

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.

#### 1559-Pos Board B403

##### **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.

#### 1560-Pos Board B404

##### **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.

#### 1561-Pos Board B405

##### **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.

#### 1562-Pos Board B406

##### **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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#### 1563-Pos Board B407

##### **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.

#### 1564-Pos Board B408

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

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The phenomenon of cardiac memory refers to the property of cardiac tissue whereby the effect of an external electrical activation outlasts the duration of presentation of stimulus by significant margin. Several molecular mechanisms have been proposed in literature to explain the possible basis of this memory. Electrophysiological models of cardiac cells coupled by GJ conductances are studied. Simulations include cell pair models and grid models. Memory effect is shown in cell pair as a lasting change in phase difference between the oscillations of two autorhythmic type of cardiac cells. Memory effect is demonstrated in grid models also where an external current input presented for prolonged duration induces long term changes in activation pattern of the grid. These lasting changes are also reflected in computed Electrocardiogram. Physiological validity of the proposed mechanism of adaptation of GJs is also addressed. The proposed mechanism is inspired by results from learning and memory literature in neuroscience and comparing the same with the cardiac case. Just as neuronal signaling is mediated by synapses, cardiac cells electrically interact with each other via GJs. Activity-dependent adaptation of synaptic “strength” is generally considered an important biological substrate of learning and memory in the brain. Similarly, according to the proposed mechanism of GJ adaptation, the GJ conductance varies as a function of membrane voltages of the cells coupled by the GJ. But from biophysical literature, GJs are known to depend on junctional voltage between a pair of coupled cells. The link between biophysics of GJs and the proposed mechanism is explored. It is demonstrated with the help of a theoretical model of voltage-sensitive dynamics of GJ channel, followed up by simulation studies, that the proposed dynamics of GJs is compatible with biophysics of GJs.

#### 1565-Pos Board B409

##### A Mathematical and Computational Approach for Integrating the Major Sources of Cell Population Heterogeneity

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Several approaches have been used in the past to model heterogeneity in bacterial cell populations, with each approach focusing on different source(s) of heterogeneity. However, a holistic approach that integrates all the major sources into a generic framework applicable to cell populations is still lacking.

In this work we present the mathematical formulation of a Master equation that pertains to a single cell and takes into account the major sources of heterogeneity, namely stochasticity in reaction, division, and DNA duplication. The formulation also takes into account cell growth and respects the discrete nature of the molecular contents. We further extend the framework to cell populations and develop Monte Carlo algorithms for the simulation of the stochastic processes considered here. Using this approach we demonstrate the effect of each source of heterogeneity on the overall phenotypic variability for the two-promoter system used experimentally by Elowitz et al. (2002) to quantify intrinsic versus extrinsic noise.

Elowitz, M. B., A. J. Levine, E. D. Siggia and P. S. Swain (2002). “Stochastic gene expression in a single cell.” *Science* **297** (5584): 1183-1186.

#### 1566-Pos Board B410

##### Using Optimal Transformations and Multi-Experiment Fitting to Detect and Reduce Effects of Non-Identifiable Parameters in Non-Linear Dynamical Models

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Mathematical models of the dynamics of cellular processes promise to yield new insights into the underlying cell biology and their systems’ properties. Since the processes are usually high-dimensional and time-resolved experimental data of the processes are sparse, parameter estimation faces the challenges of structural and practical non-identifiability of the parameters. Non-identifiabilities might render the systems analysis of the model difficult. Non-identifiability results usually in non-linear dependencies of the estimated parameters. To infer (non-)identifiability elegant analytical approaches exist which are, however, due to their computational complexity limited to low-dimensional systems. Established methods for high-dimensional systems rely on linear approximations which renders the interpretation of their results difficult.

We show that identifiability analysis can be reduced to an intuitive geometric issue. To operationalise this intuition, we propose a data-based non-parametric approach for identifiability analysis that is based on the bootstrap. It applies the alternating conditional expectation algorithm to estimate so-called optimal transformations. Statistical analysis of the optimal transformations allows for identifiability analysis regardless of model size or complexity. The algorithm identifies dependent, i.e. non-identifiable, groups of parameters, as well as the identifiable ones. We exemplify the proposed procedure by applications to dynamical models of cellular signalling pathways.

#### 1567-Pos Board B411

##### Modeling The Endosomal Stage Of Viral Infection

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Many viruses are endocytosed to enter the cell cytoplasm. To pursue their replication cycle, they have to escape endosome before being digested by lysosomal enzymes. Escape mechanisms are triggered by conformational change of either glycoproteins that deploy a fusogenic activity in the enveloped-viruses case or capsid “penetration” proteins that locally disrupt endosomal membrane in the nude-viruses case. These conformational changes, that can be multistep processes, are linked, directly or not, with endosomal acidification. Moreover, it is increasingly clear that the “fitness” of the escaping virus, that can be the number of bound specific enzymes, is crucial for infection next steps. Consequently, because endocytosed virus must escape in a certain state, before being entirely digested and because escape process, that is a complex chemical process triggered by endosomal acidification, is intrinsically variable and non deterministic, endosomal stage of viral infection calls for quantitative analysis. From biophysical considerations, we present here a general framework to model viral escape and estimate its mean escape time and its corresponding fitness as functions of various parameters such as the the number of viruses and the various rate constants. We apply more specifically the present analysis to the case of the adeno associated virus (AAV), a promising gene carrier in gene delivery.

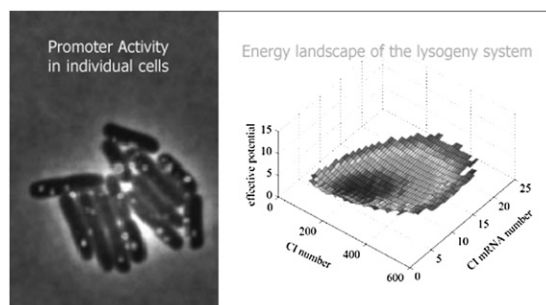
#### 1568-Pos Board B412

##### The Energy Landscape of an Epigenetic System

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The bacteriophage lambda lysis/lysogeny system serves as a paradigm for epigenetic stability and switching. However, the system still lacks a quantitative narrative based on direct experimental measurements, and theoretical studies have often relied on semi-free parameterization of key processes. By counting *cI* and *cro* mRNA numbers in individual lysogenic *E. coli*, we are able to describe experimentally the “phase plane” of the lysogenic system. The data is used to construct and calibrate a new theoretical model for the lysogeny maintenance circuitry, in which the discrete, pulsatile nature of promoter activity plays an important role. The model enables us to describe the “energy landscape” of the lysis/lysogeny system and the kinetics observed on this landscape—in particular, the extraordinary stability of the lysogenic phenotype.



#### 1569-Pos Board B413

##### Spatiotemporal Pattern Formation and Effects of Fluctuations and Stochasticity in Molecular Machinery

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University of Berlin, Berlin, Germany, <sup>3</sup>Fritz Haber Institute of the Max

Planck Society, Berlin, Germany. Cellular activity is supported by molecular machines such as enzymes, and can be seen as behavior of a reaction-diffusion system. However, such biomolecular machines are usually very large and of great internal complexity; reaction events sometimes involve intramolecular motion and take a long time (milliseconds to seconds). Moreover, due to the small cell volume and a great variety of molecules, some chemical species are so rare that their finite size fluctuations in number and molecular discreteness may be significant. Classical models using partial differential equations cannot take into account these characteristics of biochemical systems and need an extension.

As an example, we adopt reaction-diffusion systems with allosteric enzymes. Each enzyme is modeled as a cyclic machine, releasing a diffusible product at a certain phase in the cycle; binding of the product to an enzyme raises