Minisymposium 26

Mathematics in the Biosciences

Leiter des Symposiums:

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During the last years, modern biosciences have opened their doors widely: they do not only call for informatics and data processing techniques in order to master their huge amounts of experimental results, but they particularly need and want to implement appropriate tools of mathematical modelling and analysis. This minisymposium is intended to offer a selected view into this still growing field of “Biomathematics”, by presenting a series of talks on some typical biological questions together with the suggested mathematical solutions. In-between the presentations, enough time will be reserved for critical discussion and fruitful exchange of ideas.

The talks shall show that, for modelling biological processes and for understanding their particular theoretical stuctures, interesting and often newly stimulated mathematical methods are required, used and invented. The presented topics include: Nonlinear renewal equations for structured population dynamics, models for cell-cell communication in immune systems, stochastic and continuum descriptions of cell movement and membrane deformation as well as statistics of polymer cleavage fragmentation, multiple sequence alignment, and genetic association analysis.

Donnerstag, 21. September

Übungsraum 4, Geographisches Institut, Meckenheimer Allee 166

15:00 – 15:50 **Odo Diekmann** *(Utrecht)*
General Theory of Nonlinear Renewal Equations with Applications

16:00 – 16:20 **Thomas Hoefer** *(HU Berlin)*
Cell Communication in Immune Systems

16:30 – 16:50 **Sven Rahman** *(Bielefeld)*
Cleavage fragment statistics

17:00 – 17:20 **Tobias Müller** *(Würzburg)*
A New View on Multiple Alignment

17:30 – 17:50 **Tim Becker** *(Bonn)*
Haplotype Sharing and Association Analysis

Donnerstag, 21. September

Übungsraum 4, Geographisches Institut, Meckenheimer Allee 166

15:00 – 15:50 **Benoit Perthame** *(ENS, Paris)*
Cell Movement and Interactions

16:00 – 16:20 **Florentin Wörgötter** *(Göttingen)*
Predicitve Mechanisms in Closed-Loop Sensori-Motor Systems: The Convergence of Differential Hebbian Learning

16:30 – 16:50 **Axel Voigt** *(caeser, Bonn)*
Surface Flow Models for Biomembranes

Vortragsauszüge

Odo Diekmann *(Utrecht)*
General Theory of Nonlinear Renewal Equations with Applications

By doing the bookkeeping for structured populations in terms of the history of the population birth rate and the history of the environmental interaction variables, one obtains delay equations.
A delay equation is a rule for extending (in one direction, the future) a function that is originally defined on an interval. The rule either specifies the derivative in the right end point or the function itself. Perturbation theory for dual semigroups (also called sun-star calculus) provides a convenient abstract framework for dealing with both of these cases in a unified manner.
Sun-star versions of the Principle of Linearized Stability and the Hopf Bifurcation Theorem therefore apply to structured population models and one can make rigorous inferences concerning dynamic behaviour from information about the position of the roots of a characteristic equation in the complex plane, and how these change as a function of a parameter.
As an example, we show how variable maturation delay can lead to oscillations.

The lecture is based on joint work with Philipp Getto, Mats Gyllenberg and Hans Metz.

Thomas Hoefer *(HU Berlin)*
Cell Communication in Immune Systems

T cells are critical players in immune responses whose activation is tightly regulated. I will discuss networks of gene regulation and intercellular signalling involved in the control of T cell proliferation and differentiation of memory T cells. Cell-biological research has identified multiple feedbacks loops acting both within the cells and in an autocrine fashion via secreted signals. Mathematical models will be introduced that demonstrate how feedbacks can support all-or-none cellular decisions and the imprinting of immunological memory. Moreover, a model of intercellular communication between T cell subsets suggests that signalling via readily diffusible cytokines –the main messengers in the immune system– can be strongly controlled in spatial range by autocrine feedbacks. Experimental approaches that were triggered by the theoretical work will be discussed.

Sven Rahman *(Bielefeld)*
Cleavage fragment statistics

Peptide mass fingerprinting is a technique to identify a protein from its fragment masses obtained by mass spectrometry after enzymatic fragmentation: An experimental mass fingerprint is compared with reference fingerprints obtained from protein databases by in-silico digestion. Recently, much attention has been given to the questions of how to score such an alignment of mass spectra and how to evaluate its significance; results have been developed mostly from a combinatorial perspective. In particular, existing methods generally do not (or only at the price of a combinatorial explosion) capture the fact that the same amino acid can have different masses because of, e.g., isotopic distributions or variable chemical modifications.
We offer several new contributions: We introduce the notions of a probabilistically weighted alphabet, where each character can have different masses according to a specified probability distribution, and the notion of a random weighted string as a fundamental model for a random protein. We then develop a general computational framework, which we call Weight Accumulating Markov Models (WAMMs), to obtain various cleavage fragment statistics of random proteins. We obtain general formulas for the length distribution of a fragment, the number of fragments, the joint length-mass distribution, and for fragment mass occurrence probabilities, and special results for so-called standard cleavage schemes (e.g., for the enzyme Trypsin).

Tobias Müller *(Würzburg)*
A New View on Multiple Alignment

Many molecular sequence analyses start with a collection of aligned homologous sequences to infer certain features of the considered group or subgroup of sequences. We focus on the general question: what are the general sequence pattern inside the multiple sequence alignment discriminating and defining subgroups. Such patterns could later be mapped to structioral or functional features of the sequence family. The proposed problem becomes more and more challenging when the number resp. the length of the considered sequences increases. We propose a singular value based approach based on paramters of a Hidden Markov Model to give a structured view of the multiple sequence alignment. Finally we show and discuss biological examples.

Tim Becker *(Bonn)*
Haplotype Sharing and Association Analysis

Ziel der Genetischen Epidemiologie ist es, Veränderungen im Genom zu finden, die für das Entstehen einer bestimmten Krankheit verantwortlich sind. Formal gesehen ist das Genom eine Sequenz aus den vier chemischen Grundbausteinen Adenin, Cytosin, Guanin und Thymin. Der Austausch eines einzigen Bausteins kann bereits das Erkrankungsrisiko einer Person ändern. Fixe Stellen im Genom die zwischen Personen variieren, bezeichnet man als SNPs, deren Ausprügungen A,C,G ,T als Allele. Der einfachste Ansatz kausale SNPs zu identifizieren, besteht darin, die Allelverteilung aller SNPs zwischen Fällen und Kontrollen zu vergleichen. Da es im Genom 3 Millionen verschiedene SNPs gibt, ist dieser Ansatz nicht durchführbar. Aufgrund der Entstehungsgeschichte sind SNPs jedoch lokal hoch korreliert. Dadurch ergibt sich zum einen die Möglichkeit ohne einen zu großen Powerverlust nur eine Auswahl der SNPs zu testen. Zu anderen ist es sinnvoll die lokalen Abfolgen der Ausprägungen der SNPs zu betrachten. Diese werden als Haplotyp bezeichnet. Die Assoziationsanalyse mit Haplotypen stellt einige statistische Herausforderungen: der Mensch ist diploid, d.h. er trägt die Sequenzfolge der Grundbausteine in doppelter Ausführung. Selbst wenn also für verschiedene SNPs die Allele eine Person bekannt sind, so ist i.A. unbekannt, wie sie sich in zwei Haplotypen, aufteilen. Es sind deshalb statistische Methoden nötig, um Haplotypfrequenzen zu schätzen. Für die Assoziationsanalyse muss die zusätzliche Varianz beachtet werden. Es werden Monte-Carlo-Simulationen zur P-Wert-Bestimmung eingesetzt. Darüber hinaus muss die zu betrachtende Länge der Haplotypen festgelegt werden. Eine Möglichkeit besteht darin, alle Längen innerhalb eines zu betrachten und eine Korrektur für multiples Testen anzuwenden, die die Korrelation angemessen berücksichtigt. Andere Ansätze versuchen die Entstehungsgeschichte der SNPs und Haplotypen zu rekonstruieren und somit zu sinnvoll zu betrachtenden Einheiten zu kommen.

Benoit Perthame *(ENS, Paris)*
Cell Movement and Interactions

Several evolution equations arising in biology share the same qualitative aspect. When some parameters of the model are small, the solutions concentrate as Dirac masses that moves with a finite speed. This occurs in two examples:

(i) Adaptative evolution at the population level. This describes the selection of individuals with a trait that is better adapted to an environment shared by all the population when 'small' mutations occur.
(ii) Nonlinear parabolic equations that exhibit a Turing type instability.

We will give mathematical models of such dynamics and show that an asymptotic method allows us to describe the evolution of the 'concentration points' . Numerically, we can observ jumps in the Dirac locations, bifurcations (which lead to the cohabitation of two different populations) ot transition from dimorphism to monomorphism. In the regular regime, we obtain a canonical equation where the drift is given by a nonlinear problem.
The asymptotic method leads to evaluate the weight and position of a moving Dirac mass desribing the population. We will show that a Hamilton-Jacobi equation with constraints naturally describes this asymptotic. Some more theoretical questions as uniqueness for the limiting H.-J. equation will also be addressed.

Florentin Wörgötter *(ENS, Paris)*
Predicitve Mechanisms in Closed-Loop Sensori-Motor Systems: The Convergence of Differential Hebbian Learning

During the lifetime of a creature there are often events where two sensor signals follow each other in time, which refer to the same situation. Hence the earlier signal acts predictive in comparison to the later signal. For example, heat radiation predicts pain on touching a hot surface. This general situation is due to the fact that we have near sensors like touch, taste and far sensors, like smell, hearing and vision. It is evident that it is advantageous for a creature to react to the earlier far-sensor signal without having to wait for a (potentially damaging) near-sensor signal. Often this requires learning, because, prior to having experienced the first such sensor-signal sequence, the relevance of the correlation between paired signals is unknown to the animal. It is possible to employ differential hebbian plasticity at single simulated synapses to emulate such a learning process. We will specifically show that such a mechanism will lead to improved behavior in closed-loop sensori-motor systems, using some robots for demonstration. Furthermore, it can be proven that the employed mechanism will converge to appropriate synaptic weights which will stabilize as soon as the newly learned behavior has also become stable.

Axel Voigt *(caesar, Bonn)*

Surface Flow Models for Biomembranes

We derive a thermodynamically consistent model for phase seperation in multicomponent vesicles. The model is a refinement of the classical Helfrich model and mathematically can be viewed as a Cahn-Hilliard like equation on an evolving surface, where the evolution is determined through a Willmore like flow. Numerical algorithms for this system of coupled 4th order equations are presented and first simulation results are shown.

This is joint work with Frank Haußer, John Lowengrub and Andreas Rätz.