 1987; 146: 29-39.
10. Hildebrand JA, Rugar EL Measurement of cellular elastic propertiesby acoustic microscopy. J Microscopy 1983; 134: 245-60.
11. Akashi A, Kushibiki J, Chubachi N, Dunn F. Considerations for quantitative characterization of biological tissues by scanning acoustic microscopy. In: Shimizu, H. (Ed.), Acoustic Imaging. New York: Plenum Press, 1989: 17:183-91.
12. Briggs GAD, Wang J, Gundle R. Quantitative acoustic microscopy of individual living human cells. J Microscopy 1993; 172 (Pt1): 3-12.

13. Jørgensen CS, Knauss D, Hager H, Briggs GAD. Sonography and quantitative measurements. A preliminary study of coronary artery wall topography and mechanical properties. IEEE Med Biol 1996; 15: 35-41.
14. Jørgensen CS, Paaske W. Physical and mechanical properties of ePTFE stretch vascular grafts determined by time-resolved scanning acoustic microscopy. Eur J Vasc Endovasc Surg, In press.
15. Kolodziejczyk E, Saurel JM, Bagnol J *et al.* Transmission acoustic microscopy of tissue sections (1 GHz). Histoacoustics and acoustic staining. Histochemistry 1988; 88: 165-69.
16. Wickline SA, Barzilai B, Thomas LJI, Saffitz J. Quantification of intimal and medial thickness in excised human coronary arteries with 50 MHz acoustic microscopy. Coron Artery Dis 1990; 1: 375-81.
17. Wickline SA Advances in ultrasound methods for High-resolution imaging of the cardiovascular system. Trends in Cardiovascular Medicine 1997; 7: 168-73.
18. Shephard RK, Miller JG, Wickline SA. Quantification of atherosclerotic plaque composition in cholesterol-fed rabbits with 50 MHz acoustic microscopy. Arterioscler Thromb 1992; 12: 1227-34.
19. O-Brien WD, Sagar KB, Warltier DC, Rhyne TL. Acoustic propagation properties of normal, stunned and infarcted myocardium: morphological and biochemical determinants. Circulation 1995; 91: 154-60.
20. Chandraratna PA, Choudhary S, Jones JP *et al.* Visualization of myocardial cellular architechture using acoustic microscopy. Am Heart J 1992; 124: 1358-64.
21. Katz JL, Meunier A. Scanning acoustic microscope studies of the elastic properties of osteons and osteon lamellae. J Biomech Eng 1993; 115: 543-48.
22. Meunier A, Katz JL, Christel P, Sedel L. A reflection scanning acoustic microscope for bone and bone-biomaterials interface studies. J Orthop Res 1988; 6: 770-75.
23. Hasegawa K, Turner CH, Recker RR, Wu E, Burr DB Elastic properties of osteoporotic bone measured by scanning acoustic microscopy. Bone 1995; 16: 85-90.
24. Veselý P, Lüers H, Riehle M, Bereiter-Hahn J. Subtraction scanning acoustic microscopy reveals motility domains in cells in vitro. Cell Mot Cytoskel 1994; 29: 231-40.
25. Mizutani K, Tsukamoto Y, Goto H, Hase S, Niwa Y, Ohashi S. Evaluation of acetic acid-induced gastric ulcers in rats by scanning acoustic microscopy. Scand J Gastroenterol 1991; 26: 313-20.
26. Hiro T, Leung CY, De Guzman S *et al.* Are soft echoes really soft? Intravascular ultrasound assessment of mechanical properties in human atherosclerotic tissue. Am Heart J 1997; 133: 1-7.

Reference: Jørgensen CS, Gregersen H. Scanning acoustic microscopy in biomedical research. In: The Danish Society for Biomedical Engineering, ed. Aspects of biomedical engineering in Denmark. Copenhagen, 1998: 61-69.

Images of the mind

New technical approaches

HANS STØDKILDE-JØRGENSEN

The MR Research Centre, Aarhus University Hospital, Skejby Sygehus, Denmark

Key words: EEG; fMRI; MEG; PET.

Hans Stødkilde-Jørgensen, Dr.M.Sc., associate professor, The MR Research Centre, Aarhus University Hospital, Skejby Sygehus, DK-8200 Aarhus N, Denmark.

Modern neuroscience posits that the human behavioral processes represent an integration of constitutional mental operations. There are numerous elementary operations but among the more prominent are cerebral handling of afferent pulses, use of cerebral memory, cognitive actions and neuroendocrinological processes. However, it is important to realize that what makes cerebral function of humans superior to that of other species, is not only the number of neurons on the cortical surface but also factors like the functionally well-organized infrastructure of the brain. The challenge is to identify the groups of cortical areas performing the elementary operations which by integration forms the observable human behavior.

By applying modern imaging methods, complex cerebral operations such as motoric functions and perception, interpretation of images and sounds and language generation and memory can be mapped. These color images of the working brain show specific regions of the brain "lit up" as a result of vascular dilatation in the cortical region taking part in a specific task. The so-called neurofunctional images give a deeper understanding of basic neurophysiological processes and their interaction and furthermore, they have added significantly to the understanding of mental illnesses such as depression and schizophrenia.

The neurobiological basis for mapping of the brain is dependent on the technology applied. Common to all is the aim of tracking neural activity by registration of vascular, metabolic or electric changes in the activated neurons. Functional magnetic resonance (fMRI) and positron emission tomography (PET) both record the electrical activity of the neurons indirectly; primarily blood flow in the case of PET and blood oxygenation in fMRI (Fig. 1). This means that both techniques suffer from a delay in onset of the vascular response initiated by the increased neuronal electrical activity (Fig. 2). This delay is in the order of 4-7 seconds. Contrary to these two techniques, others such as electroencephalography (EEG) and magnetoencephalography (MEG) register the electrical activity directly without any delay. However, the cortical origin of the recorded signals is

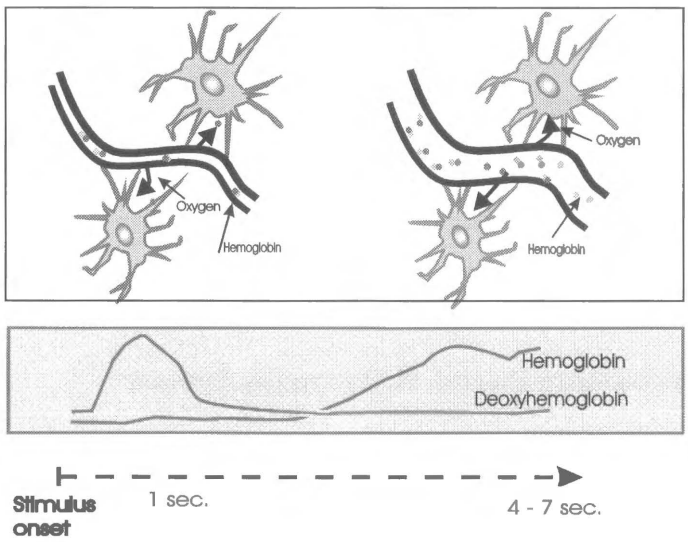


FIG. 1. Less than one second after the initiation of focal cortex activity, the oxygen extraction from the blood increases resulting in a rise in deoxyhemoglobin. Much later - 4 to 7 sec - the neurovascular tonus relaxes and the dilated arteries result in an increased blood flow and regional blood volume. The increased concentration of oxyhemoglobin which follows is the cause of the BOLD-signal which can be recorded by MRI.

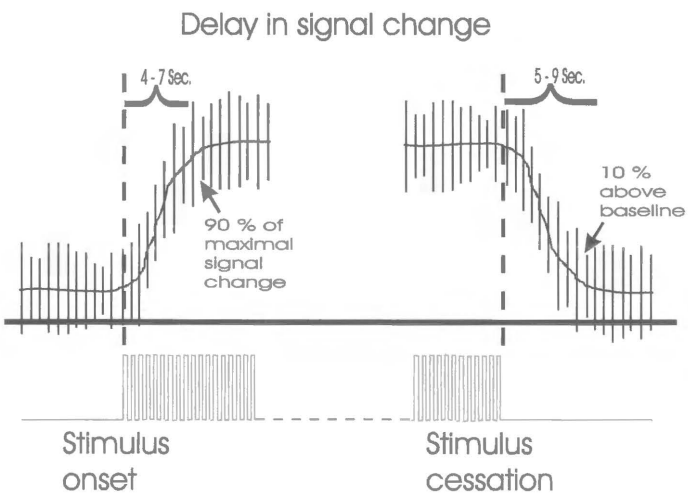


FIG. 2. Delay in hemodynamic response in respect to the beginning and end of the external stimulus.

often unclear. Thus, none of these techniques are without drawbacks. However, with their limitations in mind, they have all added substantially to the understanding of what goes on in the brain.

The imaging method that got the field running 20 years ago was PET. Lately fMRI has eclipsed PET as the method which adds the most to new knowledge on cortical activity in various tasks. However, it must be emphazied that without a full understanding of how PET and fMRI signals relate to the underlying neurobiology, misinterpretation may coincide. The fMRI technique is based on changes in magnetization when oxyhemoglobin release oxygen. Deoxyhemoglobin has pronounced paramagnetic properties which mean less signal intensity in areas where deoxyhemoglobin accumulates. This so-called blood-oxygen-level-dependent (BOLD) phenomenon can be identified in many areas of the cortex, but the more pronounced signals seem to appear in the visual cortex.

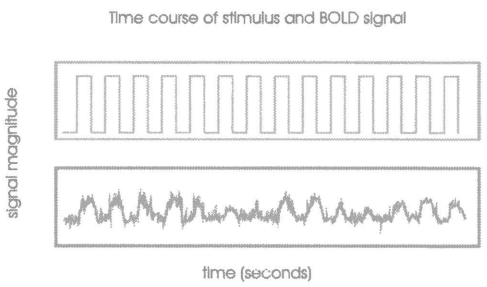


FIG. 3. Repetitive stimulus paradigm in neurofunctional imaging. By applying statistical tests which looks for image pixels with intensities varying synchronously with the stimulus paradigm, activated neuron groups can be identified.

Due to poor signal to noise ratio in both fMRI and in PET, repetitive stimulation paradigms are applied. Thus, by statistical maneuvers such as autocorrelation tests, the activated brain areas can be identified (Fig. 3). The stimulation paradigms applied are primarily visual, auditive and/or more complicated motoric movements. Common to all is the repetitive character of the paradigm. Light flickering with a frequency of 6-12 Hz is projected into the eyes with intervals of 15-30 sec. Repeated finger tapping intervalled by short resting periods can be used for visualization of the motoric cortex. Certain kinds of stimulation regimes such as pharmacological activation experiments can only be done once within a reasonable time horizon. Therefore, new processing techniques for the identification of activated pixels by one-shot stimulation are to be introduced. More sophisticated paradigms such as generation and interpretation of language and manipulation of the mood are also applied. In the later years, sophisticated neuropsychiatric and behavioral stimulation paradigms have been applied [12,14]. Now not only the basic neurofunctional mechanisms but also cognitive patterns are demonstrable. Thus, the methods are relevant not only for understanding basic neurobiology but also for the disclosure of neuropsychiatric reaction patterns during diseases such as depression or schizophrenia [11].

An important question is whether the areas which exhibit increased flow and BOLD phenomena really represent the full truth about areas with neuronal activity. The neurovascular changes are considered a response to an increased demand for oxygen and glucose. Since the middle of the eighties, it has been assumed that the activation of a neuron did not increase its oxygen consumption [16]. However, new research has changed this perception. By analyzing the light spectra reflected directly from the cortical surface in anesthetized animals, an increase in deoxyhemoglobin in the visual cortex has been demonstrated less than 1 sec after light was projected into the eyes [10]. Three to four seconds later, this effect was swamped by a rise in oxyhemoglobin caused by the following increased blood flow which, furthermore, seemed to cover a larger area of cortex than the one exhibiting the initial increase in deoxyhemoglobin. This subsequent inverse response mainly represented the accumulation of oxyhemoglobin downstream in the venules and small veins draining the active area - the effect registered by fMRI and PET.

This means that it is the response time for a number of hemodynamic parameters which determines the maximum temporal resolution achievable in PET and fMRI. The neurovascular delay in changes of flow and in the BOLD signal of 4-7 sec can be compared to the about 10 msec it takes for signals to be transported from one hemisphere of the brain to another. Thus, many neural activities have been carried out long before they can be detected in changed hemodynamic profiles. Therefore, neither

PET nor fNMR based on the BOLD effect will be able to follow the "conversation" between various brain areas.

The only methods responding efficiently and quickly enough for a direct identification of neuron communication patterns are those based on a direct monitoring of the neural electrical activity or the magnet field generated in relation to this. However, the EEG and the MEG method are not just used by everybody due to their limited spatial resolution and sensitivity. The deeper in the brain tissue one does the measurements, the lesser is the quality. Neither PET or fNMRI are encombranced by these limitations. However, in recent years, the MEG technique has undergone a major technical development, which may reduce the limitations significantly. Several studies of functional localization in the brain have been published [9].

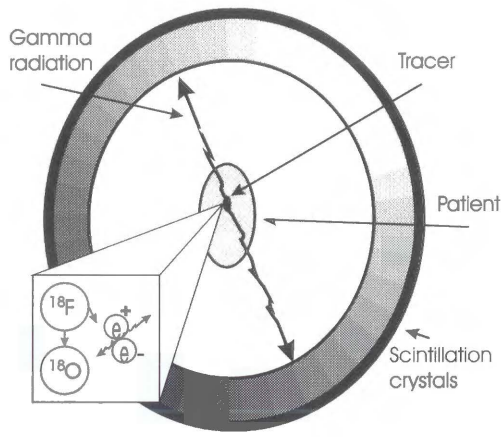


FIG. 4. A transformation of ^{18}F into ^{18}O by emitting positrons result in an antimatter-matter annihilation with a negative electron whereby two photons are created. The gamma radiation generated by this is recorded in crystals orientated in a circle around the subject. Only radiation appearing in diametrically opposite crystals are interpreted as true hits.

POSITRON EMISSION TOMOGRAPHY

The PET technique is based on intravasal injection of short-lifed isotopes. The variety of these isotopes opens for a number of studies on biochemical and metabolic processes [1]. Substances taking part in various physiological reactions are marked with an isotope lacking one neutron compared to stable nuclei of the same element. By emitting positrons and thus converting protons to neutrons, these unstable nuclei decay spontaneously. For example ^{18}F will be transformed to ^{18}O because the nine protons and nine neutrons of the fluor nuclei will be changed to eight protons and ten neutrons. The positron which can be viewed as a positive electron, is ejected and after three millimeters of travelling, an antimatter-matter annihilation with a negative electron will occur creating two photons. This process generates about 511 keV in the form of gamma radiation which penetrates the tissue and can be registered in scintillation crystals placed in a circle around the person measured on (Fig. 4). The crystals are connected in such a way that the radiation which does not appear diametrically opposite, is filtered away. More than a million decays appear during the period of one examination (1-15 min), and these form the basis for the reconstruction of tomographical images containing the spatial distribution of the radioactivity. By comparing these with the blood's reactivity before and after the examination, dynamical processes can be quantitated.

The most important feature of the PET technique is the huge signal sensitivity. Concentrations of substances all the way down to the picomolar interval can be detected. Furthermore, there are a lot of different tracers which can be incorporated in a very large number of different biological active molecules. Most PET tracers

are incorporated just by changing a biological active molecule with the isotope bearing equivalent. By this, the biochemical kinetic pattern is not changed compared to the natural version of the matter. The total amount of radiation given to a person during a PET examination is reduced due to the very short-lifed isotopes used. On the other hand, this means that PET scanners rely on a cyclotron installation only minutes away.

NUCLEAR MAGNETIC RESONANCE

Magnetic resonance is based on the precessing movements of spinning nuclei when they are exposed to a strong magnetic field. In magnetic resonance scanners, this field is produced by a coil of super-conducting wires in which current was introduced when the magnet was installed. The stationary field goes along the magnet bore and is denoted B_0. For a fullbody scanner, B_0 is between 0.5 and 1.5 Tesla. Nuclei with spin will due to B_0 experience a torque which forces them to rotate around the direction of B_0 with a frequency, which for protons in a 1.5 Tesla system is about 63 MHz, - the so-called Larmor resonance frequency.

Under conditions with no magnetic field, each of the charged nuclei will be orientated in random fashion due to the motion produced by thermal energy. No macro-scopic magnetic moment can be observed then. However, placed in a magnetic field, this will interact with the magnetic moments of the individual nuclei and produce a net magnetic moment (M) along the axis of the main field. M is the average of all the magnetic moments and can be viewed as a vector quantity possessing both magnitude and direction - a longitudinal magnetization vector (M_z).

In order to record the magnetization, M_z is perturbed by an additional magnetic field B_1 applied perpendicular to B_0 and rotating at the Larmor frequency. The B_1 is introduced by a transmitter coil and makes the magnetization precess further away from the B_0 direction depending on the duration and intensity of the RF (radio frequency) signal applied on the transmitter coil. The orientation of the magnetization is spiraling down towards the transverse x-y-plane (flip angle 90°) and may go down 180° in respect to B_0. Thus, the magnetization vector M has the components M_z and M_{xy}.

After terminating the excitation the so-called relaxation process starts. The spins return to their original orientation by transferring the absorbed energy to the surrounding molecules. This re-establishes the longitudinal magnetization. The transverse magnetization decays exponentially due to the dephasing of the processing spins. However, even though both M_z and M_{xy} 'relaxes' exponentially towards their starting values, the two should not be viewed simply as component vectors of M. There is no simple correlation between M_z and M_{xy}, but in practice, the longitudinal relaxation is always faster than the transverse.

The MR response signal is received in a coil where current is induced by M. To separate the transmitter and the receiver, coils can be used. In practice, the same coil is often used for the same purpose (Fig. 5). Thus, the coil hardware handles kilovolts during excitation and in the next second registers currents in the microvolt interval. This exerts major demands on the electronics. The registered signal called FID (free induction decay) decays accordingly with the transverse relaxation process. The FID oscillates with the magnetization components at the resonance frequency and the initial intensity depends on the number of nuclei that participate. However, the duration of the signal is influenced by the chemical environment of the nuclei. Thus,

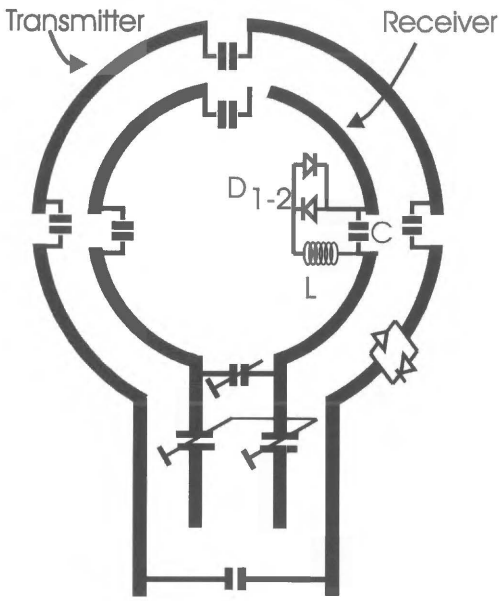


FIG. 5. A transmitter and receiver surface coil. In order to prevent interference with the receiver coil during transmission, short circuit diodes are added. The receiver coil is connected to a tune and match circuit consisting of variocapacitors. By adjusting these, a high Q value is secured and a resonance frequency identical to the precessing frequency of the spins can be adjusted.

the FID carries information about the individual nucleus' molecular environment (Fig. 6). In biological tissue, primarily nuclei types such as hydrogen, phosphor, fluorine and isotopes of carbon, nitrogen and oxygen are of interest.

The spatial resolution is limited by the signal to noise ratio. In a 1.5 Tesla fullbody system, the practically obtainable spatial resolution is about 1.5 × 1.5 × 3.0 mm per pixel. Systems with even higher field strengths such as 4 or 7 Tesla are often used in animal experiments and here the spatial resolution can go down to 50 × 50 × 100 micrometers. On the fastest scanner systems, a magnetic resonance image can be recorded very fast (50-100 ms). This is

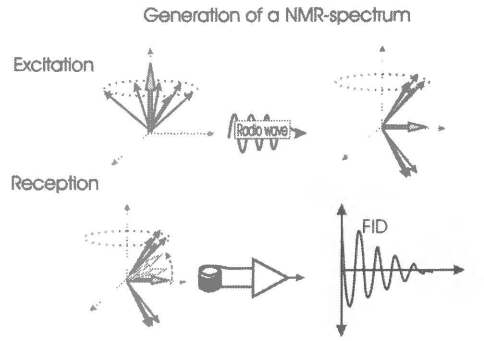


Fig. 6. By excitation with radiowaves and the precessing frequencies of the spins, some of these are forced to be orientated anti-parallelly in relation to B_0. At the same time, the spins start to precess in phase. This results in a reduced longitudinal magnetization. An up-coming transversal magnetization can after ending the excitation induce current in a coil (FID). The FID forms the basis for the image construction by a set of two-dimensional Fourier transformations.

exploited in fMRI, which demands a high temporal resolution.

ELECTROENCEPHALOGRAPHY (EEG)

EEG is a technique which has been known for years. By this, differences in the electrical potential on the cranium surface are measured. The signals are recorded in a variable number of channels, e.g. 21, placed in the skin over key points on the cranium. Thus, the activity in different parts of the brain can be identified separately. An absolute strength of the EEG-technique is its potential for registration of physiological signals of even very short duration, i.e., down to millisecond intervals. On this point, the EEG-technique is superior to both the fNMRI and the PET technique. Furthermore, the EEG technique is much less sensitive to movement artifacts compared to other methods. The drawback of the EEG technique, especially in relation to fNMR, is the poor spatial resolution obtainable. To

some extent, this explains the relative sturdiness towards head movements during the examination.

The origin of the EEG signals seems to come from fluctuations in the resting membrane potential of the dendrite tree in cortical neurons. It is created by synoptic activity such as excitatory and inhibitatory postsynoptic potentials. Fluctuations in the membrane potential result in compensating passive current floating both intracellulary and extracellulary. Especially extracellular currents spread through the surface of the skull from where the EEG electrodes can register them. However, here the signals are to some extent contaminated with currents from depolarization of muscle membranes, e.g., from the muscles on the surface of the cranium or from the heart.

MAGNETOENCEPHALOGRAPHY (MEG)

MEG recordings are based on a non-invasive registration of weak magnet fields appearing from neural electrical currents [8,2,3]. They are actually the same currents which generate the electrical potentials on the cranial surface registered by EEG, but while EEG measures currents in the extracellular volume, the MEG technique primarily rely on magnet fields appearing due to intracellular currents. These magnet fields are quite weak - typically in the area of 10^{-13} to 10^{-12} Tesla. This means that the magnet field introduced by the neuron currents is about one billion times smaller than the magnet field of the earth. Signals are acquired by superconducting fluxtrans-formers and are detected in so-called SQUIDS (Superconducting Quantum Interference Devices) which are extremely sensitive towards changes in magnet fields (Fagaly 1990). Among other things, SQUIDs contain superconducting materials

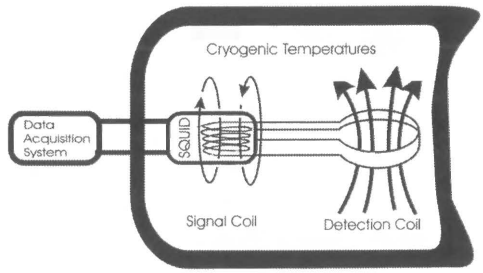


FIG. 7. Principal diagram of SQUID magnetometer. The externally applied flux passes through the loop of the detection coil. The current induced in this superconducting flux transformer by the external magnetic field couples to the SQUID.

which means that even very small magnet fields can introduce currents in the SQUID circuit (Fig. 7).

The registration of very weak magnet fields implies that the equipment has to be installed in some kind of open area without interfering magnet fields, e.g., from cars, or alternatively measurements should be made in a magnet shielded room. Together with the necessary signal technology, this means that the MEG technique is relatively expensive to establish.

Primarily, the origin of the EEG signals is in a direction parallel to the dipole axis whereas the shift in negative and positive potentials are limited to the direction perpendicular to the dipole. This is opposed to the MEG technique, and in practice this means that EEG recordings from the cranial surface detect both tangential and radial signal sources, e.g., the activity both in sulci and on gyri, whereas the MEG technique selectively registers the tangential sources, i.e., the electrical activity related to sulci [5].

As with EEG, the poor spatial resolution is also the weakness of the MEG technique. However, today MEG's resolution is about $^1/_3$ better than surface EEG because the magnetic field is not distorted by different

resistance in the cranium and the skin above [6]. PET and especially NMR operate with a much higher spatial resolution but in contrast to these, the MEG technique has a significantly better temporal resolution which is fully sufficient for the registration of even the shortest action potentials. The spatial resolution of the MEG scanner systems are now being improved by the introduction of more SQUID channels. While the first instruments were based on sequential mapping on the cranial surface with up to seven channels, it is now possible to record signals simultaneously from the entire cortical area by 122 channel systems. (Fig. 8).

The limitation in interpretation of MEG signals is the ambiguity of the mathematical so-called inverse problem [7]. While a function only has one solution for each projection, some inverse functions have several solutions and are thus not defined as a function in these areas where more than one solution appear. In practice this means that by MEG, several current distribution patterns inside the brain can produce identical signals outside the brain. Thus, MEG signals, which at first seem identical, can originate from totally different areas in the brain. Therefore, phantom examinations are always necessary in MEG.

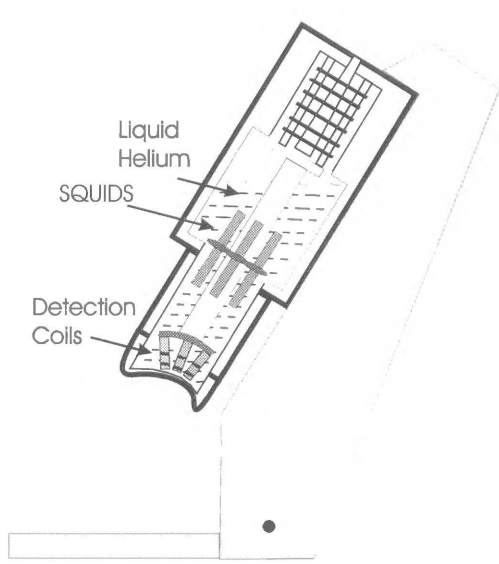


FIG. 8. Schematic illustration of a wholehead neuromagnetometer. It consists primarily of a dewar containing the cryogens for maintaining the squid centers superconducting. Today more than 120 channel devices can be purchased.

THE FUTURE

New techniques for neurofunctional imaging which overcome the neurovascular delay of today's PET and fMRI techniques are coming up [15]. One is fMRI based on the sodium magnetic resonance signal. These ions cross the cellmembrane of the neurons when they activate and fire. By flowing into the neurons, the magnetization properties of sodium is changed in a way which is detectable in a magnetic resonance scanner. However, the signals are very weak and to improve the signal to noise ratio, a huge amount of repetitive excitations have to be performed. This of course reduces the temporal resolution, but technical improvements might change this drastically.

Another functional imaging technique coming up is technically much simpler and, compared to high field magnetic resonance scanners, far less expensive. Near-infrared light from a fiberoptic source placed on the scalp can penetrate into the brain tissue [13]. Some light is reflected by the cortical tissue and can be captured by light sensors placed a few centimeters from the light emitter encircling it. The lightscattering is influenced by the activity in cortical neurongroups responding to sensory stimulation activity. The temporal resolution is of the same magnitude as seen in EEG.

Improved imaging methods are providing new insight on our brain functions. Timing is the more important factor in order to further this field of research. Both fNMRI

based on sodium, MEG and light reflectance are candidates for this. However, one thing, which we have all learnt from the very fast technical development during the last five years, is that it is impossible to predict technical improvements favoring one of the candidates.

REFERENCES

1. Phelps ME. Positron emission tomography (PET). In: Clinical Brain Imaging: Principles and Applications. Mazziotta JC, Gilman S (eds.). Philadelphia: F.A. Davis Company, 1992: 71-107.
2. Hari, R. Magnetoencephalography as a tool of clinical neurophysiology. Electroencephalography. Basic principles, clinical applications and related fields, 1993, 3: 1035-61.
3. Singh KD. Functional imaging of the brain using superconducting magnetometry. Endeavour 1995; 19,1: 39-44.
4. Fagaly RL. Neuromagnetic instrumentation. In: Susumu Sato (ed.). Advances in neurology, Vol.54: Magnetoencephalography. New York: Raven Press, 1990: 11-32.
5. Rose DF, Ducla-Soares E. Comparison of electroencephalography and magnetoencephalography. Adv Neurol 1990; 54: 33-37.
6. Cohen D, Cuffin BN, Yunokuchi K, Maniewski R, Purcell C, Cosgrove GR, Ives J, *et al.* MEG *versus* EEG localization test using implanted sources in the human brain. Ann Neurol 1990; 28: 811-17.
7. Balish M, Muratore R. The inverse problem in electroencephalography and magnetoencephalography. Adv Neurol 1990; 54: 79-88.
8. Pizella V, Romani GL Principles of magneto-encephalography. In: Susumu Sato (ed.). Advances in neurology, Vol. 54: Magnetoencephalography. New York: Raven Press, 1990: 1-9.
9. Hari R. Human cortical functions revealed by magneto-encephalography. Prog Brain Res 1994; 100: 163-68.
10. Grindval A, Frostig RD, Siegel RM, Bartfeld E. High resolution optical imaging of functional brain architecture in the awake monkey. Proc Natl Acad Sci U S A 1991; 88: 11559 - 63.
11. Andreasen NC. Linking mind and brain in the study of mental illnesses: a project for a scientific psychopathology. Science 1997; 275: 1586-93.
12. Wickelgren I. Getting a grasp on working memory. Science 1997; 275: 1580-82.
13. Taubes G. Play of light opens a new window into the body. Science 1997; 276: 1991-93.
14. Barinaga M. Visual system provides clues to how the brain perceives. Science 1997; 275: 1583-85.
15. Barinaga M. New imaging methods provide a better view into the brain. Science 1997; 276: 1974-76.
16 Barinaga M. What makes brain neurons run? Science 1997; 276: 196-98.

Reference: Images of the mind - New technical approaches. Stødkilde-Jørgensen H. In: The Danish Society for Biomedical Engineering, ed. Aspects of biomedical engineering in Denmark. Copenhagen, 1998: 71-79.

Virtual Reality in medicine

JØRGEN ERIK ASSENTOFT

Carl Bro Informatics, Risskov, Denmark

Virtual Reality technology enables an individual to become actively immersed in a simulated environment. This offspring of computer graphics will rely increasingly on the development of more sophisticated hardware and software programs as efforts intensify to make the environments more "real". The presentation of Virtual Reality environments ranges from theatre style viewing on large screens to those displayed on computer monitors, and through helmets with stereoscopic screens and headphones. The experience is multisensory: sight, sound, and touch are the most common. The technology facilitates the viewer's understanding of interrelationships among contextual elements, and provides a means by which the viewer can learn to respond effectively and efficiently to the available data.

Key words: CAVE™*; cardiac catheterization; cybersickness; disabilities; endoscopic retrograde cholangio; eye surgery; virtual hospitals; virtual navigation.

Jørgen Erik Assentoft, biomedical engineer, senior member of IEEE, Carl Bro Informatics, Nordlandsvej 60, DK-8240 Risskov, Denmark.

INTRODUCTION

Virtual Reality is one of the hottest research and development areas in the computer industry today. Its potential applications range from medical imaging and interior design to intercontinental videoconferencing and the exploration of future worlds.

Virtual Reality is often thought of as new technology, but its development actually dates back almost 50 years to flight simulators built by the aircraft industry and the U.S. Air Force during and after World War II [1]. Student pilots learned how to maneuver airplanes by manipulating the controls in specially built airplane cockpits. These

* CAVE™ is a trademark of the Board of Trustees of the University of Illinois, USA. CAVE™ is registered in the USA.

cockpits, which were actually removed from the airplanes themselves, were mounted on movable platforms that tilted and rolled based on the pilot's actions on the controls.

One area of artificial intelligence research conducted in the late 1950s and 1960s explored building better interfaces between people and machines. In the early 1960s a graduate student named Ivan Sutherland presented a Ph.D. thesis in this area that demonstrated a new way to interact with computers. Sutherland believed that display screens and digital computers could offer a means of gaining familiarity with concepts not realizable in the physical world by providing a window, or looking glass of sorts, into the mathematical wonderland of a computer. Sketchpad [2], the program Sutherland developed and described in his thesis, used computer technology to create images from abstract ideas. Using Sketchpad and a penlike device, a computer could create sophisticated images on a display screen resembling a television set. The system responded by rapidly updating the drawing so that the relationship between the user's action and the graphical display was clear. Computer-aided design (CAD) grew out of Sutherland's thesis and became one of the most powerful components of Virtual Reality development in the 1990s.

Sutherland next focused on developing technology that would allow computer users to actually enter the world of computer-generated graphics. In 1965, with support from the Department of Defense's Advanced Research Projects Agency (ARPA) and the Office of Naval Research Sutherland unveiled the head-mounted display (HMD), which took users inside a three-dimensional world by limiting visual contact to the displays shown by small computer screens mounted in binocular glasses. It became a cornerstone of Virtual Reality technology. Today Sutherland has a company supporting image processing and Virtual Reality.

In the mid-1980s, the different technologies that enabled the development of Virtual Reality converged to create the first true Virtual Reality system; Virtual Interface Environment Workstation. It was the first system that combined such standard Virtual Reality elements as computer graphics and video imaging, 3-D sound, voice recognition and synthesis, and a head-mounted display. A data glove, based on an invention designed to play air guitar, completed the system.

From there, it was only a matter of time before Virtual Reality programs began appearing in settings ranging from Virtual Reality theme parks to operating rooms, largely aided by products developed by Jaron Lanier [3], whose programming language operated the first data glove at the NASA research center. Lanier's company, VPL Research, was the first company to focus its efforts on developing products for the infant Virtual Reality industry, and provided the headgear and gloves used in many early Virtual Realities applications.

The computer generated environment, or virtual world, consists of a 3-D graphics model that is implemented as a spatially-organized object-oriented database in which each object in the database represents an object in the virtual world. A separate modeling program is used to create the individual objects for the virtual world. For greater realism, these modeling programs apply state of the art computer graphics techniques, such as texture mapping and shading, to all objects of the scene. The object database is manipulated using a real-time dynamic controller, which specifies how objects behave within the world according to natural laws, such as gravity, inertia, or material properties. These laws are application specific. The dynamics control-

ler also tracks the position and orientation of the user's head and hand.

Although original applications in Virtual Reality for medicine pertained to the planning of surgeries, efforts have now shifted to the use of data fusion, i.e., to fuse virtual patients onto real patients as a navigational aid in surgery. Medical care with multiple professionals will be provided in a shared virtual environment in different locations via high speed network that incorporates shared decision making for an actual surgical intervention or a rehearsal. Historically, physicians learn new surgical procedures through observation, practicing on animals and cadavers, and then performing the procedure on patients under the supervision of an experienced surgeon. With the computer simulation, physicians can train in a virtual environment in which there are no risk to patients, and the procedure can be reviewed from new insightful perspectives that are difficult if not impossible in the real world.

Current Virtual Reality in medicine and surgical simulation

Several research efforts in Virtual Reality are described below. First is a description of CAVE Automatic Virtual Environment from University of Illinois [4], which is a big room with video projectors on 3 walls and floor, then from Georgia Institute of Technology descriptions of endoscopic retrograde cholangio-pancreatography simulation, eye surgery simulation, simulated cardiac catheterization. The last section is about cybersickness.

Use of the CAVE by persons with disabilities

Common Virtual Reality systems use head mounted displays that require duplicating user input devices in virtual space for interactive environments. A major advantage of projection based Virtual Reality systems such as the CAVE Automatic Virtual Environment (CAVE) is the ability of the user to see his/her own body and real objects in a virtual environment, an example is shown in Fig. 1. The developments of specialized interfaces for virtual environment exploration by people who use wheelchairs are described [5]. These real, tangible interfaces are intuitive and most appropriate for wheelchair simulations. Examples of these are interfaces that match the user's wheelchair dynamics for joystick or tiller operated electric wheelchairs. The importance of this research is in applications where users of wheelchairs analyze proposed constructed environments. Additional applications include wheelchair mobility training and wheelchair controller design.

The Virtual Reality Cave

Virtual Reality is created by a three dimensional computer graphics system using real-time interactive control and displaying viewer-centered perspective. Virtual Reality usually has panoramic binocular display with a large angle of view. These features are included in the immersive technologies of head-mounted displays (HMD), boom-mounted displays and surround-screen projection-based displays.

The Electronic Visualization Laboratory at the University of Illinois, USA has developed a new Virtual Reality interface called the CAVE [6]. It surrounds the viewer with projected images of a virtual environment. Three rear-projection screens make up three walls of a ten-foot-cube that disappear when illuminated with computer graphics. A fourth data projector illuminates the floor for complete immersion.

The projectors are high-resolution data type projecting stereo images on alternating fields. Active liquid crystal display (LCD) stereo shutter type glasses are worn by

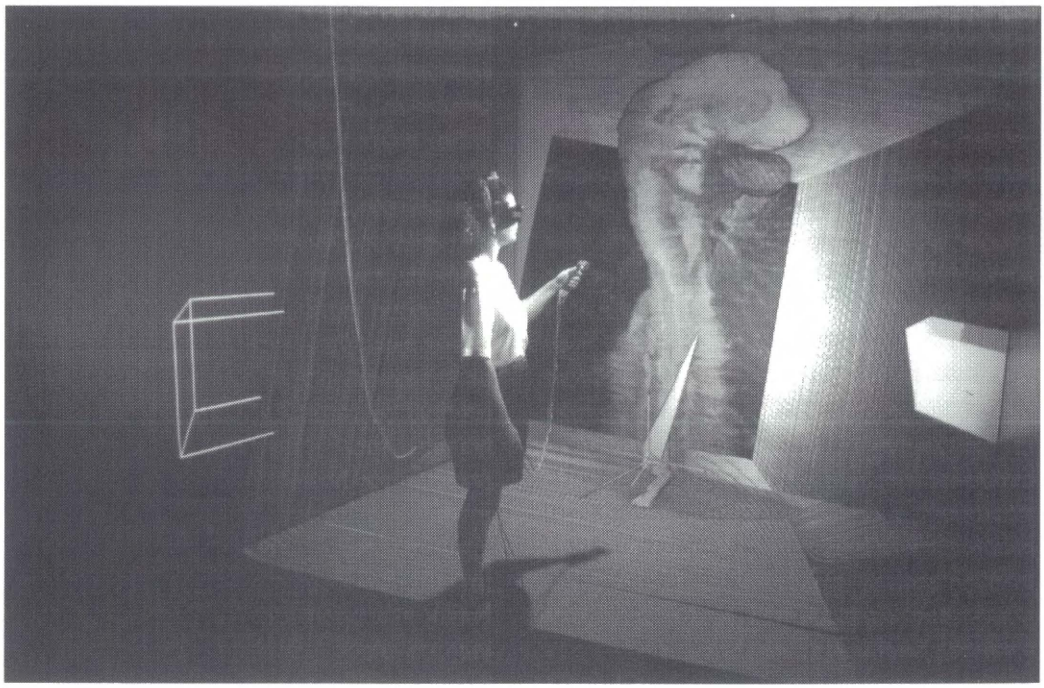


FIG. 1. National Center for Supercomputing Applications Senior Research Programmer, Rachel Brady traces a chick embryo inside the CAVE™ using Crumbs software. (Copyright University of Illinois Board of Trustees).

viewers to separate the alternate fields to the appropriate eyes, while viewer head position is tracked by an electromagnet-sensing device attached to one of the pairs of stereo glasses. A Silicon Graphics Onyx with multiple processors generates the computer graphics for each projector. The viewer can move around the virtual environment and see his own body as he interacts with real and virtual objects.

Real objects and real interfaces

With typical head-mounted or boom mounted displays the viewer is isolated from the real world. To see one's own body parts in a virtual environment, those parts must be recreated graphically [4]. A glove-input device is often used to control a representation of the hand while interacting with the virtual world. Other real world objects must also be modeled in computer graphics to include in the virtual space. These objects might involve interface devices such as vehicle controls.

Superimposition of virtual objects and real objects is possible with the use of half-silvered mirrors in head-mounted display [4]. Because the viewer sees through the virtual objects this technique is most useful for virtual objects in a real environment as opposed to real objects in a virtual environment. A useful application of this feature would be virtual overlays on real control panels for instructional purpose [7].

The CAVE also allows for combining real world objects in a virtual environment but these objects are unobstructed by the virtual environment. Real objects can, however, occlude virtual objects if the real object is behind the virtual object's virtual location.

This would be the case with virtual overlays. Alternatively, highlights can be employed with virtual outlining of a real object or adjacent graphics and text can provide directions. For example the sequence of operations in using wheelchair controls could be highlighted with animated symbols and virtual directions. Occlusion also happens if a virtual object is intended to be near the center of the CAVE and a viewer or real object is between the virtual object and the screen. Careful planning can avoid these situations.

Real navigation with real objects
For virtual environments that require less than 10 feet of movement to navigate, the user can move as normally in the CAVE. In simulating accessible interior spaces, real interfaces and real objects can be installed in the virtual environment. An example would be the interior of a mass-transit vehicle. Wheelchair securement devices such as the Seattle Red-belt can be used with a folding transit-style seat to mock up a wheelchair tie down, while the rest of the interior is modeled in Virtual Reality. The user can analyze reach requirements of the belts as well as clearances in maneuvering his/her wheelchair into the tie-down area. Using real objects, with their ability to have physical feedback and greater detail, a simulation can be made far more accurate.

Virtual navigation
Larger spaces can be virtually navigated using a joystick interface. For example a person could virtually traverse the length of a train station platform while checking accessibility features. This joystick interface was built to simulate an electric wheelchair. It can be attached to an existing wheelchair, manual or electric, or to any chair. The physical nature of this joystick interface can make a simulation very compelling. Although a "treadmill" style interface would be most appropriate for manual wheelchair [8], a joystick approach was convenient and more universal.

Shared or guided experiences
The CAVE has the ability to augment reality for multiple viewers as well. Although only one viewer would be position-tracked, additional viewers need only wear the stereo glasses to see what the other people see. This is very important for collaborative work such as analyzing design models for accessibility or evaluation of a disabled client for reach limitations. Since only one person's motion can be tracked, priority must be given to the person who is evaluating distances. For evaluation of a transit model, the tracker glasses can be passed between the person in a wheelchair and the person who is checking clearances. For training or therapy situations the client can be guided through a session in a truly shared experience with effective communication, not second hand interpretation. Guided sessions are also important for the potential occurrence of cybersickness and the need for intervention.

Input devices for Virtual Reality
Access to Virtual Reality interfaces by persons with disabilities is similar to the problems of access to computers in general. For people with physical disabilities the input devices of greatest concern have been the keyboard and mouse. A variety of keyboard and mouse aids and substitutes are now available. These devices are typically used for text and numeric data entry and cursor steering. In Virtual Reality these functions also exist with an emphasis on three dimensional cursor steering or navigation.

Another common adaptive input technique is head control. With this technique an ultrasonic device is strapped to the user's head

for cursor steering. Since a position tracker would normally be mounted to the CAVE user's head, gaze monitoring is automatic. With 3D-position tracking, gesture recognition techniques can be used for head gesture, hand gesture or wand gesture as an alternative input method. Gestures can be small and subtle or large and obvious.

The digital wand

Until recently a prototype wand input device was used that contains a position sensing device and three digital button switches. The position-sensing device is the same as the device attached to the stereo glasses for head position monitoring. The three buttons were simply wired in parallel to the buttons of a mouse attached to one of the workstations. In many ways it can function as a "3D mouse" for cursor steering in three dimensions. Navigation is accomplished by pointing in the desired direction of travel while pushing the appropriate button to move. Object manipulation is accomplished by pointing at the object and intersecting it with a virtual wand extension.

The analog wand

Connecting to the existing mouse interface of a workstation, although expedient, did not allow for more accurate navigation or precise control as afforded by analog devices. To remedy this situation an IBM PC clone was used as our input device interface. By doing this advantages could be taken of the wide variety of devices and software available on the market. For example most PC clones now include a mouse input and game port. Many types of joysticks for flight simulators or other game software exist at low cost. In addition a wide variety of digital and analog I/O boards are available at reasonable prices.

Using the PC interface also meant that the many adaptive input devices available for persons with disability could be used for virtual environments. For example chin operated track balls or foot operated joysticks can replace typical mouse operations. For text or numeric input specialized keyboards are available that replace or augment a standard keyboard (expanded keyboard, mini keyboard, key latches, key guards). Of course voice input systems hold great potential for controlling all aspects of the Virtual Reality interface by persons with movement limitations and are readily available for the PC at prices that keep falling. Head control software may also be adapted to the CAVE environment.

Wheelchair simulation

Although wheelchair simulations could be performed using the capabilities of the wand joystick we decided to develop a separate wheelchair displacement style joystick that can be mounted to the armrest of a chair or wheelchair. Navigation with this joystick can be programmed to accurately simulate electric wheelchairs of many sorts. For conventional electric wheelchairs pushing the stick forward produces forward travel while reverse travel would be controlled by pushing the stick backward. Pushing the stick further in either direction increases the speed of travel. Left/right movement of the joystick would rotate the user relative to the virtual environment as if turning the wheelchair. Simply stated, pushing the joystick in the desired direction of travel will turn and move the wheelchair in that direction at a speed proportional to the displacement of the joystick. Alternatively an omnidirectional wheelchair can be simulated by programming the joystick such that pushing the stick in the desired direction of travel will move the wheelchair in that direction without turning.

Other electric wheelchair dynamics can be simulated as well. For example different

wheelchair configurations (front or rear caster design, size of caster, etc.) or controller designs (sensitivity, oversteer, understeer, smoothing, etc.) can be programmed into the software [9].

Transportation compliance

Public transit agencies are obligated to provide access to their services to people with disabilities. Transportation providers must scramble to meet accessibility deadlines, which force them to face reconstructing facilities, which can date to the nineteenth century. Current conditions must be evaluated and design strategies developed to fit within today's limited transit budgets.

The Design Visualization Lab currently has a proposal in to the Chicago Transit Authority to develop strategies for making Key stations wheelchair accessible. Innovative new ways to raise patrons to platform level at elevated stations need to be devised. The standard method of making a station accessible is to install an elevator. At many Chicago Transit Authorities stations, this would require widening the platforms and support structure to accommodate the increased width of an elevator. This would require tearing down private and public structures making the job prohibitively expensive. By surveying state of the art accessibility equipment and developing new ideas, they hope to solve the problem. The Cave would be used extensively in this process to view and evaluate models of existing conditions and simulate new access methods. Tremendous amounts of time and money could be saved in the design and prototyping phases of the project by working bugs out of potential solutions before they are sent to an engineering firm for final planning.

Mass transit interior design

At University of Illinois at Chicago they are continuing to develop accessible vehicle interiors. Models of the University campus shuttle bus and various public transit vehicles have been built for evaluation in Virtual Reality. Bringing these models into the CAVE has allowed us to evaluate interior layouts for wheelchair accessibility. The wheelchair lift area can be inspected for clearance and the stanchions checked for position and height. By having the primary investigator wear the head-tracking device, accurate clearance measurements can be made around wheelchairs, real objects and virtual objects.

Instruction for people using wheelchairs

It also makes possible instruction before a person learns to run a wheelchair. In the safe environment of the Cave, you can make errors, which may be fatal outside of Virtual Reality. You can also try maneuvers which one is afraid to try for fear of injury, ie., crossing traffic at an intersection. In the case of teaching people to use a powered chair, much of the fear and danger can be removed from the experience, making the transition easier.

The Cave can be used for teaching ambulatory persons how people in wheelchairs function in everyday life. Designers can evaluate their ideas before committing to manufacture, and architects can see how much space is required around a chair for ease of use. Employee sensitivity training could be much more effective if participants viewed boarding a bus from the position of a passenger in a wheelchair

Endoscopic Retrograde Cholangio-Pancreatography Simulation

Endoscopic Retrograde Cholangio-Pancreatography (ERCP) is a minimally invasive technique for evaluating and treating pathologic conditions of the biliary and pancreatic ducts. The major benefit of ERCP is

that it allows patients to avoid more invasive surgical or radiological procedures, and the therapeutic applications of ERCP significantly lower the risk of infection, speed recovery time, and reduce the cost of delivering care. However, while ERCP provides the patient with substantial advantages over traditional methods, ERCP requires advanced skills and extensive experience to minimize the risk of complications. The Biomedical Interactive Technology Center (Georgia Institute of Technology [GA Tech], USA) is working with the Medical College of Georgia to develop an interactive computer simulation that will improve training of ERCP skills. The simulator consists of several physical components and several "virtual" or computer generated components. The physical components form the interface through which the physician performs the procedure in the simulated environment.

The simulated session begins as an endoscope is inserted through the "mouth" of the simulator. The endoscope is guided into position using standard endoscopic techniques. Two display options are provided: the view that would be seen through the optics on the endoscope, and a view of the endoscope in relation to the surrounding anatomy. The second view is not available in real life, but this view may help training physicians to better understand the 3D geometry and positioning maneuvers. Both views are computer generated imagery of the virtual anatomy. The stomach, duodenum, and papilla are represented by three-dimensional computer models that are texture mapped with photographic images of the anatomy acquired during endoscopic examinations.

Eye surgery simulation

The Georgia Institute of Technology, USA and the Medical College of Georgia, USA have developed a proof-of-concept eye surgery simulation that provides both visual and tactile feedback while a surgeon operates on a computer model of the eye in a virtual environment. In practice, ophthalmic surgeons operate on an eye by looking through a stereo microscope while steadying their hands (holding the surgical instruments) on a wrist rest that surrounds the patient's head. The simulator also includes a stereo operating scope and a wrist rest, but instead of looking directly at a real eye, the surgeon interacts with a virtual eye using a virtual surgical instrument controlled by a hand held 3D position tracking stylus that continuously reports position and orientation to the computer. The tip of the stylus is connected to three motors that generate component force feedback in response to the tool-tissue interaction. The simulation includes options to change instruments, record and playback training sessions, reset the models, and peel away outer layers of the eye to reveal interior anatomical components. Dials allow the surgeon to rotate the model, change transparency, zoom, and adjust stereo viewing parameters. An instrument activation switch on the stylus controls actions such as opening and closing forceps and scissors.

In the virtual environment, the eye and the surgical instruments exist only as computer models. The eye is represented by a collection of deformable three-dimensional models. The models of the sclera, iris, zonules, and retina are texture mapped with photographic images of these components. The lens and cornea are modeled as semi-transparent objects. An overhead light source included in the simulation produces specular highlights on the ocular components. Interaction between the instruments and the eye is dependent upon the currently selected tool, the location of the instrument in the anatomy, and the kind of action requested by the surgeon. For example, as the

knife makes contact, the sclera slightly deforms until the blade penetrates and starts to cut. The tactile feedback system produces a compliant resistance as the sclera deforms and then allows the blade to slice through the sclera with a small viscous resistance in the cutting direction after penetration. As the blade is cutting, a strong compliant resistance is generated at the stylus tip in the direction orthogonal to the cutting direction to produce the same type of resistance that would be experienced if the surgeon tried to lift the incision with the flat portion of the blade. Forceps can be used to grasp and stretch the sclera while opening the wound. Both visual and tactile feedback are provided to the user: if the forceps are opened during the grasp and pull action, the sclera reverts to its original shape, and the tactile resistance is removed.

Simulated cardiac catheterization

Coronary angiography is widely used to assess the extent and severity of coronary artery disease and is clinically performed by the procedure of cardiac catheterization Cardiac catheterization involves advancing a catheter under fluoroscopic guidance through the femoral and iliac arteries into the abdominal and thoracic aorta, and finally into the left and right coronary arteries. The cardiologist relies on visual feedback from the fluoroscopic display and from the resistance felt from the catheter to determine how the catheter should be advanced, withdrawn, or rotated. However, the vascular structures are essentially invisible unless dye is injected and becoming proficient in maneuvering the catheter remains a key challenge for training cardiologists. The Biomedical Interactive Technology Center, GA Tech, USA, is developing an interactive computer simulation for catheterization training. 3-D computer models of the vasculature and catheter are displayed on a monitor while the student guides a real catheter into a dummy patient on the table. A tracking system in the dummy monitors the catheter's rotation and advancement. This position and rotation information is passed to the simulation computer, which updates the display of the virtual catheter moving through the vascular tree. The vasculature can be rotated to simulate any viewing geometry. The model is rendered with flat shading to simulate the fluoroscopic display or it is rendered with full shading to provide the clear 3D visualization.

Cybersickness

Real world references assure a viewer of their balance and equilibrium. Losing a sense of location and orientation in a virtual world can lead to fear in the viewer and potential nausea (Cybersickness) [10-13]. In a projection based system like the CAVE disorientation and nausea are less of an issue because the user's view is not isolated. The viewer can be immersed in a virtual environment but still be conscious of the real world surroundings and their own body.

Cybersickness can be very important in applications involving people with disability, particularly those disabilities that affect balance and equilibrium. If Virtual Reality is used for mobility training, the user must be able to deal with the potential isolation of a virtual environment. If the user cannot maintain their equilibrium in Virtual Reality, the training will not only be useless, it could also be harmful [14,15].

FUTURE AND CONCLUSION

The hospital of the 21st century could turn out to be a real-world medical center combined with an electronic counterpart in cyberspace! That may sound like pure science fiction, but it's what physicians and others

at the University of Iowa have already started to build. They are in the midst of an ambitious project to digitally clone the university's health science colleges, library, hospitals, clinics, and medical curriculum. The architects of the "Virtual Hospital" plan to make the entire project accessible electronically in the form of a multimedia database containing text, images, audio, and video. Their long-term goal: use new computing and telecommunications technology to transform medical education and patient care in Iowa and beyond.

The Virtual Hospital relies on a very popular database format called the World Wide Web, which provides a common language for computers to share multimedia information. The WEB spawned many innovations quickly integrated with browsers through mechanisms such as Sun's Java, Microsoft's Blackbird, Macromedia's Director or Virtual Reality Modeling Language (VRML). As indicated, Java lets you download platform-independent code that enables local execution. Java is built on C and C++ languages optimized for client-server on-line applications. Code is dynamically linked on the fly through an interpreter so that an application runs without precompilation. A Java application or applet can be sent from the server to the client running HotJava, the player that automatically runs the application. The server can then continue to update the application.

In the USA the Pentagon funds a telesurgery project called MedFAST, or Medical Forward-Area Surgical Telepresence [16]. The concept is to place the surgical unit in areas of conflict, accidents or natural disasters. The surgeon, from a safe distance, controls the remote operation through force-feedback devices such as surgical instruments.

With the proper software, you can view all portions – not just text – of the Virtual Hospital. This prototype of a "ubiquitous organization" is designed to offer access to up-to-date information at the point of care – wherever that may be.

Such access to information will free physicians, health care workers, and patients from the need to go somewhere to get information or to rely on what Dr. Galvin (director of the Virtual Hospital) called "your faulty database of memory".

The Virtual Hospital (they've applied for a trademark on the name) is a prominent example of how the much-heralded information superhighway is being exploited within the health care sector. Such projects will go beyond traditional hospital information systems by making resources available electronically to a potentially unlimited audience outside hospitals.

The Virtual Hospital was originally planned only as a way to serve Iowa citizens and to help the State retain physicians in rural areas. But it soon became clear that the project could serve a much wider purpose and help build a "virtual medical community".

Soon the database will include diagnostic algorithms, clinical practice guidelines, the pharmacy formulary, selected grand rounds and lectures, course notes, a link to the hospital's patient database, and videoconferences.

On-line information from the project will also be made available to consumers and to the State school system. Patients will be able to use a physician's directory, get health education materials, or download maps to find their way to the medical center.

Behind the Virtual Hospital's high-tech glitz, lies a philosophy of medical education that Dr. Galvin calls "just-in-time learning". The problem is that physicians have trouble keeping up with current knowledge. What physicians know closely reflects what they learned in medical school. Their

knowledge tends to grow increasingly spotty and outdated after school, despite heroic efforts to keep up with the journal literature

If physicians have direct access to electronic textbooks and other on-line information tools, they can learn what they need to know when they need to know it. For example, at the University of Iowa, anatomists Drs. Bergman and Afifi are working with Teresa Chol to enter their textbook "Illustrated Encyclopedia of Human Anatomic Variation" to the Virtual Hospital program. This will have a significant impact on students and healthcare professionals. The medical knowledge base will be limitless!

The CAVE is an important and effective design tool for evaluating environments and products. The ability to include real world objects in a virtual environment sets the CAVE apart from other Virtual Reality systems, which entirely replace the viewer's environment. By being able to experience a Virtual Reality simulation with more than one person, the CAVE allows for shared or guided evaluations, which can be highly effective. Joystick navigation in the CAVE is a natural interface for all people as well as those who use joystick controlled powered wheelchairs. Additional adaptive input devices may also prove to be beneficial to nondisabled CAVE users. This allows providing a smooth transition to the virtual world. The CAVE is accessible to a larger percentage of the population by virtue of its roll-in construction and real world interfaces making it ideal for accessibility simulations.

A lot of Universities and Biomedical Engineering Departments all over are developing different applications in this area [17]. The main area investigated in Virtual Reality is surgical simulation and it is expected that this will continue. New medical imaging techniques are developed which combines MRI, CT, PET Images in such a way that it is possible to use the acquired data in simulation in real time. The next main area in Virtual Reality is the teaching of physicists.

The next couple of years will be show the areas in Virtual Reality that will survive.

In Denmark there is a tradition to develop different biomedical equipment (from chemical analysis to ultrasonic imaging equipment) from several companies. The theoretical and practical knowledge in companies and universities in Denmark is high and therefore the potential to develop new Virtual Reality equipment is there.

One of many projects could be to use the knowledge of Biomechanics to find the force for penetrating flexible tissues to make a new Virtual Reality Surgical Equipment. But before that would be possible new transducers and surgical tools should be developed. The development of new transducers based on Micro Electro Mechanical System (MEMS) should be used. The advantages of MEMS transducers are that they are very small and lightweight. These transducers mounted on a glove used by a surgeon could find the relative position and orientation of the hand (Gyroscope). The transducers would need to have a feedback correlated to the force in such a way that the surgeon can "feel" the tissue strength. Such a project is a multidisciplinary work with knowledge of Computer Science, Physics, Biomechanics, Transducers Design, Medical Science and Material Science. But this knowledge we have in Denmark and therefore new Virtual Reality projects are waiting to get started.

REFERENCES

1. Helsel SK, Judith PR. Virtual Reality: Theory, practice, and promise. New York: Information Today, Inc., New York, USA, 1991.

2. Sutherland IE. Sketchpad: a man-machine graphical communication system. New York: Garland Publishing, New York, USA, 1964.
3. Lanier J. A cyberspace Renaissance man reveals his current thoughts on the world wide web, virtual reality, and other silicon dreams. 29. Sept. 1997. Scientific American (only on the web): http://www.sciam.com/interview/lanier.html.
4. Cruz-Neira C, Sandin DJ, DeFanti TA, Kenyon R, Hart JC. The CAVE, audio-visual experience automatic virtual environment. Communications of the ACM 1992; 6: 67-72.
5. Browning D, Cruz-Neira C, Sandin DJ, DeFanti TA. CAVE, Projection-based virtual environments and disability. Proceedings Virtual Reality and Persons with Disabilities, California State University (CSUN) Center on Disabilities, 1993,
6. Electronic Visualization Laboratory, University of Illinois, USA: http://www.evl.uic.edu/EVL/index.html.
7. Feiner S, MacIntyre B, Seligmann D. Knowledge based augmented reality. Communications of the ACM 1993; 36: 53-62.
8. Trimble J. Virtual barrier free design. Team Rehab. Nov. 1992.
9. Collins TJ, Kauzlarich JJ. Analysis of parameters related to the directional stability of rear caster wheelchairs. University of Virginia Rehabilitation Engineering Center, 1987.
10. Cruz-Neira C, Sandin DJ, DeFanti TA. Surround-screen projection-based virtual reality: The design and implementation of the CAVE. University of Illinois, 1992.
11. Dizio P, Lackner JR. Spatial orientation, adaptation, and motion sickness in real and virtual environments. Presence 1992; 1: 323.
12. Hettinger LJ. Visually induced motion sickness in virtual environments. Presence 1992; 1: 306-07.
13. Kennedy RS, et al. Profile analysis of simulator sickness symptoms: Application to virtual environments systems. Presence 1992; 1: 296.
14. Biocca F. Will. Simulation sickness slow down the diffusion of virtual environment technology? Presence 1992; 1: 334, 337-38.
15. McCauley ME, Sharkey TJ. Cybersickness: Perception of the self motion in virtual environments. Presence 1992; 1: 311, 313.
16. Kitson FL, Malzbender T, Bhaskaran V. Opportunities for visual computing in healthcare. IEEE Multimedia 1997; 4: 55.
17. Satava RM. The role of virtual reality in medicine of the 21st Century. Virtual Reality Systems 1993; 1: 64-67.

Reference: Assentoft JE. Virtual reality in medicine. In: The Danish Society for Biomedical Engineering, ed. Aspects of biomedical engineering in Denmark. Copenhagen, 1998: 81-92.

The Vikings are coming !

JOHN GADE[1], STEEN ANDREASSEN[2] & ERLING HENNINGSEN[1]

[1]Judex Datasystemer A/S, Aalborg, Denmark, [2]Department of Medical Informatics and Image Analysis, Aalborg University, Aalborg, Denmark

The present paper describes the Viking Electromyography (EMG) systems developed jointly by the Danish company Judex Datasystemer A/S and by the US company Nicolet Biomedical. The Viking was introduced in 1985 as a totally new concept in clinical neurophysiology. The Viking was the first system to use a computer to control the signal recording and stimulation and to do real-time, on-line analysis of the EMG signal. Other innovations included the introduction of automatic measurements and simultaneous display of EMG signals and measurements on the same screen.

To achieve the necessary performance, the first generation was based on many custom-made hardware and software components. The technological development has gradually made it possible to replace these components. The shift towards less expensive standard components will be complete in the latest generation of Viking systems that, apart from amplifiers and stimulators, will use standard PC components and a standard Windows NT® operating system.

The Viking has a comprehensive repertoire of EMG tests, and has achieved a position as market-leader in the high-end EMG and intra-operative monitoring markets and a solid position in the area of evoked potentials. We believe that this position has been achieved 1) by insisting that technological expertise, combined with a thorough understanding of the clinical application, forms the best basis for the development of biomedical equipment and 2) by maintaining a long standing collaboration between companies with complementary skills.

Key words: Neurophysiology; electromyography; equipment.

John Gade, Judex Datasystemer A/S, Lyngvej 8, DK-9000 Aalborg, e-mail: jg@judex.dk

INTRODUCTION

In the late 1970s and the early 1980s microcomputers were slowly making their way into biomedical equipment. However, due to the limited data processing capacity the computers were mainly involved in controlling the equipment, e.g., the routing of the signal from the input amplifiers to analogue filters and averagers, not the signal analysis itself. In the 1980s electrocardiographs with computerized calculation of the heart rate were on the market, but analysis of signals from muscles and nerves demanded 10 to 100 times higher sampling frequencies, and thus put much higher demands on the data processing capacity of the computer.

The Danish company Judex was one of the prime actors in computerized analysis of electromyographic (EMG) signals. Judex was founded in 1981 with a basic idea of utilizing some of the research results generated at the Department of Biomedical Informatics and Image Analysis at Aalborg University. From the onset the development work in Judex was based on the assumption, that innovative equipment for the health care sector can only be developed by a team that has both a solid understanding of the medical area and expertise in the latest developments in hardware and software design.

Over the years Judex has participated in a number of national and international research projects and have been able to utilize results from these projects in commercial products. The company is specialized in research and development activities within the biomedical field and several of the development projects have been joint-venture projects with international partners. Today the main research and development activities are:

- The Viking family, a number of systems for recording and analysis of signals from nerves and muscles. The Viking products are developed in co-operation with the American company, Nicolet Biomedical Instruments.
- The Nightingale and the RespTrace, polygraphic systems for analysis of sleep and sleep-related respiratory disorders. The Nightingale is a modular system which can be configured for simultaneously recording of signals from up to four patients. The system includes software for sleep analysis, apnea analysis, video registration, EEG spectrum analysis etc. The RespTrace is a dedicated one patient system equipped with a 12 or 16 channels amplifier and an oxymeter and with software for sleep and apnea analysis.
- BLAQ (Booking Log Anesthesia Quality), a medical informatics system for registration of data for quality assurance in anesthesiology and anesthetic record keeping.
- DIAS (Diabetes Advisory System), a knowledge based system for adjustment of insulin therapy.

Of these activities the Viking family has far the longest history. The present paper describes the development of the Nicolet Viking EMG systems from the very beginning and to the latest Windows NT® based generation. An overview of the evolution of the Viking systems and the tests supplied for the systems is shown in Table I.

PRE-VIKING DEVELOPMENTS

The first system to be developed by Judex was a system for the Royal Dental College in Copenhagen [1]. The system was dedicated to quantitative analysis of the EMG of up to 8 different chewing muscles to evaluate muscular pain and results of

TABLE I. Milestones in the development of the Nicolet Viking EMG systems. For each model the operating system and the computer platform (at introduction) is listed. The dates of introduction of the tests and utilities are approximate.

Year:	Model:	Operating system:	Computer platform, Processor/speed, Memory/Storage:	New tests and utilities:
1998-	Viking and VikingQuest for Windows NT	Microsoft Windows NT	PC, Intel Pentium/233 MHz, 32 MB/6 GB	EOG, ERG, Collision Neurography
1997	VikingQuest		Portable PC, Intel Pentium/133 MHz, 16 MB/1.6 GB	MuscleNotes
1996				EP+ suite (SEP+, AEP+, VEP+), P300A
1995	Viking IV Review			Viking networking, Motor Unit Number Estimation
1994				Electrode and stimulator switching
1993	Viking IV	Intel iRMX for Windows	PC, Intel 80486/33MHz, 12 MB/100 MB	Report MSW, NCS Reference Values
1992				H-reflex, Blink Reflex, IOM with Processed EEG
1991				IntraOperative Monitoring
1990				
1989	Viking II	Intel iRMX for DOS	PC, Intel 80386/16MHz, 2 MB/32 MB	Quantitative EMG, Integrated Report
1988				
1987				MultiMode Program, Developers Kit, Automatic Decomposition EMG
1986				Repetitive Stimulation, Evoked Potentials
1985	Viking	Intel iRMX86	MultiBus computer, Intel 8086/5 MHz, 512 kB/10 MB	Motor and Sensory Nerve Conduction Studies, F-waves, Motor Unit Potentials, Spontaneous EMG, Interference Patterns, Single Fiber EMG
1984				
1983	Prototype EMG system			
1982	Dental EMG system	NUC86	MultiBus computer, Intel 8086/3 MHz, 256 kB/8" floppydisk	

dental correcting procedures. Manual analysis of these signals from paper-chart recordings was tedious and could last several days, and was thus not applicable in a routine clinical setting.

The output from the system consisted of a plot on a high-bandwidth pen-chart recorder (Siemens-Elema) of the EMG signals, their envelopes, and a set of markers indicating start, 50% 100%, 50% and stop of each chewing cycle to a pen-writer. The signal analysis involved continuous sampling of each channel at 2.5 kHz, or a total sampling frequency of 20 kHz. To find the envelope of the signals, the absolute value was calculated and the results were passed through a 2nd order digital low-pass filter. The markers were set automatically, based on the envelope of the signals (Fig. 1). In addition to output on the pen-chart recorder the system generated a statistical analysis of the signals to be used for diagnostic purposes.

All signal processing was performed by the computer, an Intel 8086 based MultiBus system. This pushed the processing speed of the computer to its limits, and to achieve such throughput using a 16-bit microcomputer a special analogue-to-digital (ADC) and digital-to-analogue (DAC) converter board with Direct Memory Access (DMA) was constructed. Likewise, since the few existing real-time operating systems were not fast and flexible enough, a real-time operating system, called NUC86, was developed. The system was controlled through an ASCII terminal.

The software of the dental-EMG system has been modified several times over the years, but the system is still in use.

THE FIRST VIKING

Based on the experience from the development of the dental system development of a general computerized EMG system was initiated. At the time, commercially available EMG equipment consisted of a collection of amplifiers, analog filters, delay lines, averagers and oscilloscopes. In the most sophisticated equipment the signal was routed between these hardware signal processing units by relays, controlled by a microprocessor. The vision was to develop an integrated EMG system where the signal routing and processing was performed by the computer, and to add the possibility of making automatic or semi-automatic measurements, directly from the screen displaying the EMG signals.

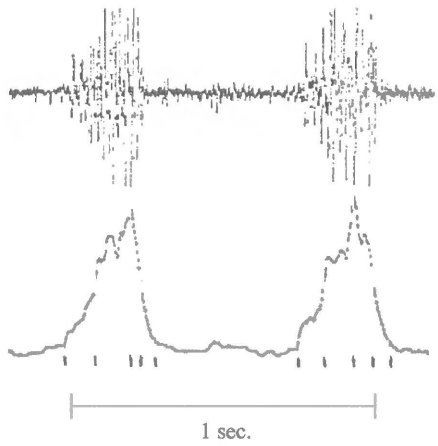


FIG. 1. The EMG signal from a chewing muscle during two chewing cycles (upper trace) and the envelope of the signal (lower trace). For each chewing cycle markers were set by the computer to indicate start of activity, 50% of maximal activity, maximal activity, 50% of maximal activity, and end of activity.

An example of this type of display, mixing EMG signals and measurements is shown in Fig. 2. Fig. 2 shows the EMG test used to determine the conduction velocity of nerves innervating skeletal muscles, in this case the median nerve innervating the abductor pollicis muscle, in the hand. The computer controls a stimulator, which delivers an electric shock to the median nerve through the skin. In the upper trace the shock is de-

livered to the median nerve at the wrist. The latency from the shock to the EMG activity in the muscle is 3.6 ms as indicated by the vertical marker, which is set automatically by the computer. By stimulation at other points along the nerve as done in the traces below the conduction velocity can be determined.

To make the EMG system clinically attractive, it was necessary to develop a system that from the onset could perform all the most commonly used EMG tests.

These ambitions made it necessary to have a high resolution color display system, that allowed fast updates of curves. Graphic boards with sufficient resolution and speed were not commercially available at the time and Judex developed a graphics board with a resolution of 1024 × 512 pixels in 256 colors, programmable in 8 individual bitplanes.

The collection of EMG tests necessitated sampling of EMG signal from up to 8 channels with sampling frequencies up to 50 kHz, both as continuous data collection and in bursts. This made it necessary to develop an ADC-board with a DMA-channel with special properties.

The computer selected for the EMG system was the Intel 8086 microprocessor in a MultiBus system, as in the dental EMG system. Fortunately the processor speed had increased, and the custom-made NUC86 operating system was replaced by Intel's iRMX86 real-time operating system. With the custom-built ADC and graphics boards the system could display the acquired EMG signals with a delay of less than 50 ms.

A prototype of a computerized EMG system was ready in the late 1982 and was sold to the Department of Clinical Neurophysiology at Aalborg Hospital. Transforming a prototype into a working clinical system was an expensive and difficult task, and since at most 10 such systems could be sold to the Danish market, the system had to be marketed internationally. This seemed an impossible task for a small company, and after negotiating with other major companies, Judex joined forces with the American company Nicolet Biomedical in 1983 to develop and market a computerized EMG system. Judex became responsible for development of the dedicated digital hardware and all software for the system, while Nicolet was responsible for analog hardware, production, sales, and marketing.

Viking I

The resulting system, called the Nicolet Viking, was put on the market in 1985, and it was the first EMG system where the built-in microcomputer was the main signal processing unit.

The Viking was launched with a number of tests divided into two groups: Nerve Conduction studies (NCS) and EMG studies. The NCS tests included Motor and Sensory Nerve Conduction studies, analysis of F-waves, and Repetitive Stimulation, all with automatic measurements of latencies and amplitudes.

The EMG tests were Spontaneous EMG (Free-running EMG or triggered traces), Turns and Amplitude (automatic calculation of mean rectified voltage, signal power and number of turns), Analysis of Motor Unit Potentials (automatic extraction of MUP's and measurement of duration, amplitude, and number of phases), and Single Fiber EMG (Jitter analysis). The basics of the Motor Unit Potentials analysis in the Viking system were the studies by Buchtal and Rosenfalck [2] on visual analysis of Motor Unit Potentials and by Andreassen [3] on computerized extraction of Motor Unit Potentials from the EMG signal.

The Viking was controlled through a control panel with dedicated keys and a set of 12 software controlled keys which could be

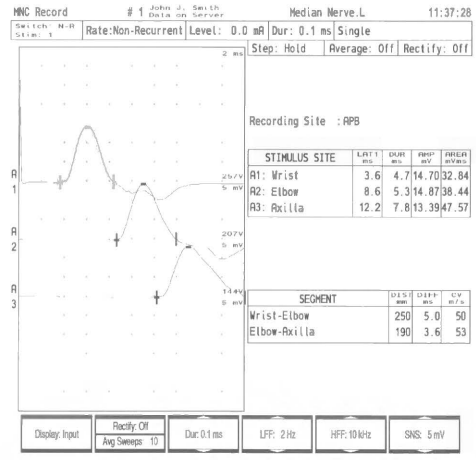


FIG. 2. The Motor Nerve Conduction test of the Viking. Left part of the screen shows the EMG responses of the abductor pollicis muscle in the hand to stimulation of the Median nerve at the wrist (upper trace), the elbow (middle trace) and the axilla (lower trace). Right part of the screen shows the measurements (latency, duration, amplitude and area) of the individual potentials. The latencies from the stimulation to the EMG activity in the muscle is meassured automatically (3.6 ms, 8.6 ms and 12.2 ms, resp.). From these latencies the nerve conduction velocities of the 2 nerve segments were calculated (50 m/s and 53 m/s, resp.).

set-up for different functions in different tests. The system was equipped with 2, 4, or 8 amplifiers, a temperature probe, two independent electrical stimulators, and audio output.

The size of the software far exceeded the 512 kBytes of memory (Table I) available in the computer. To achieve reasonably fast shifts between the different EMG tests the software was divided in a basic part, which was always loaded, and a set of overlays (comparable to a dynamic link library), which contained code specific for individual tests.

This modularity made it possible to add new tests, as an integrated part of the software. This option was exploited by researchers at Stanford University, who developed an ADEMG software package for Automatic Decomposition of the EMG signal into individual motor unit potentials [4]

This option was also used by Judex, and the most important expansion of the Viking I software was the addition of Evoked Potentials tests (Sensory, Auditory and Visual Evoked Potentials), which significantly expanded the market potential of the Viking.

A new concept in computerized biomedical signal analysis was created with the launch of the Multi Mode Program package (MMP). The MMP allowed simultaneous acquicision of free-run, triggered and stimulated traces, highly programmable by the user. The test is used e.g. for Macro EMG and autonomic system testing.

The Viking was in 1986 awarded the American IR100 award as one of the 100 most significant new technologies of the year. The award is given by a board set by the American magazine Research and Development.

Expert systems and reference values

In the period 1985 - 90 Judex participated in the project "Knowledge Based Assistant for Electromyography" supported by EU's ESPRIT program. The aim of the project was to design an expert system for diagnosis of neuromuscular disorders. The system should be able to import results from EMG systems. Based on these results the expert system should give the most probable diagnoses or suggest further tests to be performed.

In the part of the project where Judex participated, a novel technology, causal probabilistic nets, also sometimes referred to as Bayesian nets, was used. The expert system was never expanded to contain a large enough part of the anatomy to make the expert system clinically interesting, but within the limited anatomy the system performed

quite well [5,6]. The work with the system brought out some interesting observations, primarily that clinical practice was quite different in different European countries [7,8].

The differences in approach also applied to reference values for the different EMG tests, where each EMG lab tended to have its own set of reference values. Judex developed the NCS Reference Values package for the Viking, containing reference values for nerve conduction studies. Reference values, either from a textbook [9] or the users own reference values could be accessed from the individual Nerve Conduction tests, and text and graphical instructions on how to perform a specific test were made accessible on-line.

THE NEXT GENERATIONS

Viking II

The Viking had changed the appearance of EMG systems. By 1989 other manufacturers had developed EMG systems that could mix the presentation of EMG signals and text and measurements on the display. It had also become standard practice to use the EMG system's computer to do the required signal processing.

It was decided to introduce a new generation of Vikings, the Viking II. Throughout its lifetime, the Viking had been expensive, compared to traditional equipment from other manufacturers, and for the Viking II the goal was to obtain a substantial reduction in price. On the medical side the goal was to develop a system that had a full range of EMG tests.

The reduction in price could only be achieved by replacing some of the expensive custom-built components with less expensive standard hardware and software. The IBM-compatible Personal Computer (PC) had become a *de-facto* standard computer in the late 1980's. For the PC a wide range of add-on boards, including fast graphics controllers, were available. These standard units replaced the MultiBus-based computer and the custom-made graphics board in the Viking II. The operating system was changed to Intel iRMX for DOS, that allowed the users to run DOS programs on the computer along with the Viking software.

To ensure that the Viking II had a full range of EMG tests the nerve conduction tests were supplemented with specialized tests for H-reflex and Blink Reflex studies. The EMG tests underwent a major revision and expansion. They were reorganized into the Quantitative EMG package which contained tests for basic motor unit analysis and recruitment interval analysis, EMG signal power analysis and evoked EMG signal analysis in addition to the existing Single Fiber EMG and Automatic Motor Unit Potentials tests.

A new application area for the Viking came with the Intra-Operative Monitoring (IOM) Package for monitoring surgical procedures in which the brain and nervous system are at risk. The IOM package was developed in collaboration with the Mayo Clinic. This package allows simultaneous recording of a variety of neurophysiological signals, both free-running and evoked responses at different timebases. The IOM package was later supplemented with a package (IOM with processed EEG) for frequency analysis of EEG signals including calculation of activity in the traditional frequency bands (delta, theta, alpha, beta) and Color Density Spectral Arrays.

Viking IV

In the summer of 1993 the Viking IV generation was introduced. The goals for the Viking IV was

1. to continue the trend towards use of inexpensive standard hardware and soft-

ware components, including Windows, to make the price of the systems even more competitive
2. to make the facilities offered by Windows available as an integrated part of the EMG system and
3. to extend the success of the Viking as an EMG system into the adjacent areas, intra-operative monitoring and evoked potentials.

The Viking IV was based on a PC platform and updated amplifiers, stimulators and ADC-board. With a new operating system, the Intel iRMX for Windows, it became possible to use Microsoft Windows 3.1 for the user interface and still obtain the real-time, multitasking capabilities of the iRMX operating system. It also became possible to use the Windows mouse or other pointing devices in addition to the control panel. From a developmental point of view the use of Microsoft Windows removed the burden of having to develop new drivers for the ever-changing graphics adapters and printers, since these could be controlled through Windows drivers supplied by the manufactures. Together these changes reduced both hardware costs and the cost of software maintenance.

The facilities for clinical reporting of the results of the EMG tests, which had been part of the Viking since its introduction, were replaced by the Report MSW package, which generated reports from the Viking tests using a standard word processing program (Microsoft Word). Using this reporting tool it became convenient for the users to design the layout of their reports and to add curves from selected tests to the reports. The use of the Windows operating system also made it possible to let Vikings operate in local area networks with centralized data storage and printing facilities.

The Viking II had established itself as one of the most sold computerized EMG systems in the world. To secure this position, the existing EMG tests were updated and extended with the Motor Unit Number Estimation test, developed in collaboration with the Mayo Clinic, and with MuscleNotes, a special notepad for rapid scoring of EMG findings.

The facilities offered by the Viking II for intra-operative monitoring had turned out to be quite successful, and in the Viking IV this facility was enhanced with new hardware for switching of stimulators between 16 stimulation sites and amplifiers between 32 recording electrodes. On the software side, intra-operative monitoring became networked, allowing clinicians outside the operating theater to monitor IOM recordings on-line on standard PCs.

Most EMG labs also perform evoked potential testing. In the Viking IV the relatively simple averager for evoked potential studies offered by previous Viking generations was replaced in 1996 by a suite of programs with support for the three standard modalities (sensory, auditory and visual evoked potentials) and a more specialized test, the P300A.

VikingQuest

The tests offered in the areas of EMG, intra-operative monitoring and evoked potentials has allowed the Vikings to achieve prominent market positions in EMG and intra-operative monitoring and an increasing role in evoked potentials. The Vikings are addressing the upper end of these markets, and with the Vikings firmly established in that segment of the market, Nicolet saw the opportunity for introducing a less expensive EMG system for smaller EMG clinics. Such a system was introduced in the form of the portable VikingQuest in 1997. The VikingQuest was based on different hardware, where up to 4 amplifiers, electrical

and auditory stimulators and control panel is contained in one unit functioning as a base for a portable computer. The tests are in general simplified versions of the EMG, nerve conduction and evoked potential tests running on the Viking IV.

CONCLUSION

In the future the basic strategies that have guided the development of the Viking systems will be continued. The work at Judex will continue to be based on the conviction that technological expertise, combined with a thorough understanding of the clinical application, forms the best basis for the development of biomedical equipment.

In Viking generations to be introduced in the near future, the gradual transition from custom-made hardware and software towards inexpensive standard hardware and software components will be completed, for example by replacing the old iRMX operating system by Windows NT.

Judex will also continue to update the software and add new tests as required by the clinical applications. An example of this will be the expansion of the software for evoked potentials by specialized tests for analysis of the ElectroOculoGram (EOG), and the ElectroRetinogram (ERG).

The Viking family have now been on the market for more than 10 years. Over that period, the Vikings have repeatedly set trends in the technological and medical development of the EMG market. The Viking has obtained a position as a market leader in the high-end EMG market. The positive reception of the less expensive VikingQuest may in the years to come provide a similar position in the low-end market. The strategy of expanding in adjacent areas, such as intra-operative monitoring, evoked potentials and oculography also seems successful.

This could not have been achieved by a small company alone. The basis for the development has been a long standing collaboration with a major company, Nicolet Biomedical, which has the production facilities and a sales network that can effectively market the Vikings worldwide. We believe that such a strategy of collaboration may be a good solution for many small companies and it is a strategy that will be considered when Judex is developing other business areas.

REFERENCES

1. Andreassen S. Microcomputer for on-line signal analysis. (*In Danish: Mikrodatamat til on-line signalanalyse*) Elektronik 1982; 4: 24-25.
2. Buchtal F, Rosenfalck P, Action Potential Parameters in Different Human Muscles, Acta Psychiatr Neurol Scand 1955; 30: 125.
3. Andreassen S. Interval pattern of single motor units. PhD. Thesis, Aalborg University Press, 1978.
4 McGill KC, Dorfman LJ. Automatic decomposition electromyography (ADEMG): Methodologic and technical considerations. In: Computer-aided surface or needle electromyography and expert systems in diagnosis. Desmedt JE (Ed.). Amsterdam: Elsevier, 1989.
5. Andreassen S, Falck B and Olesen KG. Diagnostic function of the microhuman prototype of the expert system - MUNIN. Electroencephalography and Clinical Neurophysiology 1992; 85: 143-57.
6. Andreassen S, Rosenfalck A, Falck B, Olesen KG, and Andersen SK. Evaluation of the diagnostic performance of the expert EMG assistant MUNIN. Electroencephalography and Clinical Neurophysiology 1996; 101: 129-44.
7. Fuglsang-Frederiksen A, Johnsen B, Vingtoft S, Carvalho M, Fawcett P, Liguori R, Nix W, Otte G, Schofield I, Veloso M and Vila A. Inter- and intraobserver variation in the interpretation of electromyographic tests. Electroencepha-

lography and Clinical Neurophysiology 1995; 97: 432-43.
8. Johnsen B, Fuglsang-Frederiksen A, Vingtoft S, Fawcett P, Liguori R, Nix W, Schofield I, Veloso M and Vila A. Variation in performance of the EMG examination at six European laboratories. Electroencephalography and Clinical Neurophysiology 1995; 97: 444-50.
9. Liveson JA, Dong MM. Laboratory References for Clinical Neurophysiology. F.A.Davis Co., 1992.

Reference: Gade J, Andreassen S, Henningsen E. The Vikings are coming! In: The Danish Society for Biomedical Engineering, ed. Aspects of biomedical engineering in Denmark. Copenhagen, 1998: 93-102.

The Cognitive Function Scanner®* Research and development

PETER LAURSEN[1], THOMAS SAMS[2] & LEENA ESKELINEN[1]

[1]Cognitive Research Scandinavia, Symbion Science Park, Copenhagen, Denmark,
[2]Fortunvej 52, Charlottenlund, Denmark

Neuropsychological diagnostic testing has developed rapidly during the last 50 years. With access to handy and powerful computers it is now possible to refine and standardize the testing to an extent far superior to what is achievable with traditional manual test tools. The Cognitive Function Scanner® is the result of extensive research and development over the past 20 years. In contrast to most psychological test systems the individual tests of the Cognitive Function Scanner® are analyzed in great detail for their sensitivity to subject related factors and factors related directly to the examination which may induce noise to the outcome. In addition, a large representative study of a sample of the general population (N=1,026) aged 30 to 70 years has supplied a substantial reference material. Today the Cognitive Function Scanner® is in service in departments of neurology, psychiatry and occupational medicine at university hospitals and district hospitals in all of the Scandinavian countries.

Key words: Aging; brain function; cognition; computerization; diagnosing; neuropsychology; neurology; occupational medicine; psychiatry; standardization.

Peter Laursen, DmedSci., DPsySci. Ph.D., Cognitive Research Scandinavia, Symbion Science Park, Fruebjergvej 3, DK-2100 Copenhagen, Denmark.

HISTORY

The Cognitive Function Scanner® is a device for testing basic neuropsychological functions, i.e., attention, concentration, memory, visuomotor and visuospatial functions, visual and auditive perception and vigilance, i.e., functions important for everyday life. The Cognitive Function Scanner® is the result of a long series of clinical

* Cognitive Function Scanner is a registered trademark of Cognitive Research Scandinavia.

experiments which started in 1976 in the Psychiatric Department at Rigshospitalet (one of the hospitals affiliated to University of Copenhagen).

In the 1970s, focus was placed on neuropsychological tests of high content validity and with sufficient differential power in relation to distinguishing between healthy functions and a beginning brain impairment (i.e., with a good balance between sensitivity and specificity). In 1977, a research project was carried out on the neuropsychological consequences of city air pollution [1]. Experience from Finland and Sweden [2,3] was a great help in composing and refining a suitable neuropsychological test battery for that particular problem. Although the new test battery worked well it could still be refined, particularly in relation to parameterization and administration. Furthermore, the project revealed a great need of representative and reliable reference values.

In 1981, when the interest in health effects of industrial chemical exposures was at its highest in Denmark, the first step was taken to computerize neuropsychological examinations. The high interest meant rather free hands and a sufficient budget. At the same time, the first true microcomputers had become available on the market. Although they had only limited power compared with the microcomputers of today, it was obvious that a combination of comprehensive series of neuropsychological tests and a comprehensive computer program would give a hitherto unknown opportunity to create standardized and precise psychometric measurements and examiner-independent test scoring.

A STEP TOWARDS COMPUTERIZATION

By the end of 1981, a plan for the following five years was ready. A sensitive computer-based test battery for the examination of brain function was to be composed. Therefore new tests and new testing procedures had to be introduced and computer programs had to be developed. In the new system high emphasis was put on:

1) test characteristics such as:
   - coverage of a number of basic cognitive functions
   - better differential power between healthy persons and impaired persons than conventional clinical tests could provide
   - highest achievable degree of standardization (instructions, recording, scoring and time-taking)
   - parameterization suitable for statistical processing
   - high motivational impact on the examinee (i.e., high face validity which is of utmost importance for cooperation and the activation of all the patient's potentials)
   - computerization without losing essential clinical information
   - language independence
   - re-examination possibilities with lowest possible experience-transfer from preceding examinations.
2) suitable hardware allowing:
   - graphic input similar to conventional paper-and-pencil tests
   - precise time measurements to $^{1}/_{10}$ of a millisecond
   - automatic result recording on magnetic media
   - ergonomic design.
3) administration, i.e., software allowing:
   - full integration of test scoring and evaluation
   - fast and compact code granting smooth and stable program execution
   - time-efficiency
   - easy operation

- simple interfacing to standard statistical packages like SAS, SPSS, etc.

4) evaluation of validity and sensitivity of all included tests on the basis of:
   a large-scale epidemiological study of the general population.
5) establishment of a set of reference values to be used in future diagnostic examinations.

The latter was probably the most ambitious goal. However, it would place the new system among the few leading international neuropsychological examination systems featuring representative norms. Although psychological testing has been used as a diagnostic tool for a century only a few internationally known test systems include representative and reliable reference values.

The experience with manual tests from the preceding five years led to a unique test selection. No other published psychological test system - manual or computer-based - featured the depth and width in relation to the functions covered, the administration and the parameterization of what was later to become the Cognitive Function Scanner®. Tests of memory and visuomotor functions were developed from scratch while existing tests of attention, concentration, perception and vigilance were modified to meet our demands. The test selection was made so that both the lateral and the longitudinal organization of the brain was considered. The covered functions are shown in Table I.

Unlike most other neuropsychological test systems the Cognitive Function Scanner® features a parameterization allowing a simultaneous threefold standardized access to performance evaluation on the basis of 1) psychometric test scores, 2) performance time and 3) response process recording. The latter two are of utmost importance for differential diagnosis, e.g., distinguishing between dementia of the Alzheimer type and depression.

The prototype was based on the Tektronix 4050/4950 desktop computer series. Although it was a very advanced computer at the time it was soon surpassed by technological development.

Already from the beginning several colleagues both in Denmark and abroad expressed interest in the system. From 1981 to 1986 the interest had become so strong that it was seriously considered to develop the system for the new types of microcomputers: the IBM PC, the IBM RT, the MacIntosh, and UNIX-operated workstations.

In 1987, it was decided to start developing a prototype for the PC, which had turned out to be the most popular type of microcomputer. The firm Cognitive Research Scandinavia was founded. With assistance from an engineering firm a new prototype was introduced to the public in the autumn of 1988 under the name: The *Cognitive Function Scanner*®. In December of that year the system was demonstrated at the Third International Symposium on Neurobehavioral Methods in Occupational and Environmental Health, Washington D.C. [5]. The first Cognitive Function Scanner® systems were sold the following year.

Along with the development of the system a representative reference material was established and standardized on age, education, and gender. It means that by the end of an examination with the Cognitive Function Scanner® the outcome is automatically related to 50 and 90 percentile values of the reference material and printed with the exact values as a profile for immediate evaluation.

RESEARCH

The first Cognitive Function Scanner® was taken into use at the Department of Pro-

TABLE I. Psychological functions covered, types of stimulus, way of presentation and response media used in the Cognitive Function Scanner®.

Psychological function	Type of stimulus and presentation		Response medium
Attention and vigilance	Visual:	print on drawing plate	Digitizer pen
	Auditive:	tones in headphones	Reaction handle
Concentration	Patterns:	separate template	Digitizer pen
Learning and memory	Verbal:	words on screen	Examinee keyboard
	Verbal:	numbers on screen	Examinee keyboard
	Non-verbal:	pictures on screen	Examinee keyboard
Reaction time	Auditive:	tones in headphones	Reaction handle
Visuomotor coordination	Continuous:	print on drawing plate	Digitizer pen
(both body sides)	Discrete:	print on drawing plate	Digitizer pen
Visuospatial capacity	Template	Print on drawing plate	Digitizer pen
Visual perception	Template	Print on drawing plate	Digitizer pen

For detailed information on the tests and their parameterization please see [4].

spective Medicine at Copenhagen County-Hospital in Glostrup in the late autumn of 1982. A total of 32 psychometric parameters could be recorded for each examination. All test parameters were made subject to a thorough analysis by means of multivariate statistical modelling including 16 independent factors. The factors were age, gender, schooling, social group, smoking and drinking habits, occupational activity status, consumption of drugs affecting the central nervous system, earlier or present diseases or injuries affecting the central nervous system, lead burden, time of day and time of year, and finally, the impact of the examiner presenting the test instructions. The analysis was based on the examination of a stratified sample (N=1,026) of the general population [4].

In 1992, the Danish Research Council on the Humanities granted funds for a follow-up study of the group examined 10 years earlier. The aim of the study was to investigate the effect of chronological aging on cognitive functions. 711 persons from the original group of 1,026 subjects were re-examined over a two year period and a comprehensive report was made [6]. Besides valuable knowledge on aging and cognitive functioning the follow-up study supplied the necessary information for the updating of test norms and new important experience on the parameterization.

With the distribution of the Cognitive Function Scanner® other teams of clinicians and researchers started doing investigations with the system. Their projects covered a spectrum from stress-induced functional brain impairment [7] and neurotoxic exposures [8] to neuropsychological deficits due to whiplash injuries [9,10] and stroke [11].

USER-PRODUCER DIALOGUE

A close dialogue between the users and Cognitive Research Scandinavia was established in order to adjust the Cognitive Function Scanner® to meet the different needs of neuropsychologists and psychologists in psychiatric wards. The system was pre-

sented and discussed at conferences and symposia of international professional associations [12-14]. The feedback led to further development, especially of the recording of qualitative information on the details of the response process which is important for the decision-making in complex differential diagnostic problems. The feedback also led to the development of a verbal learning and memory test which, together with the already existing non-verbal test, allows a balanced evaluation of the memory functioning of the two brain hemispheres.

In the prototypes and in the first two series of the Cognitive Function Scanner® the test scoring was based on decision rules incorporated into the software. However, decision rules are rather rigid and may in some cases lead to incorrect evaluation - especially in relation to the graphical information where drawing of even simple patterns elucidates very different and individual characteristics which are difficult to tackle with a rigid system. From 1992 when the capacity of PCs had become much more powerful, the Cognitive Function Scanner® featured artificial neural network technology for the evaluation of the most complex test responses [15].

Memory testing: Responding to the Face Recognition Test.

THE PRESENT COGNITIVE FUNCTION SCANNER®

The Cognitive Function Scanner® is a computer-aided diagnostic tool for examining the *functioning* of the brain. The Cognitive Function Scanner® consists of a set of psychological tests covering the functions listed in Table I. All measurements and result evaluations are controlled by specially designed software and hardware.

Software

The present Cognitive Function Scanner® software package is release 3.11 (autumn 1997). It is a full 32-bit package of executable modules compiled for operation on x86 computers driven by DOS, Windows95, etc. Each software package is linked to a particular hardware assembly. Communication with the system is user-selectable in Danish, English, Finnish, French, German, Swedish, and Turkish. A detailed manual is included in each software package. Manuals are available in Danish, English, Finnish and Swedish. Other languages are possible and may be prepared according to user specifications.

Hardware

The Cognitive Function Scanner® hardware package includes all dedicated equipment, i.e.:

- drawing plate (high resolution/high accuracy digitizer) with cordless pens
- examinee keyboard
- sound module
- reaction handle
- headphones.

All parts are prepared or supplied by subcontractors. Every system is taken through a

thorough test at Cognitive Research Scandinavia before delivery.

THE FUTURE

With the Cognitive Function Scanner®, Denmark has taken a leading position in the development of diagnostic psychological tools. From correspondence and reviews [16,17] we know that the Cognitive Function Scanner® is recognized as an extensive and reliable clinical tool in international circles within neuropsychology, neurology, occupational medicine, and psychiatry. At present, 12 units are in service at university hospitals and district hospitals in the Scandinavian countries. Most of them are updated to the latest version. Even with the very limited marketing capacity of Cognitive Research Scandinavia it has been possible to export half of the units produced. With the international interest in reliable and standardized methods for examination of brain function we have every reason to believe that it should be possible to install one Cognitive Function Scanner® per 1,000,000 inhabitants worldwide.

Cognitive Research Scandinavia, the formal developer, producer and distributor of the Cognitive Function Scanner®, is currently related to the Symbion Science Park in Copenhagen. Until now, all manpower involved has been scientists with no training in production and marketing. Yet, it has been possible to cover the Scandinavian countries. However, to reach the markets in the rest of the European Union and overseas the production and marketing should be in the hands of a well-established producer/supplier of neuro-diagnostic equipment with a good international reputation and with a well-established marketing and distribution network. A complete integration of neurophysiological and neuropsychological methodology would add a powerful dimension to the diagnostic practice of today. With the best achievable assets in our hands: a state-of-the-art system and up-to-date representative reference values, we hope to be able to negotiate such an agreement.

REFERENCES

1. Laursen P, Netterstrøm B. Psychological functions of urban busdrivers exposed to exhaust gases. Scand J Psych, 1982; 23: 283-290.
2. Hänninen H, Lindström K. Behavioral test battery for toxicopsychological studies. 1979. Helsinki: Institute of Occupational Health. 58p.
3. Sjöborg Å. Frömark A. Standardisering av ett psykologiskt testbatteri för beteendetoxikologiska undersökninger I. Stockholm: University of Stockholm, Institute of Psychotechnics, 1977.
4. Laursen P. A computer-aided technique for testing cognitive functions validated on a sample of Danes 30 to 60 years of age, Acta Neurol Scand, 1990; 82, suppl. 131. 108p.
5. Laursen P, Eskelinen L. Cognitive Function Scanner: A computer-aided psychological examination system for neurobehavioral evaluation. In: Johnson B (ed.). Advances in Neurobehavioral Toxicology. Applications in Environmental and Occupational Health. Chelsea, Michigan 1990: Lewis Publishers Inc. 512p.
6. Laursen P. The impact of aging on cognitive functions. An 11 year follow-up study of four age cohorts. Acta Neurol Scand, 1997; 96, suppl. 172. 84p.
7. Laursen P, Eskelinen L. Neuropsykologisk funktion hos lokomotivførere ved DSB. En case-referent undersøgelse, København 1989: Intern rapport udført for DSB.
8. Österberg K, Börjesson J, Gerhardsson L, Schütz A, Skerfving S. A neurobehavioral study of long-term occupational inorganic lead exposure. The Science of the Total Environment. (Accepted for publication March 12, 1997).

9. Karlsborg M, Smed A, Jespersen H. A prospective study of 39 patients with common whiplash injury. Acta Neurol Scand, 1997; 95: 65-72.
10. Smed A. Cognitive function and distress after common whiplash injury. Acta Neurol Scand, 1997; 95: 73-80.
11. Jehkonen M, Sirkka A, Laursen P, Eskelinen L. The effect of metamemory training on every-day memory problems: Group rehabilitation. III. European Congress of Psychology, Tampere, Finland, July 4-9, 1993. Tampere: The European Federation of Professional Psychologists' Association.
12. Laursen P, Eskelinen L. Cognitive Function Scanner: A computer-aided psychological examination system for neuropsychological assessment. Poster presented at the twelfth European Conference of the International Neuropsychological Society, Antwerp, 5.-8. July. J Clin Exp Neuropsych, 1989; 3: 365.
13. Laursen P, Eskelinen L. A computer-aided method for the assessment of neuropsychological functions. 8th Nordic Meeting on Medical and Biological Engineering, Aalborg, Denmark, June 10-13, 1990. Aalborg University: Proceedings, p. 50.
14. Laursen P, Eskelinen L. Information process recording and psychometrics in computer-aided neuropsychological assessment. The Fourth Nordic Neuropsychological Symposium, Espoo, Finland, August 22-24, 1991. Helsinki: The Finnish Neuropsychological Society.
15. Sams T, Laursen P, Eskelinen L. Response classification in psychological testing using a neural network. Int J Neural Systems, 1994; 3: 253-256.
16. Hessellund H. EDB for psykologer. Programmer med relevans for det daglige arbejde. Psykolog Nyt, 1994; 48: 186.
17. Kane RL, Kay GG. Computerized assessment in neuropsychology: A review of tests and test batteries. Neuropsychology Review, 1992; 3: 1-118.

Reference: Laursen P, Sams T, Eskelinen L. The Cognitive Function Scanner®. Research and development. In: The Danish Society for Biomedical Engineering, ed. Aspects of biomedical engineering in Denmark. Copenhagen, 1998: 103-09.

Development and quality documentation of miniature ultrasonic hydrophones

ALLAN NORTHEVED, CARSTEN LANGKJÆR & TORBEN SEVEL

FORCE Institute, Brøndby, Denmark

Development and testing of specialized ultrasonic systems for medical applications have been major activities first at the Danish Institute of Biomedical Engineering and later at the FORCE Institute over the past 25 years.

In the mid seventies a strong need was experienced to possess an instrumentation to measure the output characteristics of ultrasonic transducers in order to be able to make sufficient progress in the development of the new medical systems such as scanners for heart mechanisms and for ultrasound assisted biopsy. A needle type PVDF[1] miniature hydrophone was developed for this purpose.

Implementation of time delay spectrometry for substitution calibration of hydrophones has been utilized over the years for essential improvements of the performance and quality of the hydrophones. This has made the FORCE Institute one of the world's leading hydrophone manufacturers.

The main application of the hydrophone today is related to quality and safety assurance regarding labeling of the medical equipment and exposure of the patient to ultrasonic fields. The hydrophones find their way around diagnostic scanning equipment to therapeutic ultrasonic equipment and shock wave litotriptors.

Quality assurance and documentation of the hydrophones themselves is now secured by accreditation under the Danish National Accreditation Scheme DANAK to perform accredited calibrations and issue calibration certificates for ultrasonic hydrophones.

Key words: Accreditation; calibration; certificate; diagnostic scanning equipment; frequency; hydrophone; needle type PVDF hydrophone; output characteristics; quality and safety assurance; sensitivity; therapeutic ultrasonic equipment; ultrasonic transducers; ultrasound.

Torben Sevel, FORCE Institute, Park Allé 345, DK-2605 Brøndby, Denmark.

[1] PVDF: Polyvinylidene fluoride.

INTRODUCTION

In 1973 the Danish Institute of Biomedical Engineering (in Danish: "Medicoteknisk Institut") was established with the objective to act as the engineering partner in multidisciplinary research and development projects in close co-operation with medical doctors and scientists also including manufacturers of biomedical instrumentation and devices. Today the biomedical engineering field of activity forms an integral part of the FORCE Institute which is a non-profit research and service corporation affiliated to the Danish Academy of Technical Sciences working with measurements, testing, inspection, diagnostics and processing related to industry, energy, environmental and the medical sector.

Development and testing of specialized ultrasonic systems for medical applications have been major activities first at the Danish Institute of Biomedical Engineering and later at the FORCE Institute over the past 25 years.

ULTRASONIC SYSTEMS IN MEDICAL DIAGNOSTICS

In the early seventies the research and development activity within the field of diagnostic ultrasonic systems was high in Denmark. The major break through in application of the techniques was made with the fetus scanning of pregnant women. The transducers used were relatively simple, whereas the scanning mechanisms became quite sophisticated. The imaging systems were far less advanced than today mainly due to the comparatively primitive computer and dataprocessing capability. The noninvasive ultrasonic principle, however, proved its value as a diagnostic tool.

More complex problems were addressed in the mid seventies. An important example is projects concerned with scanning of the heart, which were conducted in a close co-operation between H.H. Holm, MD who at that time was affiliated to the Copenhagen Council Hospital in Gentofte, and Allan Northeved, director of the Danish Institute of Biomedical Engineering [1]. This co-operation has continued ever since, professor H.H. Holm now being professor at the Copenhagen Council Hospital in Herlev.

Scanning of the heart posed substantial challenge to the development of new transducers with improved characteristics to get efficient measurements on details in the heart chambers, because the objects are small and the mechanism to be studied dynamic.

Another early achievement in said co-operation was the development of ultrasound assisted biopsy for taking samples of inner organs like kidney and liver at the exact desired position for identification of cancer tumors. Special transducers with a central lead for the biopsy needle were developed. Similar technology was applied for sampling for amniocentesis [2].

During the seventies a co-operation between Brüel & Kjær A/S and the Danish Institute of Biomedical Engineering was established and in the late seventies Brüel & Kjær A/S took over all rights for industrial production and commercialization of the ultrasonic scanning systems. The concept is continued today in B&K Medical A/S.

In the eighties and nineties FORCE Institute, Biomedical Engineering has addressed its developments of advanced transducers and scanning systems to highly specialized purposes like dermatology scanning and bone scanning. The first issue has led to establishing of an entirely new company, Cortex Technology A/S, which produces and sells dermatology scanners worldwide.

DEVELOPMENT OF THE NEEDLE TYPE PVDF HYDROPHONES

At the time of establishing the Danish Society of Biomedical Engineering the tools for measuring the output characteristics of an ultrasonic transducer were rather simple. The main principle was based on recording of reflection from a spherical object immersed in a water tank back to the emitting transducer itself. Sensitivity, spatial resolution power, and frequency response were not optimal.

This became in particular true as the development within ultrasonic scanning systems as described above accelerated. The simple measurement systems were not able to fulfill the requirements for measurements in connection with development of transducers for heart scanning or ultrasound assisted biopsy.

Imaging of heart function required transducers focusing on small areas and dynamic response. Ultrasound assisted biopsy required high precision in guiding the systems in the right direction.

The shape of the emitted ultrasound pulses from the transducers is important for obtaining good spatial resolution and imaging power in dynamic systems. Better resolution calls for shorter pulse length relative to the ultrasound frequency which for medical systems is in the range from a few MHz to several MHz. Accurate focusing requires good and well known directional characteristics of the ultrasonic field emitted from the transducer.

No solution as to a measuring instrument for control of the properties of ultrasound transducers was available at that time, neither commercially nor in research laboratories.

The Danish Institute of Biomedical Engineering experienced a strong need to possess such an instrumentation in order to be able to make sufficient progress in development of the new medical scanning systems. The concept was to develop a measuring equipment – a hydrophone – which could operate in the ultrasound frequency domain in the same way as microphones work in the audible frequency range. A miniaturized probe was envisaged for the purpose of getting the proper frequency response and obtaining high spatial resolution.

The Danish Institute of Biomedical Engineering chose the piezoelectric polymer material, PVDF as the active sensorelement. Thin PVDF foils of 20 to 30 μm thickness were suitable for the desired frequency range, and a simple hydrophone was constructed. Piezoelectric PVDF was not commercially available at that time. Instead it was obtained from high tone loudspeaker, which was purchased and demounted to obtain a sheet of 3×5 cm^2 PVDF foil. As the area need for a hydrophone is approximately 1 mm^2 this could do for a while.

Through professor Leif Bjørnø from the Technical University of Denmark a contact was made with Dr. Peter Lewin who simultaneously had come up with a needle type ultrasonic hydrophone based on a ceramic piezoelectric material. Peter Lewin, who is now professor at the Drexel University, Philadelphia in USA, was then employed at the Danish Institute of Biomedical Engineering.

This lead to combining the choice of PVDF as sensorelement and the concept of a needle type probe yielding the miniature PVDF needle type ultrasound hydrophone.

Basically this concept from the seventies is maintained in the FORCE Institute hydrophones of today and the modern hydrophones appear much like the early ones. However, extreme improvements in the performance have been achieved over the years especially with respect to sensitivity, stability and frequency response.

Although the hydrophone was developed with the main purpose of fulfilling the internal need for assisting transducer development, a few hydrophones were sold to colleagues and research partners abroad in the early days. A breakthrough in sales, however, was only achieved after the development of improved methods for controlling and calibrating the hydrophone itself and thereby ensuring improved and uniform quality.

TIME DELAY SPECTROMETRY FOR SUBSTITUTION CALIBRATION OF HYDROPHONES

In the late seventies oscilloscopes were used for sensitivity measurements of the hydrophones. The methods were rather time consuming and only allowed measurements at a few frequencies. Any unlinearities between these test points were not discovered.

Around 1980 Carsten Langkjær invented the Time Delay Spectrometry (TDS) method for measuring the sensitivity as function of frequency for ultrasound hydrophones using electronic spectrum analyzers.

The Time Delay implies that the receiving system is delayed corresponding to the pulse travel time from the emitter. All other signals from reflections are suppressed giving the advantage that disturbances and measurement noise are minimized.

Spectrometric measurements are obtained in the frequency domain by sweeping over the range of frequencies of interest and obtaining the whole sensitivity versus frequency curve in one sweep. This gives the great advantage that the complete sensitivity variations are shown. This in turn enables constructural changes of the hydrophone to be made in order to improve the frequency characteristics. Further the measurements are fast, allowing for easy access to many measurements during the trial-and-error process of improvement of the hydrophones' quality.

Calibration of the hydrophone sensitivity was made by substitution, which implies that the sensitivity response for an unknown hydrophone is obtained by comparison with a standard hydrophone thus eliminating disturbances from the calibration set-up.

A typical example of a calibration curve is shown on Fig. 1.

The implementation of this method was not only the backbone in performance and quality improvements of the hydrophones. It also attracted considerable interest from abroad when it was published in 1981 [3].

Early in the eighties this lead to comparison measurements with Physikalisches Technisches Bundesanstalt (PTB) in Germany and National Physics Laboratory (NPL) in England. A reference hydrophone was measured by other more fundamental and more time-consuming methods thus linking the results of TDS calibrations to recognized international standards. This may be seen as an early example of metrological traceability. Co-operation especially with PTB continued over the years and is still vital.

THE NEEDLE TYPE PVDF HYDROPHONE TODAY

In the early eighties the commercial interest increased considerably, and for nearly 15 years now, an annual, worldwide sales rate of up to 100 items has been obtained. This has made the FORCE Institute one of the world's leading hydrophone manufacturers and for a number of years FORCE Institute has been the main supplier of hydrophones to the Japanese market.

Today the key specifications of the needle type miniature PVDF hydrophones from FORCE Institute are:

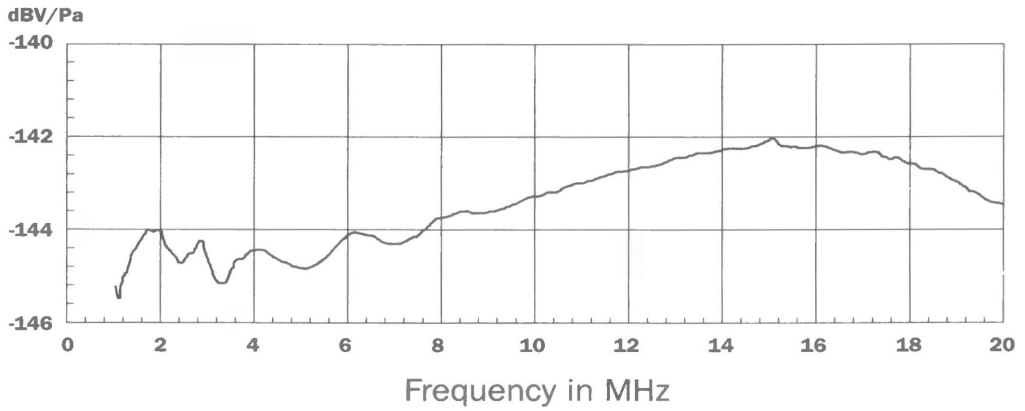


FIG. 1. Sensitivity versus frequency for a PVDF miniature ultrasonic hydrophone.

- diameter of active element: 0.4 - 1.0 mm
- sensitivity: 25 - 150 nV/Pa depending on diameter
- frequency range: 0.5 - 20 MHz
- Dynamic range: 0 to > 100 MPa.

The hydrophones comply with IEC 1102 [4].

The application of the hydrophone today is not only for development of transducers and ultrasonic systems as was the original purpose. Quality and safety assurance regarding labeling of the medical equipment and exposure of the patient to ultrasonic fields are the dominating concerns of the users. The hydrophones find their way around diagnostic scanning equipment to therapeutic ultrasonic equipment and shock wave litotriptors.

CERTIFIED CALIBRATION OF HYDROPHONES

Due to important applications of the hydrophones, the users' interest in the quality assurance and documentation of the hydrophones themselves has been ever increasing.

Already in the late eighties, a round robin was organized by the European Community, in which PTB, NPL, the Danish Institute of Biomedical Engineering and others took part. This project documented the measuring ability of the hydrophones. Since 1990 yearly comparisons have been made with PTB.

Late in 1997 FORCE Institute obtained accreditation under the Danish National Accreditation Scheme DANAK to perform accredited calibrations which implies that the calibration is in accordance with the quality assurance standard EN 45001.

An assessment of the measuring capability of the laboratory has been made by DANAK including evaluation of measurement uncertainty. This means, e.g., that the uncertainty of the sensitivity calibration of the FORCE hydrophones can be guaranteed to be within ± 1.5 dB or better over the entire frequency range from 1 to 20 MHz.

Further the FORCE Institute calibration certificates document traceability to recognized international standards.

The calibration laboratory performs initial calibration of all FORCE Institute hydrophones delivered and offers recalibration

when needed, e.g., on annual basis. Also other marks of hydrophones are calibrated with certificates.

Supplementary the laboratory makes measurements for outside customers on their ultrasound transducers and ultrasound systems for medical diagnosis and therapy using the needle type PVDF hydrophones.

REFERENCES

1. Holm HH, Kristensen JK, Pedersen JF, Hancke S, Northeved A. A new mechanical real time ultrasonic scanner, Ultrasound Med Biol 1975; 22: 147-52.
2. Bang J, Northeved A. A new ultrasonic method for transabdominal amniocentesis, Am J Obstet Gynec 1972; 114: 599-601.
3. Lewin P. Calibration and performance evaluation of miniature ultrasonic hydrophones using time delay spectrometry, IEEE Ultrasonics Symposium Proceedings 1981.
4. IEC 1102, Measurements and characterization of ultrasonic fields using hydrophones in the range 0.5 MHz to 20 MHz, 1991.

Reference: Northeved A, Langkjær C, Sevel T. Development and quality documentation of miniature ultrasonic hydrophones. In: The Danish Society for Biomedical Engineering, ed. Aspects of biomedical engineering in Denmark. Copenhagen, 1998: 111-16.

The Madsen Story

PAUL MORRISON

Madsen Electronics, Taastrup, Denmark

Key words: Audiometry; auditory evoked potentials; immittance; innovation; PC-based systems, research.

Paul Morrison, Madsen Electronics, Mårkærvej 2A, P.O. Box 119, DK-2630 Taastrup, Denmark.

AN IMPORTANT DECISION

The Danish parliament made an important decision in 1950 which resulted in a small-scale production that has developed into a worldwide export operation today.

The decision was that "defective hearing must be regarded as a handicap equal to the loss of a limb or similar afflictions". This legislation not only opened up new possibilities with regard to compensation for loss of hearing, but also led to the establishment of completely new industrial production and research activities, with the result that Denmark became the first country in the world to produce not only hearing instruments, but also instrumentation for the diagnosis of hearing loss.

Madsen Electronics was founded in 1960 by Poul Madsen in Hellerup, a small suburb of Copenhagen. He was born in 1923 in Odense (the city of the world famous writer Hans Christian Andersen), where he was educated as an electronics technician and worked for Bang & Olufsen, a Danish company renowned for the innovative and harmonious design of its hi-fi, TV and video products.

After some years with Bang & Olufsen, Poul Madsen acquired a small radio shop in Odense, and when the above-mentioned decision was made by parliament, which resulted in legislation providing free hearing instruments to all hard-of-hearing in Denmark, he was contacted by Doctor Ole Bentzen, who wanted him to produce audiometers for the first Hearing Center to be set up in Odense. A few years later, Ole Bentzen established a second Hearing Center in Aarhus, and Poul Madsen constructed the audiometers for this center as well.

A COMPANY IS FORMED

All this work was done on a free-lance basis, and the success continued when Poul Madsen was asked to build equipment for a Hearing Center in Lund, Sweden. The production of audiometers had by now become a full-time job, and Madsen found it neces-

sary to form a company and sell his radio shop. His first company (called AMPLEX) was founded in Odense in the late 1950s and produced a clinical audiometer designated "OB 1" – the OB standing for Ole Bentzen, who remained one of Poul Madsen's best friends.

In the late 1950s, a new hearing test instrument was invented by Doctor Otto Metz. This unit was a mechanical device, which could measure the acoustic impedance of the ear, and the first experimental instrument may still be seen in the Department of Audiology at the University Hospital of Copenhagen.

Dr. K. Therkildsen of the University Hospital of Copenhagen and Eng. Scott-Nielsen of the Hearing Center in Copenhagen believed it might be possible to make such an impedance tester with electronics – and they contacted the small audiometer manufacturer Poul Madsen at his company AMPLEX in Odense.

This all resulted in the company moving to Copenhagen and being renamed Madsen Electronics in 1960.

At this time, things started to move rapidly and orders for audiometers came in from many parts of the world. In the course of its first year, Madsen Electronics introduced both a small portable diagnostic audiometer "TAN 60" and a new clinical audiometer "OB 60". The following year, 1961, saw the introduction of the first commercially available electronic impedance bridge, the "ZO 61".

In the next two decades, Madsen Electronics expanded its product line to comprise other kinds of audiological test equipment including ABR and ERA instrumentation and hearing instrument fitting and test systems, but audiometers and impedance bridges remained the company's core business.

The electronic audiometer became rapidly accepted throughout the world as the natural replacement for the tuning fork, giving much more detailed and precise information about the patient's hearing loss.

However, the electro-acoustic impedance bridge, which is now known to give additional and important information concerning the function of the middle ear, was much more difficult to introduce in most parts of the world. In fact, the three inventors Poul Madsen, Scott-Nielsen and K. Therkildsen, on behalf of Madsen Electronics, spent some 8-10 years travelling around the world holding symposia on impedance in most countries throughout Europe and the U.S. until the impedance test principle was finally accepted in the late 1960s.

From the beginning, the greatest interest in impedance instruments was in the U.S., which led to the establishment of Madsen Electronics (Canada) Inc. devoted to the production of all MADSEN impedance bridges. The production of audiometers, and later of ERA equipment and Hearing Instrument Fitting and Test systems, remained in Denmark, where close cooperation with several leading scientists at hospitals in Copenhagen, Odense and Aarhus led to the development of new and exciting audiological products.

MADSEN LANDMARKS

Since the introduction of the first audiometers and the invention of the impedance bridge, Madsen Electronics has introduced many exciting products to the market, including new ideas and inventions never seen before but later copied by many other manufacturers, such as:

1972-74

The first commercially available ERA system (ERA74), which included the world's first digital calibration memory; the idea of

"post-stimulus delays" for the elimination of artifacts in ABR recordings; the data interface communication port.

1981-82
The first computerized clinical audiometer (OB802/822), including such exciting features as: two-way data communication interface, fully electronic attenuators, electronic calibration memory, electronic system for interlocking stimulus and masking to enable synchronous masking in audiometry, and "limited extended range" at certain frequencies for patient safety.

1983-84
The first computerized impedance bridge (ZO174), which was the first impedance system using a video monitor for the display of test results.

1985-86
The first menu-driven Insertion Gain (REM) Test System (IGO 1000), which was also the first multi-lingual system including the following languages: English, German, French, Italian, Spanish, Portuguese, Russian, Serbo-Croatic, Swedish, Finnish and Danish.

1988-89
The first softkey-driven clinical/diagnostic audiometer (Midimate 602/622) with user-programmable tests, non-volatile calibration memory (without battery back-up), fully click-free attenuators, multi-lingual display (English, German, French, Italian and Spanish).

1989
AUDIOCOM, the first commercially available audiological software program, with its own database for audiometric and impedance measurement data. Subsequently replaced (1990) by MateBaseI.

1992
Madsen audiometers and impedance bridges feature "connectivity", i.e., interface to PC and other Madsen instruments for communicating measurement data to audiological software programs, or for print-out.

1993
Orbiter 922 clinical audiometer replaces the best-selling OB 822 (over 4,000 units sold world-wide). In addition to providing every conceivable audiometric function, the Orbiter features direct control of a conventional CD player for presenting speech materials.

1993-1994
Introduction of the HI-PRO hardware interface box – a successful attempt to get manufacturers of hearing instruments to use the same interface for their programming software. Over 15,000 units sold to date (1998).

1995
The Aurical, a PC-based, combined audiodiagnostic and hearing instrument fitting/testing system. This system incorporates the first commercial audiometer capable of SPL audiometry and auditory area mapping by means of loudness scaling.

1995
Introduction of Voyager 522, featuring data storage on a credit-card sized memory card.

Madsen Electronics has also contributed to audiology by means of extensive educational programs during the past 30 years, such as:

1960-70
Impedance Schools throughout the world.

1974-84
ERA Schools throughout the world.

1986-89
Insertion Gain Schools throughout the U.S.

1993-95
Seminars in otoacoustic emissions (Europe/ U.S.).

1995-
Seminars in loudness scaling and SPL audiometry.

THE 1990s

The two Madsen companies in Denmark and Canada merged in 1988 to increase productivity and to reduce expenses, however, the Canadian firm proved not to be viable and became a sales office for Madsen's operations in North America in 1990. Then, in June 1990 Madsen Electronics, Denmark, was purchased by GN Danavox, a leading manufacturer of hearing instruments, and a member of the Great Nordic group.

In April 1993, Madsen Electronics and GN Danavox moved to new premises in Taastrup, near Copenhagen, a move which allowed the synergies between the two companies to flourish. With the background of GN Danavox's active role in EHIMA (the European Hearing Instrument Manufacturers' Association), the first mutual project was the HI-PRO interface box. The HI-PRO has gone on to become the industry standard for communication between PC and programmable hearing instruments. Clearly the common ground between the manufacturer of hearing instruments and the manufacturer of audiological equipment lies in the area of testing and fitting hearing instruments. Following the move to Taastrup and the subsequent integration of various functions, development of an innovative PC-based testing and fitting system, the Aurical, was commenced. This inter-company project also embraced the two companies' subsidiaries in the U.S. (in 1992, the Toronto sales office was closed down and operations were moved to the premises of GN Danavox Inc. in Minneapolis).

Launched first on the U.S. market in the summer of 1995, and later in Europe, the Aurical has proved a great success, and has even been recommended by other hearing instrument manufacturers as the system of choice for testing, fitting and programming their hearing instruments. The modular Aurical platform has been designed with subsequent software and hardware upgrades in mind, upgrades which will not only improve and update present capabilities, but actually add to the system's functions. Aurical software runs under NOAH, the software platform developed by HIMSA (a consortium owned jointly by the 3 major Danish hearing instrument manufacturers, and Phonak) for the purpose of allowing dispensers to run different brands of hearing instrument programming software at the same time. This software platform dovetails with the HI-PRO hardware interface box, and reflects GN Danavox's position as a company with a firm belief in developing industry standards for the benefit of the dispensers and users of hearing instrument technology.

By early 1998, the PC-based Aurical has made Madsen the supplier of choice for a growing number of hospitals, as well as some of the world's largest chains of hearing aid dispensers, all of which network their shops. Madsen firmly believes that the future of audiology lies in computerised technology integrated with office networks and the Internet. We will continue to harness the power of personal computers for our future products, even as we explore new ways of using this technology to improve

the precision and efficiency of modern audiology.

APPENDIX

Below some examples of audiological tests are given.

Evoked response audiometry

Evoked response audiometry (ERA) is used to assess auditory sensitivity in difficult-to-test populations, to detect neuropathologies of the auditory system, and to monitor the physiologic status of the auditory system during surgery. ERA is a type of electrophysiologic test. It makes use of the physiological activity in nerves, muscles and other biological tissues that gives rise to electrical changes. These electrical changes, or potentials, can be measured by means of an electrode placed in proximity.

Evoked potentials occur in response to a sensory stimulus, and can be extracted from the ongoing physio-electrical activity. Auditory evoked potentials are elicited by sound stimuli, and arise from different locations in the auditory system. Fig. 1 schematically illustrates the auditory pathway, and the panels to the right show examples of which auditory evoked potentials are associated with the different structures in the auditory system. The potentials shown in the bottom two panels result from peripheral (cochlea and auditory nerve) activity, and occur within 10 ms of the presentation of the stimulus. The middle panel shows potentials that arise from brainstem activity, which occur up to 15 ms post stimulus. Finally, the top two panels show potentials which come from activity in the auditory cortex.

In performing ERA, electrodes are placed either in the region of the middle ear or ear canal, or on the surface of the scalp, depending on which part of the auditory system is to be evaluated. Auditory stimuli consisting typically of clicks, filtered clicks or tone bursts are delivered via a shielded transducer to the ear, and the signal picked up by the electrodes is recorded during a specific time epoch. The signal-to-noise ratio is improved by means of differential recording, filtering, artifact rejection and time domain averaging.

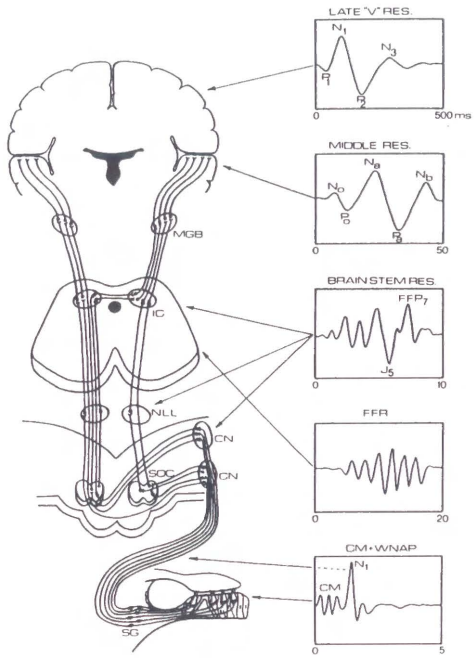


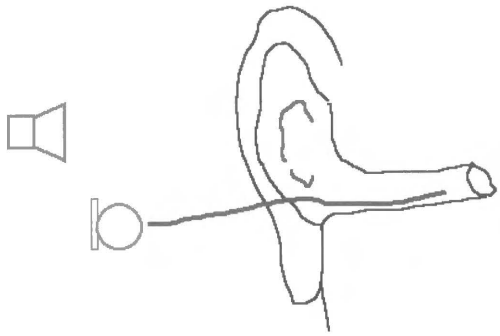
FIG. 1. Auditory evoked potentials.

Real ear measurement

The development and use of real ear measurement (REM) has greatly advanced the understanding of how the outer and middle ear influence hearing instrument fitting, as well as the impact individual differences in these structures can have on hearing instrument performance.

The term real ear measurement (REM) refers to two types of measurement:

1. the change in behavioral thresholds demonstrated when a hearing instrument is worn (a psychoacoustic measure also known as functional gain), and



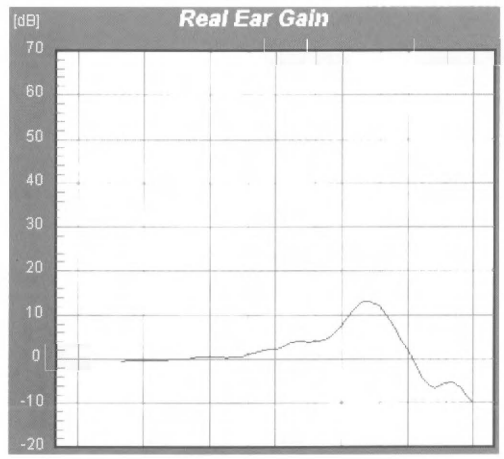


FIG. 2. Real ear unaided response (REUR).

2. the determination of sound pressure levels developed in the ear canal using a probe tube microphone (a physical measure).

The latter, also known as probe tube measurements, are accomplished by placing a narrow silicone tube, which is attached to a microphone, in the ear canal in close proximity to the eardrum. A known stimulus – typically a swept pure tone or broad-band noise signal – is presented in the free-field, and the sound pressure levels near the eardrum are simultaneously recorded. The result of this measurement is called the real ear unaided response (REUR), and demonstrates how the outer ear serves to enhance certain frequency regions. The setup and an example of an REUR are illustrated in Fig. 2.

This measurement is subsequently repeated with a hearing instrument in place in the ear canal. The resultant curve can be subtracted from the unaided response to determine the hearing instrument's effective gain, or real ear insertion gain (REIG). Fig. 3 shows the setup for this type of measurement. The bottom curve is the REUR, and the top curve is a REIG showing the relative increase in gain with a hearing instrument in place.

The primary reason for carrying out REM is that the performance of a hearing instrument on a given ear is difficult to accurately predict based on average data. Thus, REM is helpful in verifying that a hearing instrument fitting is appropriate for the individual.

Acoustic immittance

The eardrum and other middle ear structures provide a degree of opposition to the flow of acoustic energy through the system. This is referred to as the acoustic impedance of the middle ear. Conversely, the ease with which acoustic energy flows through the system is termed the acoustic admittance. Acoustic immittance is the all-encompassing term used to describe measures of middle ear impedance or admittance.

Both the acoustic impedance and acoustic admittance are governed by the mass, stiffness, and frictional resistance of the system and are influenced by frequency. Fig. 4 is a diagram of an electroacoustic immittance meter. A probe containing three tubes, which are attached to a receiver, a miniature microphone and an air pump are sealed in the ear canal using a rubber cuff. The probe is usually attached to one side of a headset, with an ordinary earphone from an audiometer attached to the other side.

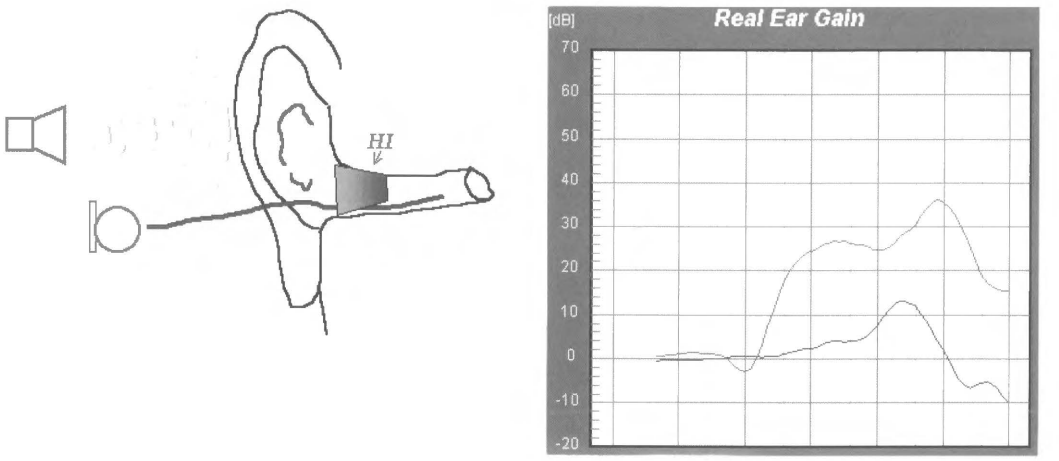


FIG. 3. Real ear insertion gain (REIG).

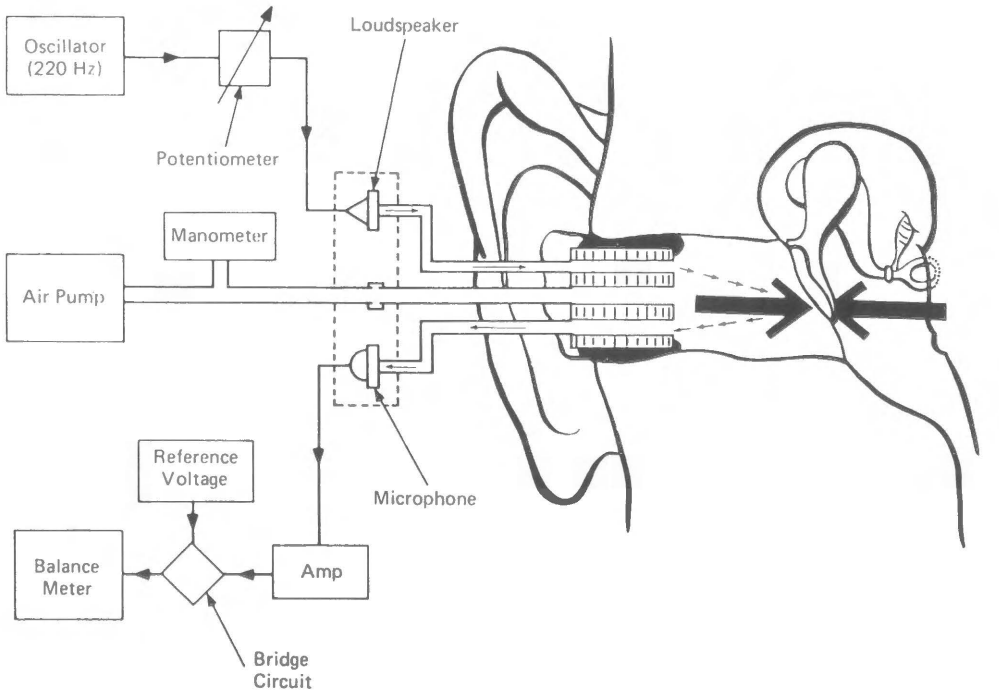


FIG. 4. Diagram of an electroacoustic immittance meter.

The receiver emits a probe tone of typically 220 Hz, and the voltage changes necessary to maintain a constant sound pressure level in the sealed ear canal are registered during the various types of measurements.

In general, three types of acoustic immittance measurements are performed:

1. static compliance, which indicates the mobility of the eardrum
2. tympanometry, which is the mobility of the eardrum as a function of pressure in the sealed ear canal, and
3. acoustic reflex, which is a contraction of the middle ear muscles in response to intense sounds, and which has the effect of increasing the impedance of the system.

Acoustic immittance measurements have become an indispensable diagnostic tool. They provide the clinician with accurate, objective information, which can be used to determine the nature of the hearing loss, to assess the integrity of the acoustic reflex pathways in the lower brain stem, and to help quantify the degree and slope of sensorineural hearing loss.

Reference: Morrison P. The Madsen story. In: The Danish Society for Biomedical Engineering, ed. Aspects of biomedical engineering in Denmark. Copenhagen, 1998: 117-24.

Bang & Olufsen Technology a/s – A new partner in Disease Management

JENS PETER ZINCK, HANS JØRGEN JENSEN, JENS KRISTIAN RASMUSSEN, PAUL ERIK FABRICIUS, TORBEN DALGAARD, KENN MELDGAARD RASMUSSEN & GITTE SCHILKOWSKI

Bang & Olufsen Technology a/s, Struer, Denmark

Key words: Acoustic analysis; diagnostic equipment; disease management; drug delivery systems; heart rate variability; home care; scattering absorption; telemedicine.

Bang & Olufsen Technology a/s, Sales & Marketing, Bødkervej 2, DK-7600 Struer, Denmark. Attn.: Manager, Sales & Marketing.

INTRODUCTION

Bang & Olufsen Technology a/s is a wholly owned subsidiary of Bang & Olufsen Holding a/s with the overall objective of strengthening earnings through the development of new business areas based on in-house competencies in markets outside the audio/video industry. When Bang & Olufsen Technology was established in 1988 the idea was to create a "nesting box" for new independent business areas.

So far this has led to the establishment of independent companies such as Ericsson Diax a/s, Bang & Olufsen Telecom a/s and Beologic a/s.

Very early on the Health Care market was identified as an area of interest.

Following the establishment of Bang & Olufsen Telecom and Beologic as independent companies, the Health Care business has become the main activity of Bang & Olufsen Technology.

Until recently Bang & Olufsen Technology's involvement with the Health Care business has mainly been the manufacture of durable injection pens for Novo Nordisk A/S. The co-operation with Novo Nordisk has over the years expanded to include product engineering and manufacturing of several products for Novo Nordisk. See Fig. 1.

The platform which Bang & Olufsen Technology has established during its co-operation with Novo Nordisk has been the starting point for a range of new activities within the area of Drug Delivery Systems. This platform is based on core skills such as project handling according to EN 46 001 standards, from basic research through concept development, product development and production engineering to manufacturing.

As it can be seen from Fig. 2, Disease Management is today a keyword for Bang & Olufsen Technology and activities are focused on developing and manufacturing non-invasive diagnostic and monitoring systems as well as advanced drug delivery

FIG. 1. NovoPen® 1.5 manufactured by Bang & Olufsen Technology for Novo Nordisk A/S.

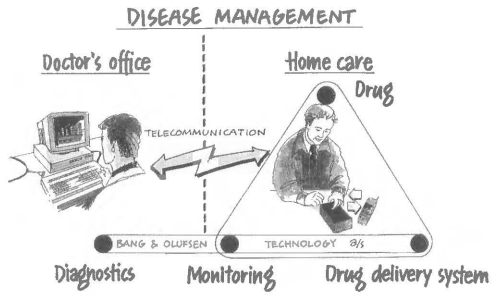


Fig. 2. An illustration of Bang & Olufsen Technology's skills within Disease Management (drug delivery systems, diagnostics, monitoring and telecommunications).

systems. By combining these skills with the skills of pharmaceutical companies, the idea is that value can be added to existing drugs. For the Home Care market, users of these drugs can be provided with easy-to-use, high quality monitoring- and drug delivery systems.

As well as aiding users in the actual drug intake, technology will also facilitate users in managing the dosage and time for administering the drugs. Telemedicine, described later in this article, could also establish an improved means for communication between patient and doctor.

On the Doctor's Office side, instruments employing non-invasive diagnostic systems, based on digital signal processing on acoustical, electrical and optical input, are also in the mold. In the future these principles could potentially be transferred to the patient's home.

Bang & Olufsen Technology aims at establishing strategic partnerships with a few, highly regarded companies in the medical market: the combination of Bang & Olufsen Technology's technological expertise with strategic partners' distribution networks, sales and marketing force and knowledge of the market, are considered a powerful means of operating in the competitive Health Care market.

Backed up by the distinct expertise of the rest of The Bang & Olufsen Group, such as simplified user interface and quality design, Bang & Olufsen Technology a/s considers itself a competent strategic partner within the Health Care market.

In the following, Bang & Olufsen Technology activity areas within drug delivery systems and non-invasive diagnostics/monitoring systems will be described further. The focus will be on the research intensive area of non-invasive technologies as well as on the emerging activities within telemedicine.

Drug delivery systems

As the demand for total Disease Management grows the area of drug delivery systems, e.g., equipment for injection or inhalation of medicine, becomes increasingly important for the pharmaceutical industry.

On the basis of many years' experience with precision mechanics and molded plastics, Bang & Olufsen Technology's operations within drug delivery systems were initiated in 1989 through the co-operation with Novo Nordisk. This co-operation has led to the establishment of a range of new activities, from basic research, concept development and product engineering to manufacturing within this field.

The prevailing focus on Home Care and Disease Management Systems gives rise to a demand for simple, reliable and discreet

drug delivery systems, while the presence of unpatented generic medicine from different suppliers, and differentiation as to how medicine is administered, has greatly sharpened the competition.

Features which allow the users of drug delivery systems to monitor precisely the number of doses remaining, the number of doses taken, the day or time that the next dose should be taken or statistics on the actual intake of medicine, are already in demand.

These increasing demands on drug delivery systems call for the implementation of advanced technologies such as the use of microelectronic control, data storage, visual communication and telecommunication. Miniaturization becomes essential in order to maintain acceptable physical dimensions for the drug delivery system.

Fig. 3 shows an example of how such features could be implemented in a future drug delivery system.

The necessary technical expertise, such as miniaturization and cost optimized design and production, required to realize these advanced delivery systems is often not available within pharmaceutical companies. Bang & Olufsen Technology has therefore focused on offering advanced turnkey technical solutions that incorporate these advanced technologies.

At present Bang & Olufsen Technology is in the process of further developing its cooperation with a number of pharmaceutical companies.

Fig. 3. Schematic of a future drug delivery system.

Monitoring / diagnostics

Acoustics

Recent advances in non-invasive and invasive cardiac imaging, along with the development of color Doppler echocardiography, provide the physician with an impressive arsenal of instruments for the diagnosis of cardiovascular diseases.

However, heart sounds and murmurs remain prime sources of essential information in the discovery and evaluation of cardiovascular diseases in general practice.

With the French physician Lennec's introduction of the stethoscope in 1816, auscultation grew into an art, providing the physician with valuable information about the functioning of the heart in a more convenient way. The stethoscope has scarcely been changed in design or functionality since 1816, and today considerable experience is still needed to perform a proper auscultation.

With this in mind, Bang & Olufsen Technology has developed VibroCard 2000, a modern, portable heart sound analyzer designed to facilitate auscultation by objectifying and quantifying the interpretation of the auscultation. See Fig. 4.

VibroCard 2000 is based on core expertise within acoustics and digital signal processing, and features simultaneous display of sound wave patterns and ecg data, sound analysis including display of total energy distribution and sound windowing functions.

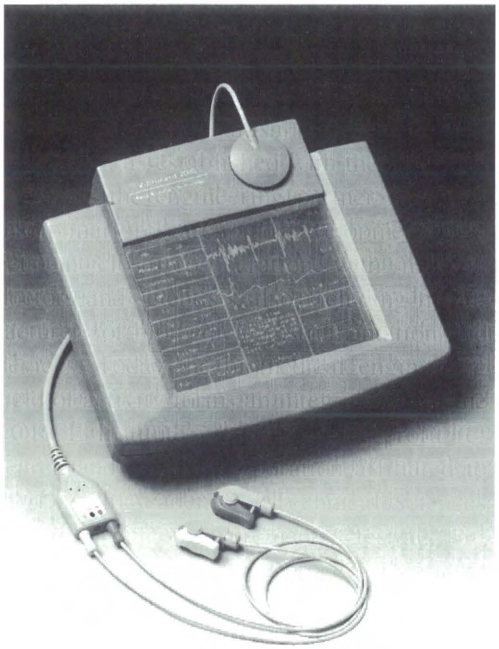


Fig. 4. VibroCard 2000, a heart sound analyzer, developed by Bang & Olufsen Technology.

VibroCard 2000 has formed the basis for a general digital signal processor platform designed for exploring new application areas employing sound analysis.

The prime activity within biomedical acoustics is basic research into the monitoring of the heart, heart valves, implants, joints and muscles to detect changes or developments in the function of these parts.

A new project has recently been established through the Center for Biomedical Engineering at Aalborg University. The project has been initiated by the National Institute of Occupational Health and is concerned with measuring and subsequently analyzing acoustical properties of muscles in order to detect muscle fatigue.

Electrocardiography

The analysis of Heart Rate Variability (HRV) data has been the object of great interest for many years. This is because HRV is influenced by the activity of the Autonomous Nervous System (ANS). By analyzing the HRV data, the ANS activity, which has been found to be descriptive of the wellbeing of the heart, can be monitored. See Fig. 5a and 5b.

Literature shows that HRV is a strong predictor of survival after an acute myocardial infarction and is also usable for evaluation of diabetic neuropathy.

A whole range of other applications is presently being investigated by researchers worldwide.

Based on the hardware platform of VibroCard 2000, the analysis of ECG data has been further developed into the area of HRV through the development of ElectroCard 2000. ElectroCard 2000 is a portable, battery-powered, real-time HRV-analyzer, suitable for short time HRV-analysis.

ElectroCard has been used for evaluation of HRV data in several studies. Different kinds of tests has been used to identify the influence of stress and pain on the ANS. Emotions, like depression, fear, anger and joy, which are known to influence the ANS, have been induced by hypnosis to investigate the effect on HRV. In acupuncture treatment, points related to sympathicus and parasympathicus were stimulated, and HRV has then been used to classify the effect of this treatment by monitoring the change in the low frequency and high frequency component. A study on the effect of treatment of depression has also been done.
All studies show significant and promising results.

Currently, resources within this area are focused on verifying application areas and contacting potential strategic partners.

Optics

In relation to the development of minimal and non-invasive diagnostic methods, opti-

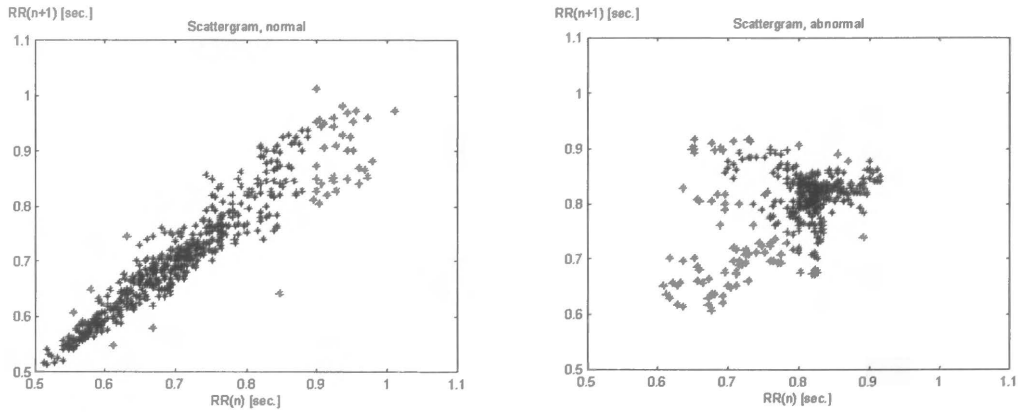


Fig. 5a and 5b. A scattergram is a visualization of the beat-to-beat variation of the heart. A normally regulated heart is characterized by the shape of a baseball bat (Fig. 5a). Other shapes (Fig. 5b) suggest abnormal regulation of the ANS.

cal principles are considered to be an area of significant potential. This is due to the ability of light to penetrate to considerable depths in tissue without inconvenience to the patient, and due to the fact that many parameters interact with light in a measurable manner by affecting absorption, scattering, refractive index and polarization.

Within the field of optics, the research at Bang & Olufsen Technology has concentrated partly on non-invasive measurements of glucose in tissue, and partly on the determination of multiple parameters in whole blood.

Both of these media scatter light which results in a complex propagation path. Efforts have therefore been directed towards establishing and developing tools for simulation of light propagation in models of real life optical systems such as the structure of tissue or an optical cuvette.

Tools for research measurements have also been designed and constructed, including a number of probes optimized for non-invasive measurements on human tissue.

Light propagation is described using either Monte Carlo simulation or diffusion theory. These tools are used to analyze realistic measurement geometrics, thereby enabling the optimum design of an instrument for a given application.

Fig. 6 shows a Monte Carlo simulation of the light absorption in a 4-layer model of human tissue. It is obvious that the wavelength used in this simulation is primarily absorbed in the capillary loops, due to the high absorption of the hemoglobin in the blood. Each layer in the model is specified by its geometrical and optical data.

The simulation tools have been used in the design of the probes that Bang & Olufsen Technology uses in clinical studies, allowing the optical front-end of the probes to be designed for optimum data acquisition. Efforts have been directed towards miniaturizing these probes by employing thickfilm techniques and wire-bonding of optoelectronic components such as LED's and detectors.

Current activities are aimed towards the optimization of whole blood measurements.

Data analysis

When extracting clinical information from raw measurement data based on acoustical, electrical, optical or ECG input, advanced data analysis is an essential discipline.

Analysis of biological systems is very of-

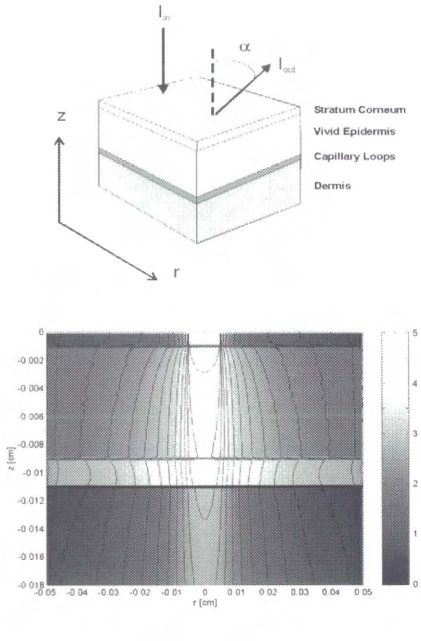


Fig. 6. A Monte Carlo simulation of the light absorption in a 4-layer model of human tissue.

ten complex, because observations are usually a result of several phenomena interacting. For instance, when analyzing whole blood, constituents in the blood have overlapping absorption spectra and some will exhibit scattering. Another example is that when characterizing murmurs and heart sounds, it is imperative to listen at various locations and to distinguish between special temporal patterns.

To extract the clinical information from the observed or measured data, multivariate mathematical techniques must be employed to extract the required signal from interfering information.

Basically, features are extracted from the transducer signals using advanced signal processing employing for example Fourier and wavelet transforms. Models are built based on these features using ordinary chemometric techniques such as partial least square and principal component regression

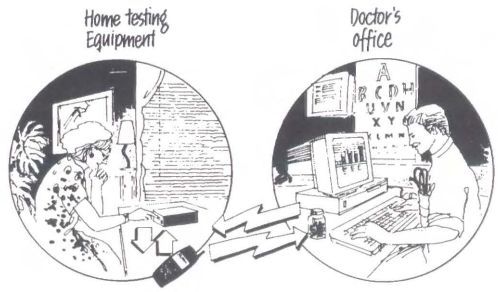


Fig. 7. Schematic of a future telemedicine application.

for linear systems. If necessary, non-linear systems such as fuzzy techniques can be applied. Further genetic algorithms are employed to optimize the models.

Telemedicine

The area of telemedicine is one of the fastest growing segments within the health sector, and as telemedicine applications are expected to be part of most medical devices in the future, Bang & Olufsen Technology has started researching this field.

Telemedicine is basically about transmitting medical data from one place to another. With the current trend towards Home Care and Disease Management Systems, the need for exchanging medical information between patient and hospital or between general practitioner and hospital becomes increasingly important. See Fig. 7.

Telemedicine is an extensive area which requires the mastery of a range of different technological disciplines such as knowledge of PC technology (Internet access), digital signal processing in telecommunications and wireless applications.

These disciplines are in-house skills attained through our close co-operation with Bang & Olufsen Telecom, with their many years of experience within both wireless and plain old telephone systems (POTS) related to the consumer end of telecommunications.

With this strong background, Bang & Olufsen Technology is now intent on incorporating telemedicine technology in a medical device.

SUMMARY

Since the identification of the Health Care market as an interesting business area in the late 1980s, Bang & Olufsen Technology has put great effort into attaining its present position as a competent strategic partner within the Health Care Market.

Bang & Olufsen Technology sees itself as a total supplier of basic research, concept development, product development and production engineering right through to manufacturing.

Based on technological skills within drug delivery systems, acoustics, electronics, optics, data analysis and telecommunications, Bang & Olufsen Technology aims at entering strategic alliances with companies concerned with drug delivery systems and non-invasive medical devices.

So far, Bang & Olufsen Technology has established strategic partnerships with several world market leaders within its focus areas.

Reference: Zinck JP, Jensen HJ, Rasmussen JK, Fabricius PE, Dalgaard T, Rasmussen KM, Schilkowski G. Bang & Olufsen Technology a/s – A new partner in Disease Management. In: The Danish Society for Biomedical Engineering, ed. Aspects of biomedical engineering in Denmark. Copenhagen, 1998: 125-31.

25 years of RADIOMETER™ blood gas analyzers

CARL C. HOLBEK

Radiometer Medical A/S, Copenhagen, Denmark

The 25 years in which the Danish Society for Biomedical Engineering has existed have been characterized by an unprecedented growth in medical technology. RADIOMETER has taken part in this process within the niche of STAT (Short-Turn-Around-Time) analyses, i.e., analyses required for patients in a critical state.

The development of RADIOMETER during these 25 years is illustrated by comparing the vintage 1973 Acid Base Laboratory, ABL1™, with the 1998 analyzer, the ABL700. ABL1 was the world's first fully microprocessor-run blood gas analyzer, and thus fittingly marked the beginning of the era of the Danish Society for Biomedical Engineering, and the ABL700 is the current top analyzer. Some obvious differences between the two instruments are the number of parameters measured as well as derived, the decreased sample volume, and the vastly increased use of Information Technology for a number of purposes. For some of these differences, the development and the idea and research behind the product are discussed in more detail. In this 25-year period RADIOMETER has successfully competed internationally, exporting 96% of its products to a large number of countries.

Key words: ABL; blood gas analysis; blood oximetry; electrolytes; glucose; history; lactate; OSM; RADIOMETER; STAT analysis.

Carl C. Holbek, Ph.D., Radiometer Medical A/S, Åkandevej 21, 2700 Brønshøj, Denmark.

INTRODUCTION

Until 1973, analysis of pH and blood gases (pCO_2 and pO_2) was a manual process, requiring highly trained laboratory technicians. It was therefore typically carried out in a centralized laboratory function often far away from the clinical departments. From a practical, clinical point of view this was less than ideal: these particular parameters were often needed within minutes to decide on a possibly life-saving therapy to be initiated or adjusted. On the technical front, attempts had been made to produce analyzers, which

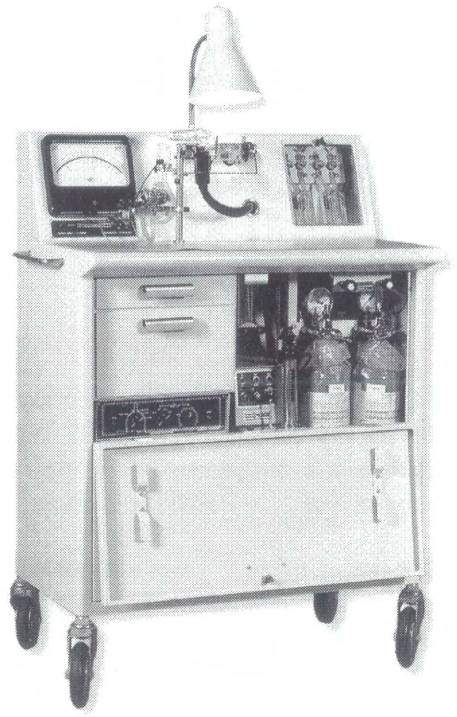


FIG. 1. The Astrup Micro Equipment (AME1) for measurement of pH and pCO_2 was introduced in 1959.

were suited for use outside the laboratory. However, these met with limited practical success because the basic complexity and consequent need for technically trained personnel remained. Fig. 1 shows an example, the AME1 Astrup Micro Equipment from 1959-60.

For RADIOMETER, the era can be illustrated by the development in the pH/blood gas analyzers, leaving a discussion of other areas such as the evolution of transcutaneous pO_2 and pCO_2 measurements, for the future. The introduction of the world's first fully microprocessor run 'Acid-Base Laboratory' ABL1, late 1973, marked the beginning of a long process where microprocessors gradually took over more and more of the technically demanding processes. Thus the analyzers gradually became suited for placement close to the patient. For the ABL1 itself, even though an operator with no technical training but just a few minutes' instructions could obtain accurate results, the analyzer still required a high level of technical training for daily maintenance and quality control. The analyzer of today is much more technologically advanced and much simpler to use and service.

Being a part of this process of development has been exciting and rewarding for RADIOMETER. The process has been demanding and has brought about significant changes in the company, just as it has in hospitals. Part of the process and some of these changes as seen from the vantage point of RADIOMETER, will be described in the next few pages.

Before 1973: History and status

RADIOMETER was founded in 1935 as an electronics company with a 'mission' to build analytical equipment for the growing radio-industry, hence the name. After only two years, RADIOMETER received an important request from Gotfred Haugaard (1894-1969), one of the assistants to the famous S.P.L. Sørensen of the Carlsberg Laboratory, to build a high-impedance voltmeter for use with a glass electrode. Even though the original request to build pH meters was well within the scope of the electronics company, subsequent requests for pH electrodes expanded the field into chemistry. Over the next several years RADIOMETER developed an expertise in electrochemistry, not only in the theory of the subject but also concerning the practical problems of making pH electrodes in glass. From then on, the combination of electrochemistry, electronics and mechanics formed a second platform on which further developments were based, in parallel with the company's original line.

In 1954, the next crucial year in the formation of RADIOMETER of today, electrochemistry was still the junior brother, seen from a commercial point of view. That year, RADIOMETER was once more approached with a request for a specialized equipment, this time by Poul Astrup, then newly appointed head and later professor, of the clinical chemistry laboratory at Rigshospitalet, the main University Hospital in Copenhagen. Like much of the world, Denmark had been hit hard by the polio epidemics, and the condition of patients was difficult to explain from just pH and total CO_2 measurements. Astrup had a brilliant idea of how to obtain the necessary information, which required the construction of an analyzer for the 'Astrup' equilibration method. Fortunately for RADIOMETER, we were the ones asked, and within a few months the first device, named E50101 The Astrup Apparatus, was delivered. For RADIOMETER this was the first highly significant step into the area of building analyzers specifically for the medical field. Within the following years the medical part of the business grew by leaps and bounds.

1973

Characteristics of the market

The pH/blood gases belong to the STAT (Short-Turn-Around-Time) parameters, where the results are often needed within minutes, rather than hours or days. The majority of tests requested from the clinical laboratory, however, are not urgently needed. Hence, the work in the laboratory is organized with other priorities, such as offering a large variety of tests, a large sample throughput, economic operation, and adequate quality control. All of these require fairly complex analyzers attended by highly trained specialists. Rapid response to individual tests, however, does not belong in the mainstream of the laboratory operation, even though some laboratories offer such services.

The requirements of STAT analyzers differ significantly from those above as they are geared for small sample throughputs. They should be made for operators whose main concern are the patients, not the technical details. Thus, the analyzer should always be ready for the single test, be simple and reliable to use, and not require any extensive sample treatment prior to analysis, i.e., whole blood rather than serum or plasma should be accepted. These requirements combined with the clinical imperative for accurate blood gas analysis, defined by the National Committee for Clinical and Laboratory Standards (NCCLS), fitted well with the RADIOMETER tradition of small production series and good craftsmanship. NCCLS states that "Blood gas and pH analysis has more immediacy and potential impact on the patient care than any other laboratory determination. In blood gas and pH analysis, an incorrect answer can often be worse that no result at all" [1].

Obviously, such demands are reflected in the construction of the analyzers.

Birth of the ABL

In 1973, the time was ripe for change, based on the newly developed microprocessor chip. The idea to use the microprocessor to make blood gas analysis so simple that anybody could be instructed in the use in just a few minutes, had come up some years earlier during a meeting between a research and development team from RADIOMETER, and Professor Ole Secher and Dr. Erik Jacobsen from the Anesthesiology Dept. at Rigshospitalet. The final concept of the ABL1 may best be described by the very simple, four point User Manual envisioned:

The operator should

1. open the inlet flap

2. inject the blood sample
3. close the inlet flap
4. tear off the strip from the printer and walk away with the results.

Fig. 2 shows the ABL1 (Acid Base Laboratory) as it was introduced in December 1973 [2].

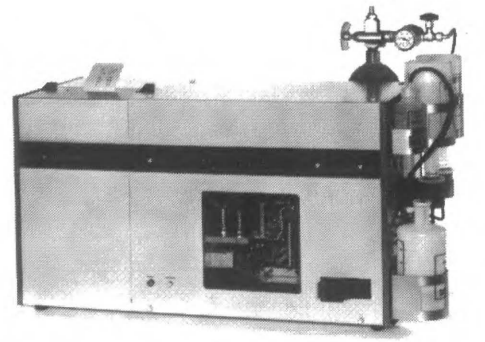


FIG. 2. ABL1, the world's first fully microprocessor run analyzer for measurement of pH, pCO_2 and pO_2 was named Acid-Base Laboratory in honour of Prof. Astrup.

Measuring technology and parameters

The measuring chamber and the equilibration towers were all thermostatted at 37.0 °C. The measurement was automatic, including a rinse. Once the sample had been injected or aspirated into the analyzer pH and pCO_2 were measured by potentiometric electrodes, pO_2 by the amperometric electrode described by Leland C. Clark jr., and the concentration of hemoglobin (*c*tHb) by measuring the absorbance at 506 nm on unhemolyzed blood. Hemoglobin was included to allow calculation of various derived parameters, which require knowledge of the hemoglobin concentration.

The microprocessor was used not only to run the analyzer but also to calculate derived parameters of interest in the clinical interpretation of the results.

Calibration

Calibration was automatic on two buffers, equilibrated inside the analyzer at 37 °C with two internally produced gas mixtures to known values of pCO_2 and pO_2. As the buffer systems were known, the pH was also known as a function of the pCO_2. The barometric pressure was measured to allow for its effect on the partial pressures. The gas mixtures were obtained by mixing 100% CO_2 in known proportions with atmospheric air. The mixing proportions were determined by the lengths of two metal capillary tubings, a principle patented some years earlier by RADIOMETER. The use of atmospheric air and 100% CO_2 rather than ready-mixed gas mixtures had the important advantage that pure CO_2 (and air) were far easier and less costly to obtain in most locations over the world than ready-mixed gases.

The choice of calibrating the gas electrodes on buffers with known gas tensions rather than directly calibrating on the gas mixture, was made to reduce errors in the pO_2 measurements. Due to the fact that pO_2 electrodes consume oxygen during measurements, the results depend on whether the sample is in the gas or liquid phase. This difference is reflected in the *gas/liquid ratio* which ranges from 1 to about 6%, making measurements on liquids based on gas calibrations somewhat uncertain. In 1973 the gas/liquid ratio varied from one electrode to the next and changed with time for the individual electrode, making corrections for the gas/liquid ratio inaccurate.

Developments 1973 to 1998

The ABL1 was an undeniably success but one that carried costs along with the more obvious rewards.

Consequences of the success

The introduction of the ABL1 and its wide-

spread use revealed a number of derived needs:

1. Requests for performance specifications, raising the question as to how to define and verify these.
   - RADIOMETER established a reference system for pCO_2 and pO_2 using bubble tonometers and whole human blood, to determine the performance specifications on one series of ten analyzers from a production series, and verifying the specifications on another series of ten. Even today, the specifications presented in RADIOMETER's user documentation is the most extensive in the industry.
   - RADIOMETER set up a pH Reference Laboratory with one of the few operating Hydrogen electrode systems in the world [3]. The Chemical Reference Laboratory's Hydrogen Electrode System is accredited by the Danish Accreditation Scheme (DANAK) to certify primary buffer solutions.
   - RADIOMETER has been active in a number of international groups and committees working to define various reference systems, e.g., for pH, pCO_2 and ionized calcium.
   - reference methods for the blood gases were internationally defined at a much later date [4,5].
2. Requests for automatic monitoring of the measuring quality.
   - Today's analyzers closely monitor all essential functions.
3. Requests for quality control (QC) programs for the users.
   - The first RADIOMETER QC system for blood gas analyzers was introduced 1979. Over the years this has been expanded, responding to the addition of new parameters, the developments in theoretically based use of QC (e.g. the Westgard rules), and the increase in data handling capabilities. Today RADIOMETER has established a system allowing the QC results from the single analyzer to be compared to other users' analyzers (World Wide DataCheck).
4. Requests for a large number of refinements, including lower sample volume, more parameters (measured and calculated), faster cycle time, and simpler maintenance, especially of the electrodes.
   - Some of the more important RADIOMETER developments are (1) intracuvette hemolyzation which allows oximetry to be built into blood gas analyzers for a more complete description of oxygen status in arterial blood and (2) sensors for whole blood glucose and lactate measurements with a lifetime of one month and no interference from most of the commonly seen interfering substances.

The success of the ABL concept and the efforts required to solve the technical problems and continue development left little time for other product lines, a fact which over time caused the original Radiometer A/S (the parent company) to split up: one part focussing on electronics, another on the industrial analytical market, and a third, Radiometer Medical A/S serving the medical market. This article deals solely with Radiometer Medical A/S.

The 25-year period witnessed a continued cooperation with distinguished scientists and clinicians to develop top line analyzers. This cooperation was facilitated by the RADIOMETER tradition of good craftsmanship emphasizing quality: the concept had to be theoretically sound as well as technically viable. As a consequence, on several occasions RADIOMETER has not

been the first to release, for example, new sensors. On the other hand, when introduced the sensors have been well received. Two areas will be discussed in more detail: development within the electrode area, and the combination of oximetry and blood gas analysis into one analyzer.

Electrode developments

In general electrodes were miniaturized to allow for smaller samples, and many other improvements were introduced, including some that shortened the formerly tedious and demanding process of replacing the electrode membrane to a matter of seconds. The production process and the construction of the oxygen electrode were improved to the extent that the gas/liquid ratio could be accurately predicted. This allowed the simpler gas calibrations to be introduced with the ABL500 series (1989) without sacrificing accuracy.

New electrodes were developed for various electrolytes, such as potassium (needed in connection with heart transplants), ionized calcium (clinically more relevant than total calcium), sodium (to a certain extent requested by the market because sodium and potassium had a history of being measured in parallel, e.g., on the flame photometer), and chloride (traditionally used with the other electrolytes and bicarbonate to calculate a derived parameter, the anion gap). In the 1990s, a number of enzymatic electrodes for glucose and later for lactate built into blood gas analyzers were introduced on the market. The lactate electrodes in particular, however, suffered from serious drawbacks such as short lifetimes counted in days or at the most a couple of weeks, and interference caused by various substances, which often occurred in the blood samples. In a concerted effort a group of scientists at RADIOMETER has managed to significantly improve on both counts, especially by improving the immobilization of the enzyme and the membrane construction, shown in Fig. 3.

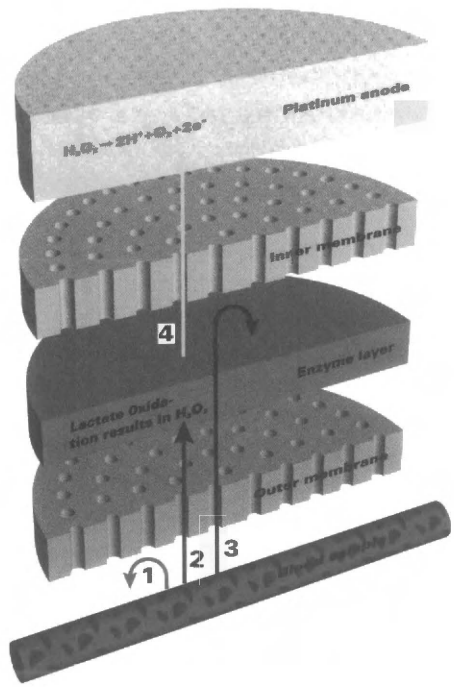


FIG. 3. The numbered arrows illustrate the flow of various sample components:
1. blood cells, 2. lactate, 3. interfering substances, 4. H_2O_2.
The outer membrane turns back the red blood cells, eliminating hematocrit as an interfering substance. The dense inner membrane blocks other types of potentially interfering substances which would otherwise diffuse through to the anode and there become oxidized. Thus, the special construction of the membrane makes the lactate measurement very robust.

Combination of oximetry and blood gas analysis

With the advent of the oxygen electrode pO_2 became the oxygen parameter of choice in spite of obvious clinical shortcomings. pO_2 which reflects the oxygen activity, does not provide any information on the 99% of the

oxygen which in normal arterial blood is transported bound to hemoglobin. According to Siggaard-Andersen [6] a complete description of the arterial oxygen status requires information on oxygen concentration (ctO_2) and the relation between pO_2 and ctO_2, in addition to pO_2. Thus measurements of the concentration of hemoglobin and other hemoglobin parameters are needed. In practice, hemoglobin and its derivatives are most easily measured by optical methods.

Optical methods

In the early 1960s, Siggaard-Andersen had developed a simple photometer (OSM™1) with RADIOMETER using absorbance spectrometry to measure hemoglobin and oxygen saturation. Accuracy required the blood to be hemolyzed before measurement, i.e., the red blood cells should be ruptured to provide an optically clear solution. At that time blood was hemolyzed in a capillary tube by freezing, before transfer to the measuring cuvette in the analyzer. The wavelengths were selected by filters.

In 1976 RADIOMETER introduced the OSM2, an automated oximeter for measuring hemoglobin and oxygen saturation [7]. One important novel feature was automatic hemolyzation, which took place inside the measuring cuvette by the application of ultrasound. This reduced the volume required to just 25 µL of whole blood (and the result was available in 25 seconds). Even though the optical system had been improved compared to OSM1, it was still based on two wavelengths selected by filters. The small volume, the speed, and the convenience of automation made this instrument a favorite in cardiac departments for more than a decade.

However, the market needed easy measurement of the dyshemoglobins, carboxyhemoglobin and methemoglobin, which were not available on the two wavelengths analyzer, OSM2. Cooperation with Professor W.G. Zijlstra in Groningen, The Netherlands, and Professor O. Siggaard-Andersen, Chief Physician N. Fogh-Andersen and P.D. Wimberley MD from the Herlev University Hospital, led to the introduction of OSM3 in 1985, a six-wavelength oximeter using gratings instead of filters to obtain the required wavelengths. Other characteristics included: a sample volume of 35 µL, ctHb, sO_2, FO_2Hb, FCOHb, and FMetHb as measured parameters, results available in 20 seconds, and the suppression of interference from intralipid and Sulfhemoglobin. Fetal hemoglobin could be estimated.

OSM3 could be electronically coupled to the ABL analyzers, allowing the calculation (estimation) of $p50$, providing the position of the oxygen dissociation curve (ODC) that relates sO_2 to pO_2, and thereby illustrates the oxygen-hemoglobin affinity. However, the accuracy of the calculation was not satisfactory for high oxygen saturation values, and was therefore not performed for these.

In 1984 Siggaard-Andersen described the ODC by use of the hyperbolic tangent function, which provided a more accurate fit between the mathematical curve and the experimental values, especially at high saturation [8]. The increased computer power available in the ABL500 Series (introduced 1989) was able to utilize this improved accuracy to determine the ODC for high saturation values as well. Then, the three parameters needed for complete description of the arterial oxygen status (pO_2, ctO_2 and the relationship between these two parameters) were available from a single sample.

1998

Todays products

The latest generation of analyzers, the ABL700, covers a lot more than just the

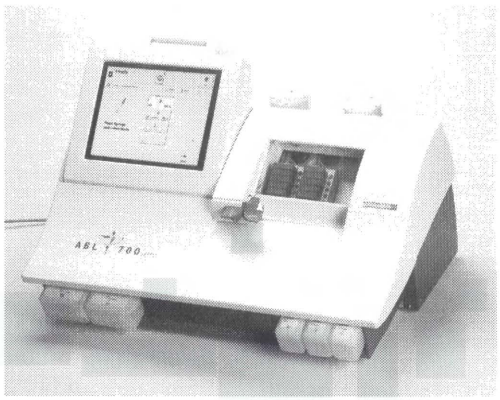


FIG. 4. The ABL700, introduced in 1998, is much more than a blood gas analyzer. The parameter panel includes hemoglobin derivatives, electrolytes and metabolites. Furthermore, it has additional space designated for future parameters, pointing towards a long useful life of the system.

blood gas parameters of 1973 (Fig. 4). It utilizes the much increased power of the microprocessors to allow the laboratory complete remote control of the analyzer, independent of its place of use. Thus the accuracy and control expected by the biochemistry can be achieved even when the analyzer is used by personnel that are not technically trained. Some of the key characteristics of the two generations of analyzers are listed in Table I.

The emphasis on the combination of oximetry parameters with the traditional blood gas parameters is continued in the ABL700 series. The oximeter, now using 128 wavelengths, automatically suppresses interference from substances such as fetal hemoglobin, intralipid, bilirubin, and various colored substances used for diagnostic purposes. The accuracy and reliability of the measured and derived parameters alike are thus increased.

The products related to the RADIOMETER STAT analyzers are all related via the Patient Focus Circle (PFC), a concept which stresses the interrelation between the preanalytical, analytical and postanalytical phases in the analytical process (Fig. 5).

Radiometer Medical A/S

Numbers and organization

In 1973 Radiometer A/S employed 873 people, all in Denmark. Sales and service were handled via sole distributors. The worldwide sales were 79 million DKK with medical products estimated to contribute less than 50% of this. 95% of the sales were outside Denmark.

In 1998 Radiometer Medical A/S has more than 1600 employees worldwide, with approximately 50% in Denmark. The sales organization spans the globe with subsidi-

TABLE I. Characteristica of the first automated RADIOMETER blood gas analyzer, ABL1 and the latest, ABL700.

Characteristica	ABL1	ABL700
Introduced, year	1973	1998
Measured parameters	pH, pCO_2, pO_2, (*c*tHb)	pH, pCO_2, pO_2, *c*tHb, sO_2, *F*COHb, *F*MetHb, *F*HHb, FO_2Hb, cNa^+, cK^+, cCa^{2+}, cCl^-, *c*Glu, *c*Lac
Sample volume, µL	500	195
No. of derived parameters	6	> 40
Time to result, sec	180	~ 60
Computer processor	4004 (4 Bit)	386 + pentium
Read out facilities	Diode display, printer	Color touch screen, printer, diskette, ringnet

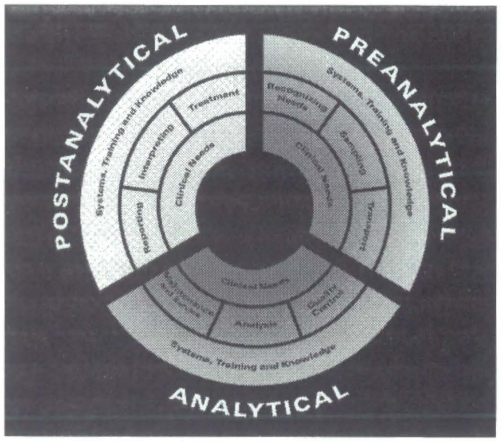


FIG. 5. The Patient Focus Circle™ (PFC) illustrates the interdependence between the various phases and activities involved in STAT analysis. The PFC serves to stress the points that while the quality of the analyzer itself is important it is by no means the only essential factor determining the overall quality of the measurement.

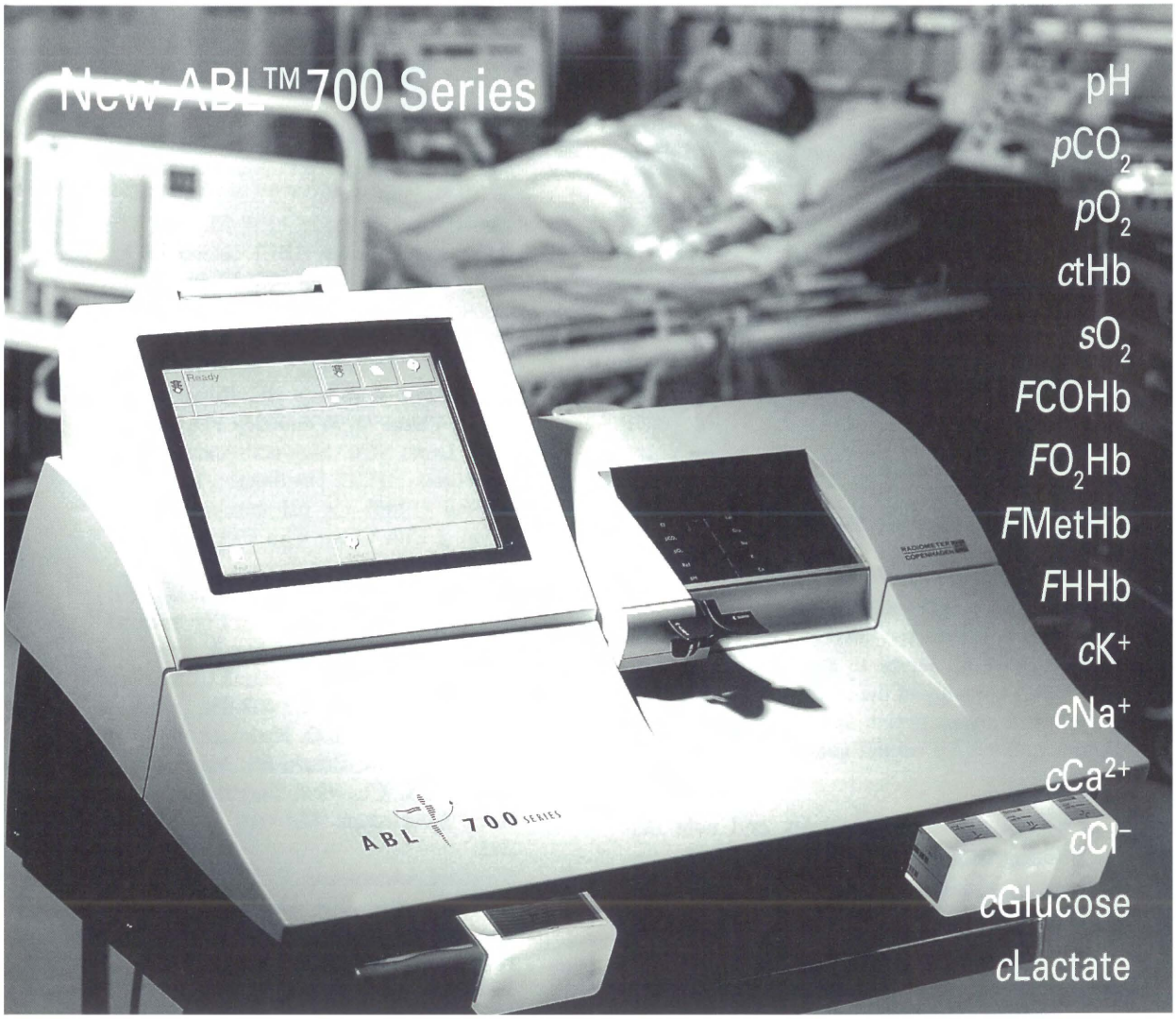
aries in some 10 countries and sole distributors covering the remainder. The annual sales are more than 1.4 billion DDK, still with more than 95% of the production is sold outside Denmark and contributing positively to the balance of payment and employment in Denmark.

The birth and growth of RADIOMETER's medical involvement are difficult to imagine without the close and fruitful cooperation between leading scientists and RADIOMETER. While this relationship has been the *sine qua non* for Radiometer Medical A/S it has at the same time served to highlight the contributions of Danish scientists, transforming their ideas to medical practice all over the world and illustrating an effective symbiosis between industry and medical research.

REFERENCES

1. Eichhorn JH, Burnett RW, Christiansen TF et al. Blood gas pre-analytical considerations: specimen collection, calibration and controls. Approved Guideline. NCCLS Publication C27-A. Villanova, Pa.: NCCLS, 1995; 13,11: 1-50.
2. Johansen E. On the ABL1. Scand J Clin Chem 1977; 37, Suppl 146: 37-40.
3. Kristensen, HB, Salomon A, Kokholm G. International pH scales and certification of pH. Anal Chem 1991; 63,18: 885A-91A.
4. Maas AHJ, Weisberg HF, Burnett RW, Müller-Plathe O, Wimberley PD, Zijlstra WG, Durst RA, Siggaard-Andersen O. Approved IFCC methods. Reference method (1986) for pH measurement in blood. J Clin Chem Clin Biochem 1987; 25,4: 281-89.
5. Burnett RW, Covington AK, Maas AHJ, Müller-Plathe O, et al. IFCC method (1988) for tonometry of blood: reference materials for pCO_2 and pO_2. J Clin Chem Clin Biochem 1989; 27: 403-08.
6. Siggaard-Andersen O. Hydrogen ions and blood gases. In: Brown SS, Mitchell FL, Young DS. Chemical diagnosis of disease. Amsterdam: Elsevier, 1979: 181-245.
7. Siggaard-Andersen O. Experiences with a New Direct-reading Oxygen Saturation Photometer Using Ultrasound for Hemolyzing the Blood. Scand J Clin Chem 1977; 37, Suppl 146: 45-50.
8. Siggaard-Andersen O, Wimberley PD, Gøthgen IH, Siggaard-Andersen, M. A Mathematical Model of the Hemoglobin-Oxygen Dissociation Curve of Human Blood and of the Oxygen Partial Pressure as a Function of Temperature. Clinical Chemistry 1984; 30, 10: 1646-51.

Reference: Holbek CC. 25 years of RADIOMETER blood gas analyzers. In: The Danish Society for Biomedical Engineering, ed. Aspects of biomedical engineering in Denmark. Copenhagen, 1998: 133-41.



The STAT analyzer for all testing sites

The new ABL700 Series analyzers offers the best of both worlds in STAT testing - the ease of use, fast turnaround time, and low maintenance of point-of-care instruments, as well as the accuracy, data control, automation and cost efficiency of laboratory testing.

- **Only 95 µL for 15 parameters**
- **Completely flexible parameter configurations**
- **Windows®95 based software and touch screen**
- **Automated hands-free inlet**
- **Automatic built-in quality control**
- **Remote control from one central PC**
- **Integration with your information system**
- **Unique interference free accuracy**
- **Maintenance reduced by 90 % to only two hours a year**

For more information, call toll-free 1-800-736-0600 or visit our internet site at: www.radiometer.com., e-mail: rame@en.com.
RADIOMETER AMERICA INC.

RED SYSTEM™
IN DIALOGUE WITH RADIOMETER

RADIOMETER COPENHAGEN

The Electromyograph – a success in Danish industry

"From a biomedical engineering point of view the electromyography is an exciting experience"

POUL BOELT[1]

Hvidovre Hospital, Biomedical and Engineering IT-Dept., Hvidovre, Denmark

The article describes DISA's motives for starting development and production of electromyographs and also describes how the technological development within electronics during the last fifty years has had great influence upon the generations of electromyographs that Danish industry has introduced successfully worldwide.

Key words: Action potentials; averaging; concentric needle electrode; DISA; electrolytical treatment; freqency range; multielectrode.

Poul Boelt, Hvidovre Hospital, Biomedical and Engineering IT-Dept., Kettegaard Allé 30, DK-2650 Hvidovre, Denmark.

One of the success stories in Danish biomedical engineering is the development within the field of electromyography.

The Danish Industry Syndicate (DISA), once known as the "rifle" syndicate (automatic gun factory), intended by the end of the 1940s to change their activities to a more civil production. Thus DISA established a special electronics laboratory.

Initially DISA started development and production of electronic therapeutic stimulators. After a successful introduction of these stimulators, DISA settled a close cooperation with professor in neurophysiology, Fritz Buchthal, at the University Hospital of Copenhagen. This close cooperation resulted early in the 1950s that DISA introduced the first commercial electromyograph in the world. Fig. 1 shows professor F. Buchthal standing by the prototype of the above mentioned electromyograph.

From a technological point of view the system was at that time a unique equipment within the biomedical engineering for research purposes as well as for use within the neurophysiological clinic.

The action potentials of the muscles and

[1]From 1965-82 leader of DISA's development department for medical equipment.

FIG. 1. Fritz Buchthal, professor at the Institute of neurophysiology, University of Copenhagen, standing by the prototype of the electromyograph.

FIG. 2. The simplest concentric needle electrode with a diameter from 0.30-0.65 mm.

nerves should be recorded, and this task did not only require the development of a new electronic system, but also the development of a wide range of electrodes from the simplest concentric needle electrode with diameters from 0.30-0.65 mm (Fig. 2) to the most complex multielectrodes provided with up to 16 leading-off surfaces arranged with different distances in a thin slot in the cannula tube with diameters from 0.6 – 1.6 mm (Fig. 3). The requirements of the insulation resistance between the respective leading-off surfaces was more than 1,000 MΩ!

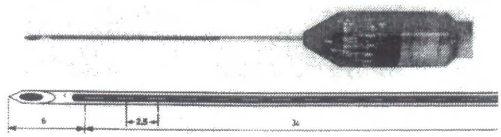


FIG. 3. The most complex multielectrode provided with up to 16 leading-off surfaces arranged with different distances in a thin slot in the cannula tube with diameters from 0.6 – 1.6 mm.

Up till the middle of the 1960s an electromyograph was first of all used for research purposes and for examination of the peripheral muscle system. Amplitudes of muscular action potentials range from 50 μV to a few mV peak-to-peak and with a frequency range from 2 Hz to 10 kHz.

Vacuum tubes were the only items available for amplification, and the noise level of the EMG amplifier had to be less than 5 μV peak-peak with shorted input. It was hard to fit.

The electromyograph was provided with 3 similar recording channels, and as monitor they had to use three 1-inch cathode ray tubes which were placed in a horizontal line. As user you had no difficulty in comparing the noise level of the respective amplifiers. Therefore, in production more than one hundred vacuum tubes were tested, just to rend three tube pairs suitable for the differential amplifier of the EMG pre-amplifier.

Exact measurements of the duration of the action potentials (5 to 20 msec) as well as the number of phases (1-10) are important information when diagnosing neurophysiological diseases. Consequently these detailed analyzes involved permanent recording of the action potentials. When recording other physiological signals (EEG, ECG and

blood pressure), pen recorder systems could be used, but when running EMG's, you had to develop a special recording system due to the wide frequency range of the EMG. The solution to this problem was to place another three 1-inch cathode ray tubes next to each other and let a paper film, 10 cm wide and 10 m long, pass by. When exposed, the paper film was lead into a big metal box, and later it was sent to a darkroom for development and drying. Not until finishing the above process you were really sure that the examination was successful!

The second generation of DISA's EMG was developed in the middle of the 1960s, and I participated from the very start. For me this was also the beginning of many years' excellent co-operation with professor Buchthal. Every Thursday the professor himself examined patients at the University Hospital of Copenhagen, and I often had the opportunity to attend these examinations. I soon learned from the professor the importance of a detailed knowledge of working methods in the clinic if you should develop and design biomedical systems. As a biomedical engineer, you must have a thorough knowledge of this if you shall co-operate successfully with the clinicians.

In the EMG of the second generation the most important news was the use of transistors in a large scale as well as the three recording channels which could now be observed below each other on a 17-inch monitor. From a clinical point of view it was certainly an improvement! Due to the fact that the input impedance must be very high (100 MΩ), special vacuum tubes still had to be used in the pre-amplifiers and the "camera" using the 10 cm wide paper strip was basically used unchanged in the new model.

In the 1960s professor Buchthal also started research in sensory neurography. The amplitude of the potentials were here between 2 to 3 decades lower than the muscles potentials and the signals were often below the noise level of the amplifier. The sensitivity was increased through development of a very special transformer which had a turns ratio of 1:30. But as the electrode impedance consequently was increased by 30^2, a new range of sensory needle electrodes had to be developed. These were constructed of stainless steel, but as even the slightest oxidation increased the electrode impedance, the electrodes had to undergo an electrolytical treatment before use in order to ensure an impedance less than 5 kΩ, which was the condition for a correct frequency range for the transformer cobbled to the input of the EMG amplifier. The electrolytical treatment consisted of placing the electrode into a physiological saline solution and allowing a current of 10 mA/mm^2 to flow until a few bobbles rise.

Worldwide there was an increasing interest for sensory neurography studies, so within the biomedical engineering there was an intensive development of equipment that could improve the signal-to-noise ratio. One of the solutions was the use of electronic averaging.

Averaging serves to improve the signal-to-noise ratio of the signals triggered by stimuli – synchronized to the memory circuit in the averager. When averaging, the amplitude of the signals increases linearly with the number (n) which represents the number of the evoked responses resulting from summation of the responses, while the noise amplitude increases by the square root of this number – consequently the signal-to-noise ratio is improved by the factor ($\sqrt{n}$).

DISA also succeeded in developing the sensory amplifier. It had a maximum sensitivity of 0.5 μV/div and a special feature called stimulus artifact compensation. With this feature, in counter phase to the stimulus artifact, it was possible to enter a signal so

that the blocking problem from a stimulus artifact in the sensory amplifier was reduced considerably.

In DISA's averager sold at the end of the1960s, digital technology was used, and at the same time the range of components for the design of digital circuits exploded.

This saturated DISA's third generation EMG's, The 1500 System. Digital technique was used in a large scale: 4-channel monitor with a separate storage function on 4 traces, digital delay lines with variable delay from 1 – 20 msec, two channel averager function, and the great news: the Disagraph.

This was a 4-channel recording system with a frequency range of DC – 10 kHz! With the background in the multielectrode technology, a recording electrode was constructed with approximately 300 steel pins placed in a row of 10 cm. The aim was that a special film should pass by this multielectrode, constructed of a basis paper inked in a black color liquid and coated with a thin aluminum foil. Across a reference electrode and the 300 steel pins, pulses were switched (100 volts, 5 µsec and 50 kHz). During this process, the aluminum foil was burned away when in contact with the active steel pins. On-line EMG curves, expanded action potentials as well as text could be recorded in this system as required.

The 1500 System was in the early 1970s marketed as the first digital EMG system in the world!

From the beginning of the 1960s and the next 10 years the EMG passed through three major technological changes: transistors, operational amplifiers and digital technique. The next big jump was the microprocessor.

With this technology the door was opened for new advanced features in the EMG, and the software controlled electromyograph was introduced as Neuromatic 2000. Automatic programming of the EMG for specific examinations, and on-line calculation was carried out.

DISA changed their name to Dantec, and they have succeeded in installing more and more programs in the electromyograph which is a great help for the increasing number of clinical users.

The electromyographs from DISA (now Dantec) has from the start of the fifties and until today been the leader in the world market. The reason for this success is a close co-operation with the leading scientists within the neurophysiology, beginning with professor Fritz Buchthal. Further reasons for the success is the fact that DISA always has developed complete measuring instruments, i.e., electrodes/transducer, equipment for measurement and recording as well as documentation including not only users manual but also excellent application papers.

This profile and product concept is also characteristic for other Danish firms that have succeeded in manufacturing medical equipment.

The neurophysiology over the past 30 years has really undergone many changes! As a medicoengineer who has followed the changes within this area, I find especially the neurophysiology very exciting, as it makes the greatest demands concerning physiological measurements!

Reference: Boelt P. The Electromyograph – a success in Danish industry. In: The Danish Society for Biomedical Engineering, ed. Aspects of biomedical engineering in Denmark. Copenhagen, 1998: 143-46.

Efficient workflow management for radiology

WERNER OFFENMÜLLER, NIKOLAS WIRSZ, ERWIN WIRSZ & HELLMUT GNOYKE

Siemens Medical Engineering Group, 91052 Erlangen, Germany

The pre-requirements for instituting a comprehensive workflow management in radiology are described. Besides the connectivity of systems and modalities based on international standards, interoperability must be guaranteed. The workflow will be explained using the example of the total radiological process and in detail the radiological reporting process. In the second part, practical solutions using SIENET®[1], Siemens PACS, are explained. Today's current RIS/PACS applications, the description of an optimal workflow during softcopy reporting and solutions for image distribution are discussed. The last chapter rounds off with an overview of routinely used integration functions in SIENET installations.

Key words: DICOM; image distribution; integration; PACS; softcopy reporting; workflow management.

Contact address: Kim Heuschkel, Siemens Medico A/S, Borupvang 3, 2750 Ballerup, Denmark

Abbreviations:

SIENET:	Siemens brandname for their PACS product line	MR:	Magnetic Resonance
PACS:	Picture Archiving and Communication System	PET:	Positron Emission Tomography
RIS:	Radiological Information System	NM:	Nuclear Medicin
DICOM:	Digital Image Communication (standard)	US:	Ultrasound
CT:	Computed Tomography	MIP:	Maximum Intensity Projection
		MPR:	Multiplanar Reconstruction
		HIS:	Hospital Information System
		HL7:	Health level 7 (standard)

1. INTRODUCTION

Digitalization of radiology departments has been an ongoing process worldwide during the last 10-15 years. Denmark was one of few countries in Europe where this process

[1] SIENET® is a trademark of Siemens AG, Erlangen, Germany.

was started very early. In the late 1980s three sites were planning total digital radiology departments: Viborg Sygehus, Skejby Sygehus, Bispebjerg Hospital. All three sites started working with digital radiology in the years 1991-92. Viborg and Skejby are today two sites which work only on a digital basis.

Today we have worldwide a situation where a remarkable number of departments and institutions have gone through this process. Due to lack of finance the role of radiology as a service department within healthcare has been subjected to considerable change. An increase of efficiency in the performance of many individual examinations is needed. And this may not only be achieved through digitalization alone, but system integration in a much larger scale than today is needed to achieve the new demands for higher efficiency in a service department as radiology. However, the quality of the medical results should be maintained even if there is a tendency to reduce resources. These problems can only be mastered by applying new Information and Communication Technologies. In this case the successful integration of all information systems and examination-related equipment is a prime requirement.

This need for system integration has also been considered at the two major Danish sites, and Siemens has been developing and working on even better solutions through the last 5 years together with the hospitals. Therefore some of the new possibilities described in this article on workflow management are also discussed and in the process of getting more routinely used in the daily praxis.

2. AUTOMATED WORKFLOW IN RADIOLOGY

The most important aim in radiology is to examine a given medical question efficiently and rapidly, using to the full all available resources and to transmit the result to the referring person. The coordination of all the necessary actions, the readiness of the doctors and paramedicals concerned to cooperate and the availability of relevant information greatly affect this process. In conventionally run departments, these necessary tasks are, by experience, well distributed and their realization known. When changing over departmental operation to a primarily DP supported workflow, processes must be re-thought and re-organized. The better this is undertaken, the more the efficiency of the department can be increased subsequently.

2.1 Including and networking all systems and modalities installed

The integration of all systems is the basis for the establishment of an electronic workflow. In today's mainly heterogeneous product landscape this should be based on standards in order to safeguard the investment and to remain open for the future. For this, DICOM offers an excellent basis to connect systems to one another. The DICOM standard covers all medical image formats (e.g., CT, MR, CR, angiography, radiofluoroscopy, PET, NM, US). In addition, network communications such as SEND, RECEIVE, QUERY/RETRIEVE or PRINT images are standardized, but also further non-image related parts are incorporated. For example, worklists (between RIS and modalities) or reports can be exchanged with DICOM. Realizing a successful connection (Plug) as well as performing data transfer (Exchange) are a reality with DICOM [1].

Certainly, the user primarily wants to use the captured data to support his daily work to the very best. This will then be possible when the respective application functions

can also receive and use all the data. Interoperability, i.e., "the ability to exchange medical information which has clinical utility on both sides of the connection" can not be automatically guaranteed with DICOM. Therefore, individual cases must be checked to see if it is possible to process and manipulate the data received (e.g., for 3D reconstruction, MIP, MPR, diagnosing, adequate identification of the data for a patient folder).

Older generations of equipment can be connected using special solutions for non-DICOM compatible systems.

2.2 Acquisition and presentation of workflows

The connection of two systems and, thus, their functional integration, is an important pre-requirement for complete integration [2].

An understanding of the total workflow in radiology to perform the diverse patient examinations is the center point of comprehensive workflow management. For this, the individual working steps must be analyzed and described in order to illustrate the interplay of all the resources involved.

This is best done by workflow modelling to

- systematically describe all tasks and sub-processes
- record the information and results resulting from the tasks
- record the person who performed the task.

In the so-called process model, all radiological main and partial tasks are presented dynamically, where the tasks are linked with the information, see Fig. 1. After this the working processes can be transferred to information technology systems and related to persons.

The acquisition and understanding of all radiological processes before and after the introduction of systems to automate the workflow helps users during the change and is the basis for future process optimization.

2.3 Control Information - Basis of efficient workflow management

The complete working process is controlled and monitored by some relevant basic information:

- subsequent process steps will be dictated by the construction of flexible, sortable workplace lists on RIS-PC's, modalities, workstations or viewing stations
- after completion of individual work processes the various status information is collated throughout the system. This gives the people involved the decision base for the following work process.

Examples for control information are:

- from the point of view of the examination: "Exam requested", "Exam scheduled", "Exam performed", "Exam quality checked", "Exam read", "Result dictated", "Result transcribed", "Result approved", etc.
- from the point of view of the patient: "Patient admitted", "Patient arrived", "Patient examined", "Patient left", "Patient discharged", etc.

The more completely this information can be exchanged between the systems involved and made accessible, the more efficient is the departmental operation.

3. EFFICIENT DATA AND WORKFLOW MANAGEMENT BY SIENET®

Siemens as the world-wide leading PACS-supplier offers networking and system integration expertise to enable intelligent connections between RIS/HIS/workstations,

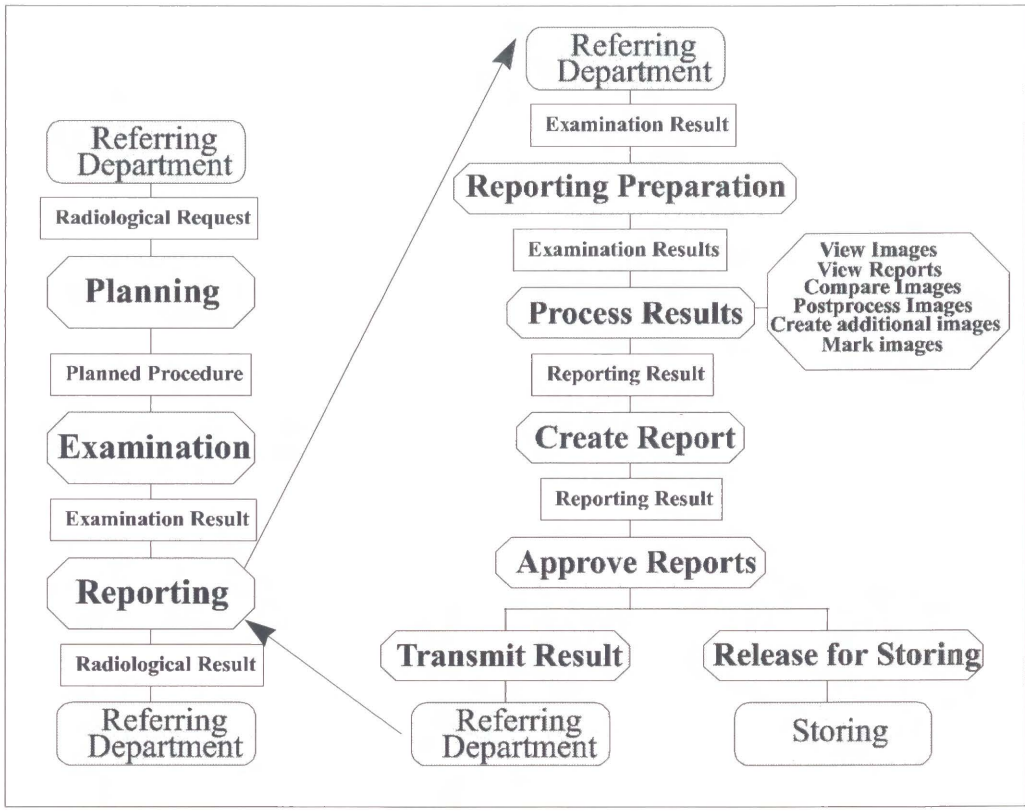


FIG. 1. Radiological workflow with detailed reporting sub-process.

archives and modalities from different vendors.

In the following sections some SIENET examples of data and workflow solutions are shown, these cover the areas RIS/PACS-integration, optimized workflow for softcopy reporting and intelligent image and report distribution [3].

3.1 Integrating different radiology and hospital information systems

The main functional emphases are on the bi-directional exchange of text-related medical data such as patient data, reports, worklists and the control of important processes such as prefetching of previous images and information about new examinations. Various interface protocols based on DICOM, HL7 or project solutions are used to connect as many RIS systems as possible, Fig.2.

3.2 Optimized workflow at the reporting workstation

The layout of the workflow at reporting workstations must meet the highest demands in order to offer the doctor optimal working conditions [4].

Reporting can be divided into three sub-processes:

a) Preparations for reporting

Three solutions are available for preloading old images:

- Each RIS can actively trigger prefetching, i.e., preloading images from the SIENET long-term store MagicStore to

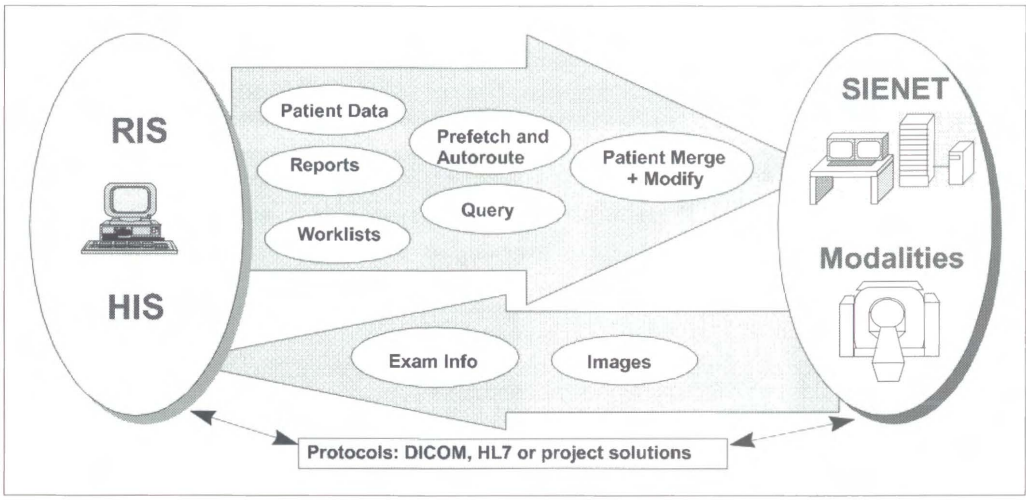


FIG. 2. Important RIS-SIENET connectivity applications.

the fast harddisk and further transmission to the reporting workstation.

- If a new examination arrives at a MagicView reporting workstation, previous examinations are automatically requested. Rules for each preloading event can be formulated depending on modality type, organ or period of time.
- MagicStore can also undertake prefetching and autorouting according to similar rules, after receiving a worklist from RIS.

The report is made available through the following steps:

- Automatic preloading the report occurs either automatically after receipt of new images or when actively released by the user
- the related report is shown next to the images if a study related identification number is present on the images. If the assignment is equivocal, then all the patient's reports are offered.

b) Softcopy reporting

- The user should only see those functions which are required for reporting: Doctor and examination dependent MagicView Tool cards can be easily generated, Fig. 3.
- The really relevant information about the examination should be shown on the monitor: a user dependent construction (what will be shown) and the flexible sorting of the workplace lists (via various criteria like modality type, organ type, physician, disciplines or location) are the basis for this. Over and above this, local worklists (workstation dependent) or shared worklists (location independent) can be configured.
- Automatic arrangement of image series on the monitor: monitor division is automatic depending on type of modality and number of examinations to be opened.
- Combination of individual, repetitive operating steps: compilation of macros from all functions available produces enormous time savings.
- Other doctors are informed about the reporting status when selecting the report status of the study (e.g., new, pre-

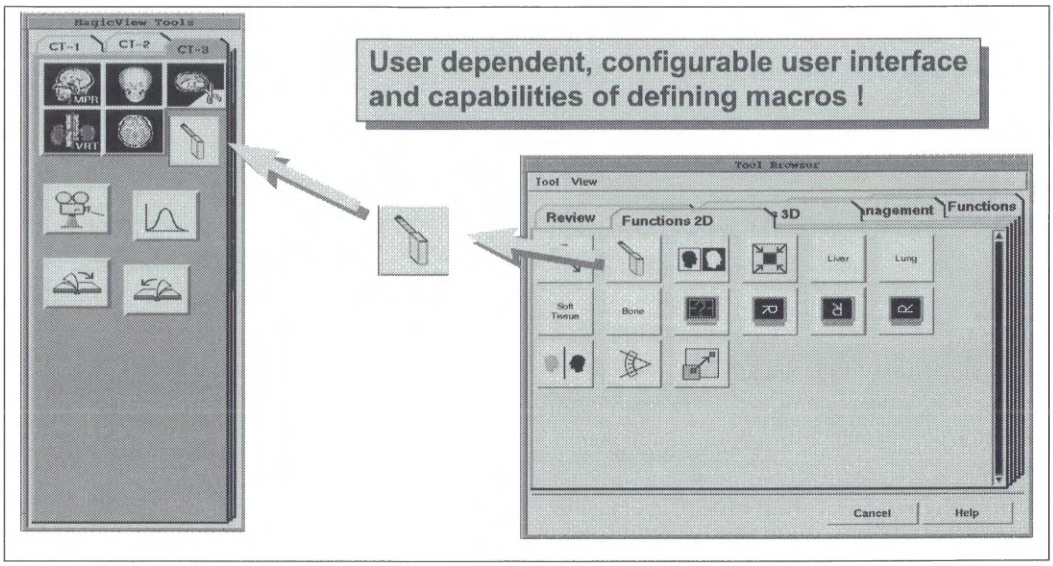


FIG. 3. Flexible structure of toolcards.

pared, reported, signed off, transcribed).

c) Report postprocessing

- Examinations from the MagicView can be distributed to any destination depending on configurable rules: MagicView can send images automatically depending on the ward information from RIS. In addition, the data flow can be controlled automatically in compressed/uncompressed form, depending on the examination status (e.g., study new, prepared, reported, signed off, transcribed).
- The SIENET multimedia report provides quick and complete radiological information to clinical areas. For fast report transmission, it combines images, written text and digital voice recordings with dynamic annotations.

3.3 Optimized data and workflow for image distribution

The radiological results should be sent back to the referrer as soon as possible after completion of the examination or report. Various possibilities for efficient image distribution are available:

- SIENET MagicServe is an intelligent distribution service in and outside the hospital. Depending on the respective modality type or selected organ, compressed or uncompressed images can be routed to many working places with DICOM-receive capabilities. Every source of images can call on this service.
- Constructing ward servers allows the results produced daily to be exchanged between the reporting workstations and the clinics and or referrers.
- The RIS can also initiate prefetching and autoroute images to the viewing consoles, Fig. 4.

4. EXPERIENCE GAINED FROM SIENET INSTALLATIONS

SIENET has been in successful clinical operation, world-wide for several years. The

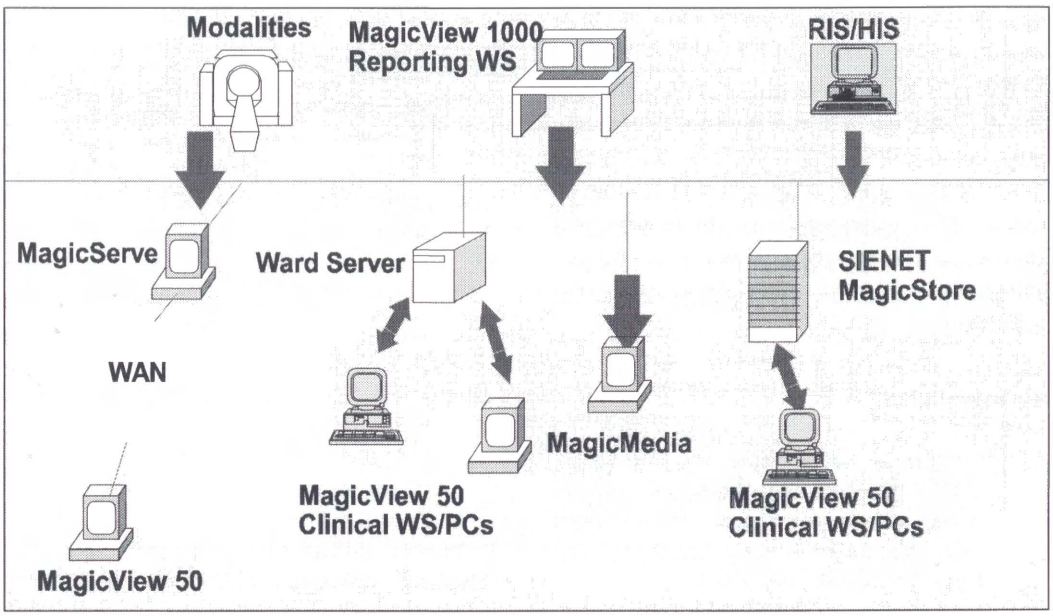


FIG. 4. Examples of SIENET Image Distribution Solutions.

Integration Functions	In operation / implementation
Softcopy Reporting	100% / 100%
Worklists (RIS-Modality-Interface) Display of Reports on MagicView	88% / 92%
DICOM-based Integration Image Distribution	29% / 62%
Prefetching and Autoroute	18% / 85%

Percentages based on 30 out of 250 major SIENET installations

FIG. 5. Usage of important SIENET workflow-related functions.

technological requirements exist to adequately fulfil the demands of radiology. The wish for the increased integration of various systems can be seen from the continuously increasing number of projects. Fig. 5 sheds light on selected SIENET installations or projects as to the extent of the integration of important functions.

5. CONCLUSION

The basis for the workflow is the total inte-

gration of all systems. DICOM and other standards supply a good foundation for this, however, interoperability has to be improved. SIENET offers various solutions for optimal dataflow and workflow which can be routinely applied in many departments today. The efficiency of all radiological processes can be greatly increased by the consequent analysis and conversion of the workflow.

REFERENCES

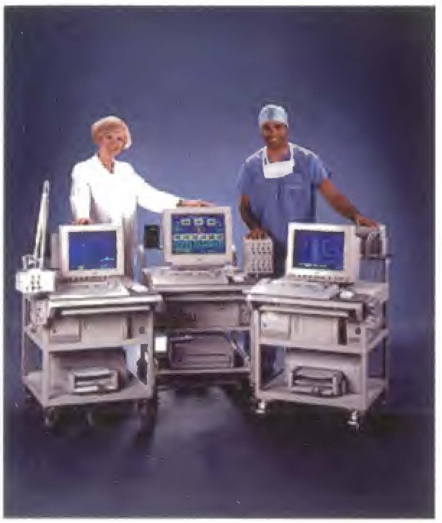
1. Gnoyke H, Offenmüller W, Thieme R. DICOM/MEDICOM Standard supplements for the integration of modalities with information systems and IMAC systems. Proc CAR 1996, Paris.
2. Offenmüller W. Managed workflow between HIS, RIS, Modalities and PACS: Now - with DICOM and beyond? Proc SPIE 1996; 2711: 144-55.
3. Haufe G, Jakob R, Northrup S. PACS at work: A multimedia e-mail tool for the integration of images, voice and dynamic annotations. Proc CAR 1996, Paris.
4. Morin RL, Berquist TH, Rueger W. The Mayo Clinic Jacksonville Electronic Radiology Practice. Proc SPIE 1996; 2711: 384-93.

Reference: Offenmüller W, Wirsz N, Wirsz E, Gnoyke H. Efficient workflow management for radiology In: The Danish Society for Biomedical Engineering, ed. Aspects of biomedical engineering in Denmark. Copenhagen, 1998: 147-54.

Notes

JUDEX

- specialists in Electrodiagnostics



The legendary Nicolet Viking provides full capabilities in EMG and Evoked Potential testing, with unparalleled features for intra-operative monitoring. High performance and unmatched advantages have made the Nicolet Viking a consistent leader among electro-physiological systems.
Nicolet offers a large range of products for the electrodiagnostic area: EMG, ENG, and Evoked Potentials testing, Digital EEG and video, and Transcranial Doppler.
Judex is your Nicolet representative in Norway, Sweden and Denmark.
To complement the high performance products offered by Nicolet, Judex offers a full line of quality electrodes and supplies.

The Magstim Company is manufacturing a large range of Magstim® magnetic stimulators and Neurosign® intra-operative motor nerve monitors. Judex is your Magstim representative in Norway, Sweden and Denmark.
Ellipse urodynamic workstation and AUDACT urodynamic evaluation software are manufactured by Andromeda. Judex is your Andromeda representative in Sweden and Denmark.

Judex is manufacturing two systems for analysis of sleep and sleep-related respiratory disorders: Nightingale and RespTrace. RespTrace is a dedicated, one patient system, fully equipped with amplifiers, oxymeter and software for sleep and apnea analysis. The Nightingale is a modular system which can be configured after your needs: 1, 2, or 4 patients simultaneously recording, sleep and apnea analysis, video registration, EEG spectral analysis, etc. Nightingale and RespTrace are sold world-wide through representatives.

NIGHTINGALE

Special solutions in electrodiagnostics or in the area of medical information technology are developed by Judex on request.

More information is available at our Homepage: http:\\www.judex.dk or contact the sales department: sales@judex.dk.

Lyngvej 8, DK-9000 Aalborg, Denmark

Phone: +45 98 18 69 00, Fax: +45 98 18 80 19

JUDEX
DATASYSTEMER

ISBN 87-987005-0-2