

Parallel Session

Cell and Intra-Cell Dynamics IV

LIMITS ON INFORMATION TRANSMISSION THROUGH BIOCHEMICAL NETWORKS IN RESPONSE TO THE PULSED STIMULI

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Keywords: Channel information capacity, Binary responses, Bandwidth, Relaxation, MAPK pathway.

Two important regulatory pathways of NF- κ B and MAPK were found to transmit merely one bit of information about the level of constant stimulation with, respectively, TNF and EGF [1, 2]. This somewhat surprising result may suggest that these pathways evolved to process analog inputs into physiologically interpretable binary outputs. In the case of NF- κ B, at small TNF doses, information is restricted by intrinsic noise, whereas at large TNF doses, by saturability of pathway components [3]. The MAPK signaling system combines a fast positive feedback with a slow negative feedback, and exhibits relaxation oscillations or pulsed responses of predefined amplitude [4]. Although being capable of transmitting a single bit about the stimulation dose, both NF- κ B and MAPK pathways can respond in a pulsatory manner to the repeated pulses of the stimuli.

Here, based on an experimentally verified computational model [4], we estimated MAPK channel information capacity C , defined as a maximal mutual information that can be transmitted over a sufficiently long time t , divided by t [5]:

$$C = \lim_{t \rightarrow \infty} \max_{p(x)} \frac{1}{t} \iint p(x, y) \log \left(\frac{p(x, y)}{p(x)p(y)} \right) dx dy, \quad (1)$$

where, in our case, $x(t)$ are EGF binary input sequences, and $y(t)$ is the output, i.e. the level of bisphosphorylated ERK. The MAPK pathway is capable of responding (by activation of kinase ERK) to short EGF pulses of period not shorter than $T=50$ minutes. As the response is nearly binary, one could expect that the information transmission rate is equal to the classical bandwidth, $1/T$. We found however, that the upper bound on information transmission rate is substantially higher and can be achieved for sequences of EGF pulses with carrying frequency higher than $1/T$. This result follows from the fact that the width of the ERK activity pulse, about 20 min, is shorter than T , and thus the distances between subsequent ERK pulses can be used for information coding. We expect that the reported

effect can be even more pronounced for information carried by short neural spikes. Because the responses are nearly binary, we found that channel information capacity slowly decreases both with extrinsic noise (i.e., variability of concentration of pathway components) and an additive intrinsic noise component.

It remains an open question whether in physiological conditions cells are exposed to EGF pulses secreted by their immediate neighbors or to slowly varying EGF concentration averaged over tissue.

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UNRAVELLING THE CONTRIBUTION OF CELL CYCLE AND CELL EXPANSION IN AN INTEGRATED MODEL OF TOMATO FRUIT DEVELOPMENT

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Keywords: Cell division, Cell growth, Development.

The development of a new organ is the result of coordinated events of cell division and expansion. Fruit growth starts immediately after bloom with intensive cell division. As development proceeds, the proliferative activity of cells progressively slows down giving the way to a phase of cell enlargement in which cells undergo an impressive volume increase, up to a few thousand-fold, via turgor-driven processes. In many species the transition from cell division to expansion phases is accompanied by a repeated DNA duplications without mitosis, a process called endoreduplication. The exact role of endoreduplication is still unknown but a strong correlation between cell ploidy (i.e number of DNA copies) and final cell size has been observed in different species, suggesting a role of endoreduplication into the control of cell growth [1, 2].

Modeling the way cell cycle and cell expansion interact together is crucial to describe early fruit development and to understand the emergence of specific morphological traits (fruit size, weight, shape and texture) in relation to environmental and genetic factors. Here a combination of theoretical and computational approaches are used to investigate the interplay among cell-cycle and biophysical processes in the control of cell and organ growth.

The Lockhart equation relating the rate of volume increase to the cell's internal pressure [3] is coupled to the description of carbon and water flows across the cell membrane, based on thermodynamic equations. The model shows that cell strategy for resources uptake and allocation may have important consequences on the resulting cell expansion rate.

At the organ level, the emergence of cell-size variability from observed kinematic patterns of cell division and endoreduplication is investigated. In particular, the possibility of a coordinated organ-level control of cell expansion capabilities, as predicted by the neo-cellular theory [4, 5] is tested and compared real data. The model suggests that a pure cell-autonomous control fails to reproduce the observed cell size distribution, and that an organ-level coordination is needed in order to get realistic results.

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LONG TERM BEHAVIOR OF SOME NON-REGULAR STOCHASTIC REACTION NETWORKS

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Keywords: Stochastic reaction network, (Complex balanced, Mono-molecular) reaction network, Stationary distribution, Gene autoregulation, Stochastic recurrence equation.

Stochastic models [1] are used to understand count dynamics of interacting species in a biochemical reaction network where an explicit form of stationary distribution is only available for a particular class known as complex balanced networks [3]. Motivated by **Gene autoregulation networks** we studied long time asymptotics of a stochastic reaction network that is not complex balanced. The species set of the proposed network is partitioned in two disjoint subsets based on an inherent causal structure. We call them as **host-parasite** reaction network since the evolution of parasite species depends only on presence of host species whose counts are assumed to be marginally ergodic. We showed that for a mono-molecular type of reactions of parasites (i.e birth, death, and conversion of parasite species P_1, P_2 represented as



where C_1, C_2, C_3 are host species) an explicit **mixture** of Poisson distribution appears as the stationary distribution. We further extended the ergodicity result to a class of more general single species parasite networks (beyond mono-molecular type). The aforementioned mixture distribution can be represented as a fixed point of a stochastic recurrence equation [2] which can be constructed from the dynamics of host species.

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INVESTIGATION OF BOOLEAN MONOTONIC MODEL POOLS

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Keywords: Boolean networks, Qualitative differential equations, Dynamical systems.

Mathematical models for bioregulatory networks can be based on different formalisms, depending on the quality of available data and the research question to be answered. Discrete Boolean models can be constructed based on qualitative data, which are frequently available. On the other hand, continuous models in terms of ordinary differential equations (ODEs) can incorporate time-series data and give more detailed insight into the dynamics of the underlying system. Several ideas have been developed in the past to link these approaches in order to benefit from the advantages of both modeling frameworks (e.g. [3, 1]). Drawing from ideas developed in qualitative differential equation theory, we present here another approach to analyze sets of monotonic Boolean models or ODE-models consistent with given signed interactions between systems components. This approach constitutes a further link between ODE-models and discrete models. We will report on our recent work partially published already in [2] focusing mainly on the Boolean side.

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STOCHASTIC GENE EXPRESSION IN GROWING CELL POPULATIONS

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Keywords: Agent-based modelling, Master equation, Gene expression noise, Population dynamics, Ergodic principle.

Population growth is often ignored when quantifying gene expression levels across clonal cell populations. We develop a framework for obtaining the molecule number distributions in an exponentially growing cell population taking into account its age structure. In the presence of generation time variability, the average acquired across a population snapshot does not obey the average of a dividing cell over time, apparently contradicting ergodicity between single cells and the population. Instead, we show that the variation observed across snapshots with known cell age is captured by cell histories, a single-cell measure obtained from tracking an arbitrary cell of the population back to the ancestor from which it originated. The correspondence between cells of known age in a population with their histories represents an ergodic principle that provides a new interpretation of population snapshot data. We illustrate the principle using analytical solutions of stochastic gene expression models in cell populations with arbitrary generation time distributions. We further elucidate that the principle breaks down for biochemical reactions that are under selection, such as the expression of genes conveying antibiotic resistance, which gives rise to an experimental criterion with which to probe selection on gene expression fluctuations.

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