Stochastic Processes in Complex Bio-Systems

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Degradation of mRNA and Translational Control

Degradation of mRNA is one of the key processes that control gene expression in the cells. Traditionally, this process has been thought to be governed by a decay rate constant. Biochemists, however, have unveiled a large number of complex mechanisms underlying mRNA degradation. In addition, several measurements of mRNA turnover have shown that mRNA decay is rarely simple. The turnover of mRNA molecules introduces new timescales that interact with the timescales of translation and of cell division. In **[1]** we have considered the interaction of the lifetime distribution of an mRNA species with the timescale needed by ribosomes to build a stable polysome (**Fig. 1**). The latter timescale is proportional to the length of the mRNA. We have found out that for very long mRNAs with a high turnover, the transient time until protein synthesis begins may be comparable with the lifetime of the mRNA thus affecting both the protein synthesis rate and the size of the polysome.

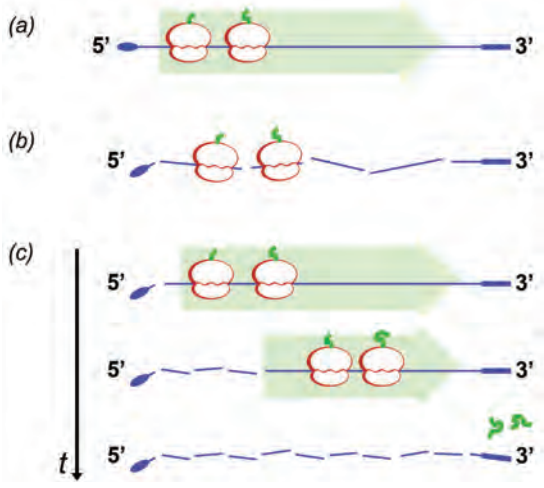

Fig. 1: Translation and degradation of mRNA. (a) Prokaryotic mRNA and (b) the effect of endonucleolitic degradation on the polysome. (c) Eukaryotic mRNA. Degradation occurs in the 5′ to the 3′ direction.

The analysis of experimental data from E. coli shows that longer mRNA produce, in general, fewer proteins than shorter mRNA if the lifetime distribution of the mRNA is short and exponential (**Fig. 2**).

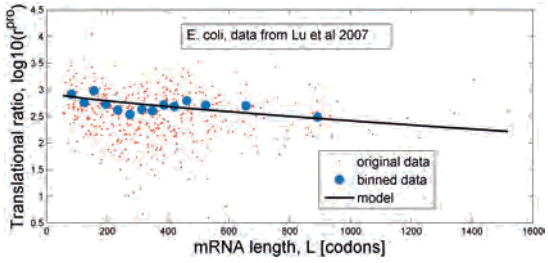

Fig. 2: The interplay between degradation and loading of the polysome can produce a negative correlation between the number of proteins per mRNA and its length.

There is also an indication that mRNA degradation may affect the spatial distribution of the ribosomes on the mRNA. This point was investigated in **[2]** using flux balance equations and stochastic simulations. Since the lifetime distribution of the mRNA is not exponential, in **[3]** we have looked at the interplay between the shape of the lifetime distribution and the timescales necessary to reach a steady state expression level (**Fig. 3**).

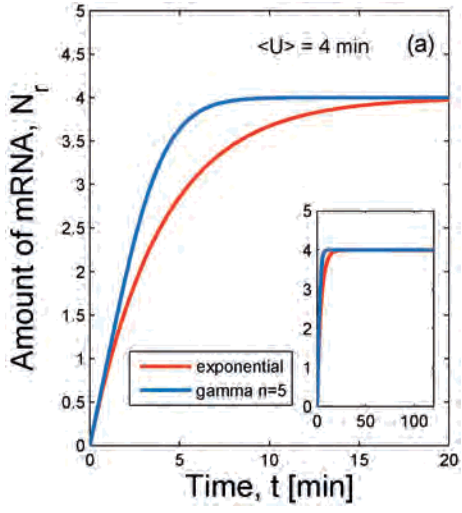

Fig. 3: Two assumptions for the mRNA lifetime distributions lead to different transient times. In E. coli the average mRNA lifetime is about four minutes and its cell cycle has duration of twenty minutes.

We found that mRNA characterized by broadly distributed lifetimes take longer to reach a steady state copy number so that especially in bacteria certain mRNAs may never reach a steady state copy number before cell division. In **[3]** we did not investigate the origin of the different lifetime distributions, a topic that was left for further investigations published in **[4]**.

Ribosomal profiling is a new experimental technique that provides an *in vivo* picture of the translational state of the cell. With this technique one can investigate the various mechanisms of translational control, which include the initiation rate by ribosomes and the codon dependent elongation rate. One important question that we wanted to address concerns the differential translational state of organisms under different growth or stress conditions. To address this ques-

tion, in the framework of the Marie-Curie ITN "NICHE" Prof Zoya Ignatova and her lab at the University of Potsdam have worked on the ribosomal profiles of *E. coli* cell cultures under four different growth conditions. The analysis of the data produced with advanced bioinformatics tools **[5]**, will be further statistically analyzed in a manuscript in preparation **[6]** to provide the most complete picture of the differential gene expression in *E. coli* so far. This data will then become a useful benchmark for modelling the interaction of ribosome with the mRNA.

Heterogeneity of Chlamy Cell Populations

Chlamydomonas reinhardtii (chlamy) is a unicellular photosynthetic alga. The cells of this organism have the special property to 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 (**Fig. 4**). Since cell volume is often considered as a proxy for the cellular metabolic state, one first objective has been to develop a model for the cell size distribution under time-independent conditions such as those created in some bioreactors. The model can be used to calculate and compare stationary distributions for the common binary and the multiple division processes **[7]**. The model has left many questions open. One biologically important question is whether the experimentally observed diversity is solely given by the stochastic nature of cell growth and division or to the heterogeneous mixture over the phases of the cell cycle. Furthermore, we wanted to investigate if the volume of the mother cells is the only determinant of the number of daughter cells.

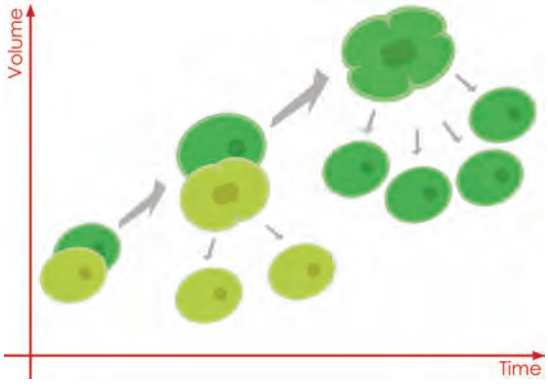

Fig. 4: Two chlamy daughter cells (bottom left) grow in time but divide at two different time points. Although the number of daughter cells is different, their sizes are very similar.

To investigate these points, Prof. Martin Steup and his lab at the University of Potsdam have performed a set of experiments with synchronized chlamy cells. The synchronization is obtained by cultivating the cells with fixed periods of light and darkness, in a growth 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. Clearly, at the beginning of each light period all the cells are in the same point of the cell cycle. The experiments showed us that DNA replication occurs stochastically during the light period according to relatively simple rules that we have been able to cast in a stochastic model of cell growth and division. The conclusion of this study **[8]**, is that DNA replication is one major determinant of the number of daughter cells and that its stochastic nature maintains the population heterogeneous even under synchronization conditions.

Markov Chains in Biological Processes

Markov chains are a very common tool to mathematically model biological processes.

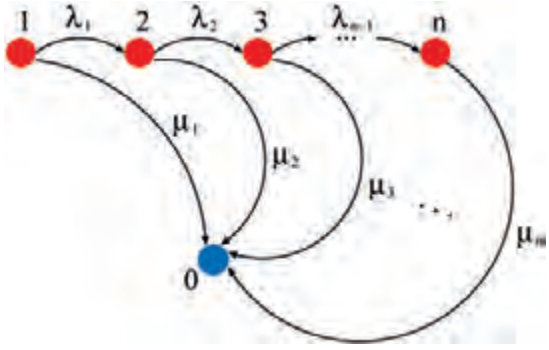

Fig. 5: The stochastic life of a single mRNA molecule is made of specific biochemical states. At each state, a transition to the next state or to absorption is possible.

The recent application of this tool in our group covers modelling the complex life time of mRNA, where each molecule undergoes several biochemical transitions until degradation takes place (**Fig. 5**, from Ref. **[4]**), and the stochastic lifetime of trabecular bones **[9]**, within a project led by Dr. Richard Weinkamer in the Biomaterials department. We have considered also mathematical models of molecular motors. In one particularly instructive work **[10]**, we have considered a simple model of molecular motors interacting with the fuel substrate. When the amount of fuel molecules is not constant, due to its stochastic consumption and replacement, the rate by which a motor receives the fuel varies stochastically in time. We could derive an analytical expression of the distribution of the time that a motor has to wait for a fuel molecule and found that it is not exponential. This implies that at low molecule number the law of mass action does not hold. Models of molecular motors like Kinesin have also inspired several problems in the mathematical theory of Markov chains that we have investigated in collaboration with Prof Sylvie Rœlly at the Institute of Mathematics of the University of Potsdam and are going to be submitted soon **[11,12]**.

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