Stochastic models of protein production with cell division and gene replication

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Presentation

Biological context

Classical models for protein production

Model with cell division and gene replication

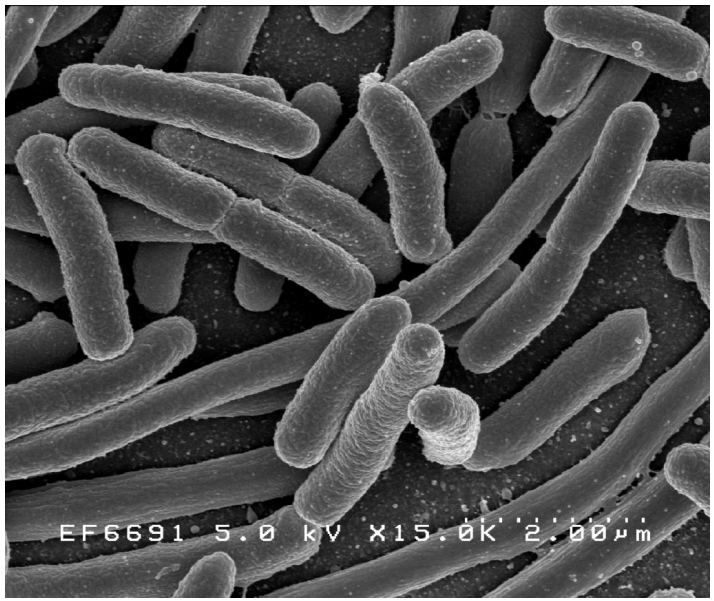
Results and further work

Part 1

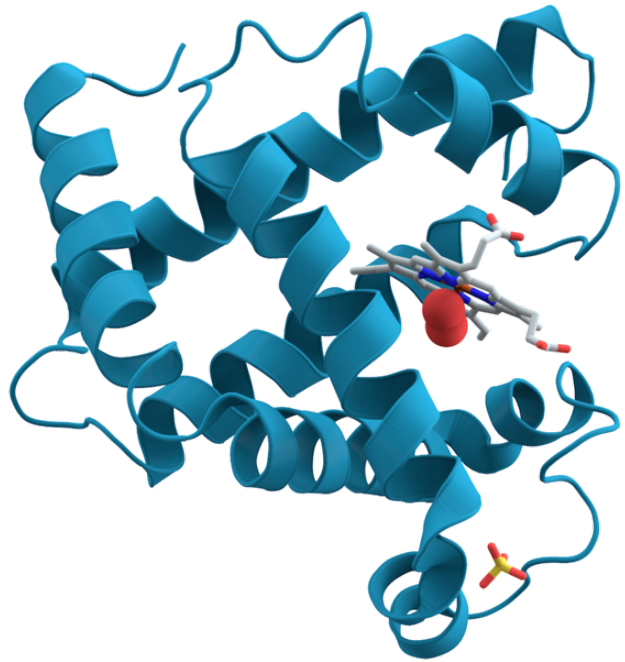
Biological context

Cells and proteins

- Cells: unit of life.
- Its goal: grow and divide.



- Functional molecules: *proteins*
  - enzymes, wall, energy, etc.
- Produced from the genes



Protein production: A central mechanism

Proteins represents:

- 50% of the dry mass
- ~ 3 million molecules
- ~ 2000 different types
- from few dozens up to 10^5 proteins per type

It needs to be duplicated in one cell cycle (approx. 30 *min*)

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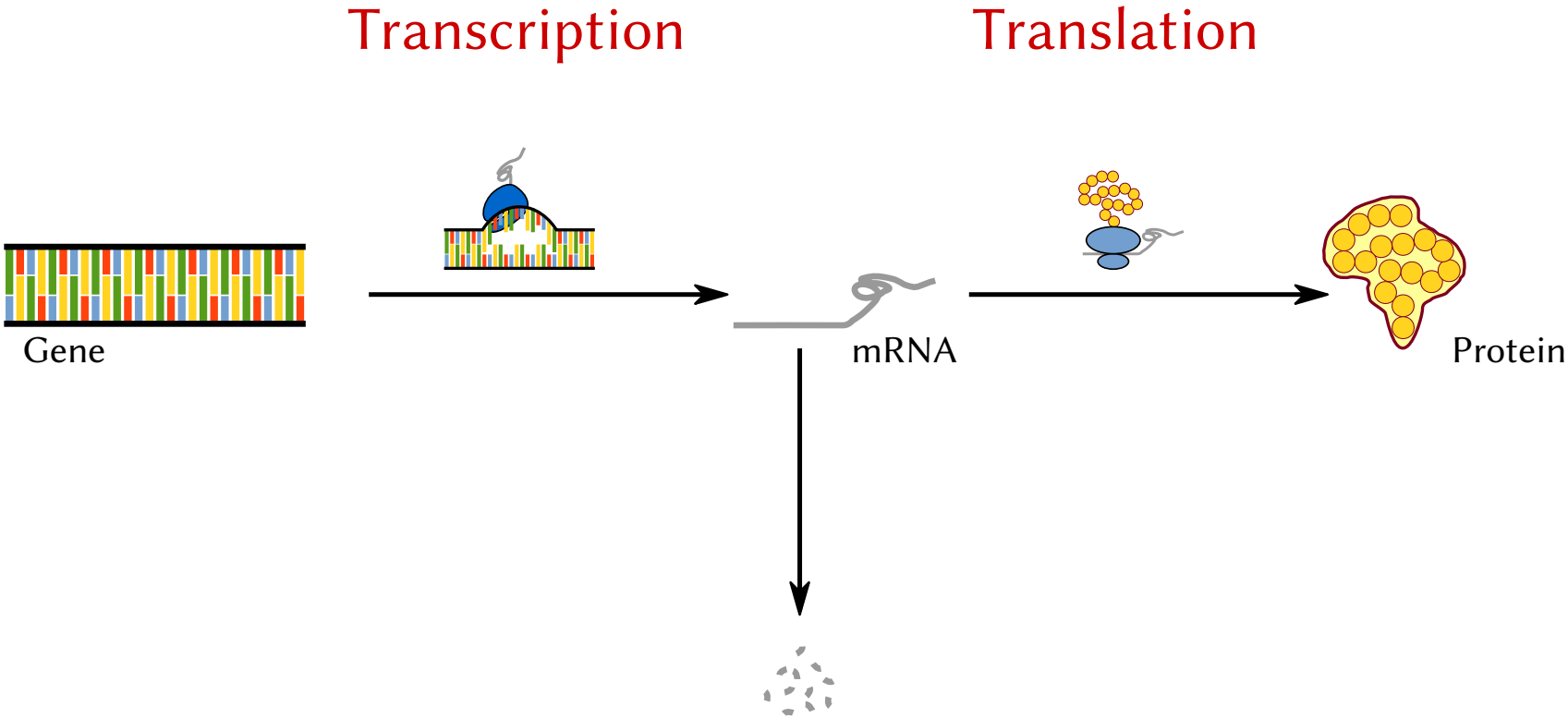
67% of the resources for protein production

Classic protein production mechanism

Two main steps in protein production:

1. Transcription: to produce mRNA
2. Translation: to produce proteins



Highly variable process

The protein production subject to high variability:

- Thermal noise (random collision between molecules)
- Cell events (division, gene replication)
- Fluctuations in of common resources

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- Thermal noise (random collision between molecules)
- Cell events (division, gene replication)
- Fluctuations in of common resources

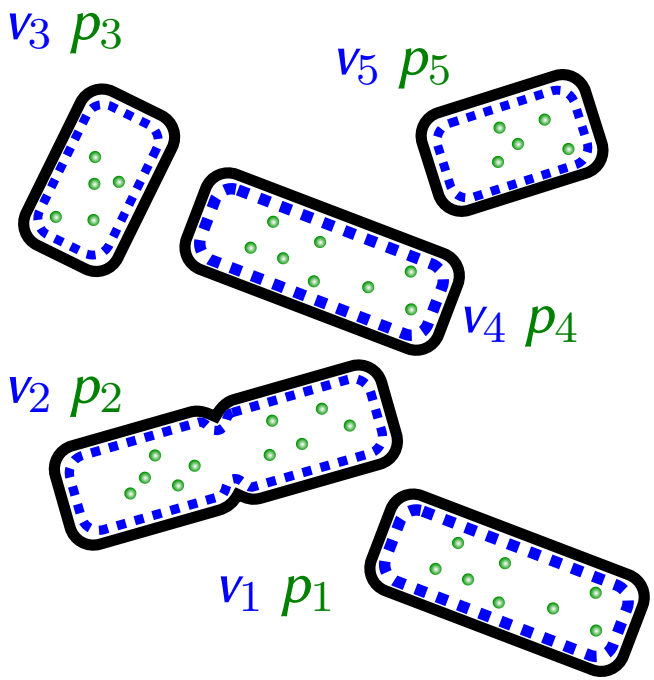
Problem: the main mechanism of the cell, impacted by a large variability.

”How the cell deals with this variability?”
A main topic for experimental research.

Taniguchi et al. (2010) experimental measures

Population of cells

- Measure volume v_i
- Measure of prot. number p_i



Interest in concentrations

Empirical mean:

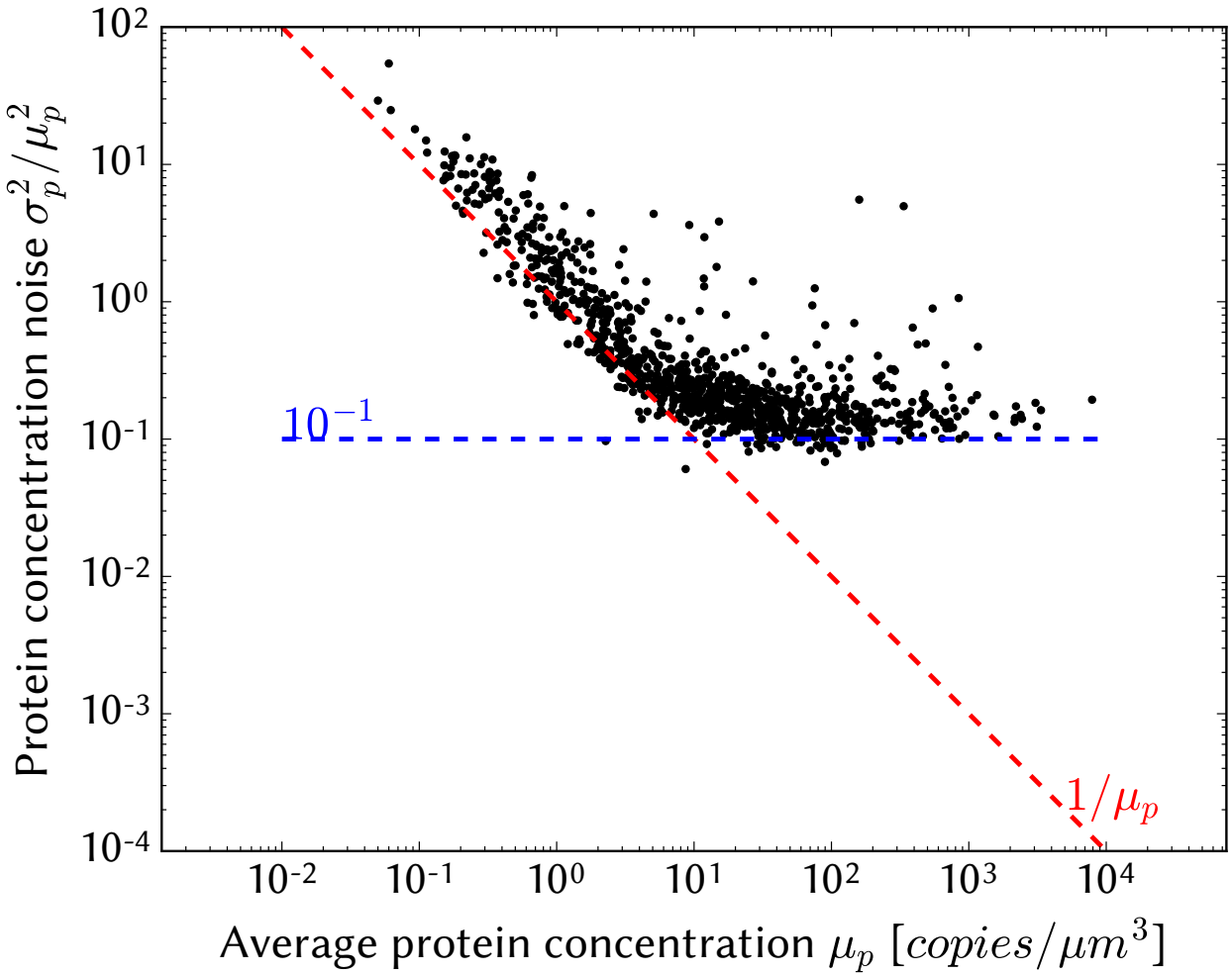
$$\mu_p = \frac{1}{N}\sum_{i=1}^{N}\frac{p_i}{v_i}$$

Empirical variance:

$$\sigma_p^2 = \frac{1}{N}\sum_{i=0}^{N}\left(\frac{p_i}{v_i}\right)^2 - \mu_p^2$$

Taniguchi et al. (2010) experimental measures

Two regimes in the protein variability:



Taniguchi et al. (2010)

Goal: modelling the protein production

- Models to describe the stochastic protein variability.
- Confront the models to real experiments (two regimes)

Part 2

Classical models for protein production

Markovian description

Framework for protein production modeling:

- Rigney and Schieve (1977)
- Berg (1978)
- Paulsson (2005)

Three types of events:

- Encounter between molecules
- mRNA and protein creation
- Lifetime of molecules

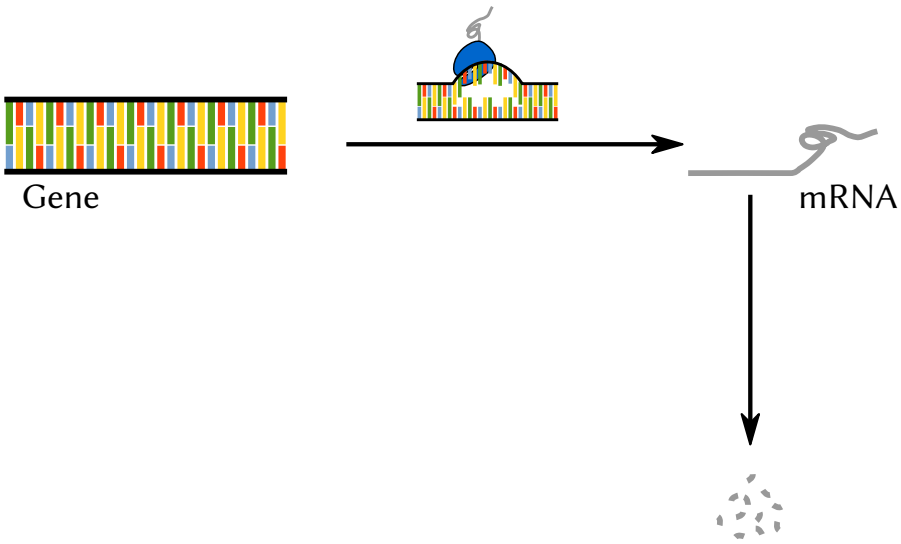
Assumption: Exponential times

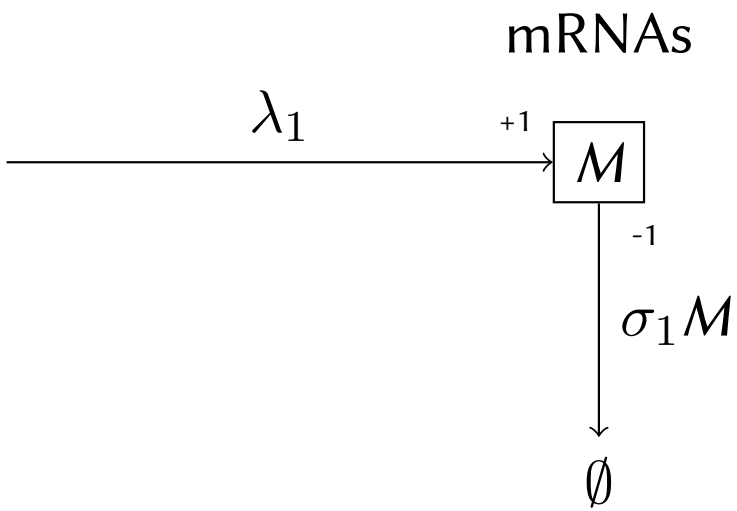
Each event occurs at exponentially distributed time.

The classical model

The classical model

Transcription





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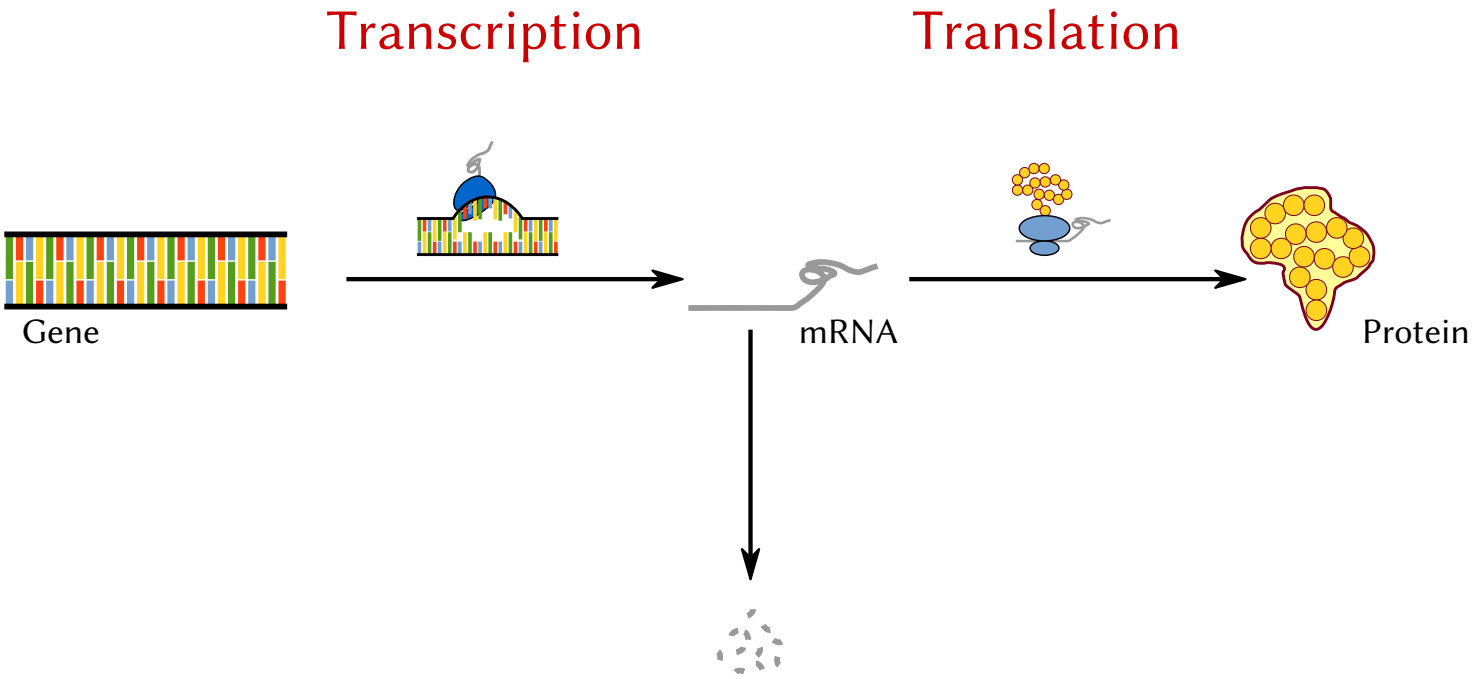

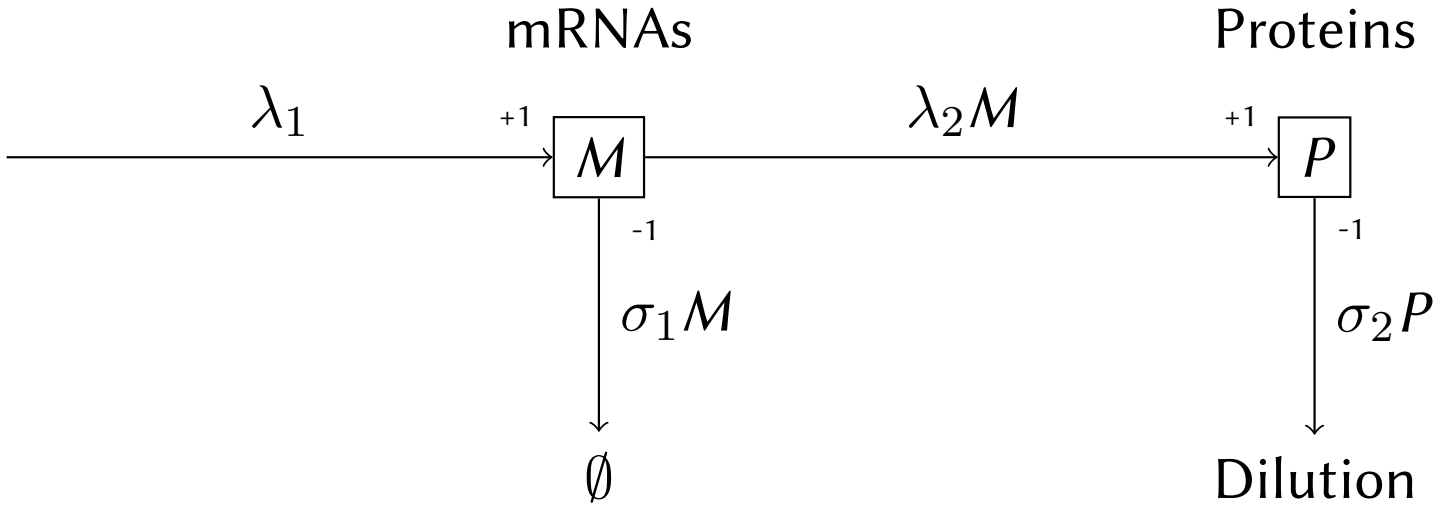

Limitations of classical models

Classical model, at equilibrium mean $\mathbb{E}[P]$ and the variance $\mathbb{V}ar[P]$ are known Paulsson (2005).
But this model has some limitations:

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- it does not consider gene replication
- it represents numbers and not concentrations

We need to have a model with the notion of cell cycle.

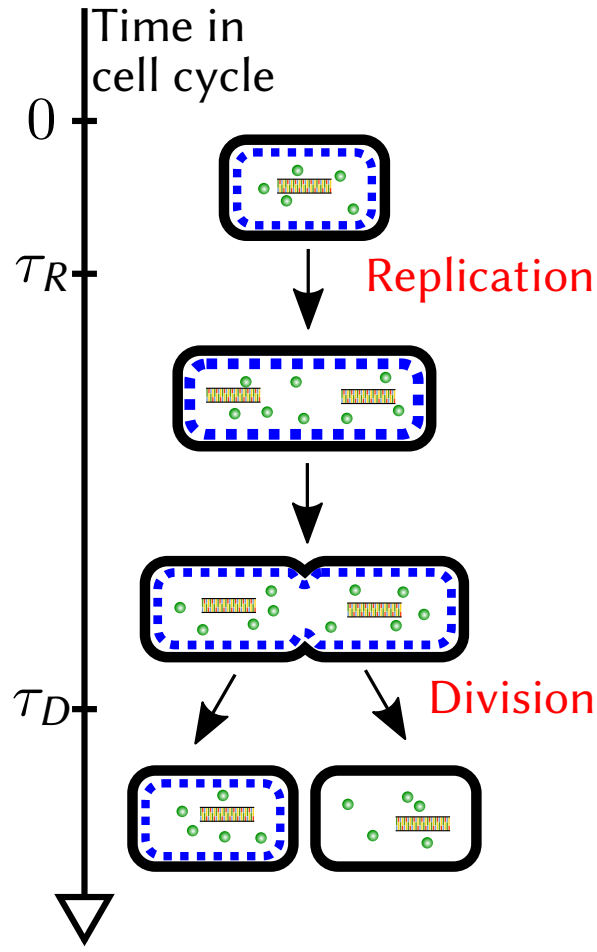
Part 3

Model with cell division and gene replication

Features of the model

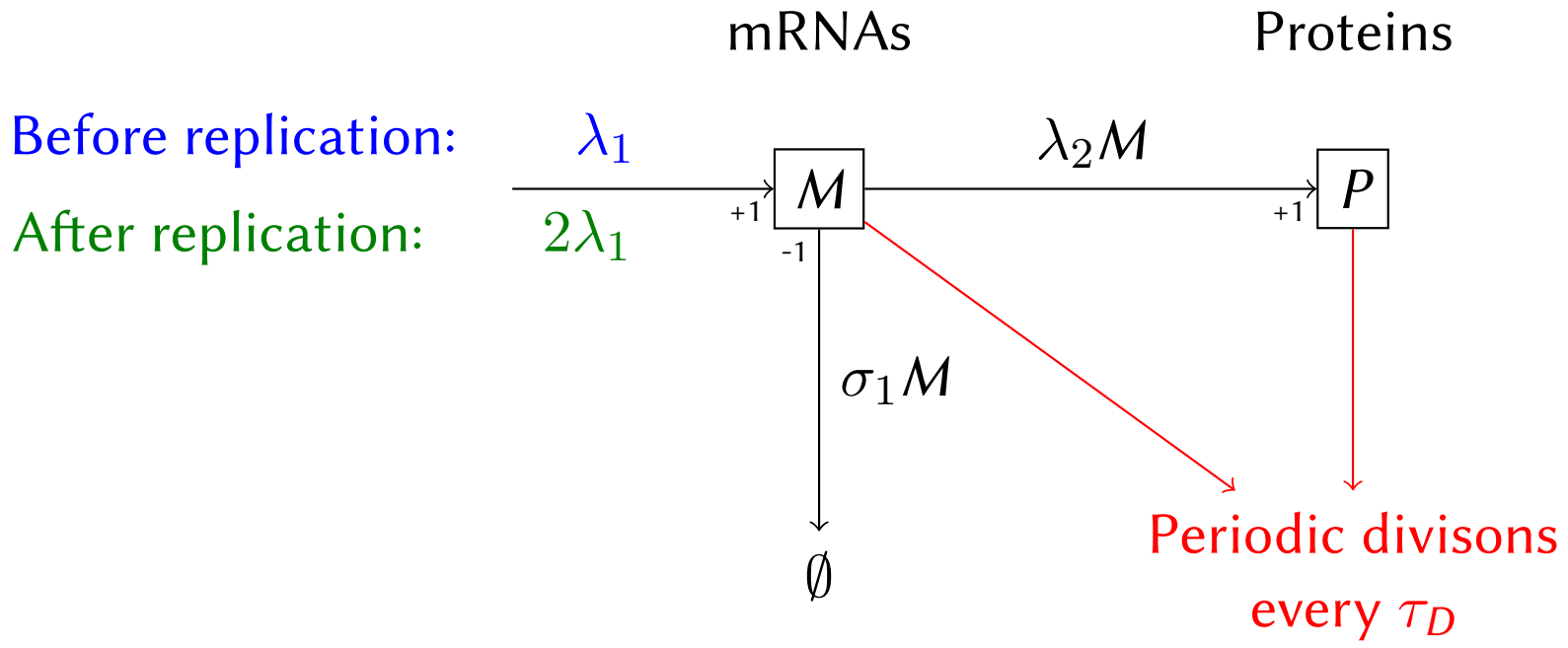
A model with cell cycle:

- Considering a growing cell
- Gene replication at τ_R
- Division at τ_D



Times τ_R and τ_D are consider as deterministic.

Presentation of the model



Volume growth:

$$V(s) = V(0)2^{s/\tau_D}$$

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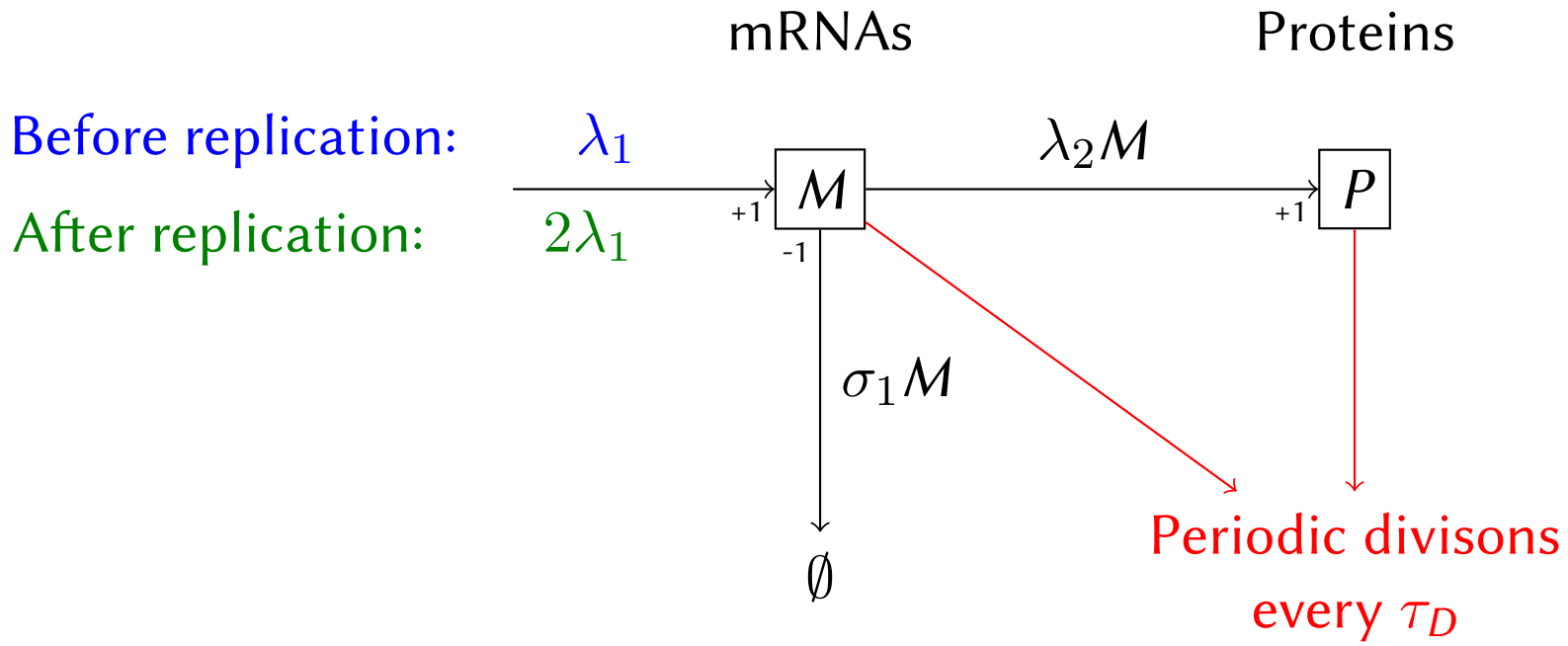

Volume growth:

$$V(s) = V(0)2^{s/\tau_D}$$

Concentrations can be considered:

$$P_s/V(s) \quad \text{and} \quad M_s/V(s)$$

Explicit solution for the number of mRNAs

For any time s of the cell cycle the distribution of M_s is known.

Theorem

At equilibrium, at a time s in the cell cycle, the mRNA number M_s follows a Poisson distribution of parameter

$$x_s = \frac{\lambda_1}{\sigma_1}\left[1 - \frac{e^{-(s+\tau_D-\tau_R)\sigma_1}}{2 - e^{-\tau_D\sigma_1}} + \mathbb{1}_{s\geq\tau_R}\left(1 - e^{-(s-\tau_R)\sigma_1}\right)\right].$$

We need to use Marked Poisson Point Process for the proof.

Explicit solution for the mean and the variance

With more calculus, the first two moments of P_s are known.

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Theorem

At equilibrium, at any time s of the cell cycle, the mean and the variance of the protein number P_s are

$$\begin{aligned}
\mathbb{E}[P_s] &= \lambda_2 \left(f_1(\tau_R) + f_2(\tau_D) + f_1(\tau_R \wedge s) + \mathbb{1}_{s \geq \tau_R} f_2(s) \right) \\
\mathbb{V}ar[P_s] &= \mathbb{V}ar[P_0] + 2\lambda_2 \frac{1 - e^{-\sigma_1 s \wedge \tau_R}}{\sigma_1} \mathbb{C}ov[P_0, M_0] + g_1(s \wedge \tau_R) \\
&\quad + \mathbb{1}_{s \geq \tau_R} \left(2\lambda_2 \frac{1 - e^{-\sigma_1 (s - \tau_R)}}{\sigma_1} \mathbb{C}ov[P_{\tau_R}, M_{\tau_R}] + g_2(s) \right)
\end{aligned}$$

with f_1, f_2, g_1, g_2, $\mathbb{V}ar[P_0]$, $\mathbb{C}ov[P_0, M_0]$ and $\mathbb{C}ov[P_{\tau_R}, M_{\tau_R}]$ explicitly depending on λ_1,σ_1, λ_2, τ_R and τ_D.

Part 4

Results and further work

Parameters

We use the empirical mean and variance of proteins in Taniguchi et al. (2010) to fit the parameters.

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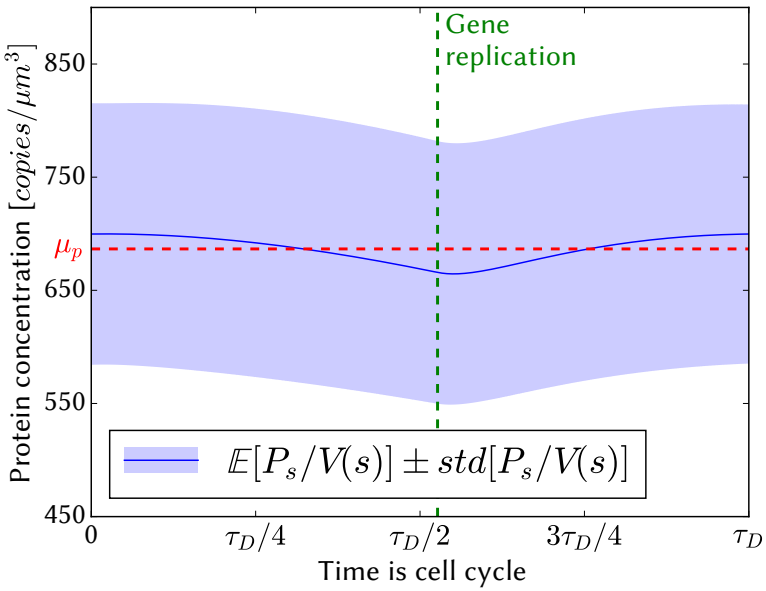
For each type of protein:

$$\mu_p = \frac{1}{\tau_D} \int_0^{\tau_D} \frac{\mathbb{E}\left[P_s\right]}{V(s)}\, ds.$$

Protein profile

The previous theorem can predict the protein variability:

Simulations



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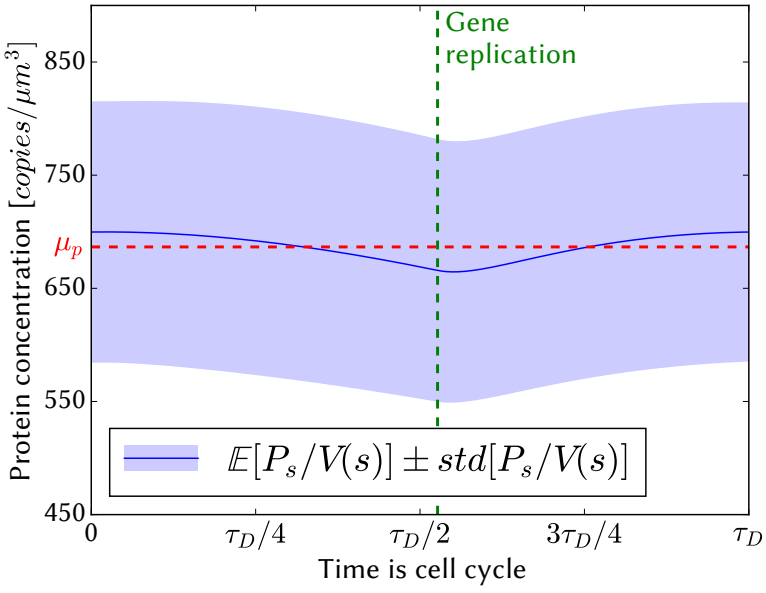
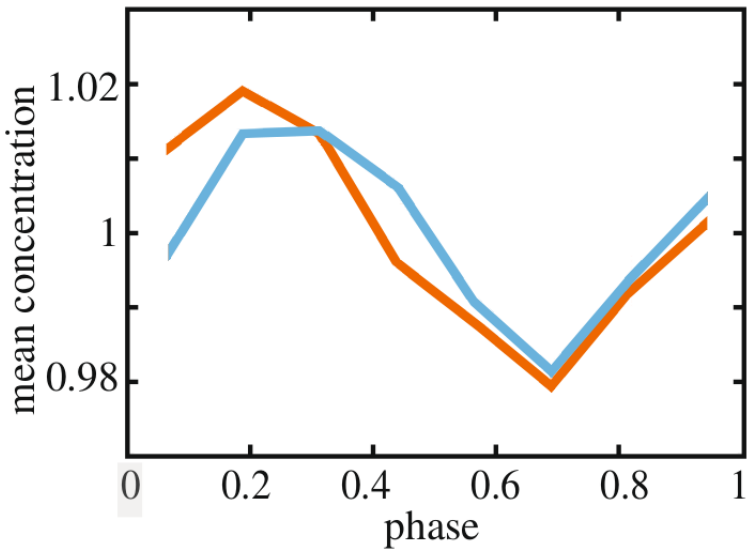


Experiments

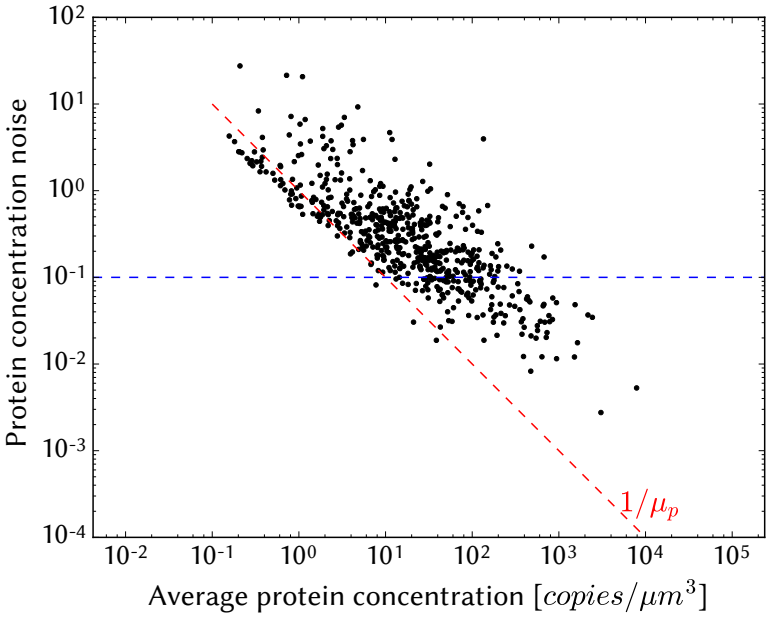


adapted from fig 4.b of Walker et al. (2016)

Protein noise

Direct comparison with Taniguchi et al. (2010)

Simulations



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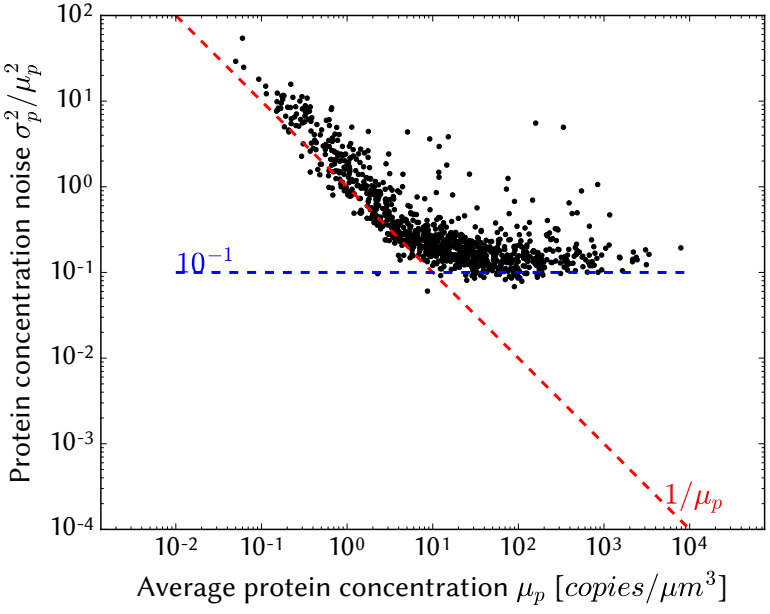

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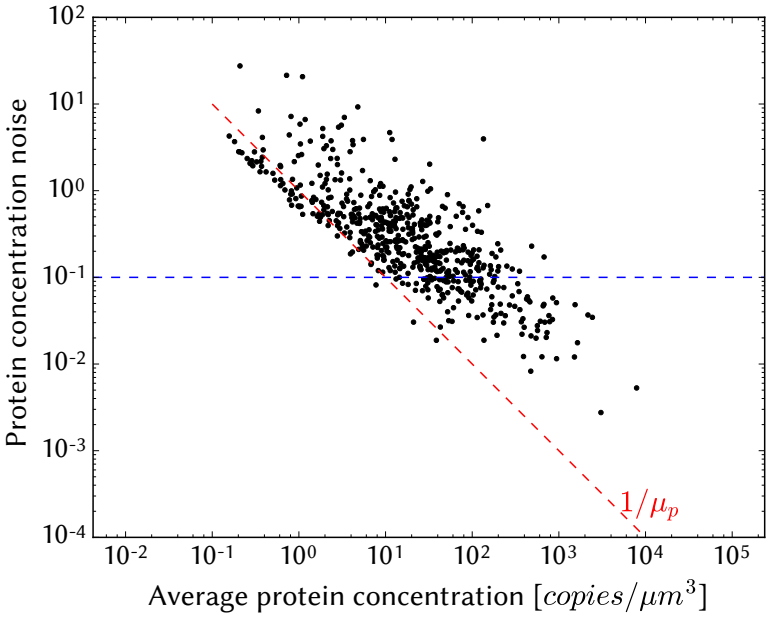

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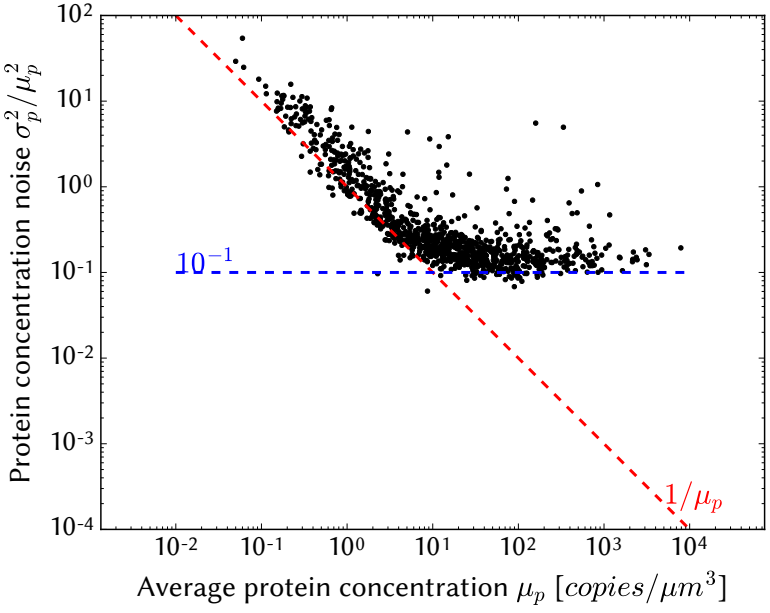
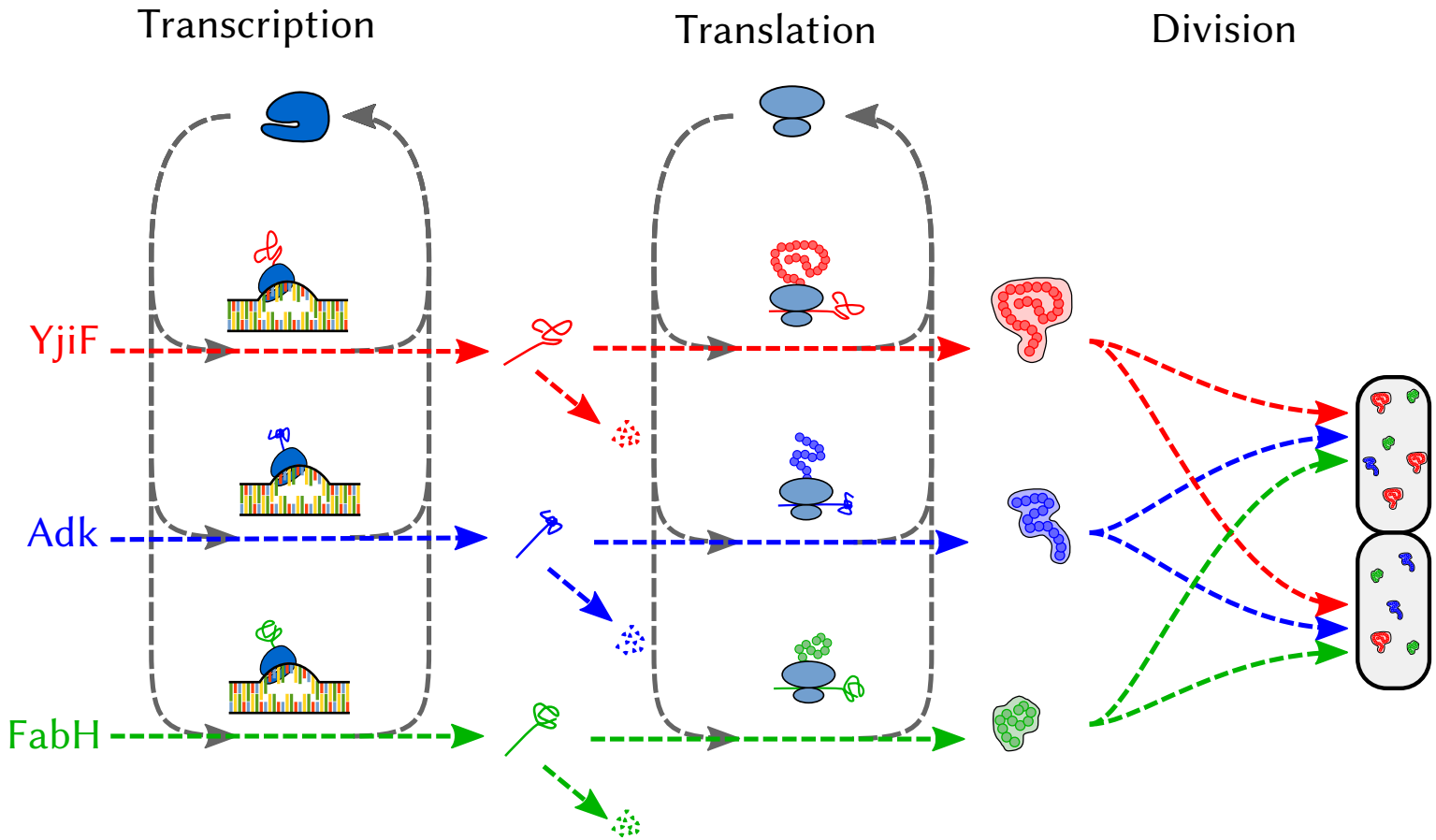


A more complex model is needed

Multi-protein model

Model with a sharing of common ressources: RNA-polymerases and ribosomes:



Conclusions

In this work:

- A model with division and replication
- Analytical results for protein mean and variances
- On average, coherent with experiments

But it does not reproduce all of the protein variability.

Thank you for you attention

PhD work supervised by

- Vincent Fromion

- Philippe Robert

For each gene, Taniguchi et al. (2010) gives:

- empirical mean of mRNA concentration: μ_m
  - empirical mean of protein concentration: μ_p
  - mRNA lifetime σ_1
  - gene position (from which τ_R can be deduced)

Main idea of the proof

Question: How many mRNAs X_s

- created since the birth of the cell
- still present at time s (with time s before replication)

Use of a Marked Poisson Point Process of intensity

$$\nu(dx, dy) = \lambda_1 dx \otimes \sigma_1 e^{-\sigma_1 y} dy.$$

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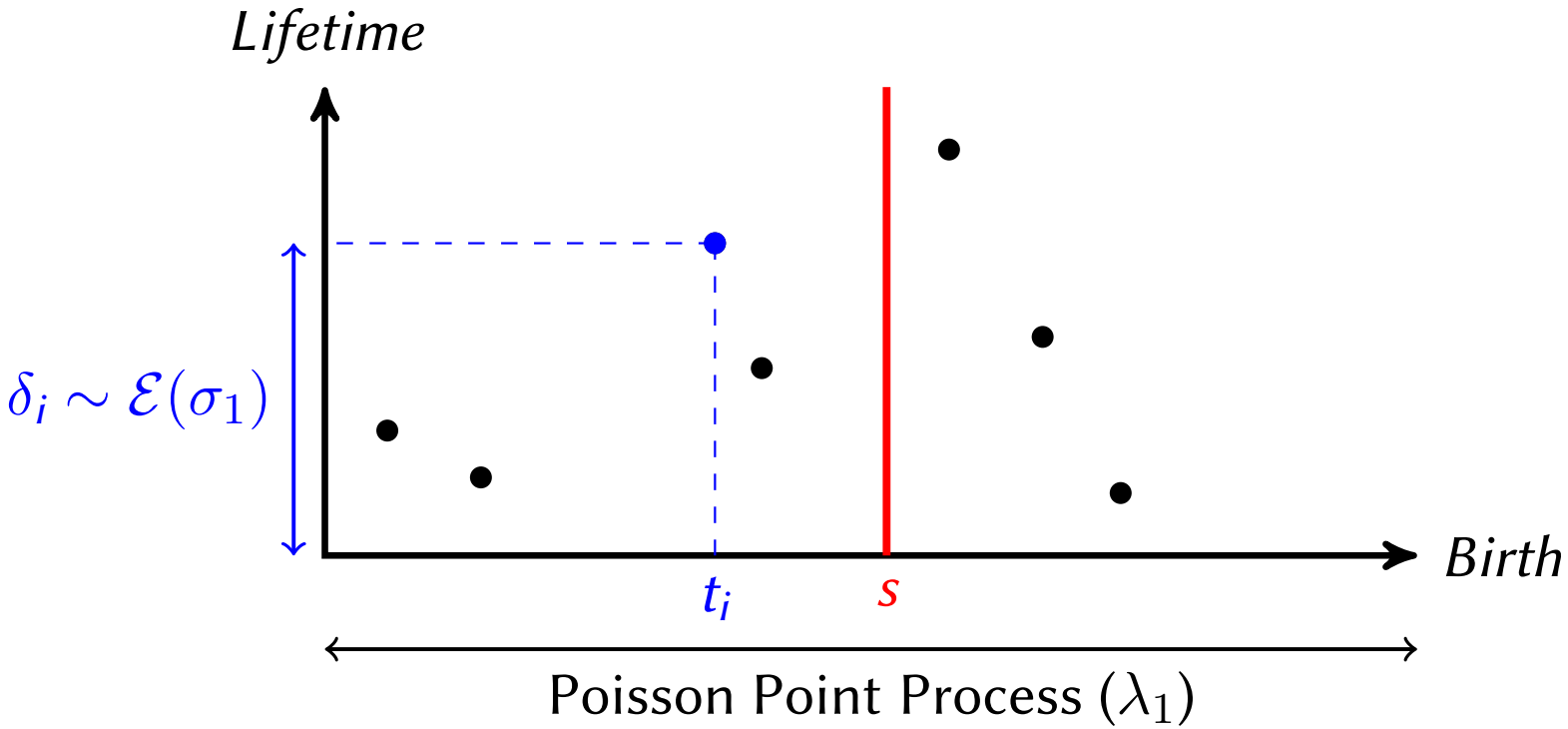

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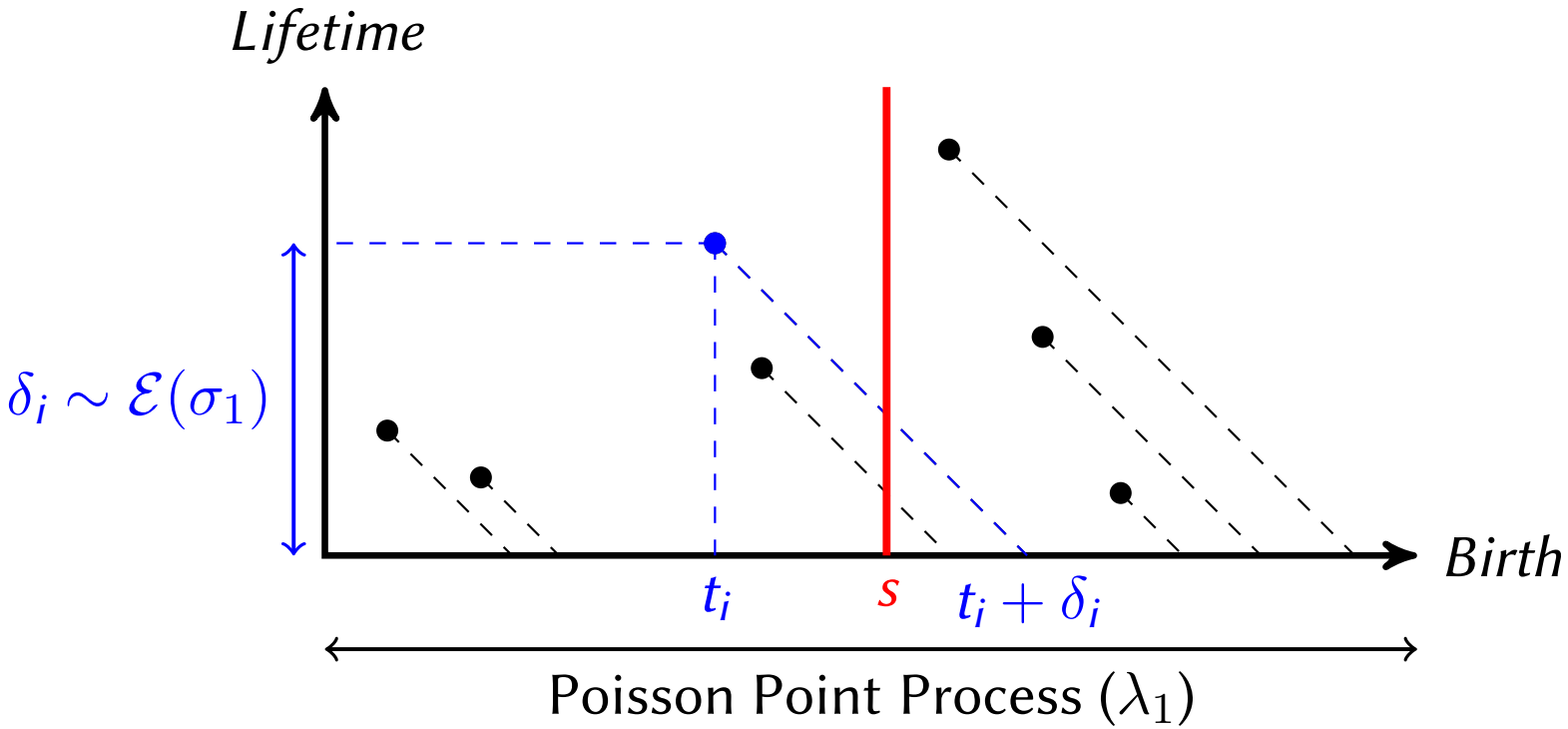

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