Stochastic Processes in Complex and Biological Systems

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Molecular Motors as Semi-Markov Chains

Kinesin is a complex molecular machine whose properties have been studied in great detail both theoretically and experimentally in our department **[1, 2]**. When we experimentally observe a kinesin molecule walking along a filament, we see a series of forward and backward steps, whose relative frequency depends on the availability of ATP, the fuel of this motor. A more detailed analysis reveals, however, that the steps of the kinesin motor are more complex. In fact, both the probability of a motor to make a step forward or backward and the time that it takes to perform one of these steps depend on whether the motor had previously performed a forward or backward step. A detailed analysis of these different probabilities was done in **[3]**, where we showed that the motor's displacements should be described in terms of pairs of steps, such as bf which means a step backward followed by a step forward. It turns out, therefore, that there are four such states indicated as *{ff, fb, bf, bb}*. In this representation, the motor is described as a stochastic chain in continuous time over these four states with the property that the dwell times are not exponentially distributed. These chains are called semi-Markov chains. Since the dwell times on these four states are also experimentally accessible and this level of description may apply to a large class of motors, we want to develop a mathematical framework to analytically compute several properties that are also easily accessible experimentally. This project is performed in collaboration with Prof Sylvie Rœlly at the University of Potsdam.

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Models for Translational Control

Translation of the messenger RNA (mRNA) is a key process in cell biology. The process of translation is performed by ribosomes, which are molecular machines walking unidirectional on the mRNA while synthesizing the proteins. The amount of proteins produced by each mRNA depends therefore on the number of ribosomes on it, which depends on the initiation rate, on the speed by which the ribosomes move along the chain, and on the termination rate. Finally, the number of ribosomes depends also on the life time of the mRNAs. Our work is mainly concerned with the bacterium *E. coli*. Experimentally, in collaboration with Prof Zoya Ignatova at the University of Potsdam, we are determining the number of ribosomes on certain mRNAs and we are preparing the samples for a ribosomal footprinting over the whole set of mRNAs in this organism. From the theoretical side, we have found out that the kind of mRNA degradation pathways in *E. coli* cells has some effect both on the number of ribosomes and also on the rate of protein synthesis and that this effect is stronger for longer mRNAs **[4, 5, 6]**. In our theory, simple models of mRNA degradation have shown that some differences in the process of degradation can have dramatic effects on the translation rate (see **Fig. 1**). We are therefore developing more complex models based on the available knowledge about the degradation process in order to finally understand the role of degradation on the rate of protein synthesis **[7]**. On the other hand, under certain circumstances the tRNAs necessary to perform the translation can become particularly rare and thus slow down the ribosomes at certain positions along the mRNA **[8]**. We are thus developing a model to take properly into account the effective concentrations of all tRNAs and thus predict the local speed of the ribosomes and compare these results with the experimental footprinting.

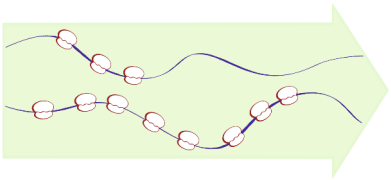

Fig. 1: Schematic diagram of mRNA translation at different times. The two chains have the same length but differ in the number of loaded ribosomes. The upper chain is young and has only few ribosomes that are close to the initiation region. The chain at the bottom is older and thus is loaded with more ribosomes. The arrow indicates the direction of motion of the ribosomes. If mRNA turn-over is very rapid, some mRNA may be degraded before producing any protein.

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Life Cycle of Chlamy Cells

Chlamydomonas reinhardtii (chlamy) is a unicellular photosynthetic alga that is studied within the ongoing systems biology project GoFORSYS, in collaboration with the University of Potsdam and the MPI of Plant Physiology (MPIMP). Chlamy cells have the special property that they remain in the growth phase for a random amount of time and attain, at a population level, a relatively broad distribution of cell sizes. One consequence is that each mother cell can produce a number of daughter cells that is roughly proportional to the logarithm of its size (see **Fig. 2**). Since cell volume is often

considered as a proxy for the cellular metabolic state, the first objective is therefore to develop a model for the cell size distribution under time-independent conditions such as those found in the bioreactor at the MPIMP. The model can be used to calculate and compare stationary distributions for the common binary and the multiple division processes **[9]**.

We have also addressed another set of experiments that were performed in the labs of Prof Martin Steup at the University of Potsdam. In these experiments, the cells are synchronized by fixed periods of light and darkness and are grown in a special medium that does not allow for cell growth in the darkness. Synchronization relies on the fact that, under certain general conditions, all cells would divide after the start of the dark period and the daughter cells would start to grow only when light is turned on again. These experiments allow determining the relationship between the cell size and the number of daughter cells as well as the cell growth rate and the timing of DNA replication. Our current aim is to use our model to predict the cell size distribution at the beginning of the light period.

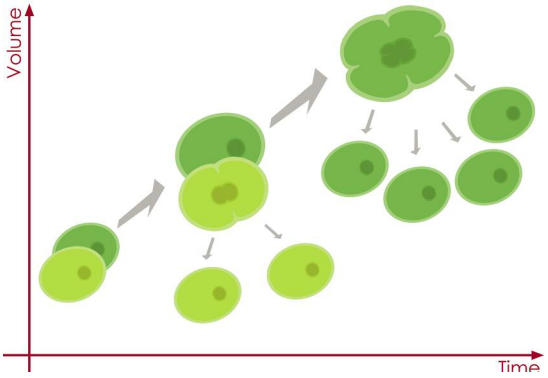

Fig. 2: Multiple cell division. Two twin cells grow in volume over time but one cell divides earlier than the other. The first dividing cell (light green) is relatively small at division time and produces only two daughter cells. The cell that divides later (dark green) attains a larger volume and can divide in four daughter cells. In the cell culture, one can observe also large mother cells producing up to 32 daughter cells.

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Patterns on Complex Networks

In this research activity, we consider networks as collections of points, called vertices, connected by bi-directional links, sometimes also called edges. Random networks are those networks in which the number of edges connected to any randomly chosen vertex, which is called the degree of the vertex, is a random variable that follows a given distribution. This distribution is called the degree distribution of the network. A special subset of these random networks is given by those characterized by a power law degree distribution. Random networks are sometimes called complex networks and all known complex networks have a direct or indirect biological origin. Prominent examples are food webs, as well as social and neural networks.

In general, the vertices of biological networks are dynamic and exhibit various properties or internal degrees of freedom that evolve with time. A proper description of the network is then obtained in terms of dynamical variables that are defined for each vertex of the network. In a neural network, for instance, the vertices represent firing and nonfiring neurons and thus switch between an active and an inactive state depending on the signals that arrive from the neurons connected to them.

In general, the dynamics of each vertex is determined by the local interactions of this vertex with its neighbors. One instructive example is provided by local majority rule dynamics which is defined as follows: If, at a certain time, most direct neighbors of a certain vertex are active or inactive, this vertex will become active or inactive at the next update of the pattern. One interesting question concerns the result of the update rule once it is repeated many times over the whole networks. In particular, we would like to estimate the number of attractors of the dynamics. We have found out that the knowledge of the degree distribution alone is not sufficient to provide a general answer. Indeed, it turns out that the degree-degree correlation between the vertices plays a major role.

It is perhaps for this reason that most naturally occurring networks have either positive or negative degree-degree correlation. In both cases, the activity patterns are governed by a large number of attractors. In fact, we have found out that in dissortative scale-free networks the number of attractors exhibits a maximum as a function of network size **[10]**, while in assortative networks the number of attractors steadily increases with network size **[11]**. We have indeed found out that the structure of the network takes a peculiar nested form that depends on whether the degree correlation is positive or negative. This structure can be visualized in terms of partially connected subnetworks or layers of different size whose dynamics can be compared with that of Ising models in different dimensions **[12]**.

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