Mini-symposium "Applications of statistical physics in quantitative biology"

Sunday June 15, 2014 - Monday June 16, 2014

Organizers:

- **Diana David-Rus, National Institute of Physics, IFIN-HH, Bucharest, Romania**

- **Alexandre V. Morozov, Department of Physics & Astronomy/BioMaPs Institute for Quantitative Biology, Rutgers University, NJ, USA**

Abstract:

The interface between statistical physics and biology is one of the most active areas of research, as shown by its rapid evolution during recent years. From regulation of gene expression in its simplest form, e.g. the rate of transcription of a gene that depends on several transcription factors acting together, to epigenetic changes and modifications that orchestrate the action of multiple chromatin-remodeling enzymes, biological cooperativity opens the possibility of non-trivial collective behavior for which statistical physics provides a well-established framework. On a larger scale, dense populations of "active particles" or "swimmers" exhibit rich collective behavior for which recent work demonstrates that hydrodynamic interactions provide a simple, generic origin of several non-equilibrium phenomena predicted or observed in the literature. Statistical mechanics is indispensable for constructing models of chemotaxis, quorum sensing, and cellular dynamics. Finally, pattern formation that occurs in both equilibrium and non-equilibrium systems is another example of a class of biological problems where concepts from statistical mechanics are routinely used. The biological systems in question range in scale from microns for cells forming an organism to hundreds of meters for flocking birds.

This symposium will address applications of statistical physics to a broad range of cutting-edge biological problems ranging from molecules to populations, with a focus on cooperativity and collective behavior in biological systems.

Venue: The mini-symposium is organized in conjunction with the 9th European Conference on Mathematical and Theoretical Biology (http://ecmtb2014.org).
It will take place in Gothenburg, Sweden at Chalmers Conference Centre, close to Chalmers University of Technology.

Registration: All symposium participants need to register through the main conference: "9th European Conference on Mathematical and Theoretical Biology" at: http://ecmtb2014.org/registration. The conference fee includes lunch on all conference & symposium days, participation at the city reception & some additional social programs. Please note that according to the rules of the meeting travel expenses are not reimbursed.

Schedule

Sunday 15 June

8:45-9:00 Opening remarks

Session 1: Collective Phenomena in Biology

09:00-10:00 Andreas Deutsch (Technical University of Dresden, Germany) **Cellular automaton models for collective cell behavior**

10:00-10:30 **Coffee break**

10:30-11:30 Michael Deem (Rice University, USA) **Emergence of Modularity in Biology**

11:30-12:30 Sorin Tanase-Nicola (University of Uppsala, Sweden) **Thermodynamic limits on noisy cellular sensing**

13:00-14:30 **Lunch**

14:30-15:30 David Schwab (Princeton University, USA) **Mechanistic models of multicellular computation**

15:30-16:00 **Coffee break**

Session 2: Statistical Mechanics: From Molecules to Insects

16:00-17:00 Alex Feigel (SAREK, Israel) **Emergence of biological-like systems, e.g. Brownian motor, by reduction of effective temperature**

17:00-18:00 Bartosz Rozycki (Institute of Physics of the Polish Academy of Sciences, Poland) **Adhesion of membranes via receptor-ligand complexes: Binding cooperativity, domain formation and line tension effects**

18:00-19:00 Elie Raphael (ESPCI, France) **Moving at the air-water interface**

Monday 16 June

Session 3: Evolution & Development

09:00-10:00 Ovidiu Radulescu (EPIGENMED, Montpelier, France) **Transcriptional bursting and bacterial adaptation**

10:00-10:30 **Coffee break**

10:30-11:30 Michael Manhart (Rutgers University, USA) **A Path-based Approach to Random Walks on Landscapes, with Applications to How Proteins Evolve New Function**

11:30-12:30 Anatoly Kolomeisky (Rice University, USA) **How to Understand Morphogen Gradients Development during Biological Development**

13:00-14:30 **Lunch**

Session 4: Chromatin

14:30-15:30 Alexandre Morozov (Rutgers University, USA) **Statistical mechanics of nucleosome crowding in yeast**

15:30-16:00 **Coffee break**

16:00-17:00 Anirvan Sengupta (Rutgers University, USA) **Regulating Looping in Genome**

Session 5: Drug Resistance in Bacteria

17:00-18:00 Namiko Mitarai (University of Copenhagen, Denmark) **Toxin-Antitoxin Battle in Bacteria**

18:00-18:30 Diana David-Rus (National Institute of Physics and Nuclear Engineering, Romania) **Stochastic approaches for understanding the impact of antibacterial drugs on bacteria population dynamics**

Abstracts (in order of presentation)

Sunday 15 June

1. Andreas Deutsch (Technical University of Dresden, Germany)
Cellular automaton models for collective cell behavior

Cellular automata are introduced as models for collective behavior in interacting cell populations. We focus on mechanisms of collective cell migration, clustering and invasion and demonstrate how analysis of the models allows for prediction of emerging properties at the individual cell and the cell population level. Finally, we discuss applications of the invasion models to glioma tumours.

Ref.: A. Deutsch, S. Dormann: Cellular Automaton Modeling of Biological Pattern Formation: Characterization, Applications, and Analysis
Birkhäuser, Boston, 2005 (2nd ed. 2014)

2. Michael Deem (Rice University, USA)
Emergence of Modularity in Biology

I will discuss the emergence of modularity in examples from the natural world. Dynamical systems typically evolve in a changing environment, and I will show that the level of modularity correlates with the rapidity and severity of environmental change. Emergence of modularity is driven by noise in the environment and is facilitated by horizontal gene transfer. This mechanism is evident in a number of systems, from viruses and bacteria to development and physiology. Bacterial metabolic networks show increasing modularity as the physical environment or horizontal gene transfer rate increases, and experimental protein interaction data shows that protein networks have become increasingly modular over the last four billion years. More recently, modularity provides early warnings in the evolution of influenza flu strains and in heart rate anomalies in physiology. I will describe a principle of least action that governs the emergence of modularity in certain limits.

1) Phys. Rev. Lett. 99 (2007) 228107
2) Phys. Rev. E 79 (2009) 031907
3) Physics of Life Reviews, invited review, 8 (2011) 129-160
4) Annual Reviews of Condensed Matter Physics 4 (2013) 287-311

3. Sorin Tanase-Nicola (University of Uppsala, Sweden)
Thermodynamic limits on noisy cellular sensing

Living systems gather and transmit information about the internal and external environments through biochemical networks of interacting molecules. The robustness and fidelity of information processing in biochemical networks can be limited by noise, the structure of biochemical interactions or numbers of participating molecules. Living cells, as a whole, are highly dissipative and it has been long recognized that information processing too require consumption of energy. Less is known about the limits and energetic cost of the capacity of information processing through biologically relevant biochemical reaction networks. Combining non-equilibrium statistical physics and learning theory perspectives we derive fundamental

constraints relating the amount of dissipated energy and the fidelity and speed of information processing in individual cell signaling modules. We also derive the limits on equilibrium modules imposed by the available complexity and cooperativity but also by the range of input signals. Finally we analyze the information processing requirements to the energy budget of the cell.

4. David Schwab (Princeton University, USA)

Mechanistic models of multicellular computation

Populations of cells exhibit a remarkable diversity of behaviors, from the reliable development of multicellular structures to complex coding in neural ensembles. Proper characterization of these phenomena requires an understanding of how dynamics at the single-cell level, when combined with intercellular signaling and environmental cues, give rise to the collective behaviors observed in populations. First, I will present results characterizing the universal signaling dynamics in individual cells of social amoebae, and discuss cell density-dependent transitions to collective, synchronized oscillations. I will then consider population coding in retinal ganglion cells. Recent experiments have shown that the distribution of spiking activity in these cells is poised near a unique critical point where the extensive parts of the entropy and energy are exactly equal. I will demonstrate how such behavior robustly arises due to shared stimulus input. Connections to the statistical mechanics of learning will also be discussed.

5. Alex Feigel (SAREK, Israel)

Emergence of biological-like systems, e.g. Brownian motor, by reduction of effective temperature

The question of emergence and optimization of living-like system is a long-standing conundrum. We will discuss emergence of Brownian motors, namely, how ability to extract energy and convert it to motion may become a preferential state of the system out of thermal equilibrium? An answer to this question may advance an analogy between Brownian motors and living systems by providing an explanation for emergence and evolution of highly fluctuating nanomachines. The emergence of motion is shown to be a general phenomenon. A motor converges to the state with the minimum of effective temperature and with the corresponding minimum in the rate of conformation changes similarly as some stochastic processes converge to the states with minimum diffusion activity. This mechanism is similar to bacterial foraging (chemotaxis). The implications include a hypothesis for the emergence of the first biological machines during the pre-Darwinian chemical evolution, deviation of stable natural or artificial machines from the minimum entropy production principle, a method for the mass production of artificial nanomachines and a framework for analysis of how energy and conformation fluctuations drive small systems away from macroscopic physical laws.

6. Bartosz Rozycki (Institute of Physics of the Polish Academy of Sciences, Poland)

Adhesion of membranes via receptor-ligand complexes: Binding cooperativity, domain formation and line tension effects

Cell membranes interact via anchored receptor and ligand molecules. Central questions on cell adhesion concern the binding affinity of these membrane-anchored molecules, the mechanisms leading to the receptor-ligand domains observed during adhesion, and the role of line tension on the boundaries of these domains. In my talk I will address these questions from a theoretical perspective. I will focus on models in which the membranes are described as elastic sheets, and the receptors and ligands as rigid objects anchored in the membranes. In these models, the thermal membrane roughness on the nanometer scale leads to a cooperative binding of the anchored receptor and ligand molecules, since the receptor-ligand binding smoothens out the membranes and facilitates the formation of additional bonds. The interactions mediated by the receptor and ligand molecules can be characterized by effective membrane adhesion potentials that depend on the concentrations and binding energies of the molecules.

7. Elie Raphael (ESPCI, France)

Moving at the air-water interface

It is generally believed that in order to generate waves, a small object (like an insect) moving at the air-water surface must exceed the minimum wave speed (about 23 centimeters per second). We show that this result is only valid for a rectilinear uniform motion, an assumption often overlooked in the literature. In the case of a steady circular motion (a situation of particular importance for the study of whirligig beetles), we demonstrate that no such velocity threshold exists and that even at small velocities a finite wave drags is experienced by the object. This wave drag originates from the emission of a spiral-like wave pattern. The results presented should be important for a better understanding of the propulsion of water-walking insects. For example, it would be very interesting to know if whirligig beetles can take advantage of such spirals for echolocation purposes.

References:

Capillary-Gravity Waves Generated by a Slow Moving Object
A. D. Chepelianskii, F. Chevy, E. Raphaël Physical Review Letters, 100 (2008) 074504

Monday 16 June

1. Ovidiu Radulescu (EPIGENMED, Montpelier, France)

Transcriptional bursting and bacterial adaptation

One of the most puzzling stories of molecular biology relates to the variability of gene expression in populations of clone cells. As discussed by Max Delbrück, this non genetic variability has a physical origin and demonstrates the discontinuous functioning of biosynthetic mechanisms. With the advent of modern fluorescence microscopy technology, this “expression noise” can be quantified with unprecedented precision. We use 2psN&B fluctuation microscopy methods for measuring cell-to-cell phenotypic variations in gene expression, even for very weakly transcribed genes under strong repression. We particularly focus on regulators of the central carbon metabolism in Bacillus subtilis. Bacterial response to changes of the carbon source is a switch between different metabolic pathways. For two promoters representing the main control points of this metabolic switch, the observed distributions of gene expression are strongly skewed, suggesting transcriptional bursting in both permissive and repressive conditions. The dynamical changes of bacterial populations under such switches have to be considered at collective and multiscale levels, that is quite a challenge for mathematical and physical modeling. We will discuss models and general rules that on one hand relate gene expression noise patterns and transcriptional regulation mechanisms and on the other hand elucidate how expression variability is exploited in bacterial adaptation strategies.

References

1) M.L. Ferguson, D. Le Coq, M. Jules, S. Aymerich, O.Radulescu, N. Declerck, C.A. Royer. Reconciling molecular regulatory mechanisms with noise patterns of bacterial metabolic promoters in induced and repressed states, Proceedings of the National Academy of Sciences USA (2012) 109:155.
2) O.Radulescu, GCP Innocentini, JEM Hornos. Relating network rigidity, time scale hierarchies, and expression noise in gene networks, Physical Reviews E 85 (2012) 041919.
3) A.Crudu, A.Debussche, O.Radulescu. Hybrid stochastic simplifications for multiscale gene networks, BMC Systems Biology (2009) 3:89.

2. Michael Manhart (Rutgers University, USA)

A Path-based Approach to Random Walks on Landscapes, with Applications to How Proteins Evolve New Function

Random walks on multidimensional landscapes are important to many areas of science and engineering. In particular, properties of adaptive trajectories on fitness landscapes determine population fates and thus play a central role in evolutionary biology. To this end we have developed a path-based approach to continuous-time random walks on discrete state spaces. I will describe an efficient numerical algorithm for calculating statistical properties of the stochastic path ensemble, including distributions of path lengths, times, and spatial structures. This approach, based on general techniques from statistical physics, is applicable to state spaces and landscapes of arbitrary complexity and structure. It is especially well-suited to quantifying the diversity of stochastic trajectories and repeatability of evolutionary events. After demonstrating our approach on two reaction rate problems, I will present a biophysical model that describes how proteins evolve new functions while maintaining thermodynamic stability. Our methodology reveals several distinct modes of adaptation depending on key biological and biophysical properties of the protein, reproducing important observations from directed evolution experiments.

3. Anatoly Kolomeisky (Rice University, USA)

How to Understand Morphogen Gradients Development during Biological Development

Concentration profiles of signaling molecules, also known as morphogen gradients, play a critical role in the development of multi-cellular organisms by determining polarity and spatial patterning that leads to further tissue differentiation. Significant advances in studying morphogen gradients have been achieved recently when the formation of signaling molecules profiles has been visualized with high temporal and spatial resolution. A widely used approach to explain the establishment of concentration gradients assumes that signaling molecules are produced locally, then spread via a free diffusion and degraded uniformly. However, recent experiments have also produced controversial observations concerning the feasibility of this theoretical description. In addition, it has been shown that time to establish the morphogen gradient yield surprising linear scaling as a function of length, not expected for the systems with unbiased diffusion processes. Current theoretical views utilize continuum models that produce unphysical behavior at limiting cases. We propose here a theoretical approach based on discrete-state stochastic analysis that provides a possible microscopic mechanism of these complex phenomena. It is argued that relaxation times are mostly determined by first-passage times and the degradation effectively accelerates diffusion of signaling particles by removing slow moving molecules. Thus the degradation works as an effective potential that drives signaling molecules away from the source. Our theoretical analysis indicates that spatial and temporal features of degradation efficiently control the establishment of signaling molecules profiles.

4. Alexandre Morozov (Rutgers University, USA)

Statistical mechanics of nucleosome crowding in yeast

Eukaryotic genomes are organized into arrays of nucleosomes. Each nucleosome consists of up to 147 base pairs (bp) of genomic DNA wrapped around a histone octamer core. The resulting complex of DNA with histones and other regulatory and structural proteins forms a multi-scale structure called chromatin. Nucleosomal DNA may transiently peel off the histone octamer surface due to thermal fluctuations or interactions with chromatin remodelers. Thus neighboring nucleosomes may invade each other's territories through DNA unwrapping and translocation, or through initial assembly in partially wrapped states. Indeed, a recent high-resolution map of inter-nucleosome distances in baker's yeast (*S. cerevisiae*) has revealed that at least 25% of all nucleosomes overlap DNA territories of their neighbors. The average length of wrapped DNA follows a stereotypical pattern: nucleosomes tend to be more unwrapped in promoters and less unwrapped in coding regions. To explain these observations, we have developed a statistical mechanics model of nucleosome unwrapping which employs a 10-11 bp periodic histone-DNA binding energy profile. Our model is in agreement with the observed genome-wide distributions of inter-dyad distances, wrapped DNA lengths, and nucleosome occupancies. Furthermore, our approach explains earlier *in vitro* measurements of accessibility of nucleosome-covered target sites and nucleosome-induced cooperativity between DNA-binding factors. We rule out several previously proposed scenarios of histone-DNA interactions as inconsistent with the genomic data. The surprising extent of nucleosome crowding in yeast

suggests that its treatment should be included in all future models of nucleosome positioning and energetics.

5. Anirvan Sengupta (Rutgers University, USA)
Regulating Looping in Genome

Regions of the chromosome that are many thousands of bases away often have to come in contact for turning some genes on or off. The specificity of such contacts is maintained by interposed boundaries or insulators, which are able to block these long distance interactions. The physical basis for the control of chromatin contact is still not well understood. We model the chromatin fiber as a semi-flexible polymer to explain how 'distant' regulatory interaction happens and how it is controlled by other sequence elements. There appears be region in the of parameters space of where mesoscopic attractive polymers fold to form branched polymer like structures, which are key to understanding our results. We will explore the connection between this regime and disordered systems treated by large N expansion. We finish by discussing how we could use the polymer model of chromatin to analyze data related to chromatin conformation and learn about regulatory contacts.

6. Namiko Mitarai (University of Copenhagen, Denmark)
Toxin-Antitoxin Battle in Bacteria

Many toxin-antitoxin operons are regulated by the toxin/antitoxin ratio by mechanisms collectively coined "conditional cooperativity". Toxin and antitoxin form heteromers with different stoichiometric ratios, and the complex with the intermediate ratio works best as a transcription repressor. This allows transcription at low toxin level, strong repression at intermediate toxin level, and then again transcription at high toxin level ([1] and references therein). Such regulation has two interesting features; firstly, it provides a non-monotonous response to the concentration of one of the proteins, and secondly, it opens for ultra-sensitivity mediated by the sequestration of the functioning heteromers. We explore possible functions of conditional regulation in simple feedback motifs, and show that it can provide bistability for wide a range of parameters [2]. We demonstrate that the conditional cooperativity in toxin-antitoxin systems combined with the growth-inhibition activity of free toxin can mediate bistability between a growing state and a dormant state. Conditional cooperativity also secures that the antitoxin dominated state has a substantial amount of toxins present, which helps the transition to the toxin dominated state under stress. These features may be relevant for understanding persister formation in *E. coli*.

References:
[1] I. Cataudella, A.Trusina, K. Sneppen, K. Gerdes, and N. Mitarai, Nucl. Acids Res. (2012) 40, 6424-6434.
[2] I. Cataudella, K. Sneppen, K. Gerdes, and N. Mitarai, Plos. Comput. Biol. (2013) 8, e1003174.

7. Diana David-Rus (National Institute of Physics and Nuclear Engineering, Romania)
Stochastic approaches for understanding the impact of antibacterial drugs on bacteria population dynamics

In most biological systems, multidimensional stochastic processes that involve some type of interaction plays an important role. For instance gene expression in both prokaryotes and eukaryotes or protein-protein interaction processes are just a few examples of inherently interacting multidimensional stochastic processes. So far most of the methods for solving the resulting stochastic equations rely on computer simulations. In this work we are developing an analytical method to analyze a general multidimensional Markov process with interaction, continues in time and discrete in a large sample space. We are using the method of dimensionality reduction in order to advance some analytical insights to the resulting stochastic equations. We discuss the model in steady state for the particular choice of states and transition rules and find exact solutions. This approach based on techniques from statistical physics is suitable when we have a multidimensional stochastic process on a large phase space. The analytical result can be used to help

developing appropriate numerical methods. We are applying this methodology on a biophysical model that describes the impact of antibacterial drugs on bacteria population dynamics and reproduces direct experimental observations.