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 examplify 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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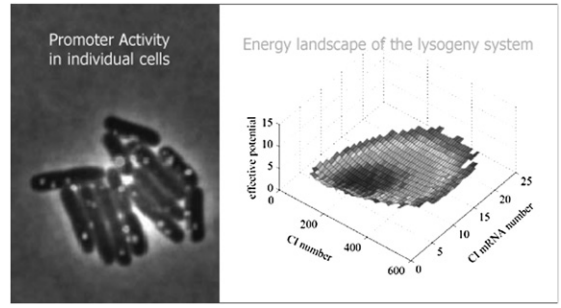
The bacteriophage lambda lysis/lysogeny system serves as a paradigm for epigenetic stability and switching. However, the system still lacks a quantitative narrative based on direct experimental measurements, and theoretical studies have often relied on semi-free parameterization of key processes. By 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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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

the enzyme activity (i.e., positive feedback). If fluctuations are absent, the system can be described by PDEs with delay. Spatiotemporal patterns such as traveling waves or spirals as well as uniform oscillations are observed.
In this work, we investigate effects of fluctuations in such systems. There are two major sources of fluctuations: conformation of each enzyme fluctuates individually and thus disperses time to finish the cycle (intramolecular fluctuations); stochastic interactions between molecules vary waiting time to start the next cycle (intermolecular fluctuations). Intermolecular fluctuations may in some cases enhance synchronization of the enzymes, while intramolecular fluctuations merely disturb it. We show that the combination of these two types of fluctuations may determine the dominant spatiotemporal pattern. Relevance to oscillatory patterns observed in vivo is also discussed.

1570-Pos Board B414
Proteome-Wide Fluctuation Analysis Of S.cerevisiae
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We measured over 40.000 single live yeast S. cerevisiae cells to determine the concentration and diffusion constants of more than 4100 proteins. These proteins account for more than 75% of the yeast proteome. We used Fluorescence Correlation Spectroscopy (FCS), Photon Counting Histograms (PCH), and Brightness & Number analysis (B&N) to analyze the intensity fluctuations of single molecules fused to GFP. The data was collected using a commercial FCS setup attached to a confocal microscope (ConfoCor3 and LSM 510 META, Carl Zeiss Jena GmbH, Germany) controlled by custom software.
The cells were imaged in transmitted light. We acquired fluorescence images, using the avalanche photo diodes of the FCS setup. This allows us to determine the localization of proteins, the cell cycle as well as cell health.
We developed a software package to automate the measurements and data analysis. We use the Open Microscopy Environment (OME) to organize our images, fluctuation measurements, and analysis results.
We calculated the protein copy number per cell, and compare the noise in concentration levels between different proteins in respect to localization and biochemical pathway.
We find that the diffusion coefficient for GFP is identical in nucleus and cytosol. But interestingly, most of the proteins localized in the nucleus diffuse slower than proteins localized in the cytoplasm.
We will present our data and compare them to information gathered with different methods like flow-cytometry and mass-spectroscopy. We will discuss conclusions derived by complementing our data with information collected in public databases like Saccharomyces Geneome Database (www.yeastgenome.org), Yeast GFP Fusion Localization Database (yeastgfp.ucsf.edu), and the General Repository for Interaction Datasets (www.thebiogrid.org).

1571-Pos Board B415
Macroscopic Singularity In Morphogen Gradient And Bioelectric Field Of Growth Control
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In embryogenesis, every physiological system is developed through a growth control system mediated by organizers and growth control boundaries. The growth control signal transduction is embedded in various physiological functions. Many physiological processes are regulated through growth control mechanisms such as hypertrophy, hyperplasia, atrophy, apoptosis and signal transduction pathways involving growth control genes such as proto-oncogenes. A model of growth control system suggests that a growth control system originates from a network of organizers which distribute at extreme points of structural surface (or interface) curvature. Organizers and growth control boundaries are macroscopic singularities (i.e. discontinuity and abrupt transition) of morphogen gradient field and bioelectric field. Small, nonspecific perturbations around singular points - organizers can have long lasting systemic effect. This offers an efficient way of manipulating the system. The growth control model further suggests that singular points - organizers and separatrices - boundaries in growth control form an undifferentiated, interconnected cellular network that regulates growth and physiology both during and after embryogenesis. Stem cells are important components of this undifferentiated network. Acupuncture points and meridians originate from organizers and growth control boundaries respectively. The model of growth control system has met the gold standard of science - the following predictions of the model have been independently confirmed: 1. Organizers have high electric conductance, high electric current density and high density of gap junctions. 2. Growth control boundaries have high electric conductance and high density of gap junctions. 3. Singularity has important role in morphogenesis. 4. Morphogens and organizers partially retain their regulatory function after embryogenesis. 5. Nonspecific stimulation at acupoints - potential organizers in adult causes extensive growth control effects.
Singularity provides a potentially efficient way of manipulating the growth control, stem cells and physiological systems.

1572-Pos Board B416
Isotopomeric 13C Labeling of Amino Acids Reveal Compartmentation in Saccharomyces uvarum
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The first step in the synthesis of the aspartic acid (Asp) methionine (Met) and threonine (Thr) can occur in close relatives of *Saccharomyces cerevisiae* such as *S. uvarum* via mitochondrial aspartate aminotransferase (AAT1) or its cytosolic homologue AAT2. Also the amination of cytosolic pyruvate in the production of alanine (Ala) in these species can occur in both compartments using cytosolic (ALT2) or mitochondrial alanine aminotransferase. The aim of this work was to reveal the compartmentation of the synthesis of these amino acids during respiratory growth using isotopomeric data derived from the ^{13}C labeling of proteinogenic amino acids. *S. uvarum* was grown under steady-state growth conditions and fed with a mixture of either $^{13}C[1,2]$ or $^{13}C[2]$ labeled acetate and unlabeled glucose at two dilution rates. Absolute and conditional labeling patterns were measured using ^{13}C NMR and compared with simulated isotopomer distributions within a least squares optimization routine that adjusted the flux parameters. Biomass composition was used to further constrain the fluxes. A software tool was created to automate the composition of the weakly non-linear isotopomer balance equations for all metabolites in the system, thus allowing us to easily test variations of any metabolic network. We properly account for symmetric and prochiral metabolites. The resulting equations are solved without the need for matrix calculations within the optimization routine making this approach a candidate for speeding up the simulation of large metabolic systems. The results of this optimization reaffirm that the precursor for Asp, Met, and Thr is mitochondrial oxaloacetate and that mitochondrial putative alanine transaminase (ALT1) is functional in the synthesis of alanine.

1573-Pos Board B417
Time recoder system of protozoa
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Unicellular animals might be cleverer than previously thought. Anticipating events are higher functions performed by the brains of higher animals; their evolutionary origins and the way they self- organize, however, remain open questions. Here we show that *Physarum polycephalum* and *Blepharisma japonicum* can anticipate the timing of periodic events. The organisms move rapidly under favourable conditions, but stops moving when transferred to less-favourable conditions. They exposed to low-temperature conditions, presented in several times consecutive pulses at constant intervals, reduced their locomotive speed in response to each episode. When subsequently subjected to favourable conditions, they spontaneously reduced their locomotive speed at the time point when the next unfavourable episode would have occurred. This implied anticipation of impending environmental change. After this behaviour had been evoked several times, the locomotion returned to normal. We explored the mechanisms underlying these behaviours from a dynamical systems perspective. We have developed a dynamical systems model that reproduces the experimentally observed phenomena. Poly-rhythmic amoeboid movement in Physarum has previously been reported by two independent research groups. Oscillations were observed with a series of different periods (600, 240, 30, 10, 2, 0.5, and 0.05 minutes), and the overall activity showed a 1/f-type power spectrum in the Fourier analysis. These results imply that there are oscillations with a series of frequencies and that the frequency distribution is wide and continuous. This is the most fundamental assumption used in the mathematical modeling. Our results hint at the cellular origins of primitive intelligence and imply that simple dynamics might be sucient to explain its emergence.

1574-Pos Board B418
Single-cell Analyses of the *Escherichia Coli* Proteome with Single-molecule Sensitivity
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Genetically identical organisms do not have the same gene expression. This stochastic difference in gene expression, also known as noise, can be the