

the noise levels in the circuit. We show that when the strength of the negative feedback is increased, the capacity to display memory of the initial galactose consumption is lost compared to the wild type strain. On the other hand, by varying the strength of the positive feedback we observe the emergence of a region with stable memory. It has been shown that the capacity for cells to display memory depends on the stochastic fluctuations of the circuit, and hence we analyze the effect of feedback strength on transition rates between the alternative states ON/OFF. In this case we demonstrate that the switching rates between the two phenotypic states can be tuned by changing the strength of the feedbacks. These results reveal that the feedback strengths of the network regulate the dynamic behavior through modulation of the stochastic fluctuations of gene expression and the stability of different states of gene expression. This suggests that the strength of feedbacks may be tuned allowing a population to enhance its fitness under a certain frequency of environmental fluctuations, by changing the rate of stochastic transitions between different states.

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Nature, Nurture Or Just Blind Chance: Stochastic Gene Expression And Its Consequences

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Life itself is a study in the contrast between randomness and determinism: from the chaos of biomolecular interactions to the precise coordination of development, living organisms are able to resolve these two seemingly contradictory aspects of their internal workings. The traditional means by which scientists reconcile the stochastic and the deterministic is by appealing to the statistics of large numbers, thus diminishing the importance of any one molecule in particular. However, cellular function often involves small numbers of molecules, of which perhaps the most important example is DNA. It is this molecule, usually present in just one or few copies per cell that gives organisms their unique genetic identity.

But what about genetically identical organisms grown in homogenous environments? To what degree are they unique? In this talk I will present experiments on bacteria, yeast and nematodes that suggest that even genetically identical individuals exposed to identical environments can be very different. Moreover, some of the most striking sources of this variability are random fluctuations in the expression of individual genes.

In some cases populations might even exploit these fluctuations to improve their chances of survival in variable environments.

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DNA Architecture and Transcriptional Regulation Exploring DNA's Mechanical Code

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DNA architecture plays a key role in determining spatial and temporal patterns of gene expression. This architecture encompasses both the nucleotide sequence (i.e., the information content) and the physical state of the DNA such as its spatial organization and mechanical properties. We explore transcriptional regulation by DNA looping in the *lac* operon, where transcriptional control is realized by the simultaneous binding of Lac repressor to two binding sites separated by hundreds of base pairs on the DNA. We develop a statistical mechanical model to quantify repression and the *in vivo* energy cost of different DNA conformations in bacteria.

Based on the falsifiable predictions generated by this model we construct a library of promoters in which their DNA architecture is varied systematically. Properties such as the length of the intervening DNA and its sequence-dependent flexibility are controlled and their resulting effect on the gene expression level and its noise are quantified at the single cell level. The goal of this work is to make a systematic and thorough comparison of theory and experiment in a parameter-free setting which strictly tests our understanding of the relation between DNA architecture and the level of gene expression.

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A Study of Cro's Role in the Induction of Phage Lambda Switch by Stochastic Probability Landscape Model

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The genetic switch of phage lambda is controlled by the double negative feedback loop of CI and Cro. Although, Cro as a repressor of the PRM promoter for CI has been studied for several decades, the role of Cro in phage lambda lytic development has not been fully understood. Evidence indicates that Cro help the induction of phage lambda by turning down lytic transcription via the binding of operator OR1 and OR2 at PR promoter and repressing the PRM promoter for CI via the strong binding at OR3. To investigate which binding of Cro is

critical in the induction of phage lambda, we compute the exact steady state probability landscape of the genetic circuit of the switch network. We demonstrate that the reduction of binding affinity of Cro on OR3 has elongated the lysogenic state and strongly inhibited the transition from lysogeny to the lytic pathway which is in good agreement with the mutations studied by Schubert et al. in 2007. The stability and sensitivity of phage lambda switch and its robustness are also analyzed in our study.

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Cellular Particle Dynamics Simulation Of Bioprinted 3d Tissue Constructs

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Previous studies have shown that under certain conditions living tissues and multicellular aggregates behave as highly visco-elastic liquids. Tissue liquidity, brought about by cellular adhesion and motility, forms the basis of the newly developed bioprinting technology, which is used to design and build 3D tissue constructs by employing computer-controlled layer-by-layer deposition of bio-ink (submillimeter size cell aggregate) droplets onto biopaper (biocompatible gel). In order to describe and predict the self-assembly process of bioprinted multicellular constructs we have developed a computer simulation method referred to as cellular particle dynamics (CPD). In CPD cells are modeled as an ensemble of cellular particles (CPs) that interact via short range contact interactions, characterized by an attractive (adhesive interaction) and a repulsive (excluded volume interaction) component. The time evolution of the spatial conformation of the multicellular system is determined directly by recording the trajectories of all CPs through integration of their equations of motion. The cellular level CP model parameters are related to the experimentally measurable tissue level biophysical quantities (e.g., surface tension, viscosity and shear modulus) by comparing the results from selected benchmark experiments (e.g., compression and fusion of spherical cell aggregates) with those from the corresponding CPD simulations. Here we apply the CPD method to describe and predict *in silico* the post-bioprinting time evolution of the formation of tubular multicellular structures (which resemble primitive blood vessels). Our CPD simulations take substantially less time and effort than the corresponding experiments and, most importantly, provide results in good agreement with the experimental ones.

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Inversion of Membrane Protein Gating Models in Bioelectricity

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In recent years we have seen a dramatic increase in the complexity of Markov model configurations. While single protein data allow to directly estimate the Markov transition rates from the data it is not possible to do so with macroscopic data. In several instances experimental constraints does not permit single protein measurements. This limitation combined with the complexity of Markov model configurations makes the estimation problem a non-trivial one.

Here we address the task of finding the Markov rates from macroscopic data. We assume the transition rates functions of one independent variable (e.g. the membrane voltage). We do not constrain the dependence to any particular form. Indeed the dependence of the transition rates with respect to the independent variable is represented with Bsplines. The method we introduce is truly non-linear. The B-spline coefficients are obtained applying a sequence of non-linear transformations to the data.

Set of currents obtained in voltage clamp stimulation protocols (or clamp of the independent variable) are represented by exponential time series. We first introduce a generalization of Prony's method that allow to obtain unambiguously the coefficients and arguments of the exponential time series associated to each current. We show that the estimation of the Markov rates from the coefficients and arguments of the exponential time series constitutes an inverse eigenvalue problem. We introduce a procedure that allows to solve this eigenvalue problem with a sequence of nonlinear transformations. We apply the method to currents produced by a given Markov model which allows us to judge the accuracy of the procedure. An interesting outcome of our analysis is that the Markov rates are not unique if a minimal and complementary data set is not produced.

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Gap Junction Adaptation as a basis of cardiac memory - A computational Study

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