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

Michail Stamatakis, Kyriacos Zygourakis.
Rice University, Houston, TX, USA.

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

Thomas Maiwald[1], Stefan Hengl[2], Clemens Kreutz[2], Peter K. Sorger[1], Jens Timmer[2].
[1]Harvard Medical School, Boston, MA, USA, [2]Freiburg Center for Data Analysis and Modeling, Freiburg, Germany.

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 examplify the proposed procedure by applications to dynamical models of cellular signalling pathways.

1567-Pos Board B411

Modeling The Endosomal Stage Of Viral Infection

Thibault Lagache[1], Olivier Danos[2], David Holcman[1].
[1]Ecole Normale Supérieure, Paris, France, [2]Hopital Necker, Paris, France.

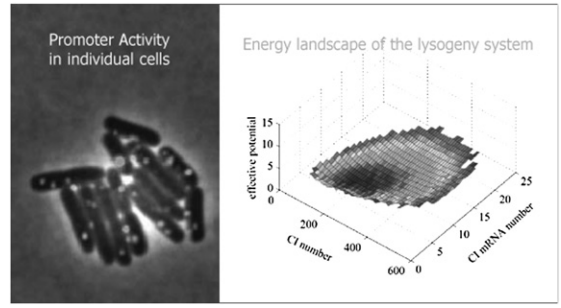
Many viruses are endocytosed to enter the cell cytoplasm. To pursue their replication cycle, they have to escape endosome before being digested by lysosomal enzymes. Escape mechanisms are triggered by conformational change of either glycoproteins that deploy a fusogenic activity in the enveloped-viruses 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

Chenghang Zong, Ido Golding.
University of Illinois at Urbana-Champaign, Urbana, IL, USA.

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

Yuichi Togashi[1], Vanessa Casagrande[2], Toshio Yanagida[1], Alexander S. Mikhailov[3].
[1]Graduate School of Frontier Biosciences, Osaka University, Suita, Osaka, Japan, [2]Bernstein Center for Computational Neuroscience, Humboldt-University of Berlin, Berlin, Germany, [3]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