Abstracts

of Plenary Lectures

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Heterogeneity of proliferating cell populations: Models and data

Recent years brought a deluge of technologies to observe biological processes at single-cell and sometimes at single-molecule levels. These include high-content microscopy as well as microfluidics and insertion of engineered fragments of genetic material into cells. Stochastic models introduced 20 or 30 years ago suffered from paucity or absence of such data. Some of these models can be now re-thought and re-applied in the new context. The talk, idiosyncratically, reviews some of these models conceived over past 20 years and confronts them with recent biological findings. This includes the pseudo-stochastic model of unequal division of cells, and the branching process model of gene amplification, Biological phenomena discussed include self-renewal and maturation of stem cells, variability of abundance of proteins in cells, and carcinogenesis.

Plenary Lecture, Saturday, July 2, 17:00

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A rigorous model for adaptive dynamics of Mendelian diploids

Adaptive dynamics so far has been put on a rigorous footing only for clonal inheritance. We extend this to sexually reproducing diploids, although admittedly still under the restriction of an unstructured population with Lotka-Volterra-like dynamics and single locus genetics (as in Kimura's infinite allele model). We prove under the usual smoothness assumptions that when advantageous mutations are rare and mutational steps are not too large the population behaves on the mutational time scale (the "long" time scale of the literature on the genetical foundations of ESS theory) as a jump process moving between homozygous states (the trait substitution sequence of the adaptive dynamics literature). Essential technical ingredients are an individual-based stochastic (birth and death) process with mutation and selection, a rigorous, geometric singular perturbation theory based, invasion implies substitution theorem and estimates for the probability of invasion in a dynamical diploid population. In the small mutational steps limit this process gives rise to a differential equation in allele or in phenotype space of a type referred to in the adaptive dynamics literature as 'canonical equation'.
(joint work with P. Collet and J.A.J. Metz)

Plenary lecture, Friday, July 1, 10:10

Rob Phillips
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Random Walks in Physical Biology

We are living through a time of explosive growth in the study of the living world that in many ways parallels advances in astronomy after the invention of the telescope. Quantitative measurements allied with physical models are providing a powerful lenses through which to view many of these biological insights. In this talk, I will give a personal view of how our understanding of living matter can be colored by appealing to ideas from statistical mechanics. In particular, these ideas are illustrated with case studies on the ways that both viruses and cells manage their genomes.

Plenary Lecture, Thursday, June 30, 8:30

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Serotonin Metabolism in Health and Disease

Because of the complexity of the central nervous system (CNS) and the difficulty of experimentation, the etiology of many neurological and neuropsychiatric disorders remains unknown. The systems of the CNS depend not only on the electrophysiology of neural networks, but also on biochemistry, gene expression, and behavior, and all four of these systems affect each other. In this circumstance, mathematical models that are based on real physiology can provide platforms on which to conduct in silico biological experiments that can test hypotheses and aid in the interpretation of experimental and clinical data. We will illustrate these ideas by discussing the serotonin system and recently constructed mathematical models for serotonin release, reuptake, and regulation. A new hypotheses about the mechanism of action of selective serotonin reuptake inhibitors used in the treatment of depression will be discussed, as well as the effects of serotonin on Parkinson's disease and levodopa treatment.

Plenary lecture, Tuesday, June 28, 9:30

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Stochasticity in biochemical networks

Biochemical systems have two sources of stochasticity: intrinsic fluctuations, inherent in the biochemistry and enhanced by low numbers of molecules, and extrinsic fluctuations, generated by interactions of the system of interest with other stochastic systems in the cell or its environment. I will discuss the definitions of intrinsic and extrinsic stochasticity and their interdependencies. I will describe ways to model, simulate, and measure both types of fluctuations and illustrate how stochasticity can be important for understanding the "design" of some biochemical networks.

Plenary Lecture, Friday, July 1, 9:20

Julie Theriot
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Quantitative analysis and modeling of cell shape during rapid movement

The crawling movement of eukaryotic cells is driven by dynamic assembly, contraction and disassembly of the actin cytoskeleton. Internal cell structural rearrangements are transduced into forward motion by dynamic cell-substrate adhesions. The forces arising from the actions of cytoskeletal and adhesive cellular components also determine the cell shape. Experimentally, we have found that cell shape and movement behavior are quantitatively coupled for several fast-moving cell types, including fish epidermal keratocytes and human neutrophils. This talk will focus on mathematical methods for quantitative analysis of cell shape changes during rapid motility, and on our current progress toward developing comprehensive physical models that link cell movement and shape determination.

Plenary Lecture, Thursday, June 30, 10:10

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System-level Understanding of Biological Timings

The logic of biological networks is difficult to elucidate without (1) comprehensive identification of network structure, (2) prediction and validation based on quantitative measurement and perturbation of network behavior, and (3) design and implementation of artificial networks of identified structure and observed dynamics. Mammalian circadian clock system is such a complex and dynamic system consisting of complicatedly integrated regulatory loops and displaying the various dynamic behaviors including i) endogenous oscillation with about 24-hour period, ii) entrainment to the external environmental changes (temperature and light cycle), and iii) temperature compensation over the wide range of temperature. In this symposium, I will take a mammalian circadian clock as an example, and introduce the systems- and synthetic-biological approaches for understanding of biological timings.

References.

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Plenary Lecture - Art Winfree Prize, Friday, July 1, 11:00

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Temporal Organization of the Cell Cycle

In his classic book on the Geometry of Biological Time, Art Winfree introduced the notions of a simple 'clock' (a periodic sequence of events) and a 'checkpoint' (a ratchet-like device). These ideas are central to understanding the logic of progression through the eukaryotic cell cycle (growth, DNA replication and cell division). Now that we know the molecular complexities of the cell cycle control system (cyclin-dependent kinases, regulated protein synthesis and degradation, etc.), we can build a realistic mathematical model of cell cycle progression. The model embodies, in terms of positive and negative feedbacks, exactly the 'clock + checkpoints' organization envisioned by Winfree. The model accounts for the fundamental physiological properties of mitotic cell divisions and provides new ways of thinking about crucial issues of the robustness and irreversibility of cell cycle transitions.

References.

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Plenary Lecture - Reinhart Heinrich Award, Friday, July 1, 17:00

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Mathematical modeling and in silico labeling with PottersWheel

Since 2005 we are developing the MATLAB toolbox PottersWheel to apply mathematical modeling in Systems Biology [1]. The software focuses on partially observed systems which can be described by biochemical reaction networks or differential equations. It comprises advanced methods to estimate unknown parameters given experimental time-resolved measurements and to identify structural and practical parameter non-identifiabilities, where several parameters may compensate each other's effect and lead to the same observed trajectories [2]. Recently, we developed a novel approach called in silico labeling to track species in complex and potentially non-linear dynamical systems, for example to determine their half-life and the transit time within system compartments. PottersWheel is freely available for academic research at www.potterswheel.de

References.

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Plenary Lecture - Reinhart Heinrich Award, Friday, July 1, 17:40

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Approximate Bayesian Computation for parameter inference and model selection in systems biology

Mathematical modelling has become an important tool in the biological sciences. Due to the overwhelming complexity of biological systems, it is not straightforward to determine the structure of the models. Moreover, the majority of parameter values are unknown and despite technological advances, these parameters are often difficult to measure experimentally. Therefore, statistical and computational techniques are needed to distinguish the good models from the unsuitable ones and to estimate unknown parameters.

In this talk we present a novel algorithm for parameter estimation and model selection of dynamical systems. The algorithm is based on Sequential Monte Carlo framework, and belongs to the class of Approximate Bayesian computation (ABC) methods. ABC methods can be used in situations where the evaluation of the likelihood is computationally prohibitive. They are thus ideally suited for analysing the complex dynamical models encountered in systems biology, where knowledge of the full (approximate) posterior is often essential.

The algorithm is applied to a variety of stochastic and deterministic biological models. We apply the model selection algorithm to distinguish between differential equation models of MAP kinase phosphorylation dynamics, the JAK-STAT signalling pathway, and the influenza infection outbreaks.

Plenary Lecture - Lee Segel Prize, Friday, July 1, 12:20

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Analysis of Winner-Loser Models of Hierarchy Formation in Animals

We review winner-loser models, the currently popular explanation for the occurrence of linear dominance hierarchies, via a three-part approach. 1) We isolate the two most significant components of the mathematical formulation of three of the most widely-cited models and rigorously evaluate the components' predictions against data collected on hierarchy formation in groups of hens. 2) We evaluate the experimental support in the literature for the basic assumptions contained in winner-loser models. 3) We apply new techniques to the hen data to uncover several behavioral dynamics of hierarchy formation not previously described. The mathematical formulations of these models do not show satisfactory agreement with the hen data; key model assumptions have either little, or no conclusive, support from experimental findings in the literature. In agreement with the latest experimental results concerning social cognition, the new behavioral dynamics of hierarchy formation discovered in the hen data suggest that members of groups are intensely aware both of their own interactions as well as interactions occurring among other members of their group. We suggest that more adequate models of hierarchy formation should be based upon behavioral dynamics that reflect more sophisticated levels of social cognition.

Plenary Lecture - Lee Segel Prize, Friday, July 1, 18:20

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Persistence and Spread of Gastro-Intestinal Infections: the Case of Enterotoxigenic *Escherichia coli* in Piglets

Several gastro-intestinal infections in animal husbandry not only greatly reduce the well-being of animals, but also have the potential to cause large economical damage. It is thus of great importance to understand the dynamics of such diseases. We will focus on the within-host aspect of the dynamics and present a model that describes the spread of the pathogen inside a single infected host. Our motivation to study the problem stems from the case of enterotoxigenic *Escherichia coli* in newly weaned piglets, but the model offers an acceptable description of within-host dynamics of several other gastro-intestinal infections. We will first deal with the case where infection is a one-time event. While the description of the problem is in this case in several ways reminiscent of the problem of the 'drift paradox' in aquatic populations, there exists an additional aspect to the problem that is not relevant for aquatic populations: the problem of reintroduction. We will thus investigate also the reinfection case, in which a fraction of the shed pathogens is reintroduced into the host's intestine. We will present the condition that guarantees persistence of colonization in the reinfection case and discuss the implications for infection control.

References.

[1] Barbara Boldin: *Persistence and spread of gastro-intestinal infections: the case of enterotoxigenic Escherichia coli in piglets.* Bulletin of Mathematical Biology, **70**, No. 7, (2008), pp. 2077-2101.