Modeling ribosome motion during genetic translation

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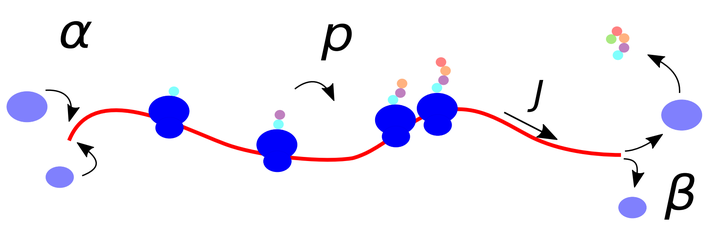
Motivation & Research Goals

Gene expression is the synthesis of proteins from the information encoded on DNA. One of the two main steps of gene expression is the translation of messenger RNA (mRNA) into polypeptide sequences of amino acids. Here, by taking into account mRNA degradation, we model the motion of ribosomes along mRNA with a ballistic model where particles advance along a filament without excluded volume interactions. Unidirectional models of transport have previously been used to fit the average density of ribosomes obtained by the experimental ribosequencing (Ribo-seq) technique in order to obtain the kinetic rates. The degradation rate is not, however, accounted for and experimental data from different experiments are needed to have enough parameters for the fit. Here, we propose to study an entirely novel experimental setup and theoretical framework consisting in splitting the mRNAs into categories depending on the number of ribosomes from one to four. We will solve analytically the ballistic model for a fixed number of ribosomes per mRNA, study the different regimes of degradation, and propose a criteria for the quality of the inverse fit. The proposed method provides a high sensitivity to the mRNA degradation rate. The additional equations coming from using the monosome (single ribosome) and polysome (arbitrary number) ribo-seq profiles will enable us to determine all the kinetic rates in terms of the experimentally accessible mRNA degradation rate.

Modeling genetic translation



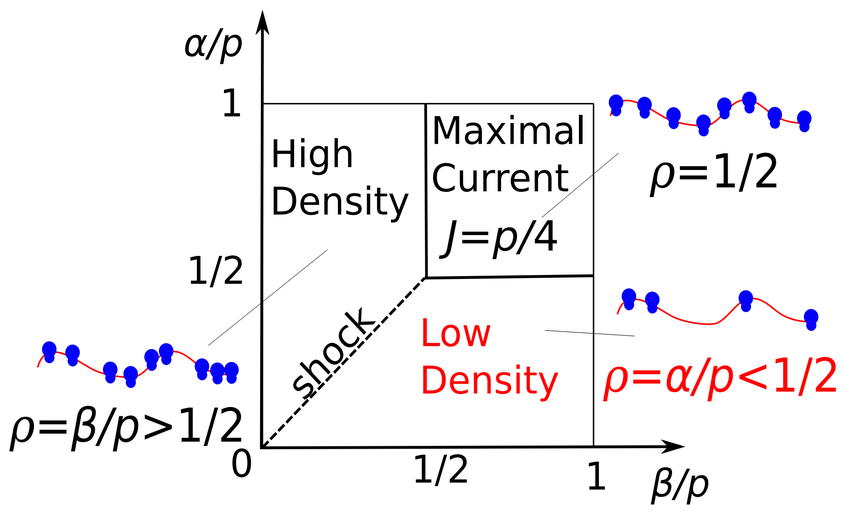


FIG.1: (top) The totally asymmetric simple exclusion process (TASEP) is the paradigmatic model for genetic transalation with initiation rate α, elongation rate p and termination rate β. (bottom) the phase diagram is governed by the value of α/p and β/p. Genetic translation is generally in the low density. The current $J = p\rho(1-\rho)$ corresponds to the protein production rate.

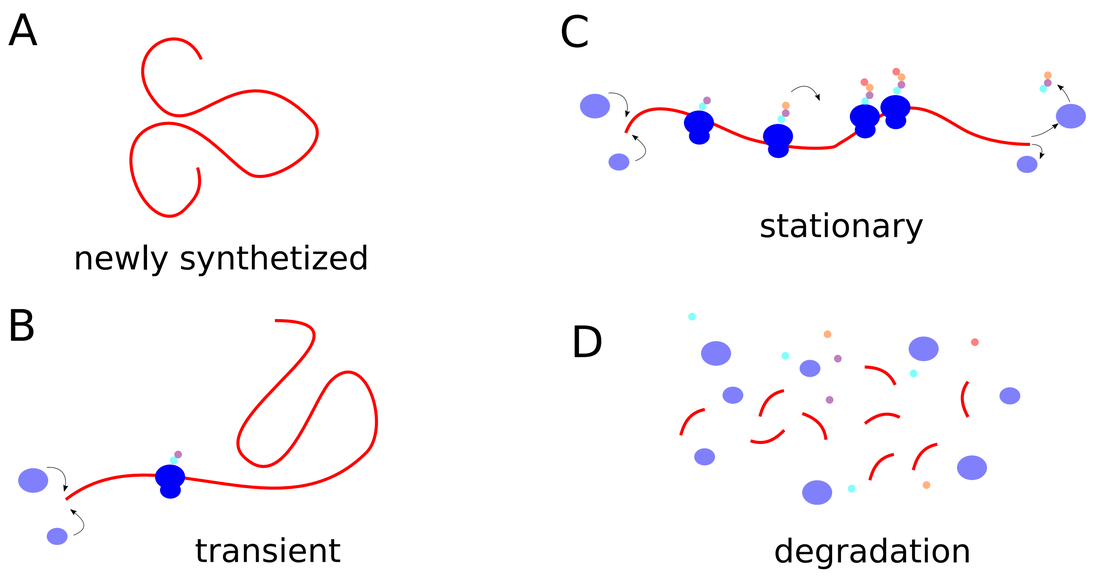


FIG.2: inside the cells, messenger RNA can be found in different kinetic state: (A) newly synthetized and empty, (B) in the process of filling up, (C) in the stationary regime and (D) in the degradation process.

Main reference and citations therein:

C. Chevalier, J. Dorignac, Y. Ibrahim, A. Choquet, A. David, J. Ripolls, E. Rivals, F. Geniet, N-O Walliser, J. Palmeri, A. Parmeggiani, J-C Walter* (2023) *Physical modeling of ribosomes along messenger RNA: estimating kinetic parameters from ribosome profiling experiments using a ballistic model* [in revision at *PLOS Comp. Biol.*]

Goal: include mRNA degradation in the modeling

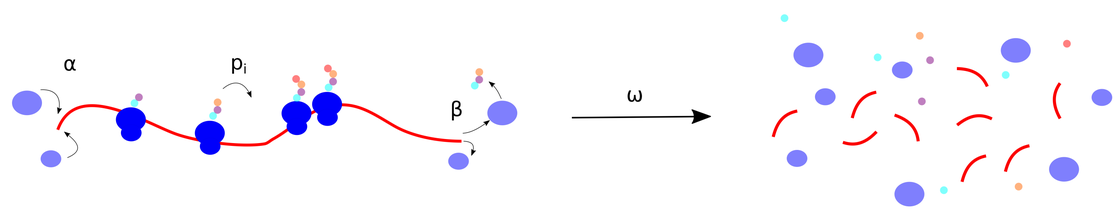


FIG.3: The TASEP can be generalized to degradation of mRNA at a rate ω.

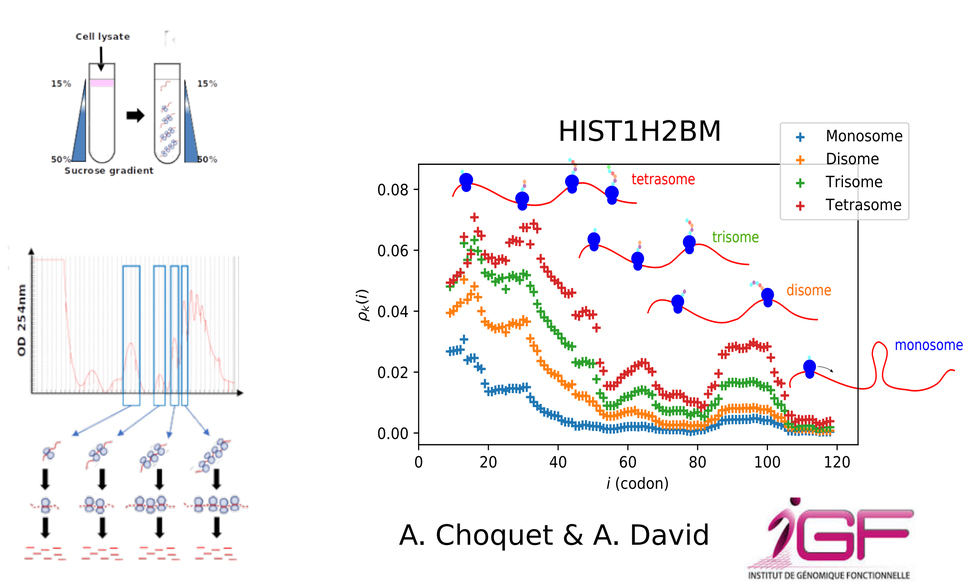


FIG.4: Ribo-seq experiments have been developed the last decade to access the density of ribosomes along the mRNA. Our collaborators, biologists at IGF, have performed Ribo-seq experiments on subsets of mRNA depending on the number k of ribosomes to probe dynamical effects: we call each family k-some. **The distribution of k-somes is directly related to the degradation rate and display an increased sensitivity to degradation. These experiments can solved issues of consistent normalization of the experimental data.**.

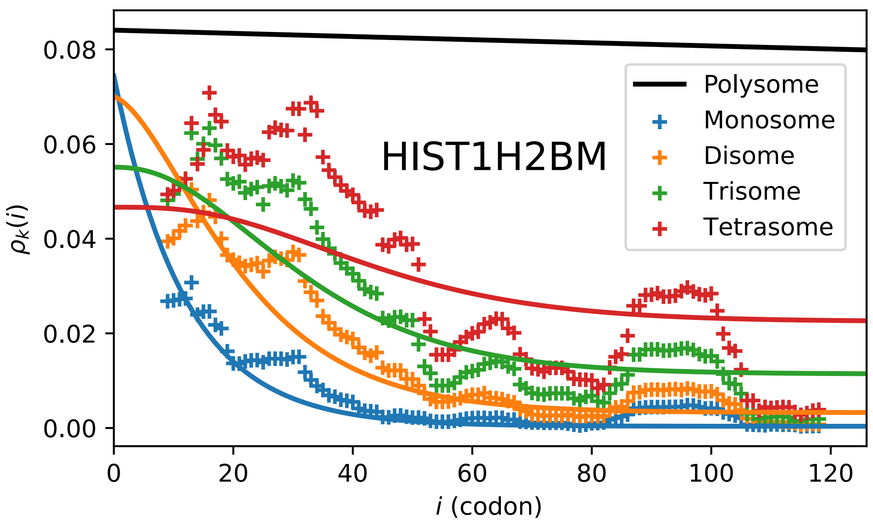


FIG.5: Preliminary results for the envelop are in good agreements with our analytical predictions.

Goal: estimate codon-dependent elongation rates and analyze new dedicated experimental data on the elongation rate.