Physical modeling of ribosomes along mRNA: estimating kinetic rates from ribosome profiling experiments

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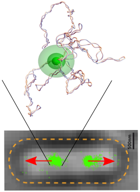
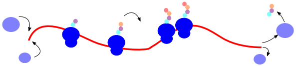
Outline

1. Introduction
2. The model
3. Results
4. Conclusion & perspectives

Genomic physics

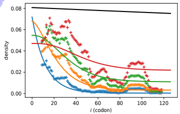




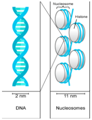
Bacterial DNA organization & segregation

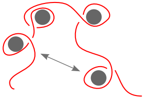
genomic physics

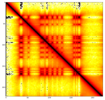
Translation of messenger RNA by ribosomes



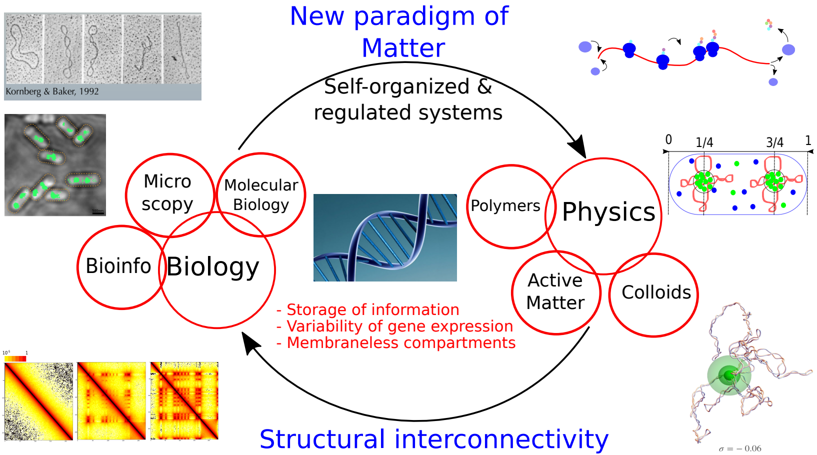
Epigenetic regulation of eukaryotic chromatin



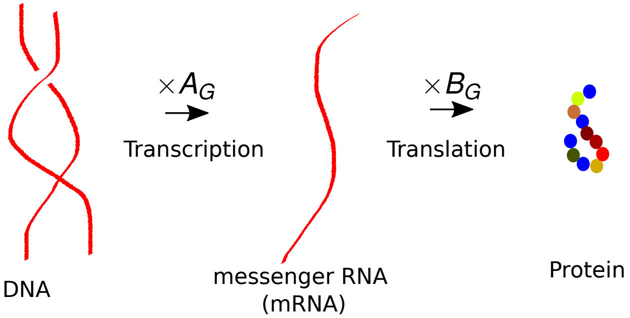




Physics of living matter



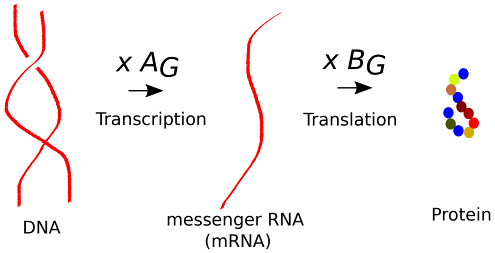
The expression of a gene depends on translation

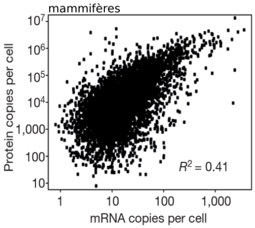


$\rightarrow$ Expression of a gene G: $A_G \times B_G$

$\rightarrow$ What are the physical interactions that determine B_G ?

The expression of a gene depends on translation



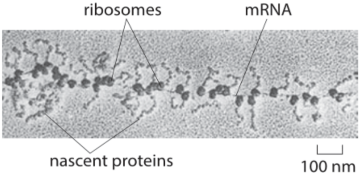


Schwanhäusser et al Nature '11

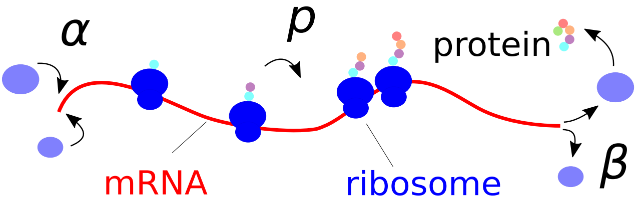
$\rightarrow$ $B_G \neq B_{G'}$ for two different genes G and G'

$\rightarrow$ What are the physical interactions that determine B_G ?

The totally asymmetric simple exclusion process

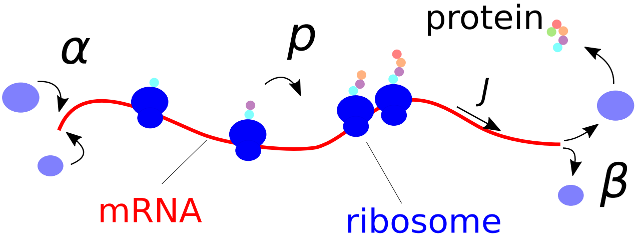


[Milo & Philips 2016]



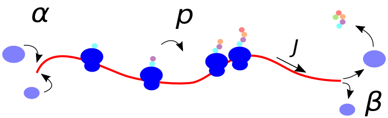
Mac Donalds 1969

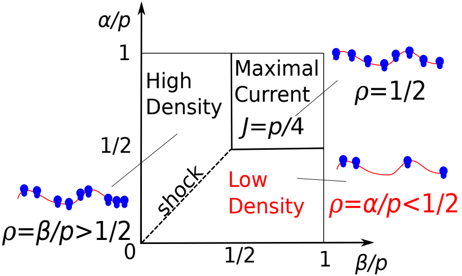
The totally asymmetric simple exclusion process



$$\rho = 1/L \sum_i \rho_i \qquad J = \rho v = p\rho(1-\rho) \approx p\rho$$

The totally asymmetric simple exclusion process

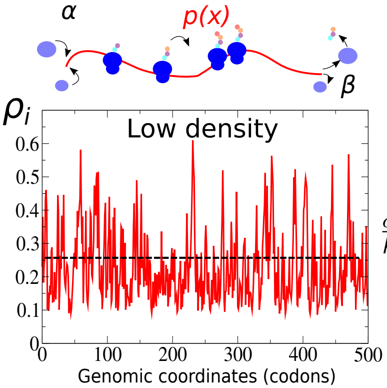




Most mRNA in Low Density

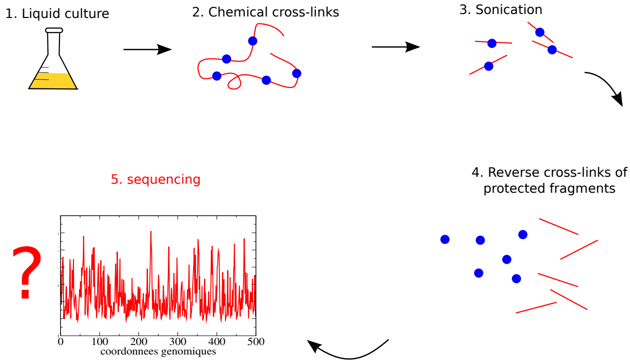
$J \sim p\rho = \alpha$

Experimental observables during genetic translation



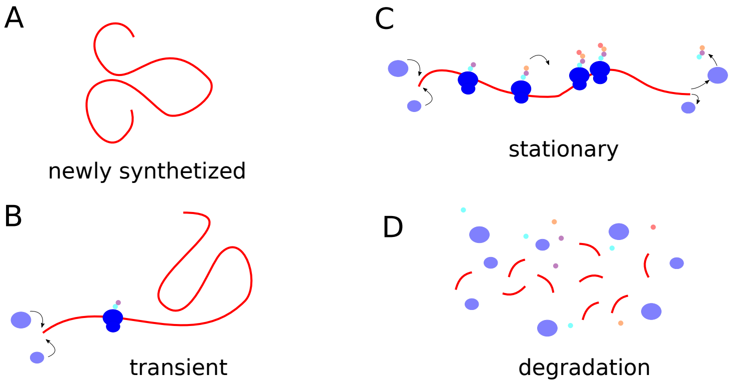
$$\frac{\alpha}{p} = \frac{1}{4}$$

Experimental observables during genetic translation



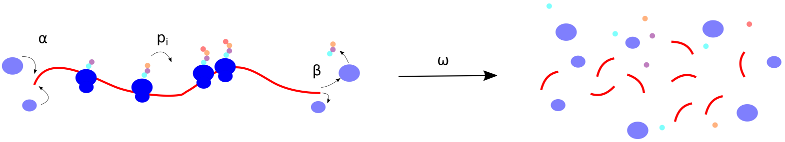
- No rigourous experimental normalization

Mixing of dynamical state in the cytoplasm



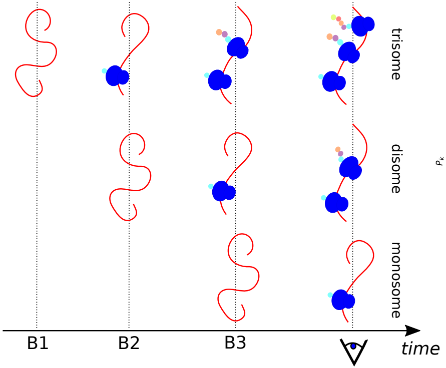
How to quantify the effect of mRNA finite lifetime (transient dynamics due to the degradation & synthesis of mRNA) with ribosome profiles ?

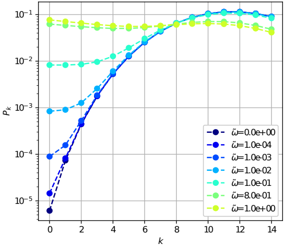
The ballistic model with degradation



1. Low density $\rightarrow$ neglect the interactions: ballistic model with Poisson injection of particles
2. Distribution of mRNA lifetime θ: $\Phi_\theta(\theta) = \omega e^{-\omega\theta}$
3. Split mRNA in k-somes according to the number of ribosomes k=1, 2, 3 & 4

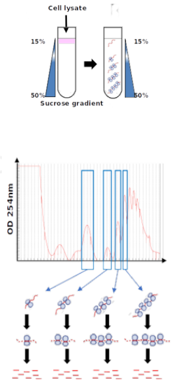
Timeline of the mRNA population

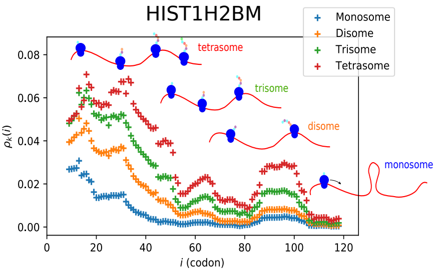




$$P_k = \frac{\tilde{\omega}}{\tilde{\alpha}+\tilde{\omega}}\left(\frac{\tilde{\alpha}}{\tilde{\alpha}+\tilde{\omega}}\right)^k \frac{\gamma(k+1,\tilde{\alpha}+\tilde{\omega})}{k!} + \frac{\tilde{\alpha}^k}{k!}e^{-(\tilde{\alpha}+\tilde{\omega})},$$

The k-some experimental protocole





1. Split mRNA in k-somes according to the number of ribosomes k=1, 2, 3 & 4
2. Sensitivity of the profile increases as k decreases
3. we define as polysomes as the whole population of mRNA (all k-somes)

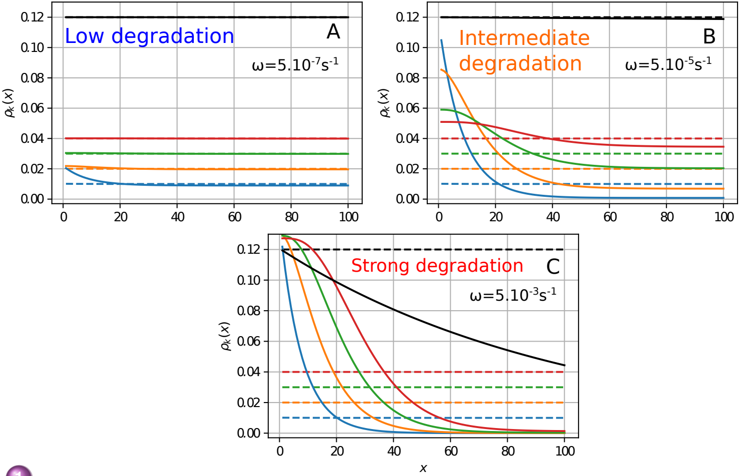
Analytically solvable model

Namely the k-some profiles:

$$
\begin{aligned}
\rho_k(x) &= \frac{\alpha^k}{P_k p(x)} \frac{e^{-(\alpha+\omega)}}{(k-1)!} + \dots \\
\dots &+ \frac{\omega}{P_k p(x)} \left(\frac{\alpha}{\alpha+\omega}\right)^k \frac{\gamma(k, \alpha+\omega) - \gamma(k, (\alpha+\omega)\tau(x))}{(k-1)!}
\end{aligned}
$$

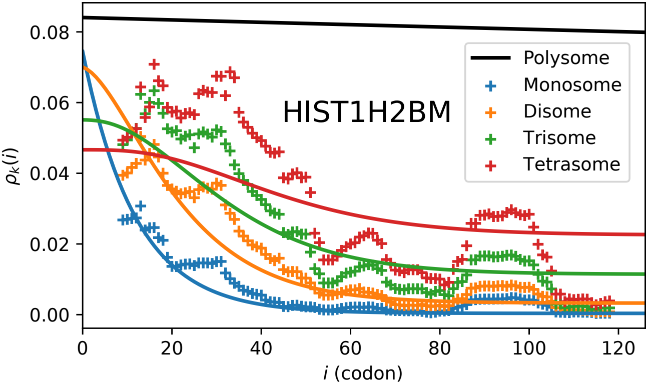
where P_k is the probability distribution of k-somes, γ is the gamma function, $\tau(x) = \mathcal{T}(x)/\mathcal{T}(L)$ and $\mathcal{T}(x) = x/L$.

3 regimes of mRNA degradation



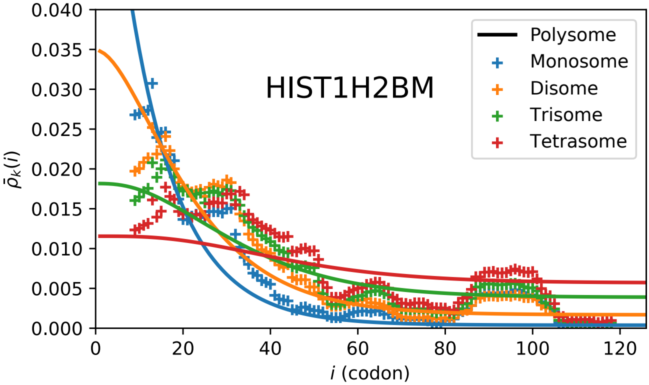
1. k-somes more sensitive than polysome (especially in the ID regime)
2. Sensitivity in ω increases as k decreases

Experiments (symbols) versus theory (full lines)



1. Fixed $\alpha = 0.06\text{s}^{-1}$, $\omega = 1\text{h}^{-1}$ $\rightarrow$ intermediate degradation
2. Fit the protein production rate $1/J = 180\text{s} \rightarrow p = 0.7\text{s}^{-1}$

Experiments versus theory (density normalized to 1)



1. Fixed $\alpha = 0.06\text{s}^{-1}$, $\omega = 1\text{h}^{-1} \rightarrow$ intermediate degradation
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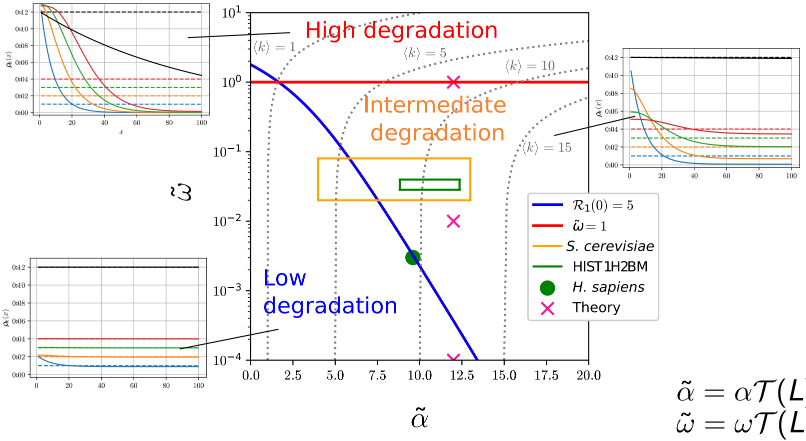
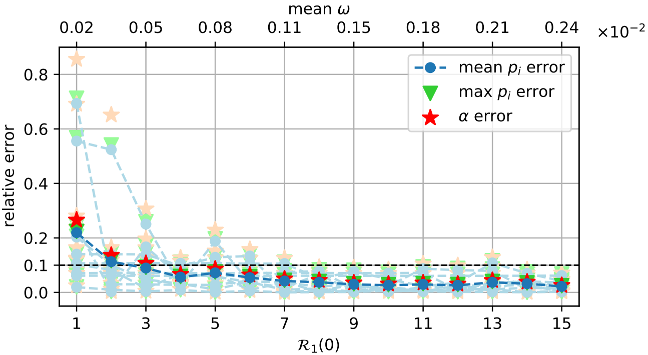
Dynamical phase diagram



$$\tilde\alpha = \alpha\mathcal{T}(L)$$
$$\tilde\omega = \omega\mathcal{T}(L)$$

- Intermediate degradation $\rightarrow$ prevalent biological regime

k-some optimize the fit in the intermediate regime



$$\chi^2 = \sum_{i=0}^{L} \left| \frac{\rho_i^{data} - \rho_i^{ballistic}}{\rho_i^{data}} \right|^2$$

1. Fit all the parameters self-consistently
2. Increased information (4 decoupled profiles) in the intermediate regime

Conclusion & perspectives

Take home message

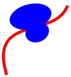
1. New *k*-some protocole: access to mRNA lifetime
2. Improve quantitative fit of kinetic rates:
   - self-consistent normalization
   - four profiles per experiments
3. Most living cells in the intermediate degradation regime

Perspectives

1. Explicit fit of initiation and elongation rates
2. Categorize cell types through kinetic rates

Reference: Chevalier C., Dorignac J., Ibrahim Y., Choquet A., Alexandre D., Ripoll J., Rivals E., Geniet F., Palmeri J., Parmeggiani A. & **JCW** (2022) *Physical modeling of ribosomes along messenger RNA: estimating kinetic rates from ribosome profiling experiments with a ballistic model*, submitted & available on ArXiv

Gene Expression Modeling project (GEM)

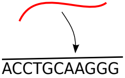


Ribosome sequencing

A. David
A. Choquet

Sequencing

E. Rivals
J. Ripoll



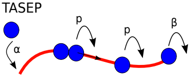
Bioinformatics

Gene Expression Modeling

ribosome profiles

Predictions & microscopic interactions

Carole Chevalier
J. Dorignac
F. Geniet
J. Palmeri
A. Parmeggiani
N-O Walliser



Biophysical modeling

k-some Probability

The mRNA age distribution is:

$$\phi_a(a) = \omega e^{-\omega a}, \; a \geq 0 . \tag{1}$$

The probability that an mRNA of age a be loaded with k ribosomes is

$$P(k|a) = \begin{cases} \frac{(\alpha a)^k}{k!} e^{-\alpha a}, \; a \leq \mathcal{T}(L) , \\ \frac{(\alpha \mathcal{T}(L))^k}{k!} e^{-\alpha \mathcal{T}(L)}, \; a \geq \mathcal{T}(L) . \end{cases} \tag{2}$$

probability P_k an mRNA be a k-some irrespective of its age:

$$P_k = \int_0^{\infty} P(k|a) \phi_a(a) \, da . \tag{3}$$

k-some Probability

$$P_k = \frac{\tilde{\omega}}{\tilde{\alpha}+\tilde{\omega}}\left(\frac{\tilde{\alpha}}{\tilde{\alpha}+\tilde{\omega}}\right)^k \frac{\gamma(k+1,\tilde{\alpha}+\tilde{\omega})}{k!} + \frac{\tilde{\alpha}^k}{k!}e^{-(\tilde{\alpha}+\tilde{\omega})}, \quad (4)$$

density of k-somes

$$\rho_k(x|a) = \begin{cases} \frac{k}{ap(x)} H(x(a) - x), \; a \leq \mathcal{T}(L)\,, \\ \frac{k}{\mathcal{T}(L)p(x)}, \; a \geq \mathcal{T}(L)\,, \end{cases} \tag{5}$$

$$\rho_k(x) = \int_0^\infty \rho_k(x|a) p(a|k)\, da, \tag{6}$$

where $p(a|k)$ is the age distribution among k-somes given by Bayes theorem, $p(a|k) = \phi_a(a) P(k|a)/P_k$.