Mathematisches Forschungsinstitut Oberwolfach

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Mathematical Biology

May 4th – May 10th, 2003

Being the tenth of the workshops on Mathematical Biology held in Oberwolfach over the last decades it brought together people studying different applications with what could be called the "eyes of a mathematical biologist".

In most of the morning sessions plenary talks gave an overview over larger areas of recent work, whereas during the afternoons the participants split up into three informal working groups focusing on detailed questions devoted to three fields:

Immunology, with a strong emphasis on the adaptive immune system, and dealing with, e.g., pattern formation between T cells and antigen presenting cells, tumour suppression, T cell recognition in the thymus, and germinal centres.

Adaptive Dynamics, both with the attempt to define an axiomatic fundament and derive phenotypic dynamics on larger scales, and applications to, e.g., mutation selection models, frequency dependent selection on polygenic traits, stability of coexistence, epidemic spread.

Interactive Motion, including various length scales from cell to macroscopic organisms, e.g., acting dynamics, cell migration, tumour growth, pattern formation by microorganisms, chemotaxis, and bird swarming.

Participants were encouraged to take part in more than only one working group over the week. Finally, plenary presentations in the evenings and during Friday morning gave an overview on the discourse in the various working groups.

Given the character of a workshop, we have tried to gather not only talk abstracts but also brief statements of research interest, to our opinion the best way to catch the various discussions and keep them to the memory of the participants. They are grouped into the three respective fields and ordered alphabetically within each group.

The history of nearly 30 years of Mathematical Biology at Oberwolfach came back to life on Wednesday evening in a celebration on stage in a theatre re-play of the first meeting in 1975. Last not least, we want to express our gratitude to the Institute and its local staff for their help in turning this one week into a most pleasant, enjoyable and productive experience.

Abstracts

The challenge of T cell activation

Nigel J. Burroghs

An overview of modelling techniques is presented tackling the intricacies of T cell activation. T cell receptor signalling is a stochastic spatial process probably involving complex spatial coupling between receptors in the membrane. We discuss simple probability models using recognition probabilities as a means to understand self:non-self discrimination, shape space models as a model for peptide binding, additive peptide profile stochastic models to model the noise inherent in the signalling process and to integrate over the diversity of presented peptides, queueing theory models as models of the activation process, adjustable threshold models and spatial immunological synapse models of the patterning observed in the cell:cell contact interface. We emphasise the utility of looking at T cell activation from different scales and through different modelling techniques; highlighting major challenges in this field.

Synaptic pattern formation during cellular recognition

Arup K. Chakraborty
(joint work with S.Y. Qi, Jay T. Groves)

Cell-cell recognition often requires the formation of a highly organized pattern of receptor proteins (a synapse) in the intercellular junction. Recent experiments [e.g., Monks & al. (1998) Nature (London) 395, 82-86; Grakoui & al. (1999) Science 285, 221-227; and Davis & al. (1999) Proc. Natl. Acad. Sci. USA 96, 15062-15067] vividly demonstrate a complex evolution of cell shape and spatial receptor-ligand patterns (several microns in size) in the intercellular junction during immunological synapse formation. The current view is that this dynamic rearrangement of proteins into organized supramolecular activation clusters is driven primarily by active cytoskeletal processes [e.g., Dustin & Cooper (2000) Nat. Immunol. 1, 23-29; and Wulfing & Davis (1998) Science 282, 2266-2269]. Here, aided by a quantitative analysis of the relevant physico-chemical processes, we demonstrate that the essential characteristics of synaptic patterns observed in living cells can result from spontaneous self-assembly processes. Active cellular interventions are superimposed on these self-organizing tendencies and may also serve to regulate the spontaneous processes. We find that the protein binding/dissociation characteristics, protein mobilities, and membrane constraints measured in the cellular environment are delicately balanced such that the length and time scales of spontaneously evolving patterns are in near-quantitative agreement with observations for synapse formation between T cells and supported membranes [Grakoui & al. (1999) Science 285, 221-227]. The model we present provides a common way of analyzing immunological synapse formation in disparate systems (e.g., T cell/antigen-presenting cell junctions with different MHC-peptides, natural killer cells, etc.).

Mathematical Models related to Tumour and Immune System Competition

Elena De Angelis

Tumour evolution is a very complex process, involving many different phenomena, which occur at different scales. Three natural scales of interest can be identified: the sub-cellular scale, the cellular scale and the macroscopic scale. Cellular models deal with the interaction between cells and are (usually) expected to describe the interactions and competition between tumours and the immune system. The evolution of the system may end up either with the blow-up of the host (with inhibition of the immune system) or with the suppression of the host due to the action of the immune system.

The mathematical structures of the equations suitable to deal with the modelling of the above system are those typical for *nonequilibrium statistical mechanics* and generalized kinetic theory.

The general idea consists in deriving an evolution equation for the first distribution function over the variable describing the microscopic internal state of the individuals. Generally, this variable may include position and velocity, but it can also refer to some additional specific microscopic features. Interactions between pairs have to be modelled taking into account not only mechanical rules but also modifications of the non-mechanical physical (internal) state. In [De Angelis & Mesin 2001] a class of integro-differential equations is proposed modelling the immune response to the evolution of the progression of endothelial cells which have lost their differentiation and start their evolution toward metastatic states. In [De Angelis & Jabin 2003] we proved the existence of solutions to the Cauchy problem related to the model. The asymptotic behaviour in time of the solutions is also investigated.

References

De Angelis, E., and Mesin, L. (2001) On the kinetic (cellular) theory. Conceptual frameworks on modelling the immune response. *Math. Models Meth. Appl. Sci.* **11**, 1609-1630.
De Angelis, E., and Jabin, P.E. (2003) Qualitative Analysis of a Mean Field Model of Tumour-Immune System Competition, *Math. Models Meth. Appl. Sci.* **13**, 187-220.

Current research interests and work:
Modelling cancer growth and progression, nonequilibrium statistical mechanics, generalized Boltzmann models, Vlasov kinetic theory, Cauchy problem.

T cell recognition

Andrew George

One of the central controlling events in the regulation of the immune system is the recognition of antigen by T cells. Thus CD4 T cells are involved in the regulation of immune responses and in activation of cells of the innate immune system. CD8 T cells are involved in killing virally infected or neoplastic cells. It is therefore important that T cell activation is a highly controlled event, as mistakes can lead either to a failure to respond to pathogens or, conversely, to autoimmune disease. Recently I have been working with Jaroslav Stark, Cliburn Chan and Simon Moon to understand aspects of this recognition event.

T cells recognise antigen as short peptides held in the groove of MHC molecules displayed on the surface of cells. The kinetics of the molecular interaction are relatively fast, when compared to antibody binding to antigen, with a $t_{1/2}$ for agonist of the order of 10-30 seconds. For T cell recognition it is important that it is highly sensitive, as the T cell may see as few as 10-100 copies of the agonist peptide held in the MHC against a background of

105-106 MHC molecules bearing irrelevant peptide. It must also be highly specific as the agonist peptide may vary from a null peptide by a single amino acid. We suggest that the sensitivity and specificity of the system must be understood at the level of the receptor, the cell and the population.

At the level of the receptor we have proposed that cycles of kinase and phosphatases (such as lck and SHP) might operate to form a molecular switch that sets a threshold for activation. In addition the bistable nature of the system allows for hysteresis, which means that once activated a T cell receptor may be maintained in an active form by small binding events that are not in themselves sufficient to activate the receptor, thus improving sensitivity. At the level of the cell we have shown that cross talk between receptors will result in an improvement in the specificity of the response. Finally we suggest that, due to the stochastic nature of T cell activation and the multiple encounters that a T cell undergoes in the periphery, that inappropriate auto-reactivity will be seen in the periphery unless there are alternative mechanisms to control it. We suggest that the induction of T cell energy by suboptimal stimulation may be important to provide a safety zone for T cell activation, so reducing the incidence of auto-reactivity.

Regulatory T-cells, lymphocyte homeostasis and immune tolerance ot tumours

Kalet León and Jorge Carneiro

The aim of my research is the understanding of the role of regulatory T cells on different immunological phenomena, following a biomathematical approach, in which theoretical models are developed, studied and confronted with experimental observations. Particularly we are currently interested on exploring the role of regulatory T cells on lymphocyte homeostasis and on the immune tolerance to tumours.

The study presented on the meeting, follows two complementary threads. On the one hand, we studied the details of the mechanism by which regulatory T cells interact with other cells and mediate the suppressive function. Here mathematical modelling was used as a tool to compare and assess the plausibility of alternative hypothetical mechanisms. On the other hand, we studied the implications of T cell mediated tolerance for the organization and operation of the immune system, with special focus on self/non-self discrimination and on the etiology of autoimmune diseases. Here modelling served as a tool to bridge different levels of organization, i.e. to understand the systemic consequences of properties of individual cells.

The main working hypothesis was that regulatory T cells effect linked suppression of their target cells when both cells are conjugated simultaneously with the antigen presenting cells (APC). Multicellular interactions are often found in biological systems but despite the general interest a formalism describing this type of interactions this was not available in the literature. Hence, we developed a simple formalism describing the formation of multicellular conjugates and quantifying the frequency distribution of conjugates with different stoichiometries. This formalism was used to represent interaction terms in population dynamic models of regulatory cells and their targets cells.

We designed four models representing the population dynamics of regulatory and target T cells, which implement alternative mechanisms of linked suppression previously proposed in the literature. We made phase plane and bifurcation analysis of each model, and identified its pros and cons in terms of the relationship with the large body of in vivo experimental observations on T cell mediated tolerance. We argued that accounting for the quantitative details of adoptive transfers of tolerance requires models that: (i) possess

bistable regimes in which either regulatory or target T cells dominate the steady state interpreted as tolerance and immunity respectively, depending on initial conditions; and (ii) possess a steady state interpreted as tolerance in which both regulatory and target cell populations coexist. We showed that only models in which the growth of regulatory T cells is strictly dependent on their target T cells bear these two properties. To further assess these candidate models, we challenged them by their capacity to explain observations in vitro. This analysis allowed us to quantify the efficiency of in vitro suppression dependent on multicellular conjugates and to show that it has an upper bound. Comparing this upper bound with the efficiency of suppression in vitro, we rejected those models in which suppression is mediated by simple competition for APCs or in which the regulatory T cell population is unable to grow. Thus, as a whole our theoretical analysis of alternative models allowed to narrow down the number of candidate hypotheses to those in which the population regulatory T cells grows as a function of the target T cells they suppress. The growth of this population may be driven by a target cell-dependent growth factor and/or may result from differentiation of target cells to the regulatory phenotype. We addressed and confirmed the first hypothesis by designing and carrying out new in vitro suppression assays in which proliferation of regulatory CD4+CD25+ and target CD4+CD25- T cells could be quantified concomitantly. This study showed for the first time that regulatory CD25+ T cells, which are unable to proliferate by themselves when stimulated in vitro, will proliferate when co-stimulated together with target CD25- T cells. Moreover, the proliferation of regulatory cells is correlated with the expansion of the target cell population suggesting that the two cell types might share a target cell-dependent growth factor, whose production is inhibited by regulatory T cells. The nature of this growth factor is discussed to be most likely IL-2 and it is argued that this would provide a mechanistic rational for the involvement of IL-2, IL-2 receptor and CD4+CD25+ T cells in self tolerance.

Having developed and shown the plausibility of our model for T cell mediated tolerance we explored its implications for the understanding of self/non-self discrimination. An issue of specificity is inescapable when considering a mechanism of tolerance by "linked recognition" of the APC: how can this "non-specific" regulation allow for tolerance to body components and immunity to invading pathogens. To tackle this issue, we simulated the thymic selection and peripheral dynamics of many T cell clones containing regulatory and target cells that interact according to our model. The simulations mimicked the capacity of the immune system to establish robust self-tolerance and reliably mount immune responses to foreign antigens. Mounting an immune response to foreign antigens requires the loss of regulatory cells in APC conjugates, which can happen because ubiquitous self-antigens are displaced from the APCs by foreign antigens and/or because there is an increase in the number of APCs upon the introduction of a foreign antigen. The simulations indicated that realistic balance between tolerance and immunity could only be achieved if the thymus shapes the repertoire so that affinities for self-antigens are upper and lower bounded, but, once this condition is fulfilled, differentiation of thymocytes to regulatory phenotype may be antigen-nonspecific. These results call for a reassessment of the role of positive and negative selection. Positive selection might be necessary to ensure a sufficiently high frequency of auto-reactivity in both regulatory and target T cells such that self-tolerance becomes reliable and robust. Negative selection may be required to avoid the emergence at the periphery of very high affinity anti-self regulatory cells that will make the tolerant state so robust that it could no be broken by the introduction of a foreign antigen.

Finally, we use our model to address the issue of the etiology of autoimmune disorders and its relation to infections. Considering that infection will lead to an increase in APCs and in the presentation of self-antigens we show that acute infections may trigger specific

autoimmune diseases but that overall microbial load may protect non-specifically against autoimmunity by reinforcing T cell mediated tolerance. These opposing consequences of infection stem from the non-linearity of the mechanism of interaction between regulatory and target cell populations. Therefore the model solves the otherwise paradox between the hygienist and antigen mimicry hypotheses for the etiology of autoimmune diseases.

Overall, this work provided the first comprehensive study of different aspects of T cell mediated tolerance by mathematical modelling. We raised and addressed some of the most outstanding problems in the field. We provided some answers and raised many new issues.

Spatio-temporal dynamics of germinal centres

Michael Meyer-Hermann

The germinal centre is an important part of the humoral immune response. Within this specialized environment the optimisation of antibodies with respect to a pathogen is realised involving intense somatic hypermutation of B-lymphocytes. The germinal centre is characterized by different zones that are dominated by specific cell types. The most important players are follicular dendritic cells, T-cells and B-cells in different stages of differentiation (centroblasts and centrocytes). During a germinal centre reaction the so-called dark zone is established and disappear after some days. The shape of the dark zone is specifically characterized and depends of the species and the organ under consideration.

The spatial organisation of germinal centre is simulated from the initiation involving a small number of B-cells until the end of the reaction. Hybrid cellular automatons are used in order to investigate the dependence of the resulting germinal centre morphology of various assumptions on the level of cellular interaction. It is found that chemotaxis providing a non-local cell interaction is for its own not sufficient in order to explain the convex shape of the dark zone. The source for the chemotaxis signal is assumed to be the follicular dendritic cell network or the corona or combinations of both. Chemotaxis is assumed to attract centrocytes or in addition centroblasts. The most promising results were found for the chemotaxis acting on centrocytes only and using a signal source as linear combination of the network and the corona. However, a rather satisfying result is found by assuming a differentiation signal which is secreted in the network and which induces the differentiation of centroblasts to centrocytes. This non-local cell interaction mechanism induces dark zones with correct shape and which disappear on the same time scale as in experiment.

The investigation of such cell-interactions with respect to an expected resulting morphology is based on rather narrow constraints from experiment. This concerns the affinity maturation as well as the general time course of the germinal centre volume that are to be respected on a quantitative level.

Additional presentation: **Delaunay triangulation for dynamical cell systems**

The method of Delaunay triangulation is introduced and discussed with respect to its potential to be applied in dynamical simulations of cell systems. The case of two and three dimensions is compared and technical difficulties are discussed. Especially the process of apostasies is focused on, which corresponds to the non-trivial deletion of vertices of a 3D triangulation. It is discussed if the interaction between cells is suitably described by the dual Voronoi tessellation naturally providing contact surfaces between neighbouring cells in a rather dense cell tissue. The advantageous (lattice free description, dynamical number of nearest neighbours, physical forces between cells) and the limits (dense tissue, cell volume considerations, convexity of cells) of this method are emphasized.

The dynamics of proteasomal cleavage process

Johannes Müller

The proteasome plays a crucial role for the immune system: Within a cell, the proteasome cuts peptides into fragments. Some of them are presented at the cell surface by the MHC complex. Other cells inspect these presented fragments. If they are derived from an alien peptide, the cell will be attacked by the immune system.

It is this reason, why the cutting behaviour of the proteasome is of interest. In this talk, we will not try to predict cuts for a given peptide but investigate the dynamics of the cleavage process. Basically, three different modes of degradation are discussed in literature:
(1) "Processive mode" of degradation: A peptide is cut from the beginning to the end and fragments are not cut further.
(2) "Slipping out": a first part of a peptide is processed in the processive mode, but then the peptide slips out of the proteasome.
(3) "Overlooking cuts": a fragment released by the proteasome may be cut later on in even smaller fragments.

In the present work, we model all of these three possibilities. Ths modelling is done first on the level of an stochastic individual based model. Then, by scaling arguments, we derive deterministic differential equations.

Of course, the distribution of fragment length is different for the three cases. Mostly, this approach is considered. Here, we emphasize a different timing in the dynamics implied by the three modes. This can be used in the analysis of HPLC data of cleavage experiments. With Bayesian statistics and Monte Carlo Markov Chain methods parameter are estimated. Furthermore, the performance of the different models are evaluated by Bayesian model selection tools. It turns out, that "slipping out" seems to describe the data best. It is possible to interpret this result in biological terms.

Discussion meetings on Mathematical Immunology

David Rand

The discussion meetings were chaired by David Rand (University of Warwick) and these notes were prepared by Hugo van den Berg.

A central issue in T cell activation is the molecular basis of the specificity of TCR, the antigen receptor found on T cells. The triggering of an individual TCR molecule occurs only after a number of molecular events have taken place, pointing to the essentially stochastic nature of TCR triggering. Jaroslav Stark (Imperial College London) argued that the classic kinetic proofreading formalism cannot accommodate all relevant aspects. It was generally agreed that molecular events such as arrival and binding of kinase or phosphorylase molecules should be included in the analysis. Dr. Stark claimed that inclusion of these effects engenders a hysteresis effect which greatly enhances the TCR's ability to discriminate between various ligands. Clemens Utzny (University of Toulouse) discussed the impact of TCR signalling on intracellular calcium, an important signal immediately downstream from the TCR. He argued that both the kinetics of TCR triggering and the eventual cellular response can be recovered from time series data on intracellular calcium, thus providing 'proof of principle' that the T cell may encode relevant aspects of TCR stimulation in this signal.

The diversity of T cell epitopes within the proteome was the subject of a lively debate. Statistical analyses were presented by Andrew George (Imperial College London) and by Nigel Burroughs (University of Warwick). T cell epitopes are derived via an intricate

intracellular trafficking pathway, which begins with degradation of the protein in a proteasome and ends with specialized MHC molecules presenting the peptide on the surface of the antigen-presenting cell. Dr. Burroughs presented evidence that peptides of at least 6 amino acid residues provide sufficient information for the immune system to distinguish harmless (self-derived) from harmful (pathogen- or tumour-derived) epitopes. The MHC presentation pathway is characterized by stringent selectivity: very few epitopes derive on average from any given protein. This selectivity may be interpreted in terms of the ability of the immune system to detect the pathogen without risking auto-recognition, as was argued by David Rand (University of Warwick), or it may be related with the size of the proteome and the cost associated with the need to eliminate self-recognizing T cell clonotypes from the repertoire, as was argued by Dr. George. Hugo van den Berg (University of Warwick) pointed out that not all auto-recognition is eliminated from the repertoire, and argued that this can be reconciled with the need to avoid autoimmunity. The group discussed the role of residual auto-recognition in the maintenance of a diverse TCR repertoire, as well as the stochasticity of the kinetics of this diversity over the life span of the host.

Johannes Müller (Technische Universität München) shed more light on the first step of the MHC presentation pathway. He presented a model-based analysis of data on proteasomal degradation of intracellular proteins. Elucidation of the precise mode of action of the proteasome is instrumental in understanding and predicting which parts of a protein are transformed by the MHC presentation pathway into potent epitopes capable of evoking a vigorous immune response. This paves the way for the rational manipulation of immune responses, enhancing them with more potent epitopes where an immune response is wanted (T cell vaccination against infection and tumour) or diminishing them where the response is unwanted (autoimmunity).

A final topic was the dynamics of immune responses at the systemic level. Jorge Carneiro and Kalet Léon (Instituto Gulbenkian de Ciencia) emphasized the role of multiple, subsequent interactions of the T cell with other cells (antigen presenting cells and regulatory T cells) during the course of the immune response. The importance of such interactions has been well studied in B cell responses, as attested by Michael Meyer-Hermann (Technische Universität Dresden), who discussed the role of cellular interactions in a spatial model of affinity maturation in germinal centres, but the role of such interactions in T cell interactions has thus far received relatively little attention. Elena DeAngelis (Politecnico do Torino) discussed the immune response against a tumour in terms of two possible outcomes (blow-up or the suppression of the tumour). She established conditions on which either one or the other occurs for a certain class of integro-differential equations which she proposed as a model for the immune response. The group discussed the merits and demerits of this particular class of equations as a suitable framework for immune response modelling, as well as ways in which more biological realism might be introduced.

T Cell Dynamics: From Single Receptor to Population Dynamics

Jaroslav Stark

T cells, and their recognition of foreign, peptides play a key role in the adaptive immune system. I have a broad range of interests in modelling various aspects of T cell behaviour in collaboration with Andrew George and Cliburn Chan of the Department of Immunology, Imperial College London and Robin Callard, Andy Yates, Martin Allan and Simon Moon at University College London. Current topics include:

1. The standard picture of how a single T cell receptor discriminates between peptides is based on kinetic proofreading. Apart from the fact that this is biologically quite implausible, mathematical analysis reveals that it is difficult to achieve levels of performance that are consistent with those observed experimentally. We are therefore developing and analysing alternative models, based on more realistic biochemical reaction schemes. In the future, we would like to extend these to incorporate signalling all the way to the nucleus, and to understand how signals from the large number of receptors on the cell membrane are integrated to determine cellular behaviour.

2. Most analysis of T cell recognition concentrates on a single encounter between a T cell and an antigen presenting cell. In reality however a T cell will make many encounters with a population of antigen presenting cells. We would like to understand the implications of this, and in particular how it affects our understanding of tolerance. More generally one needs to consider whole populations of T cells with a variety of signalling mechanisms regulating the population response, including cytokines, modulation of antigen presenting cell behaviour, and direct contact. The properties of individual T cells may well change with time, in response to various events; a particularly topical example of this is adaptation of thresholds. A related question is how to deal with division: in some cases T cells appear to require only one successful encounter with an antigen presenting cell and then undergo several rounds of proliferation, in others, continued stimulation is necessary to keep them dividing. The implications of this to auto-immunity need to be more fully explored.

3. Another important aspect of the adaptive immune system is memory, whereby previously encountered pathogens are remembered, and the response to repeated infection is much faster and stronger. This is the basis of vaccination. We still have a very poor understanding of how the T cell memory pool is regulated and how its diversity is preserved. We have recently proposed a model based on apoptosis due to cell-to-cell contact, and recently extended it to incorporate HIV infection, leading to some counterintuitive predictions. We are currently exploring other implications of this approach.

T cell activation dynamics as reflected by Ca^{2+} mobilization time series

Clemens Utzny
(joint work with M. Faroudi and S. Valitutti)

Activation of a T lymphocyte through cell-cell contact with an antigen-presenting cell (APC) is accompanied by the sustained mobilization of intracellular Ca^{2+}. This Ca^{2+} mobilization can be measured yielding time series of up 2 hours length. Since Ca^{2+} mobilization is highly sensitive to triggering of surface bound T cell receptors it constitutes a means of monitoring the receptor triggering dynamics in the cell-cell contact are. T cell

receptors are triggered after the ligation with a specific peptide presented on the surface of the APC.

We analyze several Ca^{2+} time series obtained under two different experimental conditions: low and high specific peptide concentration. Computation of several quantities such as the mean, standard deviation, autoregressive fit quality and autocorrelation demonstrates that the two different sets of time series are highly diverse and non-stationary. However, a quantitative analysis of the multivariate distribution of the upper quantities shows that the two sets of time series can be distinguished.

As a direct result of the differences in the signalling dynamics different gene expression patterns in the activated T cell population are observed: a low specific peptide concentration induces cytotoxic function, a high specific peptide concentration leads to cytotoxic function and the production of cytokines. Hence the fact that the two different types of Ca^{2+} mobilization time series can be distinguished by statistical means suggests that signal correlations as well as non-stationarity may carry the informations necessary for gene expression.

How thymic presentation determines the target of negative selection

Hugo van den Berg
(joint work with Carmen Molina-París)

Antigen recognition by the adaptive cellular immune system is based on a diverse repertoire of antigen receptors. Since this repertoire is formed by genetic recombination, a number of receptors is auto-reactive by chance, and may cause autoimmune diseases. Fortunately, potentially auto-reactive T lymphocytes (T cells) are rendered ineffective by various tolerance mechanisms. One of these mechanisms is negative selection, the deletion from the repertoire of immature auto-reactive T cells in the thymus. We propose to resolve T cell tolerance into its central and peripheral contributions by a comparative analysis of the statistics of auto-antigen presentation in the primary and secondary lymphoid tissues. Such an analysis allows an objective determination of the target of negative selection. General research interests: activation and regulation of cellular immune responses, with topics ranging from the molecular level to the systemic level. Ultimately I would like to attain a theoretical understanding of immune responses that is sufficiently accurate and quantitative to allow rational design of therapeutic manipulation of the immune system.

Mutation-selection models: Branching, ancestry, and maximum principle

Ellen Baake

$p_i(t)$ the fraction of i-individuals in a (large) population of haploid individuals at time t (so that $\sum_i p_i(t) = 1$), and $\boldsymbol{p} := (p_i)_{i\in S}$. Under the parallel mutation-selection model, the population evolves according to

$$\dot{p}_i(t) = \big(R_i - \bar{R}(t)\big)p_i(t) + \sum_j p_j(t)M_{ji}\,. \tag{1}$$

Here, R_i is the Malthusian fitness of type i, i.e., the difference between birth rate (B_i) and death rate (D_i), and $\bar{R}(t) := \langle \boldsymbol{p}(t), \boldsymbol{R}\rangle := \sum_i R_i p_i(t)$ designates the mean fitness of the population. Further, M_{ij} is the rate at which an i individual mutates to j ($j \neq i$), and $M_{ii} := -\sum_{j\in S\setminus\{i\}} M_{ij}$.

The equilibrium properties of (1) are determined by the leading eigenvalue, λ, and corresponding left eigenvector, $\boldsymbol{\pi}$, of the mutation-reproduction matrix $\mathcal{H} := \mathcal{M}+\mathcal{R}$, where $\mathcal{M} := (M_{ij})_{i,j\in S}$ is the generator of the mutation process, and $\mathcal{R} := \mathrm{diag}\{R_i \mid i \in S\}$. We will assume throughout that $\mathcal{M}$ is irreducible and reversible, and that λ is positive. If the number of types is large, little is known about the properties of λ and $\boldsymbol{\pi}$.

We now reconsider the model in terms of a multitype branching process, where individuals give birth, die and change type. Let $Z_j(t)$ be the number of j individuals (a random variable) at time t in a population that need not be large.

We investigate individuals alive at time $t+\tau$ and investigate the types of their ancestors at an earlier time, t. We can show that, when t resp. t and τ tend to infinity, both time average and population average of ancestral types converge to the *ancestral distribution* $\boldsymbol{\alpha}$ (with $\alpha_i = \pi_i h_i$, where $\boldsymbol{h}$ is the right eigenvector corresponding to λ, normalized s.t. $\langle \boldsymbol{\pi}, \boldsymbol{h}\rangle = 1$), almost surely on non-extinction. The main ingredients for our reasoning are the concept of size-biased trees, and the theory of large deviations.

Tying the forward and backward view together, we obtain the maximum principle

$$\lambda = \lim_{t\to\infty} \frac{1}{t} \log \mathbb{E}^i\big(|\boldsymbol{Z}(t)|\big) = \sup_{\boldsymbol{\nu}\in\mathcal{P}(S)} \big[\langle \boldsymbol{\nu}, \boldsymbol{R}\rangle - I_{\mathcal{M}}(\boldsymbol{\nu})\big] = \langle \boldsymbol{\alpha}, \boldsymbol{R}\rangle - I_{\mathcal{M}}(\boldsymbol{\alpha}), \tag{2}$$

where $\mathcal{P}(S)$ is the set of all probability measures on S, and $I_{\mathcal{M}}(\boldsymbol{\nu}) := \langle \sqrt{\frac{\boldsymbol{\nu}}{\boldsymbol{v}}}, \mathcal{M}\sqrt{\frac{\boldsymbol{\nu}}{\boldsymbol{v}}}\rangle_{\boldsymbol{v}}$ ($\boldsymbol{v}$ denotes the stationary distribution of $\mathcal{M}$, and the fraction is meant componentwise). Note that, due to $\lambda = \langle \boldsymbol{\pi}, \boldsymbol{R}\rangle$, the above relation establishes a connection between the present and the past.

As a simple example, consider the single-step mutation model with $S := \{1, \ldots, N\}$ and forward and backward mutation rates U_i^+ and U_i^-. Under the assumption that $U_i^\pm = u^\pm(x_i) + \mathcal{O}(1/N)$ and $R_i = r(x_i) + \mathcal{O}(1/N)$ as $N \to \infty$ with continuous functions u^+, u^-, and r on [0,1], and the new 'type variable' $x_i = i/N$, Eq. (2) leads to the scalar maximum principle

$$\lambda = \sup_{x\in[0,1]} \big(r(x) - g(x)\big) = r(\hat{x}) - g(\hat{x}) \tag{3}$$

in the limit $N \to \infty$. Here, $g(x) := (\sqrt{u^+(x)} - \sqrt{u^-(x)})^2$ is the mutational loss function, and $\hat{x} := \langle \boldsymbol{\alpha}, \boldsymbol{x}\rangle$ the mean ancestral type.

Returning to the mutation-selection equation (1), we can now use the scalar maximum principle (3) to derive exhaustive criteria for the existence of so-called error thresholds.

The Effects of Frequency-Dependent Selection on a Polygenic Trait

Reinhard Bürger

The equilibrium properties of an additive multilocus model of a quantitative trait under frequency- and density-dependent selection are investigated. Two opposing evolutionary forces are assumed to act: (i) stabilizing selection on the trait, which favours genotypes with an intermediate phenotype, and (ii) intraspecific competition mediated by that trait, which favours genotypes whose effect on the trait deviates most from that of the prevailing genotypes. Accordingly, fitnesses of genotypes have a frequency-independent component describing stabilizing selection, and a frequency- and density-dependent component modelling competition. We study how the equilibrium structure, in particular, number, polymorphism, and genetic variance of stable equilibria is affected by the strength of frequency dependence, and what role the number of loci, the amount of recombination, and the demographic parameters play. To this end, we employ a statistical and numerical approach,

complemented by analytical results, and explore how the equilibrium properties averaged over a large number of genetic systems with given number of loci and average amount of recombination depend on the ecological and demographic parameters. We identify two parameter regions with a transitory region in between, in which the equilibrium properties of genetic systems are distinctively different. These regions depend on the strength of frequency dependence relative to pure stabilizing selection and on the demographic parameters, but not on the number of loci or the amount of recombination. We further study the shape of the fitness function observed at equilibrium, the extent to which the dynamics in this model is adaptive, and we present examples of equilibrium distributions of genotypic values under strong frequency dependence. Consequences for the maintenance of genetic variation, the detection of disruptive selection, and models of sympatric speciation are discussed.

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Adaptive Dynamics après Régis Ferrière

Odo Diekmann

In adaptive dynamics, ecological interaction is the driving force of evolution. Variation is created by mutation and natural selection works by way of (apparent) competition. The distinguishing characteristic is phenotype (usually called trait or strategy) and both genes and sex are ignored. By way of time scale separation (almost faithful (clonal) reproduction, i.e., mutations are rare) one arrives at a trait substitution sequence to describe the evolution of the trait on the long time scale. By way of Pairwise Invasibility Plots one can illustrate graphically the analytical classification of singular points. The catalogue includes unbeatable strategies (ESS) as well as branching points. An (unfinished) manuscript of Régis Ferrière *et al.*, on which much of the talk is based, focuses on the mathematical challenge to give a precise underpinning that leads to a consistent formalism in which special cases of interest become tractable. The starting point is a stochastic model involving discrete individuals. The limits "population size $\to \infty$" , "mutation probability $\to 0$" and "mutation step $\to 0$" are considered in various orders and combinations. Ethier-Kurtz (Convergence of Markov Processes) yields most of the technical tools. The so-called canonical equation, the mutation-selection equation, moment equations and even super-processes can be derived, but both concerning the proofs and concerning the analysis of the resulting equations (the tractability issue !) there are many open problems.

On the coexistence of similar strategies

Stefan Geritz

The basic notion of adaptive dynamics is the invasion fitness, which is the exponential population growth rate $\rho(I, y)$ of a rare strategy y in a given environment I. Invasion by y is possible if and only if $\rho(y, I) > 0$. The environment I may be the virgin environment (i.e., if no population is established yet), but it may also be the environment modified by

and including other strategies already there. A population already present is referred to as the resident population, and the invader is called the mutant.

What does invasion of a resident population by an initially rare mutant tells us about the eventual outcome of the invasion event? Let I_x and I_y are the environments in a resident population of, respectively, strategy x and y. In adaptive dynamics it is often assumed that if $\rho(I_x, y) > 0$ and $\rho(I_y, x) \leq 0$, then after invasion y will continue to spread and eventually take over the population from x and hence become the new resident itself. A second common assumption is that if $\rho(I_x, y) > 0$ and $\rho(I_y, x) > 0$ (which will be referred to as *mutual invadability*), then both strategies remain. In general, however, neither of these assumptions need to be true, i.e., mutual invadability is neither necessary not sufficient for the coexistence of two strategies.

Previously, we have shown for a very large class of ecological models with initial conditions typical for an invasion event (i.e., low initial mutant population size and a resident population near an attractor), that the sum of the mutant and resident population sizes stays arbitrarily close to the resident attractor whenever the strategies of the resident and the mutant are sufficiently similar (Geritz *et al.* 2002). We refer to this result as the *Tube Theorem*, because the invasion dynamics stays inside a narrow tube connecting a neighbourhood of the resident attractor with a neighbourhood of the corresponding attractor for a population consisting only of mutants. Under the *Tube Theorem*, mutual invadability from opposite ends of the tube leads to coexistence if the strategies of the mutant and the resident are sufficiently similar. The problem of unprotected coexistence (i.e., coexistence without mutual invadability) remains. Is it possible to say anything at all about unprotected coexistence on the basis of invasion criteria alone without knowing the full mutant-resident population dynamics?

We show that under fairly mild conditions any form of coexistence (including unprotected coexistence) of similar one-dimensional strategies is possible only near special points in the strategy space called singular strategies. Near a singular strategy coexistence of more than two similar strategies is possible only under non-generic conditions. Some aspects of these results generalize to higher dimensional strategies. Moreover, for a two-dimensional environment we show that coexistence of two similar strategies generically requires mutual invadability.

Current research of
Philipp Getto

In the context of a formulation of the general theory of structured populations (as established by Diekmann, Gyllenberg, Huang, Kirkilionis and Metz), I work on the topics Continuous Dependence, Steady States, Bifurcation, Stability.

Results obtained under guidance of A.M. de Roos and my supervisor O. Diekmann are about to be submitted in a paper titled "On the (dis)advantages of cannibalism". There we compare the biological conclusions of a bifurcation analysis for a cannibalism model with those derived from evolutionary onset (of cannibalism) investigation. Please contact me for a copy.

Moreover I am involved in the proof of the Principle of Linearised Stability for Structured Populations as outlined and begun by members of the above group. Here, a linearised system is derived in the form of a linear Volterra convolution equation. The difficulty however seems that the Laplace transformation of the convolution kernel becomes singular in zero.

Infinitely many species cannot coexist robustly

Mats Gyllenberg

Let X be a locally compact normal Hausdorff space and let A be a not necessarily linear operator from the Banach space $M(X)$ of regular signed Borel measures on X to the Banach space $C(X)$ of bounded continuous real valued functions on X. Consider the differential equation

$$\frac{d\nu(t)}{dt}(\omega) = \int_{\omega} [r(x) - (A\nu(t))(x)]\, \nu(t)(dx), \qquad \omega \text{ a Borel set in } X, \tag{4}$$

where $r \in C(X)$ is given.

A positive measure $\nu^e \in M_+(X),\ \nu^e \neq 0$ is an equilibrium solution of (4) if and only if

$$(A\nu^e)(x) = r(x) \quad \text{for all} \quad x \in \operatorname{supp}(\nu^e). \tag{5}$$

Theorem *Suppose that $A : M(X) \to C(X)$ is continuous and compact and that there exists an equilibrium solution ν^e of (4) with an infinite number of points in its support. Then for each $\varepsilon > 0$ there exists an $r' \in C(X)$ such that*

$$\|r - r'\|_\infty < \varepsilon \tag{6}$$

and such that the equation (4) with r replaced by r' does not have a positive equilibrium solution with support $\operatorname{supp}(\nu^e)$. If r is positive on X, then r' can be chosen positive.

In applications to community dynamics X is the strategy space, ν is the state of the community, i.e., the distribution of strategies, $r(x)$ is the growth rate at low densities of strategy x and A is the interaction operator. The theorem says that if a community of infinitely many strategies exists, then an arbitrarily small perturbation can destroy the coexistence of these strategies.

Reaction diffusion equations with sedentary states: Epidemic spread and Fisher's equation

Karl Peter Hadeler

Epidemic spread in space is usually modelled by either contact distributions (a measure for the effect upon a susceptible individual of an infected at some distant position) or by random walks (moving or migrating invectives). Sometimes both mechanisms have been incorporated into one model. The two modelling approaches seem mathematically quite unrelated although in reality contacts are established by moving individuals. It should be possible to bridge the gap between the two approaches by introducing two levels of contact. Here a random walk model is proposed with an additional sedentary compartment. Infecteds switch between a sedentary and a migrating state. Then the contact distribution mechanism can be exhibited as a limiting case of the random walk mechanism, for the situation of short and rapid excursions of highly infective individuals. Special attention is given to scaling of the parameters and variables and the implications for the speed of epidemic spread for several scenarios.

These results suggest to study the influence of an additional sedentary compartment on the qualitative behaviour of reaction diffusion equations and reaction transport equations in general. An extension of the diffusive logistic equation or Fisher's equation has been studied by Mark Lewis and the author, for a situation where one part of the population is sedentary and reproducing, the other part migrating and subject to mortality. It is

shown that this system is formally equivalent to a semi-linear wave equation with viscous damping. With respect to stationary states and travelling front solutions, there are two very distinct scenarios (although distinguished by the character of the wave equation), depending on the choice of parameters. A non-trivial stationary state can exist on large domains in one case, and on arbitrarily small domains in the other. There is either an odd number of candidates (typically one) for minimal speeds of travelling fronts or an even number (typically two) in the other case.

The evolution of ecological communities: unfinished business

Vincent Jansen

Evolution in patchy environments can lead to the emergence of polymorphisms. In this way ecological communities can be formed through evolution. The species richness of the evolutionarily stable assemblages depends on the environmental conditions; different environments 'call' for different assemblages. I am trying to understand the evolution of biodiversity by studying a simplified meta-population model. In this model I assume that a second invasion in a patch leads to immediate take-over, similar to the assumptions made in super-infection models. My approach departs from previous models in that I assume that the second invader takes over the newly invaded patch with a certain probability. This probability is trade off with the ability to produce dispersers. I have employed this modelling technique to understand how the properties of parasitoid guilds are formed through the evolution of their component species and the evolution of plant communities. In this meta-population model the diversity emerges through the adaptive dynamics. This leads to an evolutionarily stable assemblage of species. The abundance of species in the stable assemblage obeys a power law. This is in accordance with known known results of macroecology, such as the species-area relationships and species abundance curves for which similar patterns have been reported.

On the beauties of the interaction operator

Géza Meszéna

A general fomulation of frequency-dependent selection is needed to establish:

- the ecological conditions of coexistence; and
- the connection between the population dynamics of a single population and of several populations of similar strategies.

The latter one is an ingredient of the description of evolutionary branching. The populations are distinguished via a heritable trait, the *strategy* x, which is an element of the *strategy space* $\mathcal{X}$, with some topology.
Population distribution is a meausre on the strategy space: $\nu \in \mathcal{M}_+(\mathcal{X})$.
Growth rate of strategy $x \in \mathcal{X}$ is affected by the population distribution:

$$r(x, \nu) = r_0(x) - A(\nu)(x),$$

where $r_0 \in C_\infty(\mathcal{X})$ is the growth rate in the virgin environment and the (not necessarily linear) *interaction operator* A maps $\mathcal{M}_+(\mathcal{X})$ into $C_\infty(\mathcal{X})$.
Distribution ν is an *equilibrium* solution if $r(x, \nu) = 0$ for any $x \in \mathrm{supp}(\nu)$. Then, we refer to the elements of $\mathrm{supp}(\nu)$ as *coexisting* strategies. A coexistence is *robust* if it survives a small enough perturbation of $r_0(x)$.
The *generalized competition kernel* is the (properly defined) functional derivative of the interaction operator which is regarded as an element of $C(\mathcal{X} \times \mathcal{X})$.

The interactions (the feed-backs) operates via the *environmental interaction variable* I, which is an element of the Banach space $\mathcal{E}$. The interaction operator can be expressed as $A = U \circ V$ where $V : \mathcal{M}(\mathcal{X}) \to \mathcal{E}$ and $U : \mathcal{E} \to C_\infty(\mathcal{X})$. The functional derivatives of U and V, denoted by e and f, are regarded as mappings $\mathcal{X} \to \mathcal{E}^\star$ and $\mathcal{X} \to \mathcal{E}$, respectively. The pair $\{e(x), f(x)\}$ is considered as the *niche* of strategy x.
Theorem 1 Suppose that A is compact. Then, only a finite number of strategies can coexist robustly.
Theorem 2 Suppose that the range of A is a K dimensional manifold. Then, at most K number of strategies can coexist robustly. Note, that $K \leq \dim \mathcal{E}$.
Theorem 3 Coexistence of the strategies $x_1, \ldots, x_K$ is sensitive for external perturbations if either $e(x_1) \wedge \cdots \wedge e(x_K)$ or $f(x_1) \wedge \cdots \wedge f(x_K)$ is small. That is, the niches of the strategies should be different enough if they are to be coexisting for a considerable range of an external parameter.
Theorem 4 The population dynamical fixed point of a singular strategy can be uniquely continued into the fixed point of the combined population dynamics of several strategies in a neighbourhood of the singular strategy, provided that a given matrix (calculated from the monomorphic adaptive dynamics) is non-singular. Stability of the polymorphic fixed point can be analysed in terms of a similar matrix.

Topics that presently have the interest of

Hans Metz

1. Development of the mathematical framework: Finding canonical forms of the invasion fitness function for higher degrees of polymorphism locally near evolutionarily singular points for higher dimensional trait spaces. Result: Up to quadratic terms the algebraic form derived on the basis of Lotka-Volterra population models is universal, or, equivalently, the monomorphic invasion fitness locally fully determines the polymorphic invasion fitnesses in a manner that does not depend on the underlying ecological model.

2. Ecological justification: Heuristically justifying the Adaptive Dynamics (AD) framework for physiologically structured (PS) population models, and more in particular the derivation of procedures for calculating the various quantities like invasion fitnesses and coefficients of the canonical equation for such models. Results: (a) For PS population models the canonical equation looks exactly the same as for simple ODE population models but for an additional multiplicative factor that relates to details of the resident life history, like the variance of the lifetime offspring production. (b) The result mentioned under 1 applies in full generality for PS population models.

3. Relationship with the Mendelian world (a): Exploring the consequences of male and female life history differences for measures of invasion fitness for polymorphic Mendelian PS populations. I do have interesting closed expressions for single locus genetics but I still have to explore their multi-locus extension, and to see what their consequences are for e.g. life-history evolution and the like.

4. Relationship with the Mendelian world (b): Exploring the influence of the genetic architecture on the choice made by Mendelian populations for the solution of ecologically posed branching problems as defined by AD theory, where the solution may be e.g. speciation, sexual role differences, random assignment of different types based on external cues, or the gradual evolutions of single locus dimorphisms with large phenotypic effect.

On diploid versus clonal ESSes in metapopulations

Kalle Parvinen
(joint work with Hans Metz)

Most studies of evolutionarily stable strategies (ESS) assume clonal reproduction. At least in the simplest cases, more realistic genetic models yield results compatible with the clonal results. As the mutant is initially rare, in well mixed populations practically all mutants come as heterozygotes. Therefore, the question whether a mutant population can invade the resident or not, does not depend on the properties of mutant homozygotes. However, the situation may be expected to differ in meta-populations with small local population sizes, as there mutants are not locally rare, even when the mutant population is still globally small. We have studied the evolution of dispersal in such a meta-population model.

It turns out that there are differences between the clonal and diploid ESS dispersal rates. In a homogenous landscape the discrepancy is minor (less than 2%). The situation is completely different in a heterogeneous landscape: the discrepancy is already significant, but more importantly, evolutionarily stability is not necessarily the same. It is possible, that the singular strategy is evolutionarily stable in the clonal case but not in the diploid case, or vice versa.

In general I am working in the field of adaptive dynamics. Especially, I have studied the evolution of dispersal in (structured) meta-population models.

K. Parvinen and J.A.J. Metz (2002) *On diploid versus clonal ESSes in meta-populations.* Interim report IR-02-044, IIASA, Laxenburg, Austria.
http://www.iiasa.ac.at/cgi-bin/pubsrch?IR02044.

Recent research interests

Andrea Pugliese

Virulence evolution, and coexistence of parasite strains. I am rather interested about evolutionary dynamics of parasites, especially concerning the evolution of virulence. Despite this interest, my only contribution to the subject is the paper [1], where I discuss whether some mechanisms (especially super-infection) proposed to explain the coexistence of several cross-immune parasite strains do explain coexistence over evolutionary time-scale.

The quick answer is that, using the framework of adaptive dynamics, it does not: evolution will generally bring virulence to an ESS. However, much depend on the details of how super-infection relates to virulence: if the function is very steep, then, for small but finite mutational steps, evolutionary dynamics may be more complex and difficult to predict.

On this subject, I would be interested in discussing the subject assuming that mutation time-scale is similar to epidemic time-scale (unlike adaptive dynamics); in proceeding to co-evolutionary dynamics of host and parasite; in putting some insight from immunology into the models.

Meta-populations. I have worked on a deterministic structured model for meta-populations, whose variables are $p_i(t)$, the fraction of sites (assumed to be infinitely many) with i individuals ($i = 0, 1, \ldots$). Together with Barbour, we proved [2] that this model always converges to an equilibrium, the extinction equilibrium below a threshold, a positive equilibrium (a

distribution of patch sizes) above the threshold. In [3] we discuss how this positive equilibrium converges (as the carrying capacity of each patch goes to infinity, while extinction rate scales appropriately) to what predicted by Levins' model.

I was concerned with limits and scalings for epidemic SIS models in meta-populations [4]. It would certainly be very interesting to understand how much these models still work reasonably with local dispersal (global dispersal is necessary for their formulation).

Other. Other models I have been working lately concern macro-parasites or tick-borne infections.

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These and other papers are available at: http://www-math.science.unitn.it/∼pugliese/

Patterns of Speciation

Martin Rost

(joint work with Michael Lässig, Ilkka Hanski, Mikko Alava)

Modes of speciation have been the subject of a century's debate. Traditionally, most speciations are believed to be caused by spatial separation of populations (*allopatry*). Recent observations [e.g. Schliewen & al. 2001] and models [e.g. Doebeli & Dieckmann 2000] show that speciation can also take place in *sympatry*, following the reproductive isolation of subpopulations. We discuss a comprehensive model of coupled differentiation in phenotype, mating, and space, showing that spatial segregation can be an induced process following a sympatric differentiation. This is found to be a generic mechanism of adaptation to heterogeneous environments. It explains the ubiquitous spatial patching of newly formed species, despite their sympatric origin [Schliewen & al. 2001, Riço & Turner 2002].

Host-parasitoid dynamics. Generally I'm interested in patterns occuring in species coexistence. Well studied examples are insect host-parasitoid dynamics. A spatially extended model [Rost & al. 2001] can explain apparent domain boundaries and their movement and location. Currently I'm working on characterisation of spatiotemporal patterns in host-parasitoid meta-populations.

Patterns at interfaces. Patterns forming at interfaces are driven by, e.g., surface tension, elasticity, capillarity. Recent examples of my work are imbibition of liquid into disordered media [Dubé & al. 2003] and phospholipid layers on lung alveoli.

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Interactive Biological Motion: Polymers, Cells and "Swarmers"

Wolfgang Alt

The focus of my current research is in describing principles and mechanisms of interaction between actively moving biological entities leading to phenomena of aggregation and collective motion.

The mainly used modelling tools are stochastic multi-particle systems, i.e., Langevin equations for positions and velocities of all interacting entities, where the terms describing mutual interaction do not only contain acceleration "forces" as attraction or repulsion, but also accelerations inducing mutual velocity adjustment. The corresponding coefficients usually depend nonlinearly on neighbour distance.

Moreover, I am interested in deriving conditions and procedures that allow to construct corresponding continuum limits, which turn out to be generalized types of nonlinear Navier-Stokes equations for density and mean velocity. Thereby I search for scaling laws, which guarantee that the stochastic perturbations are maintained in the continuum (partial differential) equations, e.g., appearing there as Gaussian noise (spatio-temporal Brownian sheets) .

For applications in standard cases (see examples below) this modelling approach is sufficient. However, for more complex interactions (as for direct cell-cell contacts or for cell interactions via extracellular matrices occurring in tissue dynamics) more elaborate models have to be considered: The interaction terms then might depend on more detailed state variables of the cells (as their extension radius, shape, adhesiveness or other surface properties) or on the eventual mechanics and dynamics of the mediating interaction field.

Example 1 (Dynamics of bird swarms)

3-dimensional bird swarms (e.g. of starlets) appear as highly dynamical "clouds" with changing their shape and flight direction. 1-dimensional chains of migrating birds (e.g. of wild geese) typically show length occillations and compression waves reminding to similar phenomena as in traffic queues.

Example 2 (Dynamics of action networks, patches or ruffles)

In migrating cells as keratinocytes or in growing cells as yeast, action polymer filaments interact via cross-linking or contracting proteins and lead to local aggregation patches or bundles which often fluctuate and dynamically change their intensity or localization. There appear quite regular periodic phenomena (as in lamellipodial "ruffle" waves) but also chaotical movement (as of actin patches in the cortex of yeast cells).

Rippling Patterns in Aggregates of Myxobacteria Arise from Cell-Cell Collisions

Uwe Börner

(joint work with Andreas Deutsch, Markus Bär)

Pattern formation in aggregates of bacteria and amoebae is a widely observed phenomenon. The emerging colonial patterns are typically modelled with continuous reaction-diffusion equations. An alternative approach uses discrete models to describe the motion of individual cells. This is the adequate approach if the number of cells is rather small and the spatial scale of the pattern is of the order of the cell size.

Myxobacteria switch from individual to social behaviour when they are starved. A complex developmental cycle is initiated culminating in a multicellular fruiting body. A variety of spatio-temporal patterns emerges such as standing wave oscillations of the cell density (rippling). Individual cells are oriented perpendicular to the ripples and move regularly back and forth, periodically reversing the gliding direction. Cell reversal is regulated by a developmental signal (C-factor) which is transmitted through close cell-cell contact and not by diffusion.

Most observed features can be captured by a cellular automaton model where cells are piled up on a fixed square lattice and move according to their orientation. Opposite oriented cells in the neighbourhood cause reversal of non-refractory cells. The refractory time can be tuned such that the wavelength and period agree with experiments.

Reference: U. Börner & al., *Phys. Rev. Lett.* **89**, 078101 (2002).

Mathematical modelling of growth regulation of fission yeast cells in space and time

Attila Csikasz-Nagy

(joint work with Wolfgang Alt, John J. Tyson, Béla Novak)

The non-spherical shape of some cells is a consequence of polarized growth. The rod-shaped cells of fission yeast provide a convenient system to study regulation of cell morphogenesis and cell cycle.

We worked out detailed mathematical models of the network of cell cycle regulation in fission yeast. Recently we also started to investigate the growth patterns of these cells. The cylindrical fission yeast cells initiate polarized growth first only at one tip of the cylinder and at later stages of the cell cycle they change to bipolar growth by turning on the growth at the other tip.

Polarized actin polymerization plays a role in the formation of the two growth zones at the tip of the rod-shaped cells. This type of pattern formation can be achieved by a simple reaction-diffusion system of two molecule types. A positive feedback on one of them and a difference in their diffusion constants are also necessary to reach a steady state when their concentration is changing in space. Polarized actin polymerization is a perfect candidate to be regulated by this Turing type pattern forming mechanism: Actin monomers are diffusing quickly in the cells and they can turn to slowly diffusing actin filaments by an autocatalytic step.

We propose a simple model for fission yeast morphogenesis based on the dynamics of this auto-catalytic actin polymerization catalyzed by a molecule which is transported to the cell tips by microtubules. We show that our model can simulate the growth pattern changes of wild type fission yeast cells. The sensitivity analysis of the model shows robustness for small changes of any parameter, while bigger changes create phenotypes which have been found experimentally.

Clamped-Filament Elongation Model for Actin-Based Motor

Richard Dickinson

Actin polymerizes by adding ATP-bound actin monomers preferentially onto barbed end (plus end) and depolymerizes by ADP-actin dissociation at the pointed end (minus end) ADP-actin. These reactions may be catalyzed by other protein components such as profilin and ADF/cofilin. Polymerization at barbed ends has long been thought to drive actin-based motility in cell crawling as well as the intracellular locomotion of organelles and certain pathogens. In this view, the force at the surface is provided by free energy of the monomer addition reaction of ATP-actin monomeric actin (ATP-G actin) to form ATP-filamentous actin (ATP-F action), and ATP hydrolysis serves to release monomers from the non-working ends to be ultimately recycled following nucleotide exchange (ADP for ATP) back to the barbed ends. Mathematical treatments of this hypothesis (e.g. Hill (1981), Mogilner & Oster's Brownian ratchet model (1996)) commonly assume conditions are such that the ATP-G-actin addition reaction (Kd 0.1 mM) is essentially irreversible, although the free energy of the reaction is less than about 1.7 kT with corresponding maximum force of less than $\sim$ 3 pN, assuming the ATP-G-actin concentration remains below the pointed-end critical concentration (Kd 0.6 mM). Moreover, the principle of detailed balance requires that profilin-ushered monomer addition followed by profilin release has the same free energy change as the direct monomer addition (assuming the resulting filaments are identical) (Kang et al. 1999), a physical constraint largely ignored in theoretical treatments relying on addition of profiling-actin complex followed by profilin dissociation. Therefore, simple monomer addition without another energy source provides a very weak driving force for actin-based motility.

A number of recent experimental observations also appear inconsistent with the Brownian ratchet model by suggesting filaments in some cases likely grow while tethered to the surface. For example, Listeria trajectories exhibit episodes of 5.4-nm stepwise motion, corresponding to the periodicity of the actin filament subunits, and extremely small positional fluctuations during the intermittent pauses (Kuo and McGrath, 2000). These finding suggest that motile bacteria remain firmly bound to actin filament ends as they elongate, probably through the host protein VASP (vasodilator-stimulated phosphoprotein) and bacterial surface protein, ActA. Upadhyaya et al. (2002) found that ActA on motile vesicles co-localize with F-actin-rich tail, also suggesting a maintained association between filaments ends and ActA, probably through VASP. SEM micro-graphs by Cameron et al. also appear to show that filament ends tethered to the surface of ActA-coated polystyrene beads; in some cases single presumably elongated filaments are seen attached to 50-nm particles.

Based on these and other observations, we have proposed a fundamentally different mechanochemical model of actin-based motility (called the Lock, Load & Fire mechanism) where force is generated by affinity-modulated, clamped-filament elongation. During the locking step, the filament's terminal ATP-containing subunit binds tightly to a clamp situated on the surface of a motile object; in the loading step, ATP-actin monomer(s) bind to the filament end, an event that triggers the firing step, wherein ATP hydrolysis on the clamped subunit attenuates the filament's affinity for the clamp. This last step initiates translocation of the new ATP-containing terminus to the clamp, whereupon another cycle begins anew. Calculation of force-dependent elongation explains how surface-tethered filaments can grow while exerting flexural or tensile force on the motile surface. Moreover, stochastic simulations of the model reproduce the signature motions of Listeria. This elongation motor, which we term actoclampin, exploits actin's intrinsic ATPase activity to

provide a simple, high-fidelity enzymatic reaction cycle for force production that does not require elongating filaments to dissociate from the motile surface. This mechanism may operate whenever actin polymerization is called upon to generate the forces that drive cell crawling or intracellular organelle motility.

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Quantification and modelling of cell migration

Peter Dieterich

Nearly everybody is fascinated by observing the dynamics, rhythms, and variations of migrating biological cells under the microscope. Biologists and medical researchers are mainly interested in the molecular mechanisms underlying cell migration which is involved in many (patho-) physiological processes as wound healing, angiogenesis, or tumour metastasis. To maintain these functions the migration machinery must coordinate spatially and temporally the cytoskeleton, cell-substrate and cell-cell interactions, and the activity of ion channels and transporters. Small modifications of molecular components typically result in sophisticated changes of locomotion which can rarely be put into a "single number" because cell migration proceeds in a highly complex way. And this is the main reason, why even physicists and mathematicians are attracted by migrating cells.

It is the aim of our work to quantify, classify, and model the system dynamics of cell migration starting from experimental observations of living single and confluent cells. Therefore, sequences of microscopic phase contrast images are acquired and analyzed under different experimental conditions. Many cells are coupled to their neighbours via cell-contact proteins and are exposed to external stimuli as chemical gradients or mechanical forces. A typical example is given by endothelial cells which cover the inner surface of the vascular system and are permanently exposed to fluid shear stress. Therefore, we have examined a 2D monolayer of confluent endothelial cells and studied the influence of constant, laminar fluid shear stress.

Defining characteristic parameters to capture migration, orientation and shape change of individual cells and the cell ensemble, we have found a typical phase-like response to the onset of shear stress with the following time-course: Resting conditions with seeming stochastic movements (phase I), change of motility with increased mean location but reduced spatial cell fluctuations (phase II), onset of alignment as rigid rotation (phase III), and

finally cell elongation (phase IV) [1]. In addition, these data provide a starting point to develop a mathematical model of cell migration in confluent cultures under the influence of fluid shear stress [2].

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Large How do tumours grow in-vitro?

Dirk Drasdo
(joint work with S. Höhme)

To what extent is tumour growth controlled by nutrients, biomechanical forces, and other factors? The main mechanisms that determine the growth dynamics of tumours at different stages and in different environments are still largely unknown [Gatenby & Maini2003]. This question is usually addressed by examining *in-vitro* model systems, which are experimentally well accessible and hence allow for systematic studies of parameter and growth condition dependencies. However, even *in-vitro* experiments are rarely free of unknown or uncontrolled influences.

Here we present a mathematical model to study the spatio-temporal growth dynamics of two-dimensional tumour monolayers and three-dimensional tumour spheroids as a complementary tool to *in-vitro* experiments. Within our model each cell is represented as an individual object and parameterized by cell-biophysical and cell-kinetic parameters that can all be experimentally determined [Drasdo & Höhme 2003]. Hence our modelling strategy allows to study which mechanisms on the microscopic level of individual cells determine the macroscopic properties of tumour growth. We quantitatively compare our *in-silico* results to published experimental observations on avascular tumour spheroids [Freyer & Sutherland 1985 and 1986] and on monolayer cultures [Bru & al. 1998]. Our findings suggest the significance of a biomechanically-mediated growth inhibition, a form of contact inhibition, during the experimentally observed transition from exponential to sub-exponential growth at sufficiently large tumour sizes. The good agreement between our *in-silico* results and the experimental data suggests that our model strategy may provide a starting point from which a quantitative modelling of *in-vivo* tumour growth under normal and therapy conditions may become feasible.

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Bifurcation analysis of an orientational aggregation model

Edith Geigant
(joint work with Michael Stoll)

We consider an integro-differential equation for the evolution of a function f on the circle, describing an orientational aggregation process. In the first part we analyze generic bifurcations of steady-state solutions when a single eigenvalue changes sign. Lyapunov-Schmidt reduction leads to the bifurcation equation which is solved explicitly by formal power series. We prove that these series have positive radius of convergence. Two examples exhibit forward and backward bifurcations, respectively. In the second part we assume that the first and second eigenvalues become positive. Again we use Lyapunov-Schmidt reduction to arrive at the reduced bifurcation system from which we get the bifurcating branches as power series. We calculate the two most important parameters of the reduced system for two examples; one of them has interesting mode interactions which lead to various kinds of time-periodic solutions.

Reference: E. Geigant and M. Stoll, J. Math. Biol. **46**, 537-563 (2003).

Stochastic Volterra Integral Equations

Frank hoppensteadt

Volterra integral equations arise in a variety of application in the life sciences and engineering. For example, renewal theory in population biology and demographics and linear time invariant systems in engineering. Linear equations of this kind have the form

$$x(t) = \phi(t) + \int_0^t h(t,t')\, x(t')\, dt'$$

where $\phi(t)$ describes external input to the system and h describes the system's impulse response function (i.e., if $x(t) = \delta(t)$ in the integral, its output is $h(t,t)$). More general nonlinar problems have the form

$$x(t) = \phi(t) + \int_0^t h(t,t',x(t'))\, dt'.$$

Extensive work has been done on such systems over the past 100 years in a variety of mathematical and applied settings [Miller 1971, Gripenberg & al. 1990].

It is of interest to investigate these models when the data (e.g., ϕ and h) involve random perturbations. Work described in detail in [Skorokhod 2002] provides some insight to these problems, and the purpose of this presentation is to describe that metthodology.

Consider a vector of random processes $y(t)$ that take values in a measurable space $\{Y, \mathcal{C}\}$, called the noise space. We suppose that this process is either Markov or stationary, satisfies a strong mixing condition and is ergodic in Y with measure ρ. If g is a measurable fuction from Y to E^1, then the ergodicity of the process y implies that

$$Eg(y(t)) = \lim_{T\to\infty} \frac{1}{T} \int_0^T g(y(t))\, dt \equiv \bar{g}$$

and the central limit theorem implies that

$$\lim_{T\to\infty} \frac{1}{\sqrt{T}} \int_0^{Tt} (g(y(t')) - \bar{g})\ dt' = b\, W(t)$$

where $W(t)$ is a diffusion process.

We consider problems in which the noise process moves on a fast time scale relative to changes in the system's state. For example consider the nonlinear renewal problem

$$x_\varepsilon(t) = \phi(t) + \int_0^t h(t, t', y(t'/\varepsilon), x_\varepsilon(t'))\ dt'$$

for the random process (system state) $x_\varepsilon(t)$. Here h is a function that is smooth with respect to t, t', and x, and is measurable with respect to the $y \in Y$. ε is a small positive constant that describes the ratio of the system time scale to the noise time scale, and the process y is as described above.

We have developed a perturbation algorithm for constructing approximations to $x_\varepsilon(t)$ which shows that

$$x_\varepsilon(t) = \bar{x}(t) + \sqrt{\varepsilon}\tilde{x}(t) + O(\varepsilon)$$

where $\bar{x}(t)$ solves the averaged problem

$$\bar{x}(t) = \phi(t) + \int_0^t \bar{h}(t, t', \bar{x}(t'))\ dt'$$

with $\bar{h}(t, t', x) = \int_Y h(t, t', y, x)\ \rho(dy)$. The first order approximation solves the linear stochastic integral equation

$$\tilde{x}(t) = z(t) + \int_0^t \bar{h}_x(t, t', \bar{x}(t'))\ \tilde{x}(t')\ dt'$$

where z is a Gaussian process. As a result $\tilde{x}(t)$ is a Gaussian process as well. The autocorrelation function of $z(t)$ can be determined directly from h and the statistics of y.

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Regulation of actin dynamics in cell motility

Leah Keshet
(joint work with Alex Mogilner)

Actin is an important component of the cytoskeleton whose functions include generation and regulation of cell shape and motion in animal cells. Actin filaments are polymers composed of monomer subunits, with two distinctly different ends. The barbed ends, which grow fastest in the present of monomers are usually oriented towards the cell edge, and are believed to push the cell membrane forward in protrusion.

The biochemistry of the actin recycling mechanism is well known, and most rate constants governing the capping, fragmentation of filaments, and the exchange of actin monomers from spent, depolymerized units to activated polymerization-competent monomers is known. I discuss a model which relates the number of barbed ends of actin filaments to the protrusion velocity. The model is based on the actin exchange cycle, the thermal ratchet mechanism for protrusion, and the nucleation of new barbed ends by Arp2/3. The model predicts that an optimal number of barbed ends is needed for fast locomotion, that speeds correlates with the total amount of actin in the cell, and that sequestering agents such as thymosin would decrease the protrusion speed.

This work appeared in Biophys J 83: 1237-1258 (2002).

From signal transduction to chemotaxis equations in *E. coli*

Hans Othmer

Evolution has provided many organisms with sophisticated sensory systems that enable them to respond to signals in their environment. The response frequently involves alteration in the pattern of movement, either by directed movement, a process called *taxis*, or by altering the speed or frequency of turning, which is called *kinesis*. Chemokinesis has been most thoroughly studied in the pretrichous bacteria *Escherichia coli*, which has 6-8 helical flagella distributed over the cell surface, and swims by rotating them. When rotated counterclockwise (CCW) the flagella coalesce into a propulsive bundle, producing a relatively straight "run", and when rotated clockwise (CW) they fly apart, resulting in a "tumble" which reorients the cell with little translocation. A stochastic process generates the runs and tumbles, and in a chemoeffector gradient runs that carry the cell in a favourable direction are extended. The cell senses spatial gradients as temporal changes in receptor occupancy and changes the probability of CCW rotation (the bias) on a fast time scale, but adaptation returns the bias to baseline on a slow time scale, enabling the cell to detect and respond to further concentration changes. The overall structure of the signal transduction pathways are well-characterized in *E. coli*, but important details are still not understood. Only recently has a source of the large gain in the response been identified experimentally, and in this talk we present a mathematical model that can explain these observations. We also address the issue of how to derive population-level equations such as the classical chemotaxis equations from single-cell descriptions that incorporate signal transduction and behavioural changes, using moment closure techniques.

The effect of growth and curvature on pattern formation

Faustino Sánchez-Garduño

During last years many publications deal with the emergence of patterns in changing domains. The way in which these authors include this is different from just putting time dependent diffusion coefficients or a source in the curved boundary. Here I present the derivation of a one and two dimensional model which takes into account the growth factor and the local geometrical changes (curvature) of the domain. These factors have a great influence in the selection of patterning. The model itself consists of two nonlinear partial differential equations, where the diffusion process includes space-time diffusion, advection and dilusion terms. The reactive part is of third order. Some numerical simulations are carried out on two dimensional simple manifolds embedded in R^3. These show us different patterns which do not apear in fix domains.

Edited by Martin Rost

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