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VISIT TO THE UNITED STATES, SPRING 1974

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UTLÅNAS EJ

VISIT TO THE UNITED STATES, SPRING 1974.

P. Hagander

ABSTRACT.

This report summarizes experiences and impressions during a stay in the United States 740203 - 740824. The research in biomedical engineering was studied, especially the computer and control applications. One month was spent in Tucson, Arizona, and the rest of the time in Los Angeles at the departments of Anesthesiology and Systems Science at UCLA.

## 1. INTRODUCTION.

During the period 740203 - 740824 I visited the United States to study and participate in interdisciplinary research projects between Medical or Biological departments and Engineering departments, mainly in the area of Control theory. Thus I studied microcirculation, pharmacokinetics and cell cycle kinetics one month with prof. Gross in Tucson, Arizona, aiming at the control of chemotherapy of cancer. I got a very good survey of the status of the field, and I also went into the cell cycle kinetics with some depth. During five months I participated in the research on the human respiratory controller at the departments of Anesthesiology and Systems Science, UCLA, California.

I also made a number of visits to other universities and research companies.

In order to summarize my main impressions I want to emphasize the resources available for interdisciplinary work. Although the administration "red tape" seems to be of the same dimensions as in Sweden the university structure is flexible enough to create faculty positions that are joint between different departments. Much research money is going to such nontraditional areas. The computer and laboratory facilities are extensive but both students and faculty have often limited experience of numerical work. They usually get it only during their thesis work, and I did not see any department with their application programs collected into a library. There is obviously little meritation in computer programming. The conventional libraries were impressing. The coverage of conferences, journals and books seemed to be almost complete both in the medical and the technical areas.

The number of bioengineering courses given by different departments are extensive. However, there are great difficulties for a PhD in bioengineering to get an adequate position, and the program at UCLA therefore requires that the student has his major in a traditional area and only has his minor and the thesis in the biology area. Many people think that the BSc in bioengineering has better possibilities at the job market. On the whole the American course system is very flexible and consequently often less job oriented.

The work was made possible by scholarships and grants from the Sweden-America Foundation, the Swedish Natural Science Research Council, the C-B Nathhorst Science Foundation, the E Lundström Foundation, the Swedish Royal Academy of Science, the University of Lund and the University of California. To all these institutions I want to express my sincere gratitude.

## 2. UNIVERSITY OF ARIZONA, TUCSON.

During the period Feb. 3 to March 3 I visited University of Arizona in Tucson. At the invitation of Prof. J.F. Gross in Chemical Engineering I followed his 2 h/week course in Bioengineering and studied his research work. I also made a number of visits to other departments. My own research resulted in a stochastic cell cycle model.

### Bioengineering Program (B Sc, M Sc, Ph D).

No formal curriculum exists in Bioengineering of University of Arizona. A number of participating departments provide a bioengineering option in their usual degrees. Supporting course work from the biological sciences is also recommended, and interdepartment research projects are going on between the Colleges of Medicine and Engineering. The BSc and MSc programs are intended also to be preparatory for the medical school, although the students seem to have some difficulties at the interviews. The participating departments have slightly formalized discussions to control and inform about the courses offered.

The bioengineering course at Chemical Engineering are taught by prof. Gross and mainly devoted to microcirculation, i.e. the flow and mass exchange in the capillaries.

### Research fields of prof. Gross.

Apart from a background in fluid mechanics and flow patterns around airplane wings, the interest of prof. Gross was concentrated in three fields: microcirculation, pharmacokinetics and cancer cell properties. Before he came to U of A in Tucson (Dec., 72) he was at Rand Corp., for

which company he is still consulting.

Microcirculation: Prof. Gross has written a number of papers on microcirculation. One is dealing with the role eddies between red blood cells in the flow through the smallest capillaries. This work relates to the work by prof. Loman in the Math. Department (see below). Then he has written about the pulsatile flow in the microcirculation, and he has made a survey paper together with Dr. J. Aroesty at Rand.

The field is also the main interest of the Physiology Dept., and during my stay they submitted (and later got approved) a 5 year joint project proposal on the regulation and exchange in the microcirculation.

An MSc student, David Reisdorff, is working with the problem of regulation of the flow in the small blood vessels.

Apart from the papers mentioned above I have notes from the bioengineering class and from discussions with prof. Gross. The field is especially interesting, if these micro models can lead to organ models (cf. the MAS project). The basic theory is well described in a book by S. Middleman, Transport Phenomena in the Cardiovascular system (Wiley, 1972), especially the Chapters 3 & 4.

The class of models dealt with are inherently partial differential equations, but under different simplifying approximations usual systems of coupled first order ordinary differential equations result. Unfortunately they are often nonlinear, particularly in the portions describing the pressure regulation.

Pharmacokinetics: There are mainly two approaches to pharmacokinetics applicable in different contexts. First there is the school with Wagner as a typical example. They build models that simulate the blood plasma levels of the drugs, and then try to relate effect of the drug mainly to these plasma levels. Sometimes those models contain compartments that are called by organ names but not necessarily reflect more than a gross behaviour, but sometimes they are combined with better models for some specific portion of the body, where a side-effect is of special importance. The models are verified by comparison with blood samples and sometimes samples from the critical organs. These measurements are therefore usually done in man.

J. Gross has been dealing with the other approach. A fairly detailed organ model is set up, where organ sizes and blood flows are typical parameters, so that the model can be adjusted to individual differences. The models are verified with animal experiments. A main assumption in the models is that the distribution of the drugs is flow limited, i.e. all diffusion within the organs is immediate. This kind of a model is usually called the Bischoff-Dedrick model after two of those who first obtained such a model in 1971. J. Gross worked with the models at RAND, and simulation was one of the main tools. An interactive simulation package for biological systems was developed there, BIOMOD (see below), which obviously facilitated the work very much. At Tucson it was continued mainly by a MSc student, Oen Nelson, who did batch simulation on their CDC machine. A terminal system was under construction based on a new PDP 10, to which probably a number of Tectronix terminals would be hooked up.

I had a number of questions to their models. First of all the verification problem. The final slopes in the logarithmic impulse responses of each measurement signal indepen-



dently determines some key parameters - the distribution ratios, and then flows, volumes, metabolism, excretion and so on are determined separately. But this does not give correct models! After that the parameters are scaled to represent man instead of an animal and the differential equations are solved to get the impulse response. The blood curves are then compared with measurements from man. Some problems with the integrations occurred because of oscillations in the system. They could not directly explain why, but they were fairly sure, that the main reason was a high affinity of the drug to the lung tissue, and the fact that the input was given intravenously. The drug was stored in the lung when the plasma concentration was high initially, and when the blood came back on its next round it received quite a lot again. It should be noted that the circulation times are assumed to be negligible, no delays, only time constants. In fact, the oscillations are inherent in flow systems with recirculation and no diffusion limitation or time delays, and it is easily demonstrated for a three tank system with recirculation (cf. KJA, Notes on identification).

The work also continues as a project together with RAND and Clinical Pharmacology at USC in Los Angeles. The main effort is concentrated at the cancer drugs as bleomycine and cytosine arabinoside (ARA-C).

I discussed with prof. Gross the possibilities to get some measurements from a certain patient that might be used to update the current parameters. Such a philosophy was suggested in a paper by Sheiner et al in Comp. and Biomed. Res. 1972. We also discussed some papers by Bellman et al in 1960 on the possibilities to get organ models from micro models. Similar models are described by Padgett and Tsokos in Math. Biosci. (1970). I also got a computer program from Rand with about 20 state variables.

Cell kinetics: The next question to be answered in order to get hold of the optimal dosage problem is the question of effect given the drug concentrations. In this area some results have been obtained by prof. Gross. At Rand they developed some preliminary models describing the effect of ARA-C on the bone marrow. The model is theoretically plausible but not quantitatively useful. The problem is that the drugs have their effect on a cell only during certain stages between its divisions. It might also happen that the drug stops the transfer of cells into susceptible stages. This means that the therapy should be intermittent in order to be as effective as possible. A couple of models are available in the literature to describe the cell cycle kinetics: Mauer et al, Baserga, Aroesty, B. Jansson and many more. Some of these are very difficult to interpret and for instance the one by Mauer et al is a discrete event simulation model, which means that a substantial number of simulations must be performed to get an estimate of the mean behaviour. It is also difficult to be able to conclude the sensitivity to the different parameters and possible controls, and consequently to do any identification. I got copies of a number of such papers.

Another difficulty is the absence of reliable measurements. For leucemia it is possible to get blood and bone marrow counts but for solid tumors even the size might be difficult to obtain. The survival rates is the most common quantity but recently it has become possible to measure some polyamines that might have some relationship to tumor growth (also Zoophysiology in Lund: Heby, Andersson, Agrell). Another complication is that the blood vessels are sometimes quite different in tumors. I got a couple of papers by Warren describing the morphology in certain tumors.

Own research.

The current models for the cell cycle kinetics did not appear to be well adapted to control purposes. In order to understand the properties of mainly the Mauer model I reformulated the single event simulation model, and I represent the number of cells in each stage during the cycle instead of representing each cell during its way through the cycle. By restricting the residence times in each phase to be one of say three or four, i.e. assuming a three or four point distribution for the residence times, and by having these times as multiples of a basic time step say two or five hours, it was possible to formulate a fairly high dimensional (n=100 or more) discrete time model, that could very easily be solved by iteration. The model is linear, and since the residence in a phase mainly consists of a delay chain, it is very easy to describe the recursion in Fortran and the computations are faster than if a big A matrix would have been formed, and a matrix vector multiplication would have been performed in each step. It was also possible to get a covariance equation. The state noise covariance is dependent of the mean value, but linearly, and the covariance equation is linear with the same dynamics as the system. The number of cells grows exponentially and the coefficient of variation approaches a constant value, which is a linear function of the initial cell distribution. The model has a number of advantages: it is first of all very fast to simulate. It also makes it possible to do some sensitivity analysis and to include controls like drug concentrations as changes in parameters. The model contains only a limited number of unknown parameters, which ought to be possible to estimate from the limited number of measurements possible to obtain using the autoradiography method with Thymidine labelling. I have performed a number of computer simulations and prepared a preliminary version of a report describing the model.

Visits to other departments of U of A.

Prof. Sidney Yakowitz, Systems and Industrial Engineering: Control is taught at many different departments in U of A. This is the department where prof. J. Casti worked before he went to Vienna. Prof. Yakowitz is currently working on projects in the water resource area, and mainly interested in identification and model building. In the past he has written a book on stochastic approximations, and he became very interested in the work by Lennart Ljung at Lund. He has also written papers on error bounds for discrete and continuous systems due to quantization errors. He has also a paper on non parametric Bayes decision theory (in all 7 reprints).

Prof. D.O. Lomen, Department of Mathematics:

Prof. Lomen is one of the members in the bioengineering committee. His background is from the aerospace industry, where he was solving fluid dynamics problem using partial differential equations. Since he came to Tucson a couple of years ago, he has been working on bio problems and especially the squeezing of red blood cells through the small capillaries (ref. Brånemark Gbg). By assuming some elasticity the stresses and the drag can be calculated. The influence of the  $O_2$  content in the cells is important (ref. Lighthill, Cambridge, Engl.), and singular perturbation theory is used since some parameters are small. A second interest is the diffusion in the lung. He is working together with R. Schroeter at Imperial College, London. Cough triggering and local regulation of respiration are studied concepts. He also calculates the lowest  $O_2$  concentration point from the alveole through the blood vessel to a lung muscle cell. If possible, closed expressions are derived and evaluated on a computer.

He is also involved in different aspects of the water resource projects.

Prof. Robert O'Malley, Department of Mathematics:

Prof. O'Malley's main interest is the singular perturbation theory ( $Ay^{(4)} + y^{(2)} = u(t)$ ,  $A$  goes to zero), and its applications to optimal control theory. He is collaborating with Cruz, Perkins and Kokotowitz at Urbana Illinois. Some results require reduced order Riccati Equations, and the uniqueness of the solutions to the algebraic equations is an interesting question.

Prof. H.A. Kamel, Aerospace and Mechanical Engineering:

Prof. Kamel is responsible for the interactive programming done at a PDP 15 mainly for finite element analysis and other problems in ship construction. The set up seems to be fairly similar to the one in Lund, but contains also a graphic pen display console. A communication link (slow) with the PDP 10 is also available. One of the programs they had developed solved the hidden line problem, so the display of three dimensional shells was very impressive (4 reprints).

Prof. T.L. Vincent, Aerospace and Mechanical Engineering:

Tom Vincent deals with two different areas: modelling of predator pray systems and collision avoidance using game theory. He has applied optimal control to the Volterra equations in different forms and describes optimal policies for fish harvest for instance. The courses in control are mainly optimal control and no statistics at all. The Volterra models would be good examples for the nonlinear courses (4 reprints).

Prof. P. Johnson, Department of Physiology:

I had only brief discussions with prof. Johnson. He showed me around the lab and I commented a PhD thesis, that he supervised, by a student in nuclear engineering.

Prof. R. Gore, Department of Physiology:

We discussed the measurement equipment available at the lab for instance for the occlusion experiment (similar to the one at Pharmacia - K.E. Arfors). We also discussed the background and experimental verification of the different theories for the regulation of flow in very small vessels. The myogenic control seems to be on a lower hierarchy than the metabolic part of the control action. The metabolic factors probably changes the myogenic action and also the vasomotor activity, frequency and amplitude modification. The pressure measurements are very difficult, especially the tissue pressure and the various osmotic pressures. The isogravimetric method is considered doubtful in some respects. He also stressed the differences between the studied tissues: basal membranes and epithale in mucosa or mesenterior. He emphasised the important work by Zweifach and Intaglietta. Prof. Gore designs and builds much of the equipment himself mainly using integrated circuits commercially available.

### 3. UNIVERSITY OF CALIFORNIA AT LOS ANGELES.

At the invitation of prof. Don Wiberg and prof. Jay Belleville I visited UCLA during the period 5/3 - 7/8, 1974, and I participated in the joint work between the departments of Systems Science and Anesthesiology on the control of respiration. Prof. G. Swanson has a joint appointment as professor in the two departments. A lot of other interdisciplinary work is going on at UCLA: the Crump fund, the bioengineering course work and so on.

The main purpose with the time at UCLA was to get involved in research collaboration between medical and engineering departments. Part of my work has been that I transferred, modified and tested a program for identification of non-linear dynamic systems.

#### Courses in bioengineering at UCLA Spring Quarter 1974.

Triggered by the donation from Ralph Crump, a former student from UCLA, who has made a fortune in biomedical instrumentation, a fairly extensive bioengineering work has evolved at UCLA. At the department of Systems Science prof. G. Swanson gives a course containing some nice material on modelling and identification with examples from the respiratory system. It also contains a number of guest lectures and a project work. At the department of Engineering Systems prof. DiStefano conducts a number of courses in biosystems both at the undergraduate and the graduate level with a main emphasis on the endocrinological systems. He is also head of the bioengineering program and administrates some survey courses where the different departments doing bioengineering research present themselves. Apart from these courses the medical program have a number of courses that are usually attended by the bioengineering

students, like the Physiology course and some of the Biochemistry courses. I got a preliminary copy by DiStefano describing the bioengineering program. I attended the course by prof. Swanson, in which I also gave two lectures. The part of the physiology course that dealt with the respiratory system was lectured by prof. Whipp, and these lectures gave me a good introduction to the research going on in the respiratory field. I listened only to a few of the lectures by prof. DiStefano. There were a number of guest seminars that I attended: by prof. Lions, prof. Frick, prof. Bar Shalom, prof. Kaniel, prof. Kallinpuru, and in most cases I had the opportunity to discuss with the lecturers.

Research by the respiratory group at UCLA, Anesthesiology.  
J.W. Belville, G.D. Swanson.

The respiratory group was formed around 1972 by prof. Belville, who came from Stanford at the invitation of the new department chairman Dr. Ron Katz. The department of Anesthesiology was undergoing a total course change towards research, and the number of faculty was increased from 6 to 20 in two years. Dr. Belville is apart from being an MD also a Chemical Engineer and has a deep interest in electronics. He has for instance developed a special purpose analog computer. The respiratory group has a close connection with the department of Systems Science, by the way one of the conditions that Dr. Belville had for coming down from Stanford. Thus there is a joint assistant professor between the departments: Dr. G. Swanson, and prof. D. Wiberg at Systems Science are participating in the work too. Two PhD students in Systems Science, Denham Ward and David Michels, are working at the laboratory.



The background to the research is the need to study the respiratory effects of analgesic and anesthetic drugs. Many drugs are respiratory depressing, one of their main side effects. A classical way of quantifying the drug effects on the respiratory controller is the so-called re-breathing technique. This is the "production method" of the lab. A bag is charged with  $O_2$  and some  $CO_2$ . The subject is breathing in this gas mixture for about 10 minutes, and his ventilation as well as his end expiratory  $CO_2$  concentration (= arterial concentration) are measured. From a plot of ventilation versus  $CO_2$  concentration the shift at a ventilation 20 l/min of a regression line is a common measure of the respiratory effects.

From control point of view this experiment shows some ramp response, and the measure is the change in gain under the assumption of equilibrium. The controller is, however, not in equilibrium. The end tidal measurement and the ventilation are calculated by a special purpose analog computer, and a PDP-8 is used to collect and analyze the results.

Another method is developed to take the dynamics of the controller into account: the so-called "dynamic forcing" technique. Using a breathing chamber, where the  $O_2$  and  $CO_2$  concentrations can be manipulated, and the end tidal measurements the arterial blood concentrations can be forced to follow certain wave forms using a digital servo, and good estimates of the controller performance can be obtained. In earlier experiments the inspired concentrations had been the input, and the slow dynamics of the rest of the body had hidden some of the controller properties. The configuration is shown on Fig. 1 and Fig. 2.

Based on such experimental data Dr. Swanson had done modelling at Stanford. Many controller models are described in the literature, but few are verified by data, and there

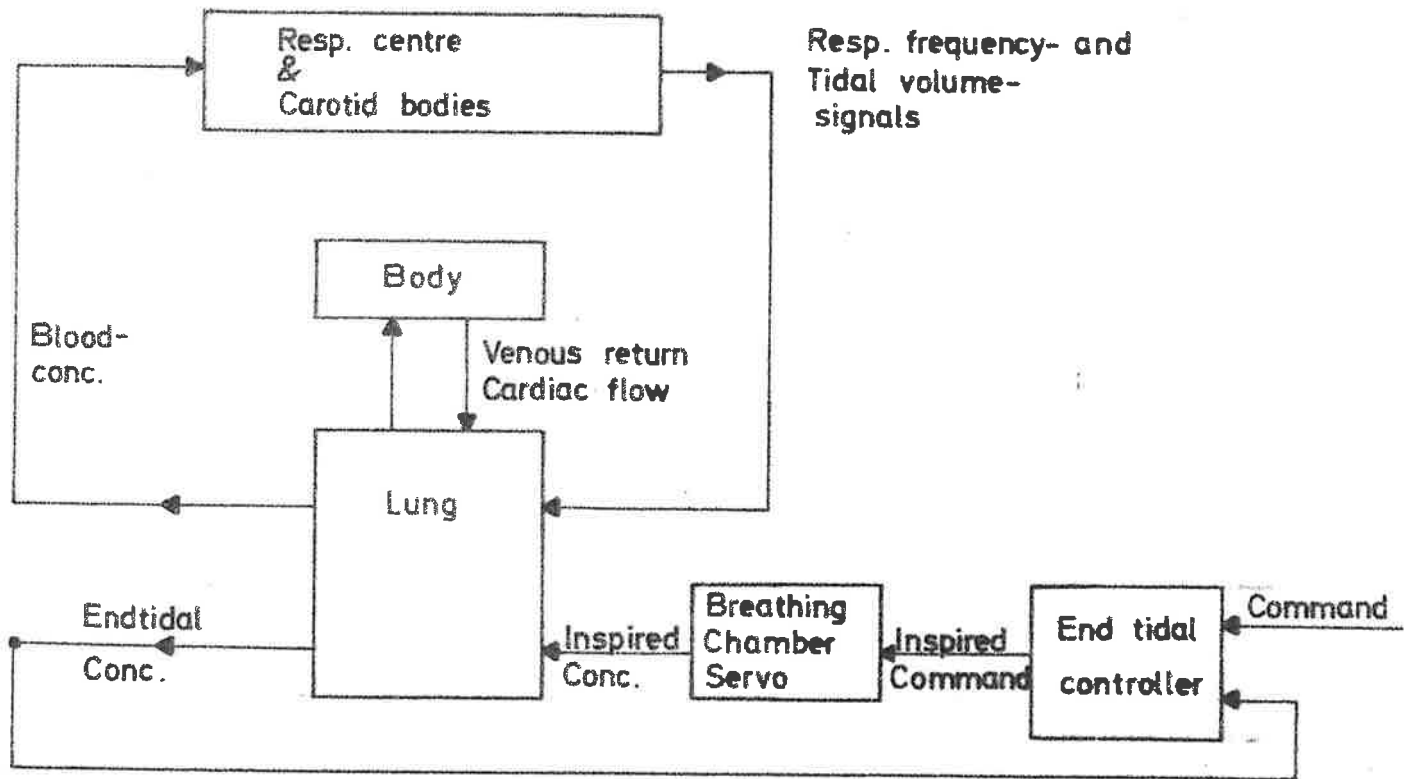


FIG. 2

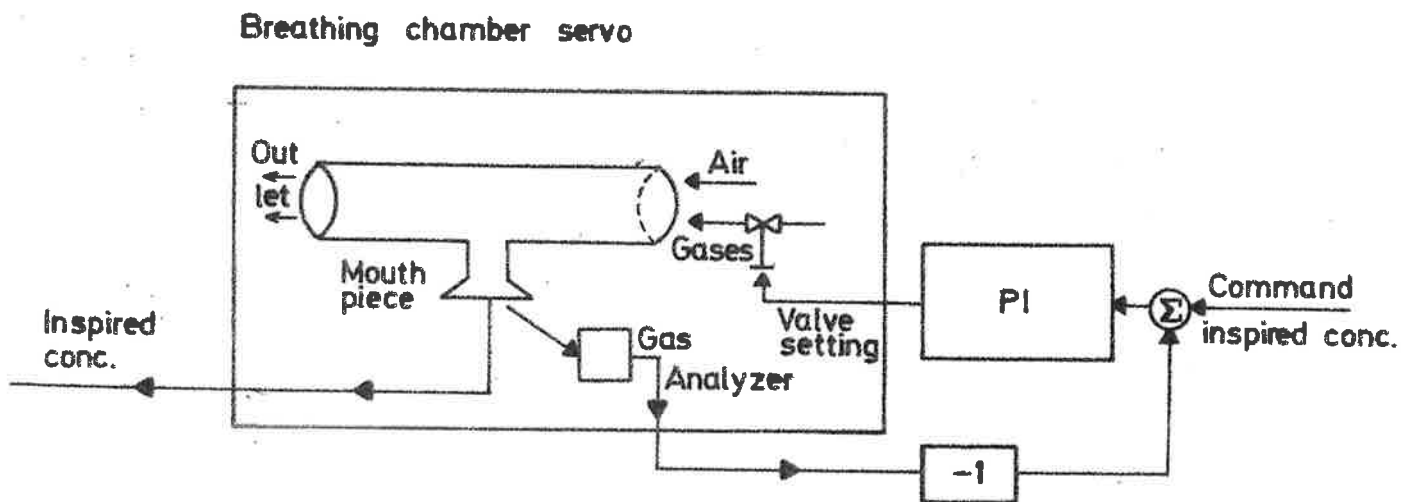


FIG. 1

are a lot of controversies both on the receptor sites and especially on the quantitative effects of various receptors.

My work in the group has mainly been in this model building sector. A number of different models have been discussed in relation to the possibilities of experimental verification.

I also implemented an identification program for nonlinear systems allowing unequal sampling rates on the Campus Network IBM 360 computer. The interactive usage through terminals was of great importance, but the graphic output on the terminals was unfortunately of bad quality, so I had to make the plots on a Calcomp plotter as batch jobs with a quite long turn around time. During my stay the lab bought another PDP-8 and a Tectronix 4010 terminal. Together with their older PDP-8 with changeable disc this made their configuration powerful both for data collection and program development. Most programming was done in FOCAL because their FORTRAN was not extended to include real time handling. The immediate execution after changes also facilitated the program writing. An observation is that the big IBM machine does not have paper tape input, so the communications between the computers had to go through another DEC installation with changeable disc and an IBM compatible magnetic tape station.

The identification results are in good agreement with the somewhat more ad hoc results by Dr. Swanson at Stanford, and his input was according to simulated data reasonably close to the optimal one for hard constraints on the input and the experiment length limited to 11 minutes. The bilinear parameters describing the change in cerebral blood flow are naturally the most difficult to obtain, and there are several local minima. Since my routine uses the analy-

tic second derivative I also encountered some difficulties with saddle points.

Although the data is described very well by these models it is dangerous to try to distinguish between all hypothetical models. It is, however, possible to exclude a number of possibilities. George Swanson and I plan to describe some models in a joint paper.

The work on the dynamic forcing is currently basic research, but the aim is to distinguish between the effects of different drugs in their dynamic responses and maybe conclude something about their site of action.

Another basic research question that recently has drawn the attention of the group is the respiratory control under exercise, and in connection to this the possible role of neural dynamics. The latter is the topic of the thesis by Denham Ward.

Research interests of Prof. A.V. Balakrishnan.

From the starting point of the IFAC Hague paper we discussed prof. Balakrishnan's new way of representing dynamical systems with a finite number of inputs and outputs. It is possible to find an infinite dimensional state space representation, that essentially is all future outputs, if no control or noise. This representation is controllable (but not observable), and the C-operator is unfortunately both unbounded and unclosable, so one has to be careful when formulating the Riccati equation with adjoint operators. Another way is the one of the Hague paper where the state space is a little modified and the C operator bounded. However, the important feature is that with this formulation it is never necessary to introduce infinite dimensional noise, even for noise without a rational spectrum. Still this is a question of interest to prof. Balakrishnan. He does not hesitate to introduce infinite dimensional white noise (with the identity as covariance operator), even if it is infinitely additive only after the noise has gone through a dynamical system, i.e. a bounded operator. Another topic of interest is the formulation of a theory around band limited white noise. Much of prof. Balakrishnan's current work is centered around ideas from the work on flight control in turbulence.

Research interests of prof. D. Wiberg, Systems Science.

The control of partial differential equations, also with boundary control and noise, constitute the main interest of prof. Wiberg. He has a number of examples of how the optimal closed loop system modes are a better basis for a finite dimensional approximation, than the usual approximations of the open loop system. He also has a nice treatment of equations where a coefficient operator in

front of the state derivatives might be singular, i.e. some modes are instantaneous. He recently became involved in the respiratory group formed by prof. Belville in Anesthesiology.

Research interest of prof. J. DiStefano, Engineering Systems.

Prof. DiStefano's research activity is concentrated in the bioengineering area and endocrinological systems in particular. Since the physiological knowledge of those multivariable systems is quite limited, identification of the dynamical parameters has been his main tool. To some extent he has been forced to use new methods for function minimization because the few data he has introduced multiple minima of the loss functions. Direct search has been found to work very well. The question of identifiability has also been treated. Many experiments made are inherently linearizing tracer experiments, and the question of design of such experiments to obtain unique estimates of parameters in the underlying nonlinear systems is very important. I had thorough discussions with prof. DiStefano on this subject and suggested modifications in a paper he was preparing. We have also plans for a joint paper.

Visit at Harbor General Hospital, Torrance.

Substantial research activity is going on in the respiratory group at Harbor General Hospital, which is affiliated to the physiology department at UCLA. The group is lead by profs. Wasserman and Whipp. Their special interest is the interaction between the control of respiration and the control of cardiac output, or stroke volume and heart frequency. A number of papers emanating from this group appeared in J. Appl. Physiol. during the recent years, advocating that much of the respiration is controlled secondary to the cardiac output. Their data analysis is done using a small computer, and a PhD from USC is employed to do the more system oriented parts of the work: Dr. Kasaburu. A striking fact was the admiration for the work by prof. Wigertz and by prof. von Euler. The computer is also used in the clinic for pulmonary function tests, as part of the clinical physiology department.

Visit to Department of Biomedical Engineering USC.

The Department of Biomedical Engineering offers a number of programs. The main degrees have been PhD or Master in Biomedical Engineering, but there is also a possibility to have biomedical engineering as a major in an electrical engineering PhD. During the last year a bachelor program has also started. It is a common opinion that the need for people with a lower degree is much higher than the need for PhD:s, who currently have great difficulties to get jobs outside the research and educational institutes.

The department is with respect to its research divided into three groups headed by the professors Grodins, Yates and

Bekey. Prof. Bekey is working on hospital administration systems as well as in identification, his earlier field of interest. Prof. Yates leads the group on Metabolic Systems, which mainly studies hormonal systems using statistical thermo dynamics and nonlinear mechanics, using for instance coupled oscillators to describe the FFA-Glucose system. Prof. Grodins is currently interested in basically two areas, both in connection with respiration: The control of the breathing pattern as an adaptive system that minimizes the work of the respiratory muscles, and in connection with this he investigates the distribution of the ventilation and perfusion using washout of  $N_2$  both from impulse responses and PRBS responses. The results are presented as the mean and the variance of the time constants or the moments of the impulse response curve. The second field is the cardiopulmonary coupling in the control of breathing during exercise. The work is done together with prof. Yamashiro, one of the first students from the biomedical engineering program at USC. Dr. Daubenspeck has done work on the response to inspired  $CO_2$  concentrations before and after denervation of certain critical nerves in order to assess the quantitative importance of the different portions of the respiratory controller.

Visit to Laboratory of Nuclear Medicine and Radiation Biology at UCLA.

The main research interest of prof. Z.H. Cho is image reconstruction of X-ray pictures. Both 2- and 3-dimensional pictures are processed using a small computer and semiconductor cameras. Both the statistical aspects of the linear superposition from different camera angles and the problem of the design of the semiconductor elements for best possible signal to noise ratio are considered. In the



latter field prof. Cho collaborated with prof. P.A. Tove from Uppsala, that I also met at the lab. Prof. Cho has been working in Stockholm for a number of years. I also got a short survey of the work going on in tracer analysis.

#### Visit to Measurex Corporation, Cupertino.

At Measurex Björn Wittenmark and I met: Dave Stepner, Al Shaikh, H.G. Wells, Eric Dahlin and Bill Robinson. Measurex delivers dedicated systems mainly for the paper industry but also for the control of textile, plastic, metal and tobacco plants. We saw their new System 2000 built around an HP computer. The operator console uses a four colour TV monitor and push buttons to select different display frames, on which certain parameters can be changed when needed.

They were very interested in adaptive control, and Nils Leffler, who was away trouble-shooting at one of their installations, had made simulations with STURE. Björn Wittenmark gave an informal seminar and answered a lot of questions.

#### Visit to Stanford University, Department of Electrical Engineering.

Together with Björn Wittenmark I visited Tom Kailath's group. Prof. Kailath was ill, but we met him the next day at Systems Control. I discussed my work on operator factorization and unknown initial values for Kalman filters with him. He had some comments with respect to the problem with correlated measurement and process noise. He also emphasized the problem when a state space repre-

sentation is not available, only the covariance functions. At Stanford we met three of prof. Kailath's PhD students: G.S. Sidhu, M. Morf and B. Dickinson, and we mainly discussed the fast computation of Kalman filter gains without using Riccati equations. They had interesting extension to their previous results, that related to Choleski factorization and square-root filters. They were also interested in the problem, when the initial covariance approaches infinity. A somewhat surprising observation was that there is no real program library at the department, and the computational experience is quite limited. M. Morf was designing his PhD thesis using a sophisticated computer text-editing system.

Visit to Systems Control Inc., Palo Alto.

Together with Björn Wittenmark I met mainly Dr. Bar-Shalom, who told us about the company. It employes about 60 people with a PhD degree. The work is concentrated around military contracts although there is currently a trend away from those. Still it is mainly projects for government or state like waste water treatment and other urban systems. Björn Wittenmark gave a seminar about STURE, and discussed dual regulators with Bar-Shalom. We also met: Bob Larson, John Anton, A. Segal, N. Gupta, and Mark Davis (visiting from Imperial College, London).

Visit to Rand Corporation, Santa Monica.

My host at Rand was Dr. Mario Juncosa, a close friend of John Casti, who gave me a survey of the activities at Rand. The great emphasis on government investigation was changed and more work in other fields like biomedicine is going on. Dr. Juncosa had his main interests in Numerical Analysis, and he had been visiting prof. Fröberg in Lund a number of times. The computer centre was impressing especially the interactive facilities built around the Rand tablet, a hardware development from Rand. An interactive simulation package for biological systems was available. It had been used extensively by prof. Ed DeLand (currently at UCLA) and prof. Gross (in Tucson), the former in his work on the ion balance in the body.

The Joint Automatic Control Conference at Austin, Texas.

For me the conference was a slight disappointment. The standard of the papers was considerably lower than what is usually published in journals. This was especially true for the contributions in the bioengineering sessions, which I tried to cover when possible. Still, most of the control groups in the US were represented, and I had a number of interesting discussions with other participants. Karl Reid from Oklahoma State University had for instance some ideas for the control of ventilators, and prof. Whisler at Austin suggested interaction between the cardiovascular system and the temperature regulation, important in diving. An impression was that a number of mechanical engineers with a background in simulation and model building are trying to find biomedical applications for their companies.

The best presentations and the most interesting contribu-

tions were in my opinion found in an invited session on applications, where prof. Bryson described the work at Stanford on helicopter controllers. He gave a pole placement solution to the problem containing 18 differential equations. I got a copy of a paper with the assumed model explicitly stated. He also showed a film of a computer simulation showing the control of a helicopter carrying a heavy load in a long wire just a few meters above the ground. The film was part of a PhD work by Narendra Gupta. The preprints from the conference are available at the Division of Automatic Control, Lund.