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Irreversible Thermodynamics of Transcriptional Regulation
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In this work we studied memory and irreversible transport phenomena in a non-equilibrium thermodynamically model for genomic transcriptional regulation. Transcriptional regulation possess an extremely complex phenomenology, and it is, of course, of foremost importance in organismal cell development and in the pathogenesis of complex diseases. A better understanding of the way in which these processes occur is mandatory to optimize the construction of gene regulatory networks, but also to connect these networks with multi-scale phenomena (e.g. metabolism, signaling pathways, etc.) under an integrative Systems Biology-like vision. We analyzed three simple mechanisms of genetic stimulation: an instant pulse, a periodic biochemical signal and a saturation process with sigmoidal kinetics and from these we derived the system's thermodynamical response, in the form of, for example, anomalous transcriptional bursts.

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Stochastic Hopf Bifurcation in Transcription Networks with Delayed Feedback
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Transcriptional regulation is an intrinsically stochastic process. There is increasing evidence, for example, of stochastic stabilization of biological clocks and oscillators relative to their classical description based on macroscopic rate equations. Elucidating the effect of randomness on biological oscillation is central to understanding the design principles of robust oscillators, or to the design of synthetic networks. We study the oscillatory instabilities of two model systems that rely on delayed negative feedback to induce oscillation: a single gene auto repressor system, and a dimer negative autoregulation system. We focus on fluctuations of intrinsic origin in the range of low copy number. The bifurcation diagram is obtained for these stochastic models, and shown to differ significantly from that of a macroscopic description that neglects fluctuations. Bifurcation lines remain sharp under fluctuations, but their location is a function of the relative size of the fluctuations. Shifts in the stability threshold of the oscillators can be traced back to the interplay between statistical correlations and delayed feedback. We finally show that there results cannot be captured by weak noise approximations (the diffusion limit), but instead result from strong fluctuations associated with low copy numbers.

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Transcription Factor Target Search Strategy at the Single Molecule Level in Eukaryotic Cells
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Transcription is the mechanism by which information encoded in genes is transmitted to an mRNA template. This process is initiated by the binding of a transcription factor (TF) to a gene promoter. TFs have to find their specific gene promoters (~20bp) within a 3.2 billion bps genome in a fast and efficient manner. A key challenge is thus to understand by which mechanisms do TFs execute target search in a crowded nucleus?
To address this question, we use a non-native doxycycline-deactivable Tet Repressor (TetR) DNA-binding domain integrated into a human cell line (U2OS). By transfecting cells with TetR tagged with the photo-convertible DENDRA2, we are able to visualize their dynamics in the nuclei of live cells using a sptPALM technique. Low UV irradiation causes stochastic conversion of DENDRA2 from the green to the red, with an event probability low enough to detect single molecules.
The nuclear dynamics of TetR exhibits three different behaviours: (I)trajectories that cross the entire nucleus, screening it predominantly with a fast motion ($16\mu m^2/s$); (II)quasi-immobile molecules($0{,}1\mu m^2/s$), and (III)an intermediate behaviour, with medium motion($1{,}4\mu m^2/s$) confined in subparts of the nucleus. When doxycycline is added, disabling TetR DNA-binding properties, there is a drastic decrease of quasi-immobile molecules and a 50% decrease of the medium-motion ones.
This suggests that the quasi-immobile molecules are unspecifically bound on DNA. Their slow motion suggests a 1dimensional screening of DNA as seen in in vitro experiments. The medium motion population shows transiant DNA unspecific binding combined with 3dimentional jumps, allowing a local search. The fast population screens in a global way the nucleus.
TFs seem to have a well established target search strategy by unspecifically binding on DNA and combining 1Dimentional and 3Dimentional motions, as suggested by previous target search theories.

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Breaking the Code of Bacteria Decision Making
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To enhance fitness in complex and changing environments, identical bacteria cells in isogenic populations have the capacity to stochastically differentiate into various phenotypes with special attributes. Stochastic fate determination guarantees variability, as it provides each cell with the freedom to choose its own fate. This hedge survival strategy allows the population to continuously deploy specialized cells in anticipation of possible drastic changes in conditions. Recently, we introduced and analyzed a novel integrative model developed for the complete decision-making signal transduction system that determines the cell fate between sporulation and competence. Here I will focus our current studies of the core decision circuit - the AbrB circuit. This circuit regulates the interplay between the sporulation master regulator, which acts as an adjustable timer whose clock rate is adjusted by the past and present stress normalized by the mean-field stress of the other cells, and the competence master regulator, which acts as a stochastic switch whose switching rate is adjusted by the normalized cell density. The decision circuit is composed of a cascade of three inhibitory genes generating oscillatory dynamics of opening the stochastic switch. The decision circuits of the individual bacteria are coupled by inter-cell signaling such that the decision-making circuits of the different cells work in coordination and amplify the noise and differences between the cells. This ingenious scheme describes how individual bacteria weigh their decisions carefully, taking into account the stress they are facing, the situation of their peers, and the statistics of how many cells are sporulating and how many are choosing competence.

Membrane Physical Chemistry II

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Anesthetic Concentrations of Halothane Change the Domain Structure of Mixed Lipid Membranes
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Binary and ternary mixtures of lipids that form separate phases (gel, fluid-ordered, and fluid disordered) may provide useful insights into the complex physics of real biological membranes. Here, we examine the mixing versus temperature of DPPC:DLPC and DPPC:DOPC:Cholesterol phase separated systems using neutron and x-ray diffraction methods. We also report the affects of inhalation anesthetics on the phase behavior of these lipid mixtures. Phase co-existence was measured by lamellar x-ray diffraction from multi-layer samples. Two distinct series of lamellar Bragg diffraction were observed demonstrating separation into distinct 3D phases. We observe a broad transition in which one phase diminishes as a function of temperature resulting in a single homogenous phase. We used isotopic contrast from chain deuterated lipids to show compositional changes in the fluid phase during the mixing transition. The changes seen in the proportion of lipids in the lamellar diffraction studies correspond to physical mixing of the lipid species shown by examining the chain diffraction at wide angles produced by deuterated lipids. Finally, we show that the anesthetic halothane shifts the temperature mixing curves and sharpens the transition of these mixtures.

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The Phase Diagram for the Four-Component DSPC/DOPC/POPC/CHOL Mixture
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When liquid-ordered (Lo) and liquid-disordered (Ld) phases coexist in mixtures of DSPC/DOPC/Chol, phase domains appear as large round domains in giant unilamellar vesicles (GUVs) examined by fluorescence microscopy. However, when liquid-ordered and liquid-disordered phases coexist in DSPC/POPC/Chol mixtures, domain size is too small to be detected by fluorescence microscopy. The phase diagram of the four-component DSPC/DOPC/POPC/Chol mixture allows for the exploration of the transition from macroscopic-to-nanoscopic domains. We have found complex shapes (modulated phase morphology) in a particular region of composition within the