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

Jean-Charles WALTER
Laboratoire Charles Coulomb (L2C)
CNRS & Université de Montpellier

RNA Club @ Genopolys
Montpellier
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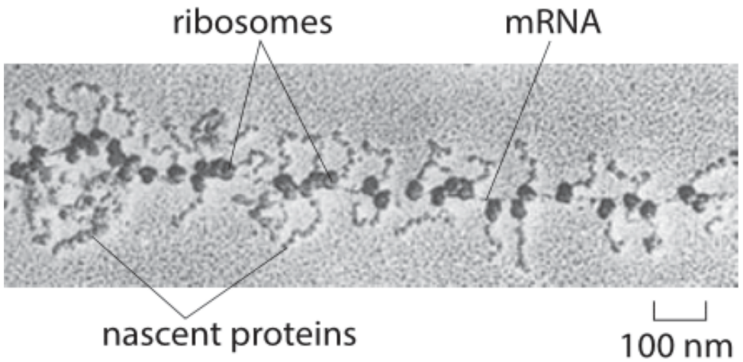
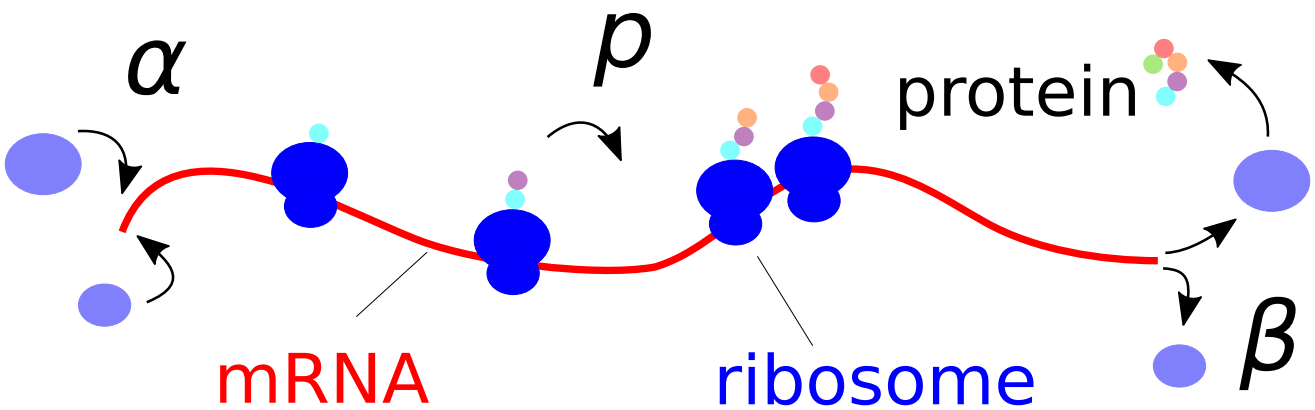
Outline

The totally asymmetric simple exclusion process

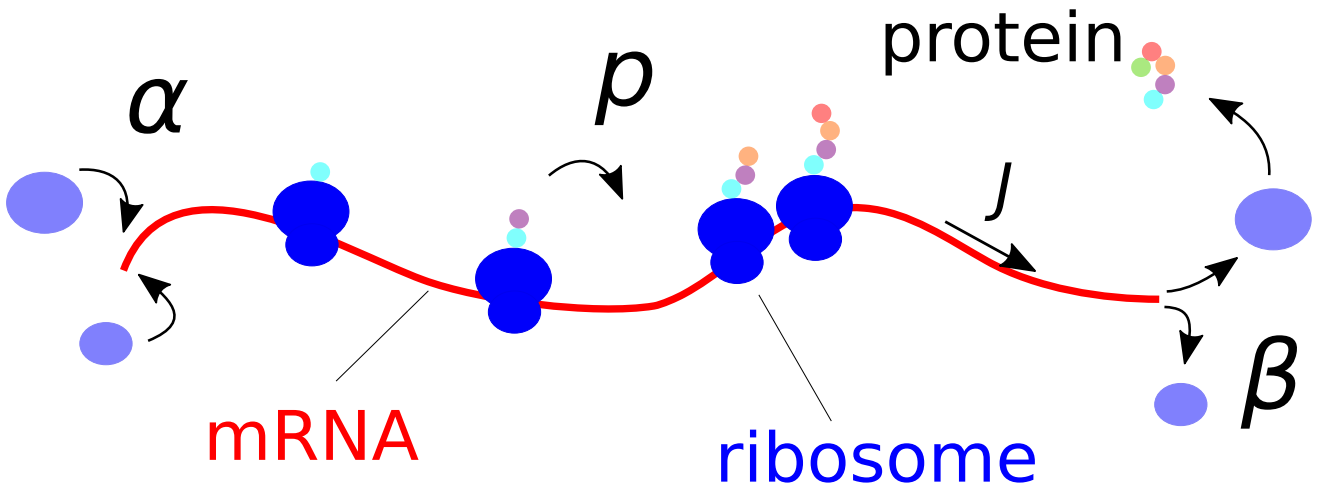


[Milo & Philips 2016]



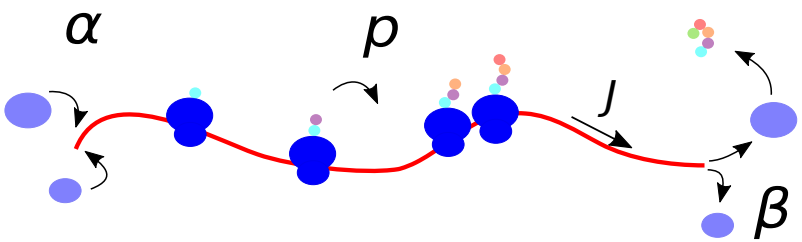
Mac Donalds 1969

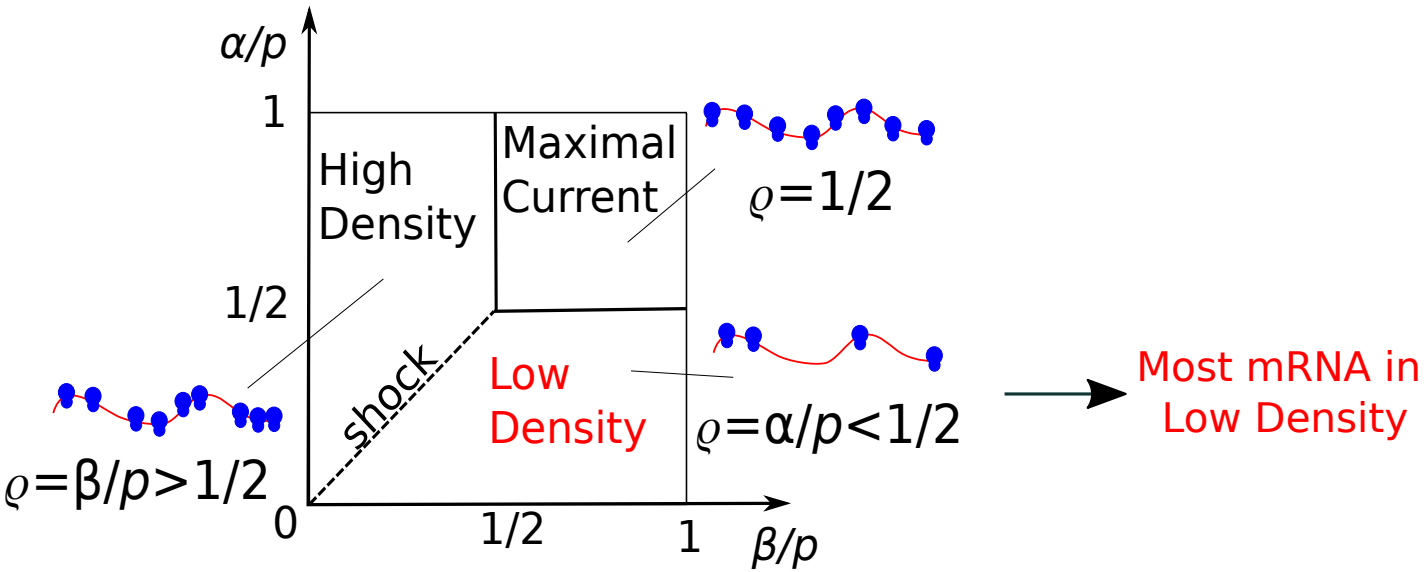
The totally asymmetric simple exclusion process



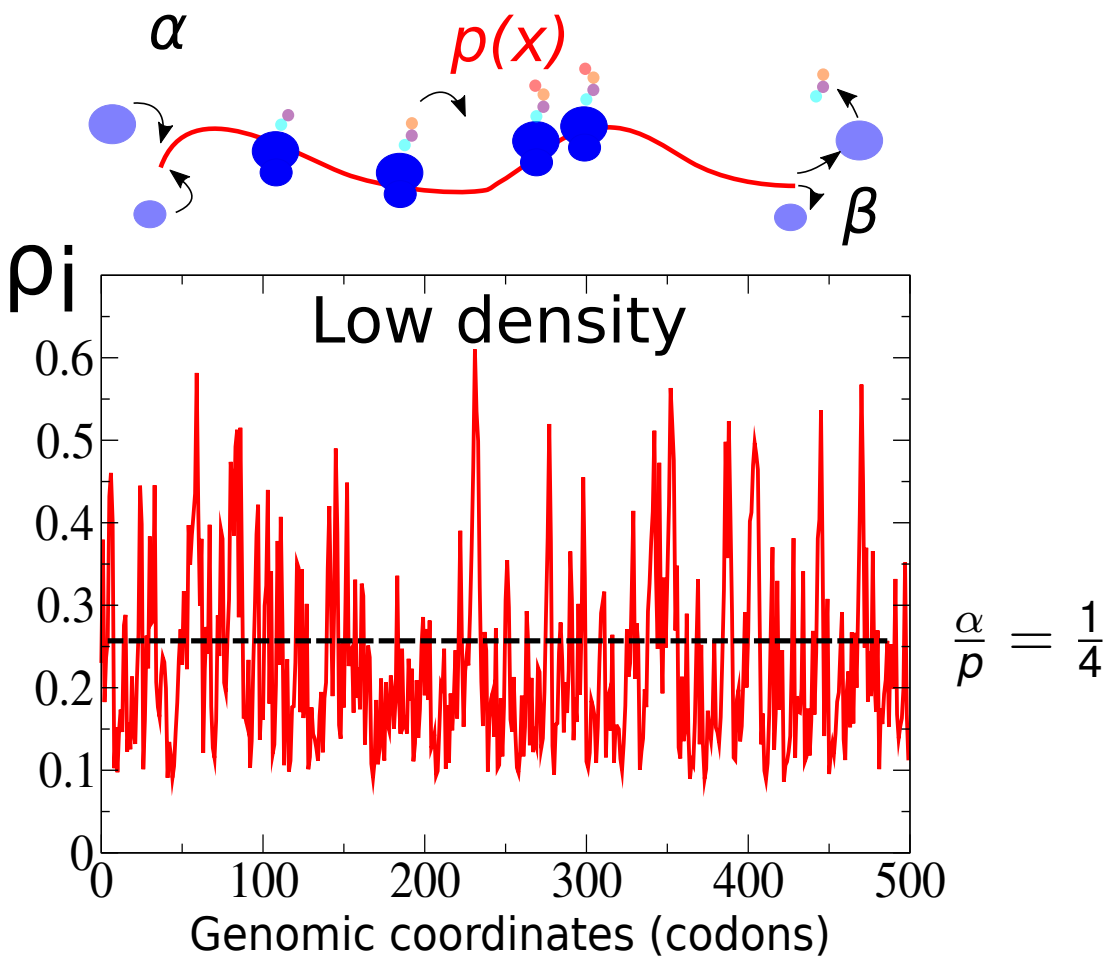
$$\rho = 1/L \sum_i \rho_i \qquad J = \rho v = p\rho(1-\rho) \approx p\rho$$

The totally asymmetric simple exclusion process





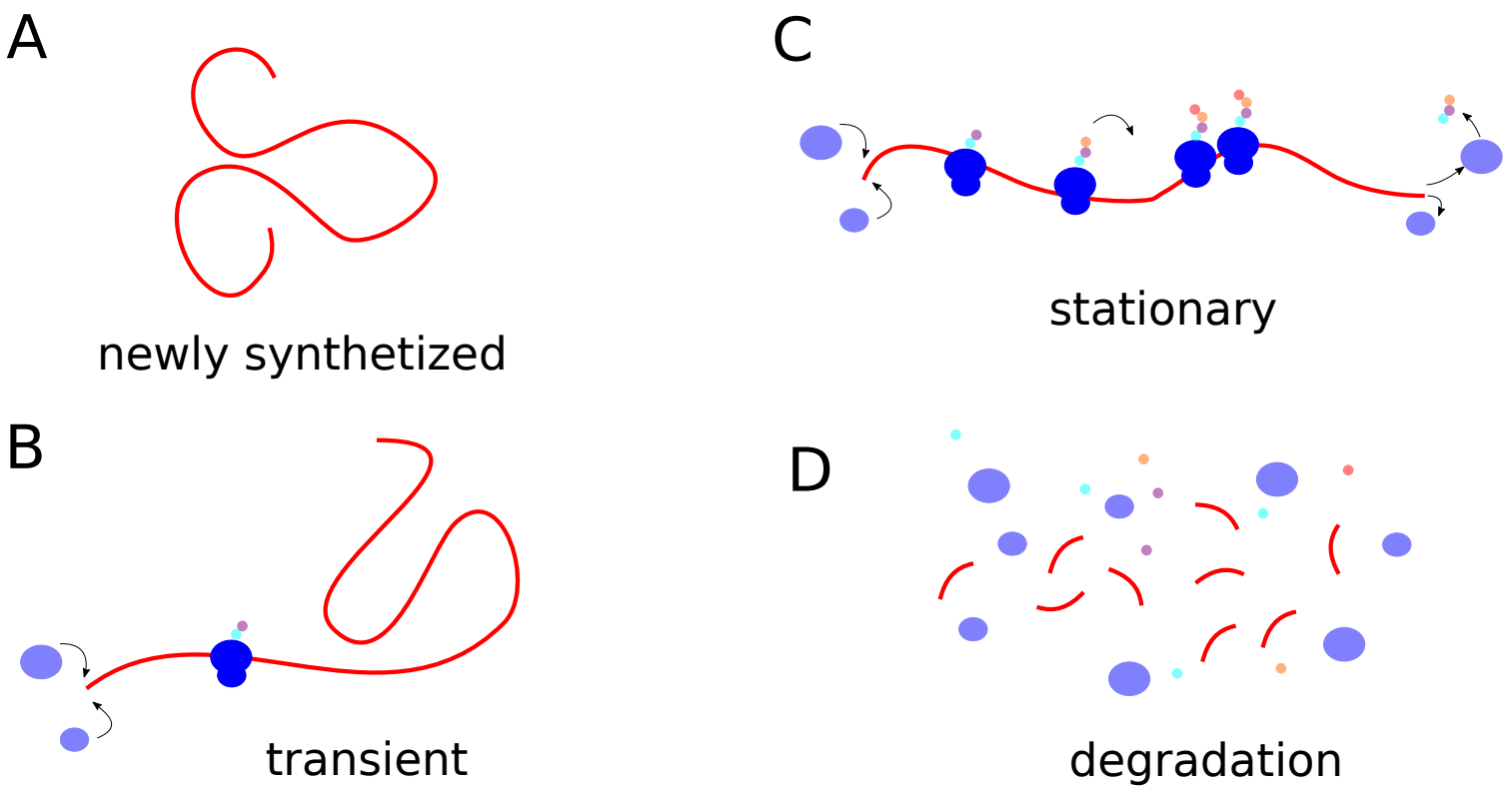
The totally asymmetric simple exclusion process



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

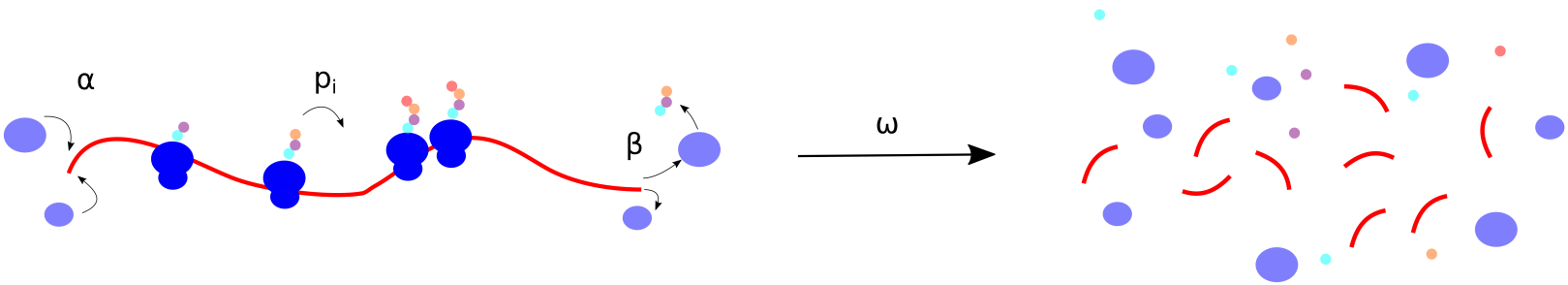
- Modeling assume infinite mRNA lifetime i.e. stationarity

Mixing of dynamical state in the cytoplasm



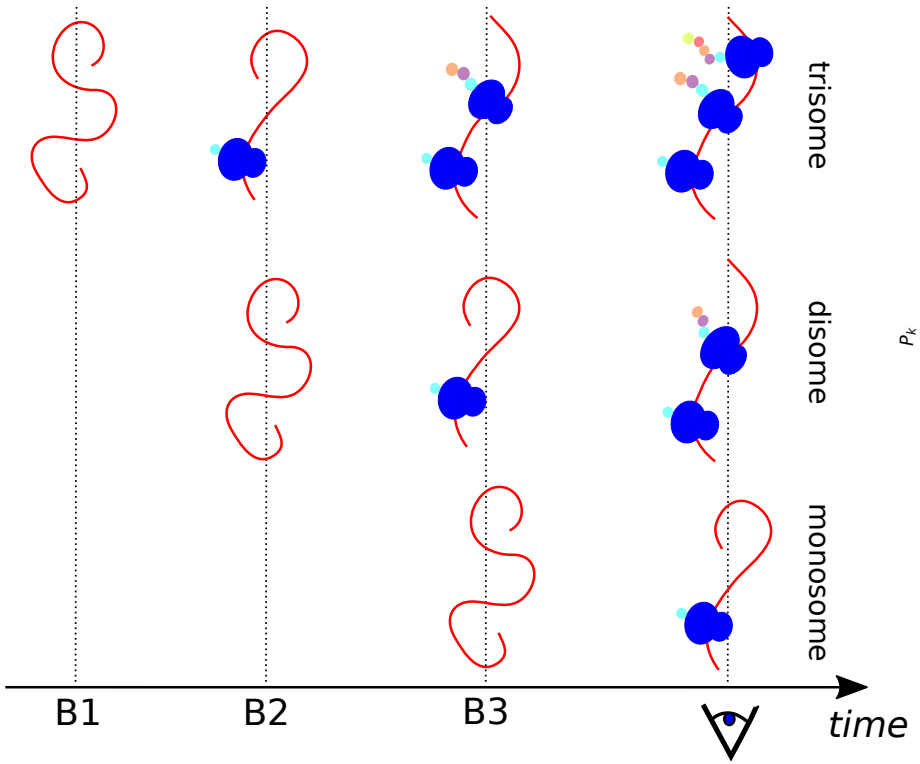
How to quantify the effect of mRNA finite lifetime (transient dynamics due to the degradation & synthesis of mRNA) with ribosome profiles ?

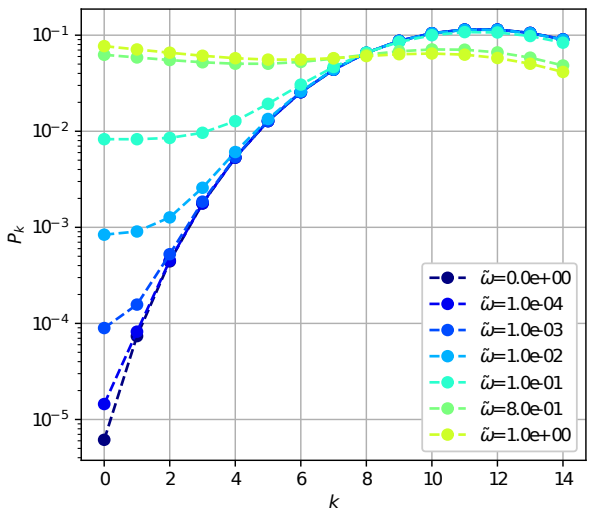
The ballistic model with degradation



1. Low density $\rightarrow$ neglect the interactions (ballistic)
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

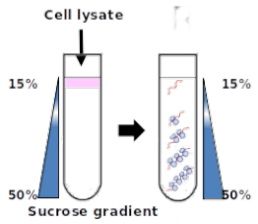
Timeline of the mRNA population

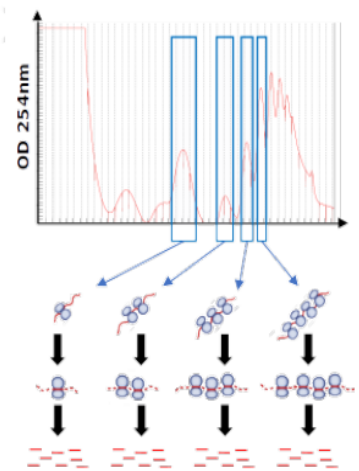


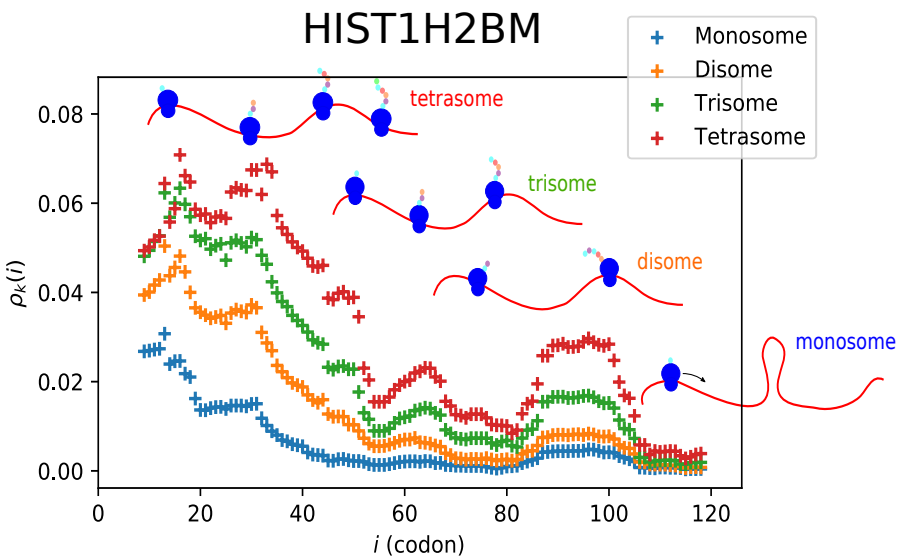


1. The smaller k the closer the ribosomes from the start
2. The proportion of “young” mRNA increases with mRNA degradation/synthesis

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)

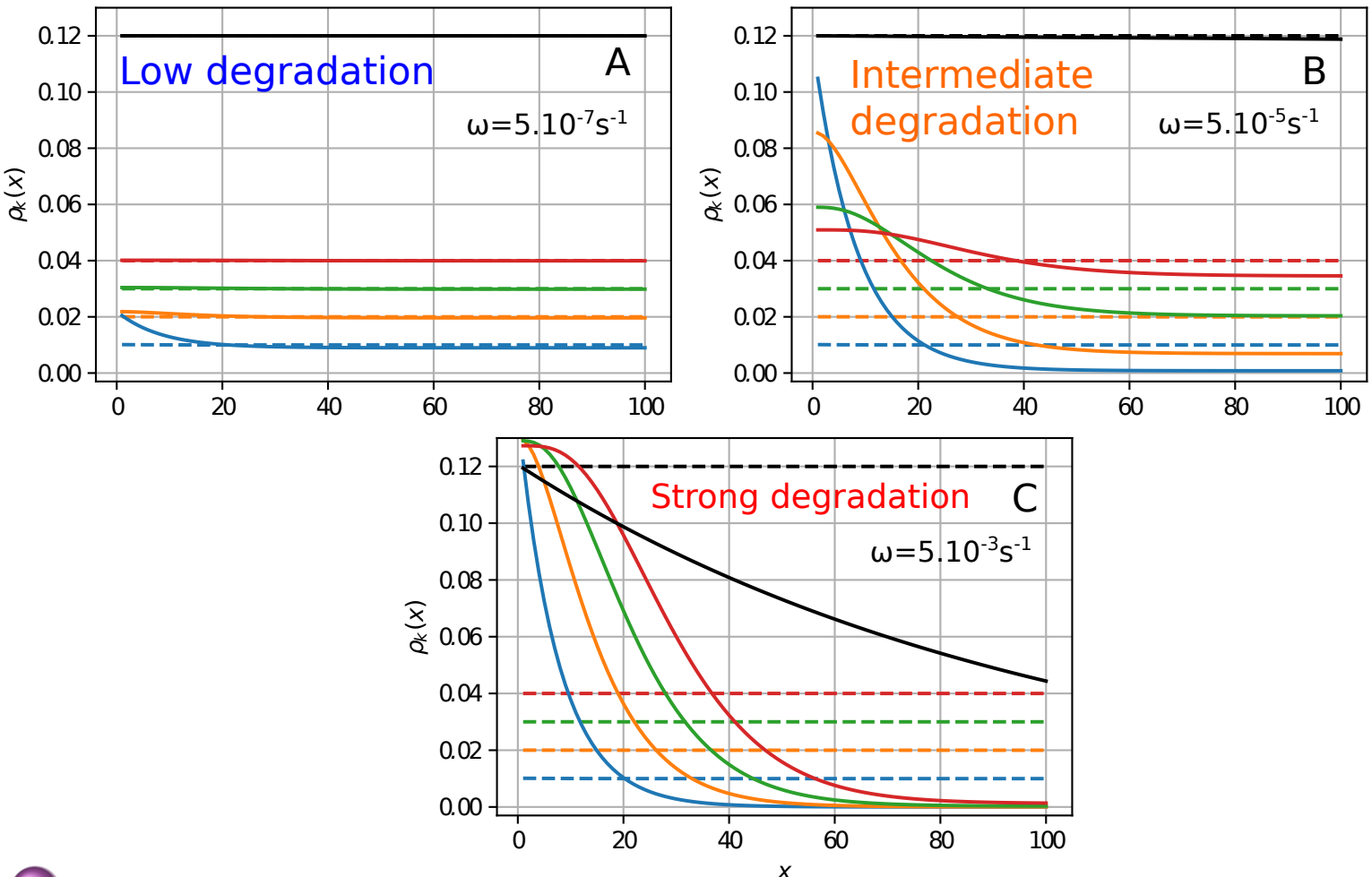
Analytically solvable model

Namely the k-some profiles:

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

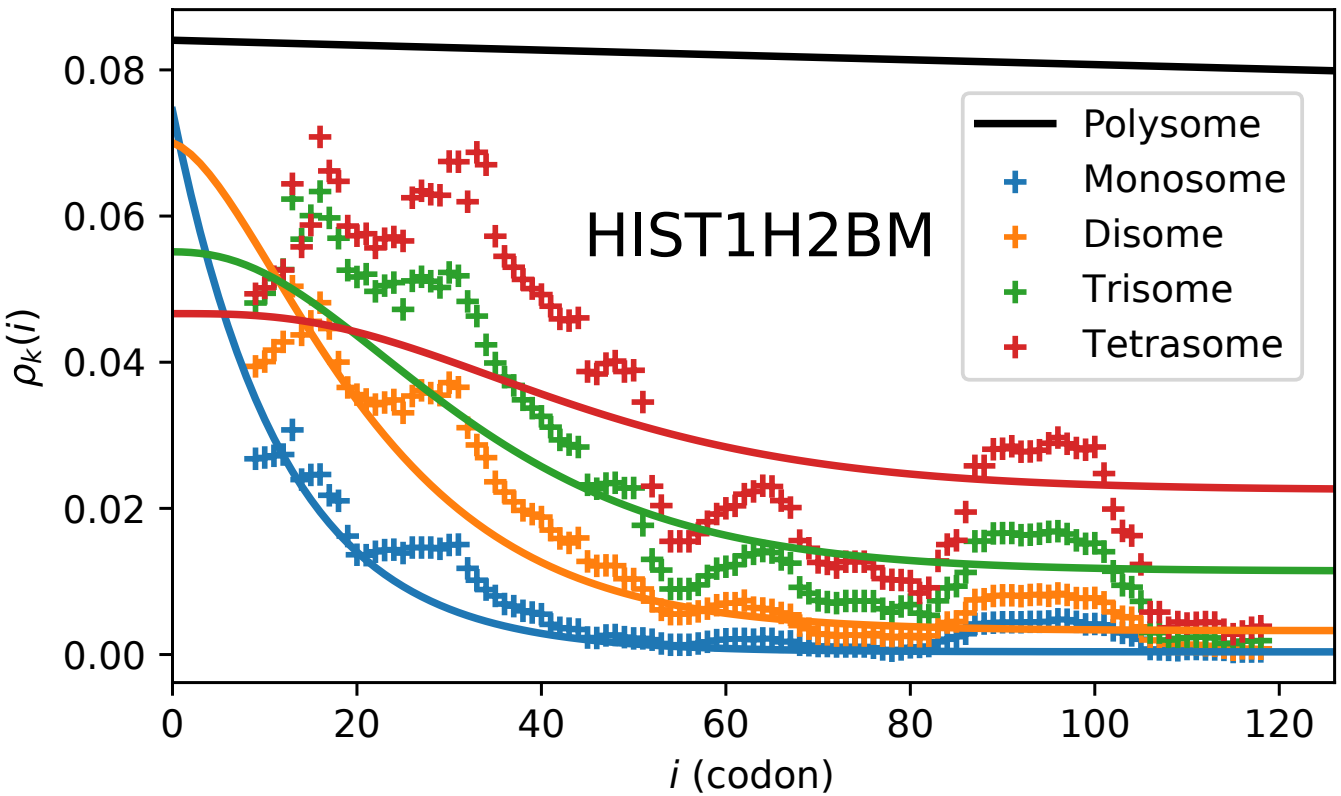
where P_k is the probability distribution of k-somes, γ is the gamma function, $\tau(x) = \mathcal{T}(x)/\mathcal{T}(L)$ and $\mathcal{T}(x) = x/L$.

3 regimes of mRNA degradation



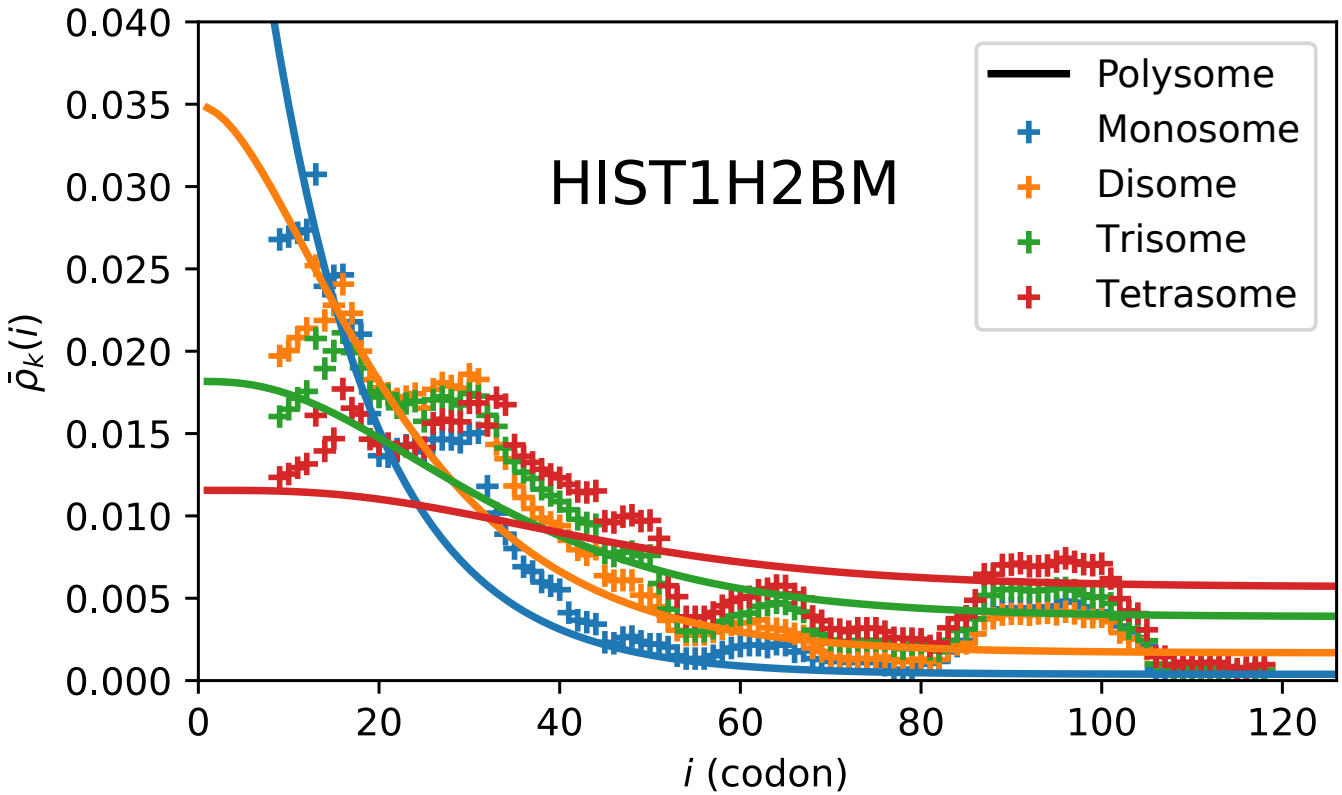
1. *k*-somes more sensitive than polysome (especially in the ID regime)
2. Sensitivity in ω increases as k decreases

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)



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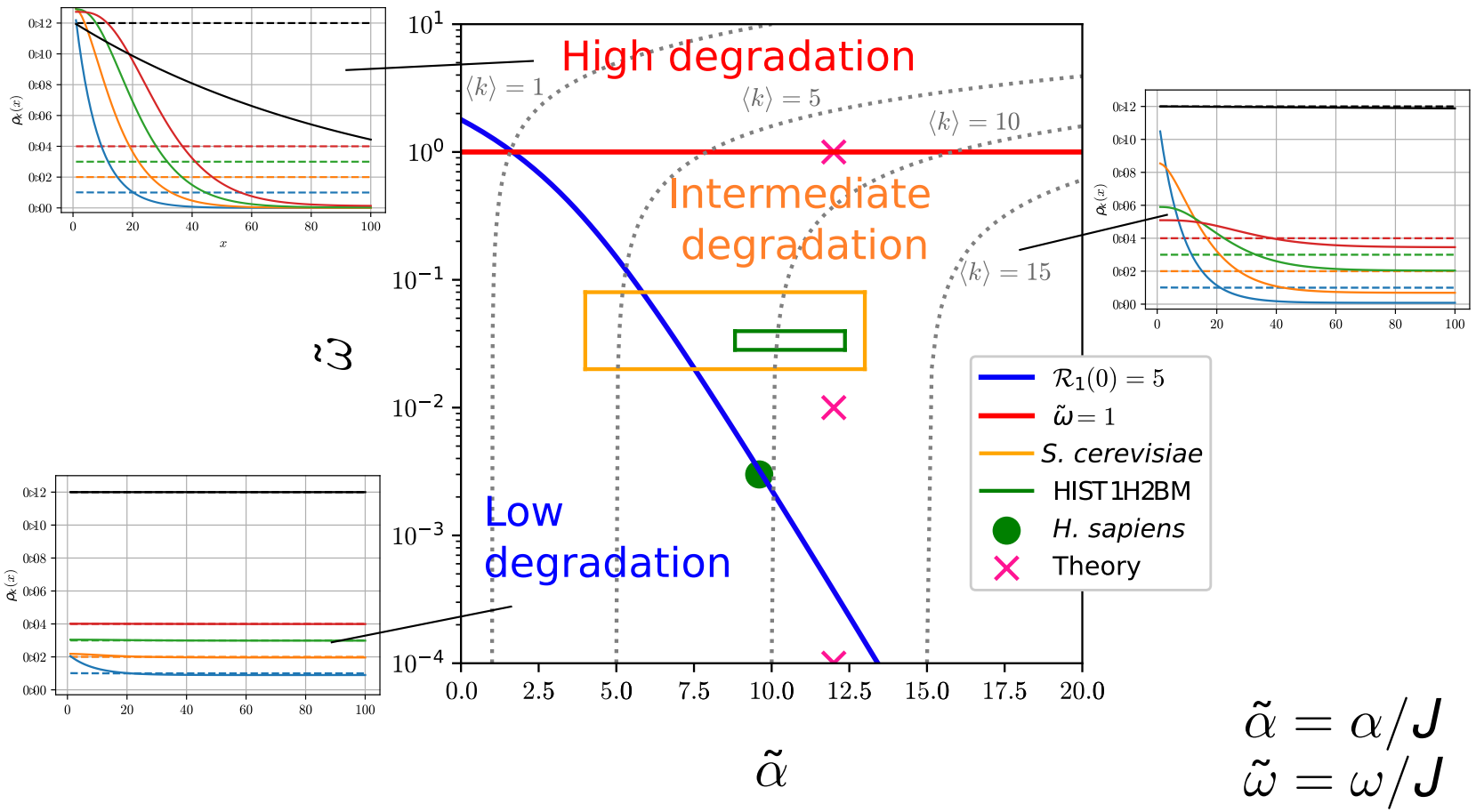
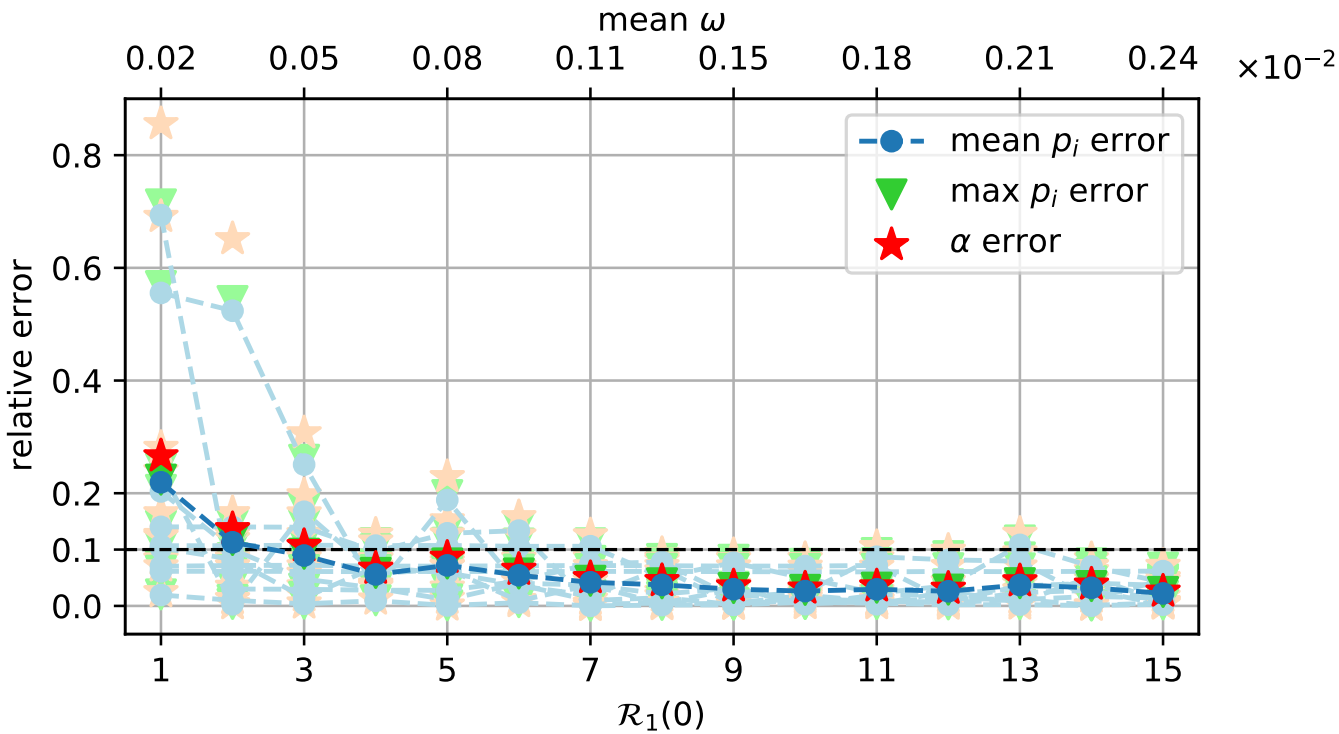
Dynamical phase diagram



$$\tilde{\alpha} = \alpha/J$$
$$\tilde{\omega} = \omega/J$$

- 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

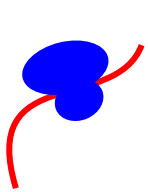
1. New *k*-some protocole: access to mRNA lifetime
2. Most living cells in the intermediate degradation regime
3. Improve quantitative fit of kinetic rates: self-consistent & four profiles per experiments)

Perspectives

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

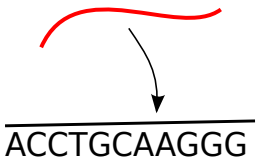
Reference: Chevalier C., Dorignac J., Ibrahim Y., Choquet A., Alexandre D., Ripoll J., Rivals E., Geniet F., Palmeri J., Parmeggiani A. & **JCW** (2022) *Physical modeling of ribosomes along messenger RNA: estimating kinetic rates from* ribosome profiling experiments with a ballistic model, submitted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

Gene Expression Modeling project (GEM)



Ribosome sequencing

Sequencing

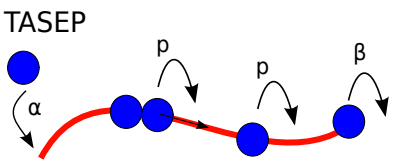


Bioinformatics

Gene Expression Modeling

ribosome profiles

Predictions & microscopic interactions



Biophysical modeling