Modelling Spatio-temporal Dynamic of Ribosome During Translation

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Flagship project GEM (Gene Expression Modeling) : physical modeling of gene transcription and translation. Coordinators : E. Rivals, J. Palmeri.

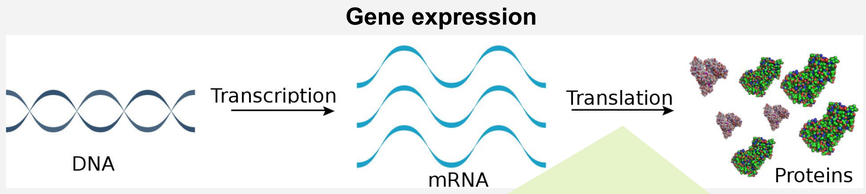
Key words : Monte Carlo, TASEP, lattice gas, mean field theory, translation, deep sequencing.

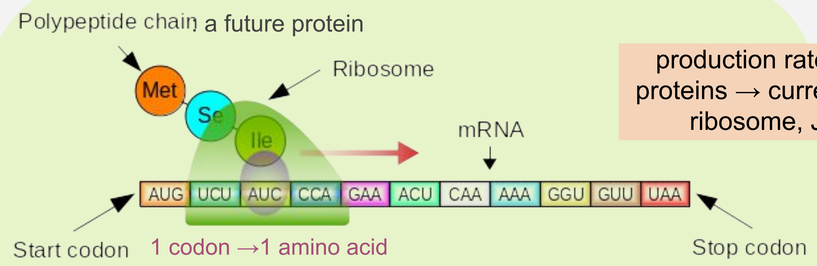
Abstract : Translation of messenger RNA (mRNA) leads to the production of proteins and is the last step of gene expression in cells. The dysregulation of translation can lead to all illnesses linked to the dysregulation of protein production, like cancer and neurodegenerative diseases. About ten years ago, was developed a ribosomal density mapping strategy (Ribo-seq). The time is therefore ripe to apply to theoretical physics methods to study translation. We model the movement of ribosomes on mRNA using the Totally Asymmetric Simple Exclusion Process (TASEP) which is an out of equilibrium one dimensional directed transport model. With Monte Carlo simulations and a mean field approach, we give a way to calculate the speed of ribosomes from experimental data. Moreover, we provide preliminary results concerning the correlation between the speed of ribosomes and the occurence rate of codons (RSCU).

DESCRIPTION : modeling of traduction

Overview of the Translation Process

Gene expression



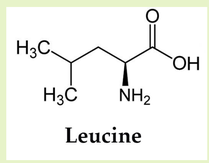


61 codons and 20 amino acids

→The genetic code has redundancy. Severals codons specify the same amino acid.

Example :

UUA
UUG
CUU
CUC
CUA
CUG

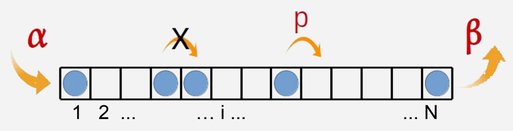


1 codon → 1 amino acid but not necessarily different

production rate of proteins → current of ribosome, J

TASEP (Totally Asymmetric Single Exclusion Process)

Translation is a one dimensional phenomenon of out of equilibrium directed transport. → lattice gas TASEP :
A particle can enter on the lattice with a rate **α**, jump from site i to site i+1 with a rate **p** and leave the lattice with the rate **β**.

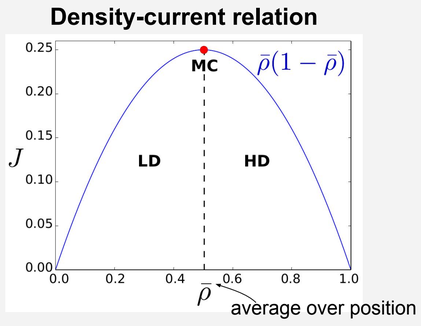


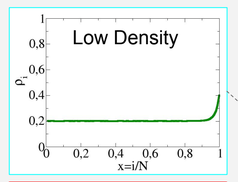
Mean Field description

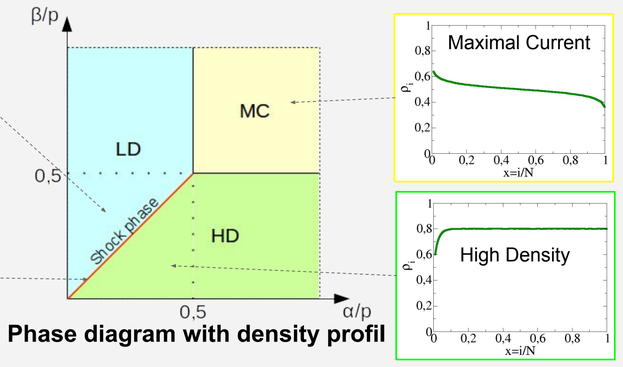
$$\frac{d}{dt}\rho_i = p\rho_{i-1}(1-\rho_i) - p\rho_i(1-\rho_{i+1}),$$

ρ_i : site dependent density

Density-current relation

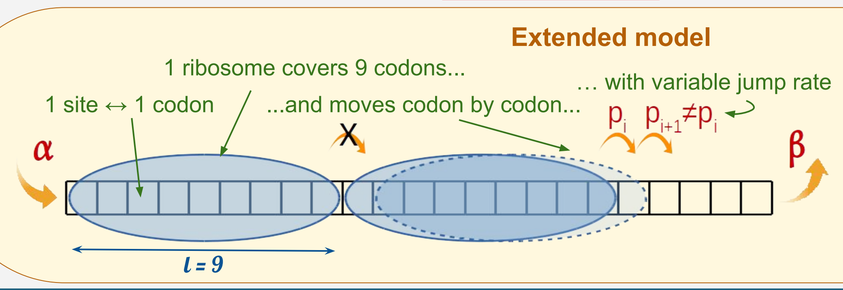


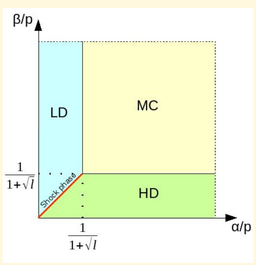




Phase diagram with density profil

Extended model

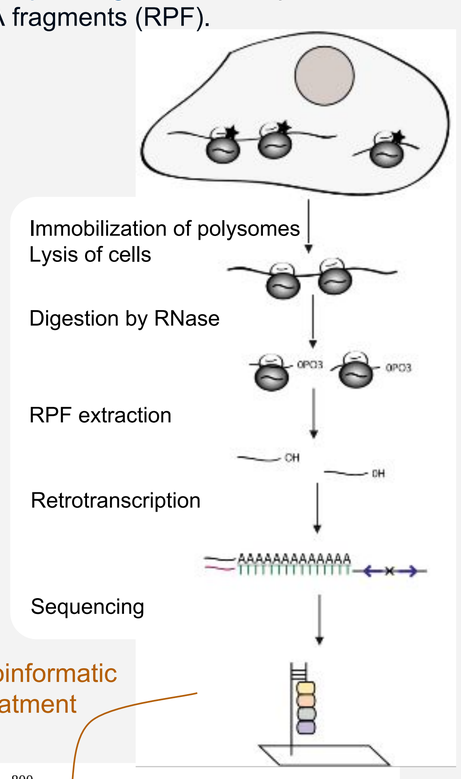




Phase diagram *l*-TASEP constant p_i

Ribo-Seq

Ribosome-profiling strategy based on the deep sequencing of ribosome-protected mRNA fragments (RPF).



MAIN RESULTS

Calculate Speed of Ribosomes

Measured physiological rates :

$$\begin{cases} \alpha = 0,1\ s^{-1} \\ \{p_i\} \in [5\ codons/s; 10\ codons/s] \\ \beta = 1\ codon/s \\ l = 9 \end{cases}$$

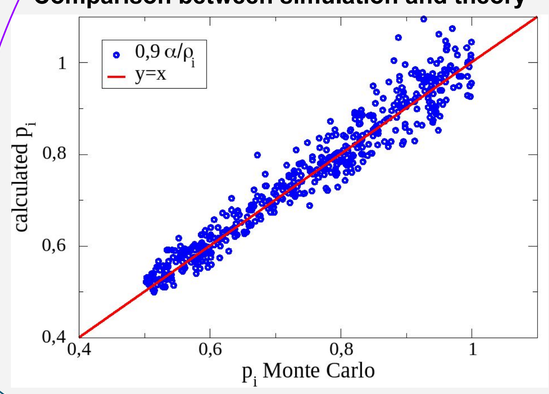
Translation is in low density phase

Mean field approximation : close neighbors correlations are neglected. We can write the speed as jump rates in low density phase :

$$p_i \approx \frac{[1-(l-1)\bar{\rho}]\alpha}{\rho_i}$$

average over position

Comparison between simulation and theory



Codon Usage Bias (CUB)

A study made by the bioinformaticians and biologists of the GEM consortium show that there is a preferred codon for each amino acid [*].

most of preferred codons are different

Strong CUB

	simple species	evolved species
high translated genes (htg)	C1	C3
low translated genes (ltg)	C2	C4

Weak CUB

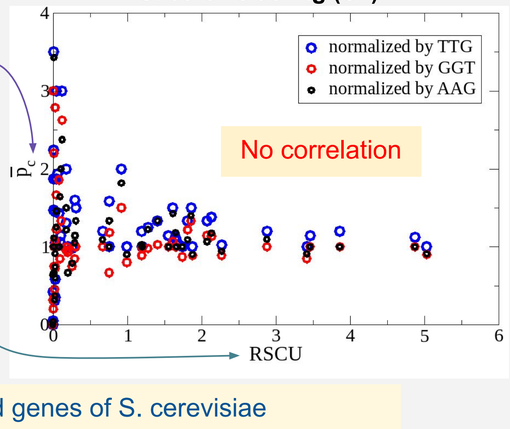
some preferred codons are different (very few for evolved species)

How are these preferred codons selected ? By their speed ?

Estimation of the relative speed (to cancel α) for each codon c :

$$\bar{p}_c = median\left\{ \frac{p_i}{p_{c_{\text{norm}}}} \mid i \in c \right\}$$

S. cerevisiae htg (C1)



Relative Synonymous Codon Usage estimation of preferred codons

$$\frac{n_a \cdot x_{a,c}}{\sum_{c=0}^{n_a} x_{a,c}}$$

n_a : number of synonymous codons for amino acid *a*
$x_{a,c}$: number of codons *c*

A similar graph for the low translated genes of S. cerevisiae
→ Preferred codons of C1 and C2 are therefore not selected by speed

[*] D. Paulet, A. David and E. Rival. Ribo-seq enlightens codon usage bias. *DNA Research 2017,* 24(3), 303-310

PERSPECTIVES :

- CUB-speed analysis with other species (simple and evolved)
- The design of Ribo-seq experiments with a finite number of ribosomes may allow one to determine alpha
- Impact of boundary layer on density variation with the length of mRNA