MATHEMATISCHES FORSCHUNGSINSTITUT OBERWOLFACH

T a g u n g s b e r i c h t 9/1990

Mathematische Modelle in der Biologie

18.2. bis 24.2.1990

Continuing the tradition of (five since 1975) meetings on Mathematical Models in Biology at Oberwolfach the Mathematical Research Institute with its experienced staff and great facilities brought together a group of mathematicians, theoretical biologists, and other scientists interested in Mathematical Biology. Among the participants there were a quite large number of young scientists, and most fortunately, many participants had close connection to experimental work or field data.

The meeting has been organized by W. Alt (Bonn), U. an der Heiden (Witten-Herdecke), K.P. Hadeler (Tübingen). Among the various topics those related to physiology (Neurophysiology, Cell Biology, Microbiology) have been emphasized, although there were quite a number of presentations on population dynamics, ecology, and epidemiology.

On the other hand this meeting again showed the role that mathematics plays in dealing with systems of different scale and complexity on all levels of Biology (molecules, cells, organs, individuals, populations, communities, ecosystems, biosphere), e.g. the dynamics of the cell cycle and the dynamics of infectious diseases lead to related, though not identical mathematical problems. Epithelial growth has much in common with spatial organization of populations of microorganisms.

It would be impossible to review all contributions (see abstracts). We just list some of the fields covered in the meeting: Cell cycle, locomotion and orientation of cells, growth of tissues and spatial organisation, receptors, epidemics, in particular the concepts of basic reproduction numbers, competing species in ecosystems, stochastic systems, cellular automata models versus numerical methods, neural networks. Some further comments seem to be appropriate. The large number of participants reflects the increasing interest in Biomathematics for scientists from various fields. On the other hand this large number has exhausted the technical facilities of the Institute and it has required a smooth organization of various sessions and informal workshops. Of course the ample facilites of the library building are very much adapted to informal workgroups. In future meetings on Mathematical Biology the organizers should stay strictly within the traditional limits, perhaps by emphasizing a particular topic.

Fortunately in Mathematical Biology the interaction between mathematicians and biologists is increasing. As far as Oberwolfach conferences are concerned, the mathematical aspects will be emphasized: Mathematics which leads to better understanding of biological phenomena, Biology which leads to further progress in Mathematics.

Mathematical Biology in Europe is still a developing field, and apparently the growth rates are very different in different countries. It can be truly said that the development so far has been enormously furthered by the Oberwolfach conference, by the interaction of scientists from all over the world.

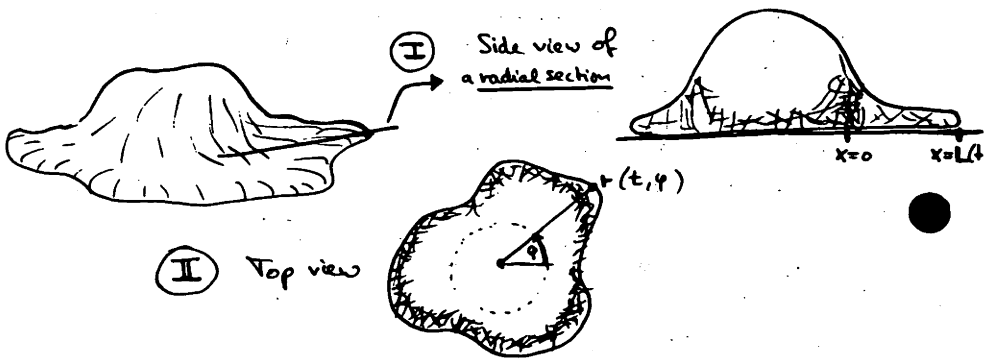
As a postscript we would like to mention that the recently installed computer facilities have been very useful, both for the organizers in producing the program and for individual participants presenting their simulations or working on joint papers.

Vortragsauszüge

Wolfgang Alt

Models for cell plasma motion and shape changes

White blood cells (in particular leukocytes) as well as various tissue cells, spread on a (glass) surface like a fried egg, show irregular protrusions and retractions of so-called lamellipods in all directions, as long as the cell stays unpolarized:



Responsable for the observed motions of the peripheral plasma membrane

surface is the interior hydrostatic pressure in relation to the (contractile) stress of the cortical actin-myosin filament network.

I: A one-dymensional fluid-dynamical model (in the high viscosity limit) for the density $a(t,x)$ of actin network and its mean translocation speed $v(t,x)$ in *radial direction* x is analyzed:

$$\partial_t a + \partial_x(av) = f(a),$$

$$\partial_x\{\mu(a)\partial_x v + s(a)\} = \varphi(a)\cdot v$$

with monotone non-linearities μ, f, φ and cubic s. The one-sided boundary condition $v(t,L(t)) \leq \dot{L}(t)$ at the free boundary, besides $v(t,0)=0$, leads to sustained periodic oscillations of extension ($\dot{L}>0$) and contraction ($\dot{L}<0$).

II: An analogous "circular model" for density $a(t,\varphi)$ and angular velocity $v(t,\varphi)$ in *tangential direction* tries to mimic the more general (and more difficult) 2-dimensional PDE- system with moving boundary: An additional stress term due to surface tension of the cortex-membrane boundary now appears in $s(a)$ and constitutes a parabolic equation for the radial extension $r(t,\varphi)$ of the cell periphery:

$$\varphi_1(a)\partial_t r = P(r,a) + \partial_\varphi(\tau a \partial_\varphi r)$$

This non-linearily coupled system of a hyperbolic, and elliptic and a parabolic equation on the unit circle exhibits characteristic properties of morphogenetic instabilities (linear stability analysis) and shows a variety of (mostly regular) oscillatory patterns of cell shape changes (numerical simulations using alternating steps with upwind resp. central difference approximations).

Ellen Baake

Modelling and parameter identification in the light reaction of photosynthesis.

The induction kinetics of chlorophyll fluorescence is one of the most important probes for studying the light reaction of photosynthesis. It exhibits a typical biphasic behaviour, which, though well-known since its discovery by Kautsky (1931), has not been understood till today.

As a first approach towards a quantitative description, a reaction scheme of photosystem 2 electron transport is combined with a description of excitation energy distribution, yielding a highly nonlinear ODE system. Its free parameters are fitted to experimental data by means of the multiple shooting algorithm as developed by Bock (1981) for parameter identification in systems of differential equations. The outcome is a very good description of the induction curves at moderate light intensities, and the estimated parameters correspond closely to physiological values. In dealing with the deviations occuring at lower intensities, model refinements are discussed with a special emphasis on photosystem 1.

Jonathan Bell

Modelling transduction in a skin receptor.

Mechanoreceptors are physiological units that convert mechanical stimuli to neural responses. The largest mechanoreceptor in the skin is the Pacinian corpuscle, which is associated with the sense of touch. A Pacinian corpuscle (PC) is basically a dentritic terminal surrounded by a capsule made up of alternating layers of viscous fluid and elastic shells. When the skin is compressed, the PC feels a compression on its outer boundary. The capsule transmits strain to the core receptor membrane of the dendrite. The receptor membrane has strain-activated ionic channels which allow current flow across the membrane. This changes the receptor potential which initiate an action potential. To model the mechanical-to-electrical process in a PC, we have developed a continuum mechanical model for the capsule, an electrophysiological model for the dendrite, and a transducer model to explain the action of the strain-activated channels. The capsule normally requires for each layer continuity and momentum equations for the fluid coupled to elastic shell equations. There are 30-60 layers, so we employ a formal homogenization technique on the capsule model to reduce the system to a two variable theory. The two variables are normalized radial displacement, and a homogenized pressure variable. Out of the model comes an expression for the hoop strain at the receptor membrane which is used in a model for the strain-activated transduction current. This is also a component of a model for the nerve. The nerve model takes account of the fact that the nerve has cytoplasmic extensions distributed over it, and our theory assumes these are the site of the transduction channels. We discuss some aspects of known PC behavior, and show that the model reproduces qualitatively this behavior. This includes the PC's ability to rapidly adapt to step in pressure stimuli, and to produce frequency and intensity characteristics, given periodic stimuli. This work represents an initial investigation into mechanisms responsible for generic properties of mechanoreceptors, and the start of a project to develop a quantitative model for the somato sensory system.

Nicola Bellomo

Solution of partial differential equations with random parameters.

I consider initial-boundary value problems for partial differential equations with random coefficients and/or random initial and boundary conditions. The solution refers to the time evolution of the moments and correlations of the dependent variable and of the first and second order probability density joined to the dependent variable.

The analysis is developed by the so called "adaptive stochastic interpolation methods" which make suitable use of the stochastic lagrange polynomials and of the stochastic splines.

Application to the analysis of biological models is dealt with.

Oana Brosteanu

Analysis of lamellipodial behaviour of leukocytes.

Leukocytes or related cells stimulated to move on a substrate show membrane protrusions (lamellipodia) in various directions. The main problem concerning lamellipodial activity is to describe and eventually model the temporal and spatial behaviour of these deformations of cell periphery (extensions resp. retractions). A first approach, using data obtained by drawing the cell outlines from film images for succesive time steps, is to quantify the peripheral change in normal direction at points on the cell outline (per fixed time step) and to calculate the auto-correlations of the displacements. This method allows to characterize spatial correlations, but only spatial, since points on the periphery are difficult to follow over several time steps. A second approach is to calculate the weighted moments (taking into account the mass distribution of the cell) and from these the momental ellipse (defined by the centralized moments of second order). This ellipse can be used as a reference shape, looking at the displacements along the normals of this ellipse. This allows to compare the displacements over multiple time-steps and to evaluate the temporal and spatio-temporal dependencies.

Stavros Busenberg

Dynamics of disease transmission in populations of varying size.

In populations of constant size, a single threshold parameter R_0 suffices to determine the initiation of an epidemic. This is no longer the case in variable size population and a finer structure of the threshold parameters needs to be obtained. For example in the $S \to I \to R \to S$ model there are essentially five distinct thresholds, $R_0, R_1^{a,b}$ and $R_2^{a,b}$, where:

$$R_0 \leq 1 \Rightarrow \frac{I(t)}{S(t)+I(t)} \to 0; \quad R_0 > 1 \Rightarrow \frac{I(t)}{S(t)+I(t)} \to i^* > 0$$

$$R_1^{a,b} < 1 \Rightarrow I(t)+S(t)+R(t) \to 0, \quad \text{and} \quad R_1^{a,b} > 1 \Rightarrow I(t)+S(t)+R(t) \to \infty$$

with a holding when $R_0 \leq 1$ and b when $R_0 > 1$.

$$R_2^{a,b} < 1 \Rightarrow I(t) \to 0; \quad R_2^{a,b} > 1 \Rightarrow I(t) \to \infty$$

with the a threshold holding if $R_0 \leq 1$ and the b when $R_0 > 1$.

Thus the disease affects the demographics, and conversely the demographics of the population affects the possibility that the disease gets established either as a proportion $I(t)/(S(t)+I(t)+R(t))$ of the total population or in absolute numbers. This type of fine structuring of the threshold criterion is necessary in understanding the dynamics of disease transmission for lethal diseases and in populations which

are undergoing demographic change. These results were obtained in joint work with P. van den Driessche, K. Cooke, and H. Thieme. They required the use of techniques from dynamical systems and in one case, the proof of a new theorem which provides a general criterion for the non-existence of periodic solutions or of orientied phase polygons on smooth oriented two-dimensional manifolds.

Vincenzo Capasso

Optimal control problems for a class of man-environment-man (MEM) epidemics modelled by reaction-diffusion systems with boundary feedback.

A class of MEM diseases which apply to coastal regions (typhoid fever, infectious hepatitis A, ...) has been modelled by the author and his collaborators, according to the following nonlinear evolution system

$$\frac{\partial u_1}{\partial t}(t,x) = \Delta u_1(t,x) - a_{11}u_1(t,x), \quad \text{in} \quad Q^\infty$$

$$\frac{\partial u_2}{\partial t}(t,x) = -a_{22}u_2(t,x) + g\big(u_1(t,x)\big), \quad \text{in} \quad Q^\infty$$

$$\frac{\partial u_1}{\partial \nu}(t,\sigma) + \alpha u_1(t,\sigma) = \int_\Omega k(\sigma,\xi)u_2(t,\xi)d\xi, \quad \text{in} \quad \Sigma_1^\infty$$

$$\frac{\partial u_1}{\partial \nu}(t,\sigma) = 0, \quad \text{in} \quad \Sigma_2^\infty$$

subject to suitable initial conditions. Here Q represents the habitat. A part Γ_1 of its boundary $\partial\Omega$ represents the coastline, where the coupling with the sea waters occurs; the other part Γ_2 being completely isolated. ($Q^T = [0,T] \times \Omega$; $\Sigma_1^T = [0,T] \times \Gamma_1; \Sigma_2^T = [0,T] \times \Gamma_2$). $\mu_1(t,x)$ represents the concentration of the infectious agent (bacteria, viruses, ...) at point $x \in \Omega$ and time $t > 0$. $u_2(t,x)$ represents the spatial density of infectives at time t in Ω.

The integral operator $\int_\Omega k(\sigma,\xi)u_2(t,\xi)d\xi$, $\sigma \in \Gamma_1$ describes the mechanism of transfer of the infectious agent produced by infectives u_2 at any point $\xi \in \Omega$, to a point σ of the coastline Γ_1, hence making it available for diffusion in the habitat. The term $g\big(u_1(t,x)\big)$ represents the force of infection of human susceptibles due to the concentration u_1 of the infectious agent. When g is strictly concave a threshold parameter can be identified

$$\vartheta = g'(0) \quad \sup \int_{\Gamma_1} k(x,\xi)d\xi$$

such that if $\vartheta < 1$ the epidemic tends to extinction, otherwise a nontrivial endemic state appears.

Optimal control problems arise based on the fact that the epidemic can be reduced by reducing the kernel $k(x,x')$ by means of a multiplicative factor $\omega(t,x)$.

The following costs have to be taken into account

$$J_1 = \int_0^T \int_\Omega f(u_2(t,x))dxdt \quad \text{(cost of the epidemic)}$$

$$J_2 = \int_0^T \int_{\Gamma_1} h(\omega(t,x))dxdt \quad \text{(cost of the sanitation program)}$$

$$J_3 = \gamma(T) \quad \text{(cost of the duration of the epidemic)}$$

$$J_4 = \int_\Omega l(u_2(T,x))dx \quad \text{(penalization due to the final value of the epidemic)}$$

An optimal control can be based on the minimization of the total cost

$$J_1 + J_2 + J_4$$

with a fixed duration T.

Another approach is based on vector optimization in which the various costs are considered in a vector form. In this context Pareto-optimality plays a major role; consider the vector cost $J = (J_1, J_2, J_3)$. $J(\omega^*)$ is P.O. iff $\exists e_i, i = 1,2,3$ s.t. $\forall i = 1,2,3, J_i(\omega^*)$ is minimum in the set $\{\omega | J_k(\omega) \leq c_k, k \neq i\}$. This is an important tool for decision-makers when the costs cannot be optimised all at the same time.

Jacques Demongeot

Use of exhaustion procedures coming from the study of the auditory system in segmentation of medical images.

The post-cochlear neural network (cochlear nucleus, geniculate body) detect and emphasize correlated trains of spikes on fibres corresponding (in the tonotopic mapping) to close frequencies; we apply this technique to exhaust homogeneous images (tumours or functional elements of the brain like the grey nuclei at the basis of the cortex) coming from the CAT - scanner or from the NMR; after we use this exhaustion in order to define a gradient and a hamiltonian related to the grey level observed after and before the image processing by the neural network. Finally, we define a differential system having as limit cycle the contour of the homogeneous image previously exhausted.

Odo Diekmann

How to decide whether an infectious disease can establish itself in a population?

The expected number of secondary cases produced by a typical infected individual during its entire period of infectiousness is mathematically defined as the

dominant eigenvalue of a positive linear (so-called "next-generation") operator. In special cases one can compute this eigenvalue in terms of ingredients for submodels describing infectivity. The case of pair-formation submodels à la Dietz & Hadeler is given special attention. Thus the lecture served as an introduction to the lecture by Klaus Dietz.

Klaus Dietz

The threshold number of partners for the transmission of HIV.

The basic reproduction number, i.e. the number of secondary cases generated by one case during the infectious period in a susceptible population, is calculated for the pairing model by Dietz & Hadeler (J.Math.Biol.1988). It is represented as a function of the number of partners during the infectious period. Variable infectiousness during the infectious period increases considerably the minimum number of partners for the persistence of HIV. The threshold number of partners is in a sensitive way dependent on the assumptions about the duration of a partnership.

Dietmar Dorninger

Predicting and reconstructing the spatial order of chromosomes.

According to Bennett's model the spatial arrangement of the chromosomes of eucaryotes is such that adjacing chromosome arms are of "most similar size". During metaphase the centromeres of the n chromosomes of a haploid genome are assumed to form a plane regular $n-$gon, whereby the arms of the chromosomes are stretched to the outside.

A graph theoretic model is presented that shows that there occur inconsistencies in Bennett's model and the cases, when this may happen, are classified. Moreover modifications of the principle of most similar arm size are discussed where such inconsistencies do not arise.

Further the $HP-$complete algorithm used by biologists to reconstruct the original order of the centromeres from the coordinates of the displaced centromere-positions which they measure are considered and eventually substituted by an algorithm that only needs polynomial time.

Friedhelm Drepper

Zufall und Kausalität im Informationsproduktionsprofil von Masern Epidemien.

Das Skalenverhalten von Informationsproduktionsraten der Renyi Ordnung 2 scheint in besonderer Weise geeignet, das komplexe Zusammenspiel von Zufall und instabilem Determinismus bei der Entstehung von Unvorhersagbarkeit

zu trennen. Die Informationsproduktion kann als Unsicherheit einer bedingten Kurzzeitvorhersage interpretiert werden. Die Bedingtheit bezieht sich hierbei auf eine gleich genaue Kenntnis der jeweils jüngsten Vergangenheit.

Die Anwendung dieser neuen Methode der nichtlinearen Zeitreihenanalyse auf die Epidemiologie zeigt, daß die Unvorhersagbarkeit der Masern Epidemien durch lokale Instabilität der zugrundeliegenden nichtlinearen "deterministischen" Dynamik wesentlich beeinflußt wird.

Herbert I. Freedman

Stage-structured models of population growth.

Models in which populations are structured into immature and mature stages are considered. The time to maturity is represented as both a constant and a density-dependent time delay. Single- species and predator-prey models are investigated in this manner.

Ursula Gaedke

Predator-mediated coexistence of calanoid copepods in a spatially heterogeneous environment.

Literature data on life history and ecology of two sympatric calanoid copepod species, *Eurytemora affinis* and *Acartia tonsa*, were analyzed for density-dependent processes and those promoting direct and indirect interactions between the two populations. The impact of these processes on competition and coexistence was examined with a complex numerical simulation model integrating comprehensive experimental evidence with theoretical concepts on species coexistence. Model results suggest that in the present case study competition is mainly caused by common predators (i.e. carnivorous zooplankton), but not by utilization of common resources. Competition for common resources is weak and diffuse, due to numerous other herbivores. Predation of it tonsa on nauplii of both species enhances intra- and interspecific competition at high abundances but despite being species specific it does not support coexistence within a reasonable parameter range. Non-selective predation by carnivorous zooplankton depending on the combined abundance of the two prey species appears as the main factor promoting competition between copepod species. At the same time, it is – at least in the model – the most important mechanism of coexistence if prey species are spatially heterogenously distributed and predation pressure relies on local prey density. Revealing this mechanism of coexistence allows a better explanation for the observed distribution of some copepod species.

Annette Grabosch

A functional analytic approach to a model of red blood cell production.

Invariance properties for closed, invariant sets play an important role in the theory of differential equations. For ordinary differential equations in $\mathbb{R}^n$ a sufficient and necessary condition for the positive cone

$$C = \{(x_i) : x_i \geq 0 \text{ for } i = 1, \ldots, n\}$$

to be invariant under the semiflow generated by the ordinary differential equation

$$x'(t) = f(x(t)), \quad x(0) = x_0 \in \mathbb{R}^n,$$

where f is locally Lipschitz continuous, is the subtangential property:

$$\underline{\lim}_{h \downarrow 0} \frac{1}{h} \operatorname{dist}(x + hf(x), C) = 0 \quad \text{for all } x \in \partial C.$$

If we consider the differential equation $x'(t) = f(x(t))$, $x(0) = x_0 \in X$ in a Banach lattice X, where $f : X \to X$ is locally Lipschitz continuous, then the same result holds. To extend this result to partial differential equations we assume that we have an operator A on a Banach lattice X which generates a linear, positive, strongly continuous semigroup $(T(t))_{t \geq 0}$. We consider the dual problem

$$u'(t) = A^* u(t), \quad u(0) = \varphi \in D(A^*),$$

which is well–posed in a weak*–sense. For $Y := \overline{D(A^*)}$ we assume that $F : Y \to X^*$ is locally Lipschitz continuous. Additionally we assume that $\Psi : X^* \to \mathbb{R}_+$ is a strictly positive, locally Lipschitz continuous, locally bounded functional. Then we consider the Cauchy problem

$$(*) \qquad u'(t) = \Psi(u(t)) A^* u(t) + F(u(t)), \quad u(0) = \varphi \in D(A^*).$$

If we additionally assume that Y is a Banach lattice and that X is separable the following result holds.

There exists a local "mild" solution $u(t;\varphi)$ of $(*)$ which satisfies the semigroup property and $\lim_{t \uparrow t_{\max}(\varphi)} \|u(t;\varphi)\| = \infty$ holds. If the subtangential property

$$\underline{\lim}_{h \downarrow 0} \frac{1}{h} \operatorname{dist}(\varphi + hF(\varphi), X_+^*) = 0$$

is satisfied for all $\varphi \in \partial X_+^*$, then $\varphi \geq 0$ implies $u(t;\varphi) \geq 0$ for all $t \in [0, t_{\max}(\varphi))$. Moreover the subtangential property is equivalent to a "positive–off–diagonal" property, that is, if $\varphi \in Y_+, x \in X_+$ with $\langle x, \varphi \rangle = 0$, then $\langle F(\varphi), x \rangle \geq 0$. Furthermore a "principle of linearized (in)stability" holds.

This result can be applied to a model for the production of red blood cells. Production takes place mainly in the bone marrow. The main stage for the "real" production process is the stem cell compartment, where cells undergo the cell cycle and have the capability to divide continuously. Some of the cells are committed to undergo a differentiation process to become blood cells. The red blood cell line is one out of three possible paths. Stem cells entering this line will undergo several divisions in a precursor cell compartment. At the same time (but independently) maturation, e.g. hemoglobin synthesis, takes place. Finally the cells will enter the blood cell compartment. Regulation of this process is not well understood. Nevertheless it has to function very precise, since every day about 1% of all cells has to be replaced by new ones and the total development of a cell from its birth to its final form takes more than 6 days. There are several possible failures of this system which lead to common diseases such as anemias, leucemias, etc.
Here the process is modelled by a system of first–order partial differential equations with several nonlinear couplings. This system can be reformulated as a Cauchy problem of the form (*) and the above result applies.

Johan Grasman

A deterministic model of the cell cycle.

The variability of the duration of the cell cycle is explained from the phenomenon of sensitive dependence upon initial conditions as it may occur in deterministic nonlinear systems. Chaotic dynamics of a system is the result of this sensitive dependence. First a deterministic system is formulated that is equivalent to the Smith-Martin transition probability model of the cell cycle. Next the model is extended to a dynamic process that ranges over the cell generations. A deterministic nonlinear relationship between the cycle time of the mother- and daughter cell is established. It clarifies the variability of mother-daughter correlations for the different cell types. The model is fitted to two different cell cultures; it shows the constancy of the nonlinear relation over different cell types.

Michael Guevara

Mechanisms of cardiac arrhythmias.

Ventricular arrhythmias - which can arise due to disturbances in the conduction of the cardiac impulse in the ventricles of the heart - are often implicated in sudden cardiac death. In a variety of circumstances the stage of induction of ventricular arrhythmias is often preceded by a phase of alternans – beat-to-beat alternation in the morphology of the action potential. We show in single ventricular cells isolated from the rabbit heart that alternans can be seen as the pacing frequency is increased. We attribute this production of alternans to a

period-doubling bifurcation. Further increase in pacing frequency leads to a second period-doubling bifurcation, which is followed by an irregular rhythm upon increasing pacing frequency still further. We show that a simple one-dimensional finite-difference equation predicts the existence of the above behaviors: moreover, the irregular rhythm is chaotic.

Karl P. Hadeler

Homogeneous evolution equations.

Motivated by problems from demography and epidemiology we study equations $\dot{x} = f(t,x)$, where $f : \mathbb{R}^n \to \mathbb{R}^n$ is homogeneous of degree 1, $f(t,\alpha x) = \alpha f(t,x)$. We derive stability criteria for the analogues of stationary and periodic solutions (exponential solutions and "spirals"). We generalize the notions of a Lyapunov function and of a gradient field, and we prove a Bendixson-Dulac criterion.

Uwe an der Heiden

A simple model of immune response.

The immune system protects the organism against foreign substances (antigens), viruses, bacteria, tumor cells etc. In order to describe the interaction between the immune system and these invaders we introduce two time-dependent variables:

$e(t)$ = amount of antigens, viruses, ... of some type.

$k(t)$ = amount of active immune cells competent for this type.

The proposed model consists of the following system of two ordinary differential equations:

$$de/dt = \alpha e - \beta ek$$
$$dk/dt = \gamma f(e) + g(k) - \delta k.$$

The time-constant parameter $\alpha, \beta, \gamma, \delta$ are positive, except α, which is positive if e-molecules or cells can reproduce, and negative if, after infection, the invadors simply decay. The function $f(e) = e/(1+e)$ describes the activation of immune cells by antigens, $g(k) = k^n/(1+k^n)$ means autocatalytic production of immune cells.

This clearly oversimplified model of immune response has the advantage that it can be studied favorably by methods of phase plane analysis and analytic discussion of the vector field, which is defined in $\mathbb{R}^2_+$ by the right hand sides of the two differential equations. This analysis exhibits a large variety of different types of solutions of the model system. Depending on parameters there can be up to four

constant solutions (equilibria). These equilibria correspond to states, described by immunologists as "virgin state", "immune state", "state of tolerance". The model successfully replicates the so-called "secondary response": A second infection (by the same type of antigen) is more quickly overcome than the first one. There may be permanent coexistence of antigen and competent immune cells in the system (corresponding to a positive equilibrium). Antigen and immune response can oscillate with either decreasing amplitude or in the form of a limit cycle oscillator. This last possibility means that the organism becomes alternatingly ill and healthy at regular intervals without being infected again from outside. Under certain values of parameters the immune system is not able to overcome the antigen attack, i.e. $\lim e(t) = \infty$ as $t \to \infty$.

Zygmunt Hejnowicz

Modeling of plant organ growth by means of the growth tensor.

Plant tissues grow in such a way that neighboring cells do not slide one past other; their walls are cemented. A growing plant organ resembles the deformation of a visco-elastic body, thus a tensor, designated as the growth tensor, (GT), is applicable. The GT is the covariant derivative of displacement velocity of markers in the growing organ. The principal directions of GT (PDGs) are represented (in a steadily growing organ) by cell walls aligned in so called periclines and anticlines which are orthogonal.

The mathematical task in describing organ growth is thus following: given is the pattern of periclines and anticlines, formulate the growth tensor such that its PDGs fit the pattern. This task was fulfilled for root apices. A paraboloid coordinate system (u, v, ϕ) was used.

The growth rate (relative) of a line element in the direction α, $r_{l(\alpha)}$, is: $r_{l(\alpha)} = (GT) \cdot \bar{e}_\alpha \cdot \bar{e}_\alpha$ where $\bar{e}_\alpha$ is the unit vector in the direction α. The α for PDG was obtained from $\frac{dr_{l(\alpha)}}{d\alpha} = 0$ as a function of $\left(\frac{du}{dt}, \frac{dv}{dt}, u, v\right)$. The point functions $\frac{du}{dt}(u,v)$, $\frac{dv}{dt}(u,v)$ were chosen so that PDGs of the corresponding ST matched the required peri/anticline pattern. The obtained GT gave a realistic distribution of volumetric growth rate (the trace of ST).

Solving the equations $\frac{du}{dt} = f(u,v)$; $\frac{dv}{dt} = g(u,v)$ with respect to time allowed modeling of the displacement of markers in the apex.

The maintenance of the peri/anticline pattern in the apex of a mature root, and the formation of new apex (transient cellular pattern) were simulated.

Josef Hofbauer

New results on the hypercycle system.

A hypercycle, as introduced by Eigen and Schuster, is a system of n self-replicating macromolecules, which are coupled together by a closed loop of catalytic reactions, such that each species catalyses the self-reproduction of the next one. Such hypercycles have been postulated as missing links in the prebiotic evolution from simple self-replicating elements with enzyme-free copying mechanism to the early forms of RNA. With the simplest form of reaction kinetics, this leads to the system of ODEs [2]:

$$\dot{x}_i = x_i(x_{i-1} - \bar{F}), \quad i = 1, \dots, n, \quad \bar{F} = \sum_{i=1}^{n} x_i x_{i-1}. \tag{1}$$

Here x_i denotes the concentration of the ith species, and i is understood modulo n. Due to the flux term $\bar{F}$ the total number of elements remains constant and (1) defines a flow on the simplex $S_n = \{x \in \mathbb{R}^n : x_i \geq 0 \text{ and } \sum_{i=1}^n x_i = 1\}$. It is known [2] that the equilibrium $p = (\frac{1}{n}, \frac{1}{n}, \dots, \frac{1}{n})$ of (1) is globally asymptotically stable if $n \leq 4$. Since the eigenvalues at p are the nth roots of unity (except 1), p is unstable for $n \geq 5$. Numerical simulations suggested convergence to a stable limit cycle (which follows the edges $123\cdots n1$ for large n). Sigmund (see [1, p. 101]) proved that (1) is *permanent*: There is a $\delta > 0$ such that for all initial values $x \in \operatorname{int} S_n$, $\liminf_{t\to\infty} x_i(t) \geq \delta > 0$.

Theorem. *Every orbit of* (1) in $\operatorname{int} S_n$ converges either to p or to a nontrivial periodic orbit.

If p is unstable (i.e. $n \geq 5$) then even the existence of an asymptotically stable periodic orbit can be shown. The theorem holds also for more general systems than (1). This result is a consequence of the recent deep work of Mallet-Paret and Smith who proved a Poincaré–Bendixson type theorem for *monotone cyclic feedback systems*. These are systems

$$\dot{x}_i = f_i(x_i, x_{i-1}) \qquad i = 1, \dots, n, \tag{2}$$

on (some open set in) $\mathbb{R}^n$ where $\frac{\partial f_i}{\partial x_{i-1}}$ does not change sign. This is a discrete version of an analogous result on reaction diffusion equations (with periodic boundary conditions). The proof uses the fact that the number of sign changes of the vector $x(t)$ decreases monotonically along solutions of the linearized problem. Using similar methods, another open problem on the competitive exclusion of hypercycles (see [1, p. 104] has been solved.

1. J. Hofbauer, J. Mallet-Paret and H. L. Smith: Stable periodic solutions for the hypercycle system. J. Dynamics Diff. Equ. (Submitted)

2. J. Hofbauer and K. Sigmund: *The Theory of Evolution and Dynamical Systems*. Cambridge Univ. Press 1988.

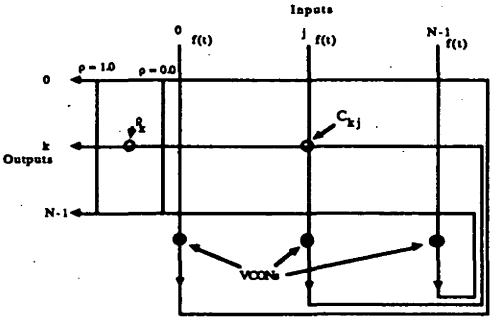
Frank C. Hoppensteadt

Analysis of a model neural network.

A network of voltage controlled oscillator neuron (VCON) models is described by the differential equations

$$\frac{dx_j}{dt} = \omega_j + \sum_{k<N} C_{kj} \cos_+ x_k \cos_+ x_j + f(t) \cos_+ x_j$$

for $0 \leq j < N$ where C_{kj} is the strength of connection from VCON k to VCON j, $f(t)$ is the external signal applied to the network, and ω_j is the center frequency of the j^{th} VCON. The following notation is useful for computer simulation since it presents at once the data, inputs and outputs.



The arrangement of the network provides a visualization of the connection stencil $C = (C_{kj})$ where the size of the circle at the intersection (k, j) is proportional to C_{kj}.

The system can be studied using the rotation vector method. If f is almost periodic, then the $\lim_{t\to\infty} x_j(t)/t = \rho_j$ exists and describes the output frequency of the j^{th} circuit, and the entropy of the distribution $x/|x|$ can provide a useful Liapunov function for the it [Proc.Nat'l Acad.Sci.(USA) May, 1989]. In turn, the network represents f as a generalized harmonic poynomial

$$f(t) \sim \sum A_k \cos_+ x_k(t)$$

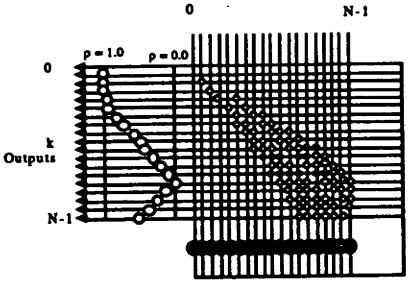
This gives the projection of f onto the output voltages, which generally are not orthogonal. However, if

$$f_j = < f \cos_+ x_j > \equiv \lim_{t\to\infty} \frac{1}{t} \int_0^t f(s) \cos_+ x_j(s) ds$$

then, $f_j = \sum A_k B_{kj}$ where $B_{kj} = < \cos_+ x_k \cos_+ x_j >$. This system can be solved for the amplitudes A_k using least squares methods and the fact that

$$\rho_j = \lim_{t\to\infty} \frac{x_j(t)}{t} = \omega_j + \frac{4}{\pi} \sum_{k<N} C_{kj} + f_j$$

Thus, a temporal signal can be coded in a spatial structure. A network that creates



a frequency gradient is described next. This lays a basis for the network to encode a variety of input signals.

Gottfried Jetschke

Speciation by stochastic transitions between stable genetic equilibria in a continuously distributed population.

Under certain selection pressure more than one genetic equilibrium can be possible. Let us consider a continuous character under disruptive selection. The effect of gene flow within a population living in a continuously extended region is described by a diffusion term. Then a nonlinear partial differential equation is obtained. The effect of the genetic drift due to the finite size of the population is included by adding a spatio-temporal white noise.

Properties of this stochastic partial differential equation are explained. If the effective population size is large most of the time the system stays near one of its stable equilibria. But in the long run stochastic transitions to another stable equilibrium are possible. The mechanism, most probable paths and mean times of such speciation processes are discussed.

James P. Keener

The effects of discrete gap junction coupling on propagation in myocardium.

The myocardium is comprised of anisotropically coupled exitable cells, through which an action potential propagates to initiate each cardiac contraction. In spite of the obvious inhomogeneity of myocardial tissue, cardiologists and physiologists have had reasonable success understanding action potential propagation using only continuous cable theory. Continuous cable theory is based on the assumption that the tissue is homogeneous, and implies that the tissue's resting space constant, the speed of propagation, and the stimulus threshold are inversely proportional to the square root of the total cable resistance.

Cardiac cells are coupled via low resistance gap junctions, the resistance of which is usually incorporated into the average cable resistance for continuous cable theory. However, because they are discrete objects, gap junctions can have important effects on propagation, especially in conditions of high resistance or before full recovery of the tissue.

The purpose of this work is to reexamine continuous cable theory, and to discuss modifications to the speed of propagation and stimulus threshold necessitated by the inclusion of gap junctions as discrete objects into a mathematical model of propagation. Of special significance is the calculation of a critical value of gap junction resistance above which action potential propagation is impossible. From the calculation of these quantities, it is possible to give an explanation of some previously unexplained experimental observations. In addition, to further test these observations, five predictions about the relationship between physically adjustable parameters and characteristics of propagation are made. These predictions all have the feature that they are counterintuitive, being in disagreement with the usual reasoning based on continuous cable theory. As a result these predictions provide an interesting test for the modified mathematical theory. To date, experiments testing these predictions have not been carried out.

Mirjam Kretzschmar

A malaria model with immunity.

In areas where malaria is highly endemic a form of immunity is observed, which is acquired very slowly in the course of repeated infections. This situation is modelled by a nonlinear system of four ordinary differential equations. The dynamic variables are the class of susceptibles S, the class of infectives I, the total immunity X in the susceptible class, and the total immunity Y in the infective class. The force of infection is described by an asymptotically homogeneous term, i.e. for low population sizes approximately by a law of mass action, for large populations the infection rate is proportional to the fraction of infectives in the

population. Depending on parameter values there can exist asymptotically exponentially growing solutions as well as stationary states. We study several variants of the model, which incorporate effects of immunity on the infection rate φ, the differential mortality α and the recovery rate γ, respectively, and compare to the dynamics of the system without effects of immunity. In the case that immunity of infectives decreases their differential mortality one can get bistability and periodic solutions. This is of interest with respect to the various epidemiological patterns (stable and unstable endemic situations) that are observed in reality.

Heike Lischke

A model to simulate the population dynamics of the codling moth.

The codling moth, one of the major apple pests, is supposed to be controlled by the means of the integrated pest management using a virus as biological pesticide. For this aim the population dynamics of the codling moth is simulated to be able to forecast the virus-sensitive stage of the pest.

Two main elements of the life cycle of the animal (development and reproduction) are formulated as deterministic submodels.

– *Development* is modeled as a stage-structured ODE-system with the maturing time for each stage depending on the stage specific developmental rate, which itself depends on temperature with an optimum-function. Simulations run with this simple model show satisfying ressemblance to phenological field data of codling moth.

– *Reproduction* is formulated as a complex behavioral ODE-model. One of its submodels describes the flight of the male moth to copulation. Parameter estimation could be made with this submodel and validation shows a good result. The estimated parameters indicate that the male moth flight-activity depends mainly on temperature, whereas humidity seems to be of less importance.

Markus Löffler

Models of temporal and spatial organisation of epithelia.

Epithelia are tissues on biological surfaces. They are characterized by very specific spatial arrangements of cells which are macroscopically stable although an underlying mechanism of cellular regeneration induces a high microscopic dynamic with a continuous replacement of individual cells. The leading questions refer to the complexity of the proliferation-differentiation program, the mechanisms of cell migration and the process that maintain the spatial stability. To investigate these questions models of the intestinal crypt system are investigated. The first model is designed to analyse cell cycle characteristics. It is based on ordinary differential equations and yields typical time parameters. In order to take temporal and spatial

aspects over a period of a few cell cycles into account a model of stochastic cellular automata is discussed. All available data can be quantitatively understood by the following assumptions:
1) Existence of an age structured population with an internally determined proliferation-differentiation program (stem cells, transient cells with a fixed number of divisions, postmitotic cells);
2) Local cell displacement ordering mechanisms based on cell to cell interaction (next neighbour).

In a third model the size distribution of entire crypts and their life cycle can be explained by a stochastic branching process of the individual stem cells in the crypts. The model involves a Galton-Watson-Process with an asymmetric division and two symmetric cell divisions as well as a threshold dependent fission process of the crypt into two with binomial distribution of cells. A comparison of model results with data shows that stem cell divisions in the biological system are almost always asymmetric. This justified the assumptions made in the second model on the age structure of the cell system.

Dimitrii Logofet

An approach to modelling structured populations.

Partitioning a population into age groups, which is typical for classical Leslie models of age-structured populations, often turns out insufficient for practical applications. An additional structure by another basis (e.g. body weight, or size, or physiological status, etc.) then generates the partition into age-"status" groups and brings about block structure of the projection matrix A in the population dynamics equation $x(t+1) = Ax(t)$, where x is a vector of age-status group sizes. Whether the additional structure introduces some new features in the asymptotic behaviour of $x(t)$ should be analyzed in terms of indecomposability and (im)primitivity properties of the block matrix A. These are equivalent respectively to strong connectedness (or strongness) of the associated digraph $D(A)$ and to a certain relationship among the lengths of all directed cycles in $D(A)$. The digraph is now to be defined on a two-dimensional lattice of vertices and the digraph theory provides the criterion for regular block structures only. Extending the theory to the general case leads to new concepts, such as the age and status factorgraphs and the factorclosure of D, and gives a constructive criterion of strongness.

The criterion can also serve as a tool to derive sufficient conditions relevant to particular classes of double-structured populations. For example, a Leslie-type model of a reindeer population under harvesting pressure includes 19 yearly age classes and 3 status groups within each age class ("weak", "normal", and "strong" animals), admits age- and status-specific vital rates, and implements the practical harvesting rule that "the weakest animals are harvested first". Under a realistic pattern of status transitions, the 57×57-matrix A is proved to be indecomposable and primitive already at the early stage of formulating the model.

Both the presence and the absence of strongness in $D(A)$ can be interpreted properly in terms of the biology of a population under concern.

Michael C. Mackey

The dynamic origin of increasing entropy.

Thermodynamic states are assumed to be characterized by densities. Recent ergodic-theory results on the evolution of densities are used to give a unified treatment of the origin of classical nonequilibrium thermo–dynamic behavior. Asymptotic periodicity is sufficient for the existence of at least one state of (metastable) thermodynamic equilibrium and for the evolution of the entropy to a relative maximum that depends on the way the system is prepared. Ergodicity is necessary and sufficient for a unique state of thermodynamic equilibrium to exist. Exactness, a property of chaotic semidynamical (irreversible) systems, is necessary and sufficient for the global evolution of the entropy to its unique maximum for all initial states. Since all of the laws of physics are formulated as (reversible) dynamical systems, it is unclear why entropy is observed to approach maximum. Setting aside the possibility that all of the laws of physics are incorrectly formulated, it is demonstrated that either observation of a subset of the complete dynamics (trivial coarse graining) or interactions with an external heat bath (addition of noise) may induce exactness with a consequent evolution of entropy to a maximal state.

Joseph M. Mahaffy

Modeling inition of DNA replication in Escherichia coli.

This work is a collaboration with Judy Zyskind, who is in the Department of Biology at San Diego University specializing in experimental work on the origin of replication, **ori C** in **E. coli**. The models examine how the protein DnaA can act as the principal control in the initiation of DNA replication, which is the first step in the cell cycle for prokaryotes. DnaA protein exists in many forms; however, only the form bound with ATP is active in the initiation process. In the models a stochastic process is used to determine when Dna-ATP becomes bound or unbound to **ori C**. When a threshold of 30 molecules bind to an origin, it replicates and is assumed to continue to completion. There is an 8 minute delay after initiation when DnaA cannot bind to **ori C**. The remaining dynamics are deterministic. The models assume that there is a reserve pool of DnaA-ATP bound to sites along the chromosome. In one model, the DnaA protein is first produced in the active form and from there it redistributes to activate **ori C**, bind to the reserve sites along the chromosome, or is inactivated. Its production is standard repression kinetics assuming excess substrates for most quantities. A second model parallels the one described above; however, it differs by having DnaA first enter as inactive DnaA from which it produces the active form. In addition,

the second model examines gene dosage of the **dnaA** gene affecting production. Numerical simulations show that both models fit data well for several growth rates. The first model is numerically very stable, but fails to properly represent the biological situation. The second model is biologically as accurate as is known to date; however, numerical simulations often lead to cells which "died" as DnaA became too dilute. Future studies hope to improve our models, so stay tuned.

Mario Markus

Isotropic automaton for the simulation of waves in excitable media.

The cellular automata proposed so far for the simulation of excitable media are based on periodic grids. These automata suffer from the drawback that the shape of the cells propagates into macroscopic scales, leading to anisotropic wave propagation. This problem is overcome in this work by setting randomly one point in each cell of a square grid. Each point may assume an integer number of states. Excitation propagates within a neighbourhood defined by a circle centered at each point. The following processes are simulated in agreement with experimental observations in the Belousov-Zhabotinskii reaction and the slime mold: spirals with different topological charges, oscillations of the distance between the tips of multi-armed spirals, the spiral core, turbulences due to interaction of chemical waves with hydrodynamic processes, an eikonal relationship, a dispersion relation, breaking of waves at inhomogeneities (as in heart tissue) and scroll waves in three dimensions.

Jim D. Murray

A wave problem with alligators.

Development of spatial pattern and form is one of the central issues in embryology. The rich spectrum of patterns and structures observed in the animal world evolve from a homogeneous mass of cells and are orchestrated by genes through the initiation and control of pattern formation mechanisms. Although there are now several mechanisms, such as reaction-diffusion models and mechanochemical models, which can generate a wide spectrum of spatial patterns, little is known about the actual mechanisms involved in any specific patterning event. One of the reasons is that it is not known *when* in development the generator is operative. The embryological development of the alligator poses the usual pattern generation problems but in particular has one of the simplest and distinctive skin patterns, namely regular stripes down the dorsal side of the animal. Fortuitously it is an animal for which there exists a large amount of embryological information. The work I discuss here was used to suggest specific experiments which provided interesting information on this specific embryological patterning process.

In the alligator embryo it is known that the stripe pattern is laid down like a travelling wave from the head to the tail tip. It is also known that there is a higher density of melanocyte cells in the dark stripe regions. So, after describing the basic features a general mechanism must have I shall take a simple cell-chemotaxis model in which the dermal cells are considered to produce their own chemoattractant and describe how spatial patterns in cell and chemoattractant density can be formed. I shall then discuss in detail the mathematical problem of a travelling wave which, as it progresses down the dorsal surface of the embryo, leaves behind a spatial pattern of regularly spaced stripes. I shall describe how a linear theory can be used to provide qualitative results for the speed of propagation and the wave length of the resulting *nonlinear* pattern.

Returning to the specific embryological problem, it is extremely difficult to determine any pattern formation mechanism experimentally since in general we do not know when in development the pattern generator is operative since the patterning mechanism has already ceased by the time the pattern is observed. I shall show how this model was used to determine *when* in development the stripe pattern generator was active and how resulting experiments provided the answer to an embryological problem of current interest.

Beate Pfistner

A one dimensional model for the swarming behavior of myxobacteria.

Myxobacteria belong to the gliding bacteria. They show coordinated movement of many cells, a process called swarming. Single cells tend to join other cells. Either they glide past each other or they move parallel in the same direction. The swarm edges of the suborder Cystobacterinae are typically fringed and build peninsulas. The outermost zone, the spreading zone, is a thin cell zone, which expands progressively. Cells at the swarm edge rarely leave the swarm totally. If they venture from the swarm edge they stop after a short distance, reverse their direction and enter the swarm again.

For one dimension this complex phenomenon is modeled by a PDE system. The density change in both directions is calculated as the difference of cells turning out of and into each direction. The turning frequencies of individual cells depend on the weighed distribution of surrounding cells. Simulations of stationary states show the influence of sensitivity to cell distributions. For linear weight functions this sensitivity increases with increasing perception radius. Then the swarm shape extends with a large spreading zone.

An-shen Qi

The application of cellular automata to biological problems.

The application of two dimensional cellular automata to the immune surveillance against cancer is explored. In the modeling, the replication and the death of normal cells and abnormal cells, the cytotoxic behavior of effector cells and the escaping or dissolving of dead cells are taken into account. A global description of the cancerous growth is obtained. A picture of the cancerous evolution can be intuitively shown on a computer screen. The affection of the cytotoxic rate on the tumoral growth is investigated. The influences of the dissolving rate of dead cells and a quantity depicting the competition between angiogenesis and the blocking of the vascular system on cancer evolution are also studied. Maxima of these two quantities are found. Aparting from them, the tumor would grow more slowly.

Klaus Reichard

Simulation of immune cell activities.

This simulation model has several cells of different types moving in a 2–dimensional plane (the surface of the computer screen). There are four types of cells:

Up: unprimed cells, they may convert into killer cells (**Ki**)
Su: supressor cells, inhibiting the conversion **Up** $\Rightarrow$ **Ki**
Tu: tumor cells, they can be destroyed and proliferate by cell division
He: helper cells, specific for **Tu**, recognizes **Tu** and actually converts **Up** $\Rightarrow$ **Ki**

The state of each cell is given by a certain set of data: individual number type, position, internal clock, preferred directional movement, state flag (attached to, destructed, free).

When cells meet, certain actions are taken:

Up $-$ $-$**Su**:	stay together for some time T_1, during which (**Up** $\rightarrow$ **Ki**) is impossible.
He $-$ $-$**Tu**:	stay together for some time T_2.
Up $-$ $-$**Tu**:	NO ACTION!
Up $\rightarrow$ (**Tu** + **He**):	conversion **Up** $\Rightarrow$ **Ki**, and destruction of **Tu**, stop doubling after that **Ki** $\Rightarrow$ **Up**, and **He** free.
Tu $\rightarrow$ (**Tu Tu**):	doubling of**Tu** with doubling time T_3.

Movements are made in an orthogonal quadratic grid. Cell moves to one of the 8 adjacent places, whose probability depends on the preferred direction. All times T_1, T_2, T_3 are chosen stochastically with predefined means and variances.

Results of the model running: Two possible results: Total elimination of **Tu**, or unlimited growing of **Tu**. Even if the model is stochastic, there is a rather sharp "jump" from success to failure, when changing parameters.

Frank Rinn

Dendroclimatology by densitometric tree ring.

A new electric-mechanical method allows the measurement of density profiles of conifers and (for the first time) of decideous trees. Time series of special tree ring parameters which can be determined in the density profiles correlate with climatic variations, fertilizations, air pollution and other growth limiting factors.

Klaus R. Schneider

Relaxation Oscillations in Belousov-Zhabotinskii - like systems.

In the first part we give a survey on recent developments in BZ- like reactions and their modelling. In particular we report on the light and oxygen sensitivity and derive the corresponding mathematical models.

In the second part we describe a general approach to establish existence, uniqueness and stability of a relaxation oscillation in singularly perturbed systems with more than two time-scales. The method under consideration is a two-stage approach. In the first step we reduce the singularity perturbed $(n+2)$- dimensional system to a singularly perturbed two-dimensional system by using integral manifold theory. In the second step we apply a window-version of a general theorem due to Mishchenko- Rozov on singularly perturbed systems to get a unique stable relaxation oscillation near some closed curve.

In the last part we apply our general approach to systems modelling BZ-like reactions. Especially we describe the mechanism of decreasing of relaxation oscillations in case of UV-radiation and oxygen influence. This mechanism is the "french duck" mechanism and its modification ("russian duck").

Lee Segel

An analytic model for the development of dominance in a population of interacting organisms.

We present an analytic treatment of hypothesis studied in computer simulations by P. Hogeweg (Utrecht) and coworkers. The work concerns the possible role of a scalar variable x, called dominance in the interaction of social organisms such as bees. There is evidence that certain bees participate in encounters that result in a winner and a loser. It is supposed that the result of an encounter is a chance event, with the more dominant more likely to win. After an encounter the dominance of the winner (loser) is incremented (decremented)— with larger changes when a result of lower probability occurs. The probability distribution function of dominance in the population $f(x,t)$ is shown to satisfy the following equation, where $\phi(\cdot,\cdot)$, $\omega(\cdot,\cdot)$, $W_1(\cdot,\cdot)$, $l(\cdot,\cdot)$ and $L_1(\cdot,\cdot)$ are given:

$$\frac{\partial f(x,t)}{\partial t} = -f(x,t)\int f(y,t)dy + \int \phi\big[\omega(p,x),p\big]\frac{f\big[\omega(p,x),t\big]}{1+W_1\big[\omega(p,x),p\big]}f(p,t)dp$$
$$+\int \phi\big[q,l(q,x)\big]\frac{f\big[l(q,x),t\big]}{1-L_1\big[l(q,x),q\big]}f(q,t)dq$$

Other versions of the basic equation are derived and compared. Various special cases are analyzed. A major goal is to find conditions under which the dominance distribution is bimodal, yielding an "automatic" way to divide the population into 2 groups.

Donatas Shvitra

Modeling of the blood sugar system.

With the help of mathematical modeling there is a possibility to verify some hypotheses on the functioning of the physiological regulation system of the normal blood sugar level as well as pathologic, ensuing in the development of diabetes mellitus and hyperinsulinism. It is most important at that to take into account oscillatory nature of the considered physiological volume, appearing as a consequence of time delay in the blood sugar system, equal to the duration of production of insulin on β-cells of the pancreas. The mathematical model of the blood sugar level regulation is constructed and investigated with the help of a system of four nonlinear difference-differential equation:

$$\dot{I}(t) = \tau_I\big[\frac{G(t)}{\kappa_G} + a\big(\frac{G(t)}{\kappa_G} - \frac{I_A(t)}{\kappa_{IA}}\big) - \frac{pI(t-h_p)+(1-p)I(t-h)}{\kappa_I}\big]I(t), \quad (1)$$

$$\dot{I}_A(t) = \tau_{IA}\big[\frac{G(t)}{\kappa_G} + b\big(\frac{G(t)}{\kappa_G} - \frac{I(t)}{\kappa_I}\big) - \frac{I_A(t)}{\kappa_{IA}}\big]I_A(t), \quad (2)$$

$$\dot{G}(t) = \tau_G\big[1 + c\big(1 - \frac{I_A(t)}{\kappa_{IA}}\big) - \frac{G(t)}{\kappa_G}\big]G(t), \quad (3)$$

$$\dot{I}_S(t) = \tau_{IS}\big[\frac{I(t)}{\kappa_I} + d\big(\frac{I(t)}{\kappa_I} - \frac{I_A(t)}{\kappa_{IA}}\big) - \frac{I_S(t)}{\kappa_{IS}}\big]I_S(t), \quad (4)$$

where $I(t), I_S(t), I_A(t)$ and $G(t)$ are levels of all the insulin produced in β-cells, joint, active insulin in plasma and blood sugar, correspondingly at the time moment t, h and h_p are delays, $\tau_I, \tau_{IA}, \tau_G$, $\tau_{IS}, \kappa_I, \kappa_{IA}$, κ_G, κ_{IS}, p, a, b, c and d are some parameters.

Within the mathematical model (1)-(4) dietary regimen is taken into account, the problem of controlling the dynamics of the blood sugar level is also stated and solved.

Angela Stevens

A model for gliding and aggregation of myxobacteria.

The myxobacteria are ubiquitous soil bacteria which glide on suitable surfaces during the vegetative state of their cell cycle. They prefer to glide on slime trails produced by themselves. The myxobacteria tend to glide cooperatively. Under starvation conditions different patterns are formed until the bacteria aggregate to form so called fruiting bodies.

Different biological hypotheses are tested by a cellular automaton model to understand the myxobacterial gliding. The results are that the following of the slime trails does not account for aggregation but for certain patterns which can be seen before the formation of fruiting bodies. So a chemo-attractant is introduced. This leads to the following equations:

Define b : density of bacteria, s : density of slime, c : density of chemo-attractant, $\gamma_s, \gamma_c \in \mathbb{R}_+, 0 \leq \varepsilon \ll 1$

$$\begin{aligned}
\partial_t b &= \nabla(a(b,s)\nabla b) - \nabla(b\nabla c),\\
\partial_t s &= \varepsilon\Delta s + \beta_s(b,s) - \gamma_s s,\\
\partial_t c &= \Delta c + \beta_c(b,c) - \gamma_c c.
\end{aligned}$$

Yurij M. Svireshev

Nonlinear models in mathematical ecology and genetics.

Non-linearity is a principal feature of models in mathematical ecology and mathematical genetics. Even the simplest classical models of mathematical ecology - the "predator-prey" system and the system of two species competing for one resource - present typical non-linear effects: Hopf cycles, relaxation cycles and hysteresis. In random environment these cycles split producing parametric resonances.

Competition and natural selection at the ecosystem level can be modelled by closed trophic chains. Taking the total amount of matter as the bifurcation parameter, one can see how its increase raises the structure complexity.

Interestingly, these same objects - closed trophic chains - demonstrate such a specific non-linear behavior as dynamic chaos.

There is a hypothesis that in ecology and genetics dissipative structures appear rather due to complexity of boundaries than due to non-linearities in assumed model equations of the "reaction- diffusion" type.

More general equations than the classical Fisher-Haldane-Wright equations are suggested as equations of population genetics. These are non-linear integral equations of a new type.

In conclusion some new problems from ecology and genetics are considered.

Horst Thieme

Stability change of the endemic equilibrium in age- structured epidemic models.

Age-structure has been introduced into epidemic models in a double meaning: as chronological age, i.e. the elapse of time since birth, and as infection age, i.e. the elapse of time since the moment of being infected. The introduction of any of the two structures can destabilize the endemic equilibrium in models where it is stable otherwise. This is shown for an infection age model for sexually transmitted diseases which can be lethal and for a model with chronological age for a non-lethal disease in a population of constant size and age distribution. It still has to be examined whether this destabilization occurs in a realistic parameter range.

Robert T. Tranquillo

Model for receptor-mediated protrusions of leukocytes.

When exposed to a receptor-specific chemical stimulus known as a chemoattractant, white blood cells exhibit amoeboid-like movement. Underlying this ability of the cell to translocate across a substratum or through a fibrous matrix is a local protrusive activity occuring over the cell surface, the protrusions being mostly associated with but not restricted to the leading front of the cell, or lamellipodium. Protrusions are the manifestation of cytoplasmic forces acting on the cell membrane, the direction and magnitude of the forces being regulated by intracellular biochemical species associated with receptor binding. Translocation is commonly believed to be the result of "competition" between protrusions which transiently adhere to a substratum or anchor around matrix fibers. To begin to understand the complicated relationship between chemoreception and directed motility, also known as chemotaxis, at the molecular level, it is proposed to model the "ruffling" behavior and consequent morphological polarization exhibited by leukocytes when initially subjected to a uniform concentration of chemoattractant.

Using a time-dependent random field model of an idealized receptor-sensing motile cell, preliminary predictions of the spatial-temporal pattern of protrusion activity in a uniform chemoattractant concentration have been made. The model synthesizes a continuum description of the actin-based contractive properties of cell cytoplasm proposed by W.Alt with a stochastic description of receptor binding and diffusion (the consequences of statistical fluctuations in receptor binding for the ability of cells to sense chemoattractant gradients have been examined in earlier work and shown to be of significance). Predictions are numerical results obtained by simulating the time-dependent random field, i.e. solving the 4^{th}-order PDE continuum equation describing the distribution of actomyosin around the annulus of an idealized circular cell, representing the cell cortex, with a finite difference algorithm, where a parameter(s) in the equation is taken to be a prescribed

function of the local (fluctuating) densitiy of bound receptors. The latter is determined by receptor binding and diffusion on the adjacent cell surface and described by a SPDE upon accounting for statistical fluctuations in those phenomena. The SPDE is approximated by an SDE system using a small noise expansion of the FDE obtained via a Kramers-Moyal expansion of the governing master equation (the steps collectively being equivalent to a van Kampen system size expansion of lowest order). Thus, the fluctuations in bound receptor density are characterized solely in terms of fundamental molecular parameters (i.e. binding kinetic constants and diffusion coefficients). The spatial-temporal correlations of bound receptor density which can be realized upon numerical integration of the SDE system (e.g. stochastic Euler algorithm) are then manifested in the actomyosin distribution around the annulus, from which protrusion is inferred.

The preliminary numerical analysis assumes that the concentration parameter in the mechanical force balance equation for the actomyosin "fluid" is a linear function of the local bound receptor density. Thus, the details of receptor signal transduction are omitted at this stage for simplicity. Prior to conducting the simulations, the expected pattern of protrusions can be easily predicted from a linear stability analysis of the deterministic PDE for the actomyosin concentration, obtained by eliminating the annular velocity from its associated conservation equation by substitution from the inviscid limit of the mechanical force balance equation. The simulations show that when all modes are predicted to be linearly stable for an appropriate choice of parameters in the continuum actomyosin model, the fluctuations in the local bound receptor density can stimulate the lowest model, progressing through a transient of low amplitude deviations of actomyosin concentration around the annulus (ruffling) to a single maximum (lamellipodium) reminiscent of the polarization observed in leukocytes. The lifetime and position of the maximum vary between realizations, suggestive of the periodic random locomotion characteristic of leukocytes in uniform chemoattractant concentrations. Other choices of parameters which cause additional modes to be linearly unstable leads to competition patterns between transiently coexisting maxima, another common feature in leukocyte random motility.

Joanna Tyrcha

Stability problems for dynamical systems with stochastic perturbations.

Consider discrete time dynamical systems

$$x_{n+1} = S(x_n, \xi_n) \qquad n = 0, 1, \ldots \tag{1}$$

where $S : A \times V \to A$ is a given transformation and $\{\xi_n\}$ is a sequence of identically distributed independent random vectors with values in V ($A \subset \mathbb{R}^d, V \subset \mathbb{R}^k$). The behaviour of system (1) is described by the sequence of distributions

$$F_n(B) = prob(x_n \in B), \qquad B \subset A, B - \text{Borelian}.$$

Our first goal is to find effective sufficient conditions for the convergence of F_n to a unique distribution F_* independent of F_0. Then we show applications of our stability results to dynamical systems appearing in the mathematical theory of the cell cycle (Lasota-Mackey and Tyson-Hannsgen models) and in the theory of the plant growth.

John J. Tyson

A cellular automaton model of excitable media

To study wave propagation in two- and three-dimensional excitable media by numerical solution of underlying partial differential equations is a costly undertaking. To provide an alternative method requiring modest computer power, we have investigated cellular automata models discrete in space, time and state variables. By carefully designing the rules of the CA to mimic the phase planes characteristic of excitable media, we obtain a fast and reliable method for exploring the behavior of waves traveling in excitable media. The behavior of CA has been compared in some detail with results of numerical integration of PDEs and of singular pertubation theory. The close agreement confirms the usefulness of the CA approach.

Roland Waldstätter

Coexistence of two types of plasmids in a prokaryotic cell population.

Selftransmissible plasmids are extra-chromosomal circular DNA-molecules in prokaryotes, for instance E.coli. These plasmids code for genes that cause the host cell to produce long, thread-like, pili which enable conjugation between the host cell and other cells. The conjugation allows the other cell to receive a copy of the plasmid DNA. Plasmids usually benefit their host cells and there seems to be selection to regulate the plasmid copy number within one cell. Furthermore there is selection on both host and plasmid genes to favour the regular transmission of plasmids into daughter cells. The model presented here is part of a co-work with S. Levin and C. Macken, where a cell population with two types of plasmids is considered. Let x be the number of cells without plasmids and y_j the cells with $n-j$ plasmids of type 1 and j plasmids of type 2. The models equations are:

$$\dot{x} = \sum_{k=0}^{n} f_k r_k y_k + rx - \tilde{\mu}(x, y_0, ..., y_n)x - \beta x \sum_{k=0}^{n} y_k,$$

$$\dot{y}_j = \sum_{k=0}^{n} (1 - f_k) p_{jk} r_k y_k - \tilde{\mu}_j(x, y_0, ..., y_n) y_j + \begin{cases} \beta x \sum_{k=0}^{n} \frac{n-k}{n} y_k, & \text{j=0,} \\ \beta x \sum_{k=0}^{n} \frac{k}{n} y_k, & \text{j=n,} \\ 0, & \text{otherwise,} \end{cases}$$

The model has several equilibria. In the special case of only one type of plasmids ($y_1 = ... = y_n = 0$) the model can be also interpreted as an epidemiological model with vertical transmission.

Gail Wolkowicz

The use of Lyapunov functions in models of competition in the chemostat.

(joint work with Lu Zhigi)

The following model of exploitative competition of n species in a chemostat for a single, essential, nonreproducing, growth-limiting substrate is considered:

$$S'(t) = (S^0 - S(t))D - \sum_{i=1}^{n} \frac{x_i(t)}{y_i} p_i(S(t))$$
$$x_i'(t) = x_i(t)(-D_i + p_i(S(t))) \qquad i = 1, 2, ..., n.$$
$$S(0) \geq 0, \quad x_i(0) > 0, \quad i = 1, 2, ..., n.$$

Here S denotes the concentration of substrate at time t and $x_i(t)$ the concentration of the i^{th} competitor. S^0 is the concentration of substrate in the feed vessel, D is the dilution rate, D_i involves the dilution rate and species specific death rate, y_i is a yield constant and p_i is a response function. Prototypes for the p_i include Michaelis-Menten, Lotka-Volterra and sigmoidal forms.

Hsu applied the LaSalle Extension Theorem of Lyapunov stability theory to study the global asymptotic behaviour of solutions in the special case that the response functions were modeled by response functions of Michaelis-Menten form thus providing a sleeken proof of the result in a previous paper by Hsu, Hubell and Waltman. They showed that all solutions approach an equilibrium concentration at which there is at most one survivor. The survivor is the competitor with the lowest break-even concentration and in order to survive the break-even concentration must be lower than S^0. Hsu used the Lyapunov function

$$V(S, x_1, ..., x_n) = S - \lambda_1 - \lambda_1 \ln(S/\lambda_1) + c_1 \left[(x_1 - x_1^*) - x_1^* \ln(x_1/x_1^*)\right] + \sum_{i=2}^{n} c_i x_i$$

with $c_i = m_i/(y_i(m_i - D_i))$. Here $(\lambda_1, x_1^*, 0, ..., 0), x_1^* > 0$ is an equilibrium concentration. (This function has also been used by Volterra and Goh in other contexts.)

We indicate the limitations of this functions and a natural extension

$$V(S, x_1, ..., x_n) = \int_{\lambda_1}^{S} \frac{p_1(\xi) - D_1}{p_i(\xi)} d\xi + k_1(x_1 - x_1^* - x_1^* \ln(x_1/x_1^*)) + \sum_{i=2}^{n} k_i x_i$$

where $k_i \geq 0$ are constants, and we show that the function

$$V(S, x_1, ..., x_n) = \int_{\lambda_1}^{S} \frac{p_1(\xi) - D_1}{S^0 - \xi} d\xi + x_1 - x_1^* - x_1^* \ln(x_1/x_1^*) + \sum_{i=2}^{n} \alpha_i x_i$$

where $\alpha_i > 0$ are constants, works for a wider class of response functions, including any combination of the three prototypes. This extends some results of Butler and Wolkowicz to allow for differential death rates.

Berichterstatter: R. Waldstätter

Tagungsteilnehmer

Prof.Dr. Wolfgang Alt
Abteilung Theoretische Biologie
Universität Bonn
Kirschallee 1

5300 Bonn 1

UNB11B@DBNRHRZ1

Prof.Dr. Stavros N. Busenberg
Dept. of Mathematics
The Claremont Colleges
Harvey Mudd College

Claremont , CA 91711
USA

BUSENBERG@HMUAX

Ellen Baake
Institut für Mathematik
Arbeitsgruppe Professor Bock
Universität Augsburg
Universitätsstr. 2

8900 Augsburg

Prof.Dr. Vincenzo Capasso
Istituto di Analisi Matematica
Universita di Bari
Palazzo Ateneo

I-70121 Bari

CAPASSO@IBACSATA

Prof.Dr. Jonathan Bell
Dept. of Mathematics
State University of New York at Buffalo
106, Diefendorf Hall

Buffalo , NY 14214-3093
USA

MTHBELL@UBVMS

Prof.Dr. Jim Cushing
Dept. of Mathematics
University of Arizona

Tucson , AZ 85721
USA

JCUSHING@ARIZRVAX

Prof.Dr. N. Bellomo
Dipartimento di Matematica
Politecnico di Torino
Corso Duca degli Abruzzi, 24

I-10129 Torino

Prof.Dr. Jacques Demongeot
IMAG
BP 53

F-38041 Grenoble Cedex

Joana Brosteanu
Abteilung Theoretische Biologie
Universität Bonn
Kirschallee 1

5300 Bonn 1

Prof.Dr. Odo Diekmann
Stichting Mathematisch Centrum
Centrum voor Wiskunde en Informatica
Kruislaan 413

NL-1098 SJ Amsterdam

Prof.Dr. Klaus Dietz
Institut für Medizinische Biometrie
Universität Tübingen
Westbahnhofstraße 55

7400 Tübingen

Prof.Dr. Dietmar Dorninger
Institut für Algebra und
Diskrete Mathematik
Technische Universität Wien
Wiedner Hauptstraße 8 - 10

A-1040 Wien

E118307@AWITUWO1

Dr. F. Drepper
Arbeitsgruppe Theoretische ökologie
Forschungszentrum KFA Jülich
Postfach 1913

5170 Jülich

TOE003@DJUKFA11

Prof.Dr. H.I. Freedman
Dept. of Mathematics
University of Alberta
632 Central Academic Building

Edmonton, Alberta T6G 2G1
CANADA

USERHIFR@UALTAMTS

Ursula Gaedke
Limnologisches Institut
Universität Konstanz
Mainaustraße 212

7750 Konstanz

Dr. Annette Grabosch
Lehrstuhl für Biomathematik
Universität Tübingen
Auf der Morgenstelle 10

7400 Tübingen 1

MIGBKA1@DTUZDV5A

Prof.Dr. J. Grasman
Vakgroep Wiskunde
Landbouwuniversiteit Wageningen
Dreijenlaan 4

NL-6703 HA Wageningen

Prof.Dr. Michael R. Guevara
Dept. of Physiology
McGill University
3655 Drummond Street

Montreal, Quebec H3G 1Y6
CANADA

Prof.Dr. Karl Peter Hadeler
Lehrstuhl für Biomathematik
Universität Tübingen
Auf der Morgenstelle 10

7400 Tübingen 1

BMHAKA1@DTUZDV5A

Prof.Dr. Uwe an der Heiden
Fakultät für Naturwissenschaften
Universität Witten/Herdecke
Stockumer Str. 10

5810 Witten -Annen

Prof.Dr. Zigmund Hejnowicz
Botanisches Institut der
Universität Bonn
Venusbergweg 22

5300 Bonn

Prof.Dr. James P. Keener
Dept. of Mathematics
University of Utah

Salt Lake City , UT 84112
USA

MA.KEENER@SCIENCE.UTAH.EDU

Dr. Josef Hofbauer
Institut für Mathematik
Universität Wien
Strudlhofgasse 4

A-1090 Wien

A8131DAI@AWIUNI11

Mirjam Kretzschmar
Center for Dynamical Systems and
Nonlinear Studies
Georgia Institute of Technology

Atlanta , GA 30332
USA

Prof.Dr. F.C. Hoppensteadt
Dept. of Mathematics
Michigan State University

East Lansing , MI 48824-1027
USA

FCHOPPEN@MSU

Heike Lischke
Institut für Angewandte Mathematik
der Universität Heidelberg
Im Neuenheimer Feld 294

6900 Heidelberg 1

AW9@DHDURZ2

Prof.Dr. Willi Jäger
Institut für Angewandte Mathematik
der Universität Heidelberg
Im Neuenheimer Feld 294

6900 Heidelberg 1

Dr. Markus Löffler
Abteilung LFI/EDV
Universitätsklinik I
Joseph Stelzmannstr. 9

5000 Köln 41

AIMI7@DKORRZKO

Dr. Gottfried Jetschke
Sektion Mathematik
Friedrich-Schiller-Universität
Jena
Universitätshochhaus, 17. OG.

DDR-6900 Jena

Prof.Dr. D.O. Logofet
Laboratory of Mathematical Ecology
Computation Center, Academy of
Sciences of USSR
ul. Vavilova 40

GSP-1 Moscow 117 967
USSR

Prof.Dr. Michael C. Mackey
Department of Physiology
McGill University
3655, Drummond Street

Montreal P. Q. H3G 1Y6
CANADA

PH25@MCGILLA

Prof.Dr. An-shen Qi
Dept. of Physics
Beijing Normal University

Beijing 100088
CHINA

Prof.Dr. Marc Mahaffy
Dept. of Mathematical Sciences
San Diego State University

San Diego , CA 92182-0314
USA

Q200041@CALSTATE

Dr. Klaus Reichard
Fakultät für Naturwissenschaften
Universität Witten/Herdecke
Stockumer Str. 10

5810 Witten -Annen

Dr. Mario Markus
Max-Planck-Institut für
Ernährungsphysiologie
Rheinlanddamm 201

4600 Dortmund 1

Frank Rinn
Institut für Umweltphysik
Universität Heidelberg
Im Neuenheimer Feld 366

6900 Heidelberg

Prof.Dr. J.D. Murray
Centre for Mathematical Biology
University of Oxford
24 - 29, St. Giles'

GB- Oxford OX1 3LB

MURRAYJD@VAX.OFORD.UK.AC

Prof.Dr. Klaus Schneider
Karl-Weierstraß-Institut für
Mathematik der Akademie der
Wissenschaften
Mohrenstr. 39, PF: 1304

DDR-1086 Berlin

Beate Pfistner
Botanisches Institut
Abteilung Theoretische Biologie
Universität Bonn
Kirschallee 1

5300 Bonn

UNB10D@DBNRHRZ1

Prof.Dr. Lee Segel
Dept. of Applied Mathematics
The Weizmann Institute of Science
P. O. Box 26

Rehovot 76 100
ISRAEL

MASEGEL@WEIZMANN

Prof.Dr. Donatas Shvitra
Institute of Mathematics and
Cybernetics
Akademijos St. 4

232600 Vilnius
USSR

Prof.Dr. John J. Tyson
Dept. of Biology
Virginia Polytechnic Institute

Blacksburg , VA 24061
USA

TYSON@VTVM1

Angela Stevens
Institut für Angewandte Mathematik
der Universität Heidelberg
Im Neuenheimer Feld 294

6900 Heidelberg 1

L39@DHDURZ2

Roland Waldstätter
Lehrstuhl für Biomathematik
Universität Tübingen
Auf der Morgenstelle 10

7400 Tübingen 1

BMWA001@DTUZDV5A

Prof.Dr. Horst R. Thieme
Department of Mathematics
Arizona State University

Tempe ,AZ 85287-1804
USA

ATHRT@ASUACAD

Prof.Dr. Paul Waltman
Dept. of Mathematics and
Computer Science
Emory University

Atlanta , GA 30322
USA

WALTMAN@MATHCS.EMORY.EDU

Prof.Dr.R.T.Tranquillo
Dept. of Chemical Engineering and
Materials Science
University of Minnesota
421, Washington Ave. S. E.

Minneapolis , MN 55455
USA

FQX6452UMNACVX

Prof.Dr. Gail S. K. Wolkowicz
Department of Mathematics and
Statistics
Mc Master University

Hamilton, Ontario L8S 4K1
CANADA

WOLKOWIC@MCMASTER

Dr. Joanna Tyrcha
Institute of Computer Science
Polish Academy of Sciences
P. O. Box 22

00-901 Warszawa PKiN
POLAND