Regulation of Bio-Processes

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Most biological processes are tightly regulated. For example, the genetic information is processed in several steps, transcription, translation, and degradation of mRNA and protein. Each of these steps may be the target of regulatory mechanisms that switch a gene on or off or fine-tune the concentration of its product. Our group is interested in the design principles behind these control mechanisms and the underlying physical constraints, with a focus on bacterial systems. In general, we attempt to use theory as a way to bridge between molecular information and its macroscopic (physiological or evolutionary) context.

Dynamics and Regulation of Transcription

The first step in gene expression is transcription by RNA polymerases (RNAPs) that move along a gene and synthesize an RNA copy of its sequence. The dynamics of this process is a complex interplay of stochastic stepping along the DNA and several types of pauses. One question we are interested in is how this complex dynamics affects transcription under conditions where a gene is transcribed by multiple RNAPs simultaneously. Dense RNAP traffic is typical for the transcription of ribosomal RNA (rRNA) in fast growing bacterial cells, as large ribosome concentrations are needed for the high rate of protein synthesis associated with rapid cell growth. Using lattice models that are related to simple exclusion processes from non-equilibrium statistical physics, we found that backtracking pauses (during which RNAPs slide backwards in a diffusive fashion) are strongly suppressed under these conditions, but that pauses without backtracking may severely limit the transcription rate (**Fig. 1**) **[1]**. Rapidly growing cells therefore need to actively suppress such pauses. In bacteria, this is achieved by the so-called ribosomal antitermination system.

The suppression of backtracking pauses in dense RNAP traffic may also be used in regulatory mechanisms: If pausing is coupled to the termination of transcription, the probability of termination can be modulated by the pause duration and, thus, by the transcription rate **[2]**. As a result, transcription can become very sensitive to changes in the rate of transcription initiation.

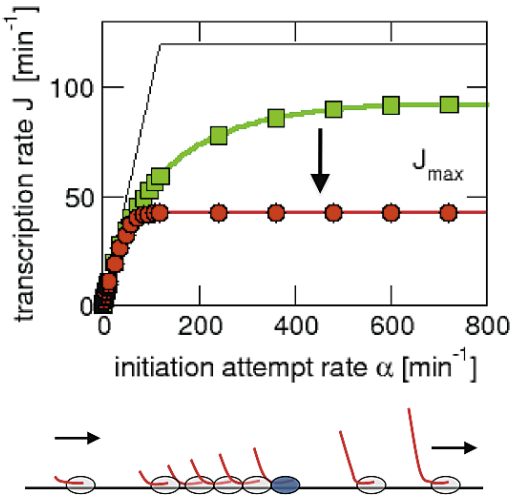

Fig. 1: Pauses during transcription reduce the maximal transcription rate (green to red) due to traffic jams behind paused RNAPs.

Economic Principles of the Transcription and Translation Machinery

RNAPs as well as ribosomes, the molecular machines of translation, are allocated by the cell to genes or classes of genes based on the requirements of their genetic program. For RNAPs, we have used a functional partitioning model (**Fig. 2**) to study this allocation. The model indicates that there is a large pool of RNAPs that are non-specifically bound to DNA. This pool buffers the concentration of free RNAPs against changes in transcription of even highly transcribed genes such as the rRNA genes. Therefore, even dramatic changes in the transcription of a class of gene only weakly affect other genes **[3]**.

Ribosomes underlie different economic principles, as most ribosomes in bacterial cells are active in translation and their activity is directly linked to cell growth. Optimizing ribosome activity therefore provides a fitness advantage, which we have used as a basis to understand the non-random usage of synonymous codons (different nucleotide triplets encoding the same amino acid). An evolution model for codon usage allows us to obtain a prediction of the abundance of a protein from codon frequencies in the sequence of its gene.

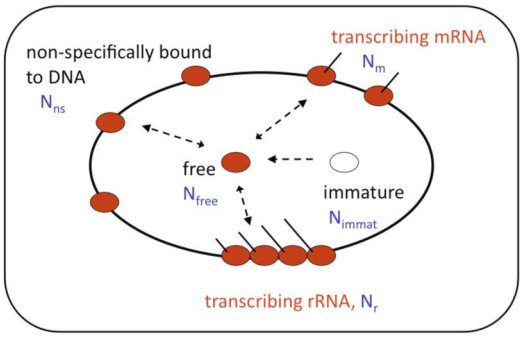

Fig. 2: Model for the partitioning of RNA polymerases into five functional classes.

Genetic Circuits and Growth-Rate Dependent Gene Expression

The control networks of genes regulating other genes are often described in analogy to electrical circuitry. However, genetic circuits remain coupled to the physiological state of their host cell, which for example provides the machinery of gene expression. As a result, the concentration of the product of a gene depends not only on its regulation but also on the state of the whole cell, which in bacteria can often by characterized by the growth rate. We have characterized the growth rate dependence of gene expression of unregulated genes (**Fig. 3**) and several simple circuits **[4]**. If the product of a gene also affects cells growth, these effects can give rise to a new feedback mechanism, mediated by a modulation of cell growth. Such feedback, due to the controlled expression of chromosomal toxins may have a role in the establishment of tolerance against antibiotics (persistence) **[4]**.

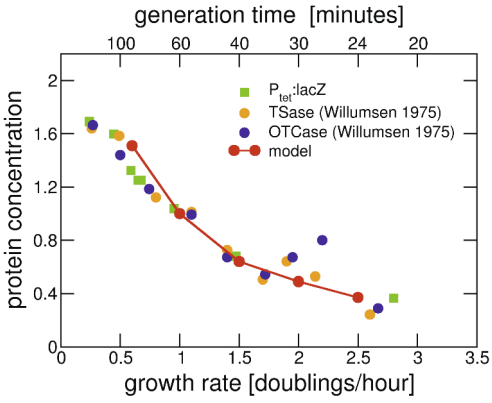

Fig. 3: Growth-rate dependence of gene expression for an unregulated gene, theoretical results (red line) and experimental data for several systems (symbols).

Cooperative Molecular Motors

We have also continued our activity in modeling the cooperative action of small teams of molecular motors. Using detailed simulations of a bead pulled by several kinesin motors **[5]**, we studied how cooperative transport depends on mechanical aspects of the system (collaboration with the group of Ulrich Schwarz, University of Heidelberg). Surprisingly, there is a rather robust relation between the average number of pulling motors and the processivity (run length) of the bead, in good agreement with our earlier model (**Fig. 4**). The increase in processivity with increasing number of motors is also found for motors pulling in opposite directions, despite the tug-of-war between two teams of motors **[6]**.

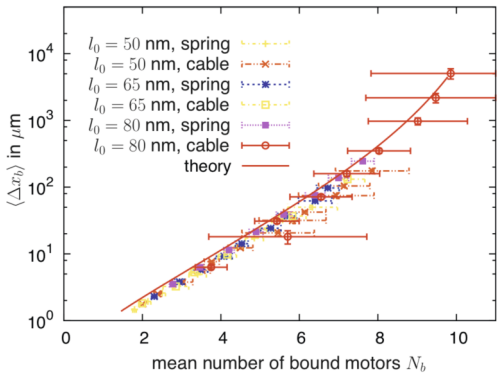

Fig. 4: Run length of a bead transported by several kinesin motors as predicted by simulations that vary the geometrical and mechanical properties of the motors.

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References:

[1] Klumpp, S., Hwa, T.: Stochasticity and traffic jams in the transcription of ribosomal RNA: Intriguing role of termination and antitermination. Proc. Natl. Acad. Sci. USA **105**, 18159-18164 (2008).

[2] Klumpp, S.: Pausing and backtracking in transcription under dense traffic conditions. J. Stat. Phys. Published online (2011), DOI: 10.1007/s10955-011-0120-3

[3] Klumpp, S., Hwa, T.: Growth-rate dependent partitioning of RNA polymerases in bacteria. Proc. Natl. Acad. Sci. USA **105**, 20245-20250 (2008).

[4] Klumpp, S., Zhang, Z., Hwa, T.: Growth-rate dependent global effects on gene expression in bacteria. Cell **139**, 1366-1375 (2009).

[5] Korn, C.B., Klumpp, S., Lipowsky, R., Schwarz, U.S.: Stochastic simulations of cargo transport by processive molecular motors. J. Chem. Phys. **131**, 245107 (2009).

[6] Müller, M.J.I., Klumpp, S., Lipowsky, R.: Bidirectional transport by molecular motors: Enhanced processivity and response to external forces. Biophys. J. **98**, 2610-2618 (2010).