Stochastic models of protein production with feedback

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(Fance)

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Presentation

Biological context

Mathematical framework

Equilibrium results

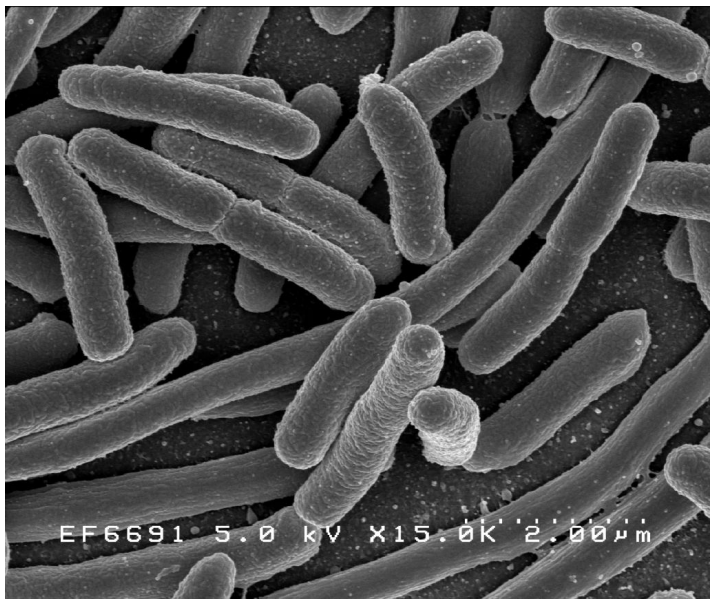
Other aspects of the controlled model

Part 1

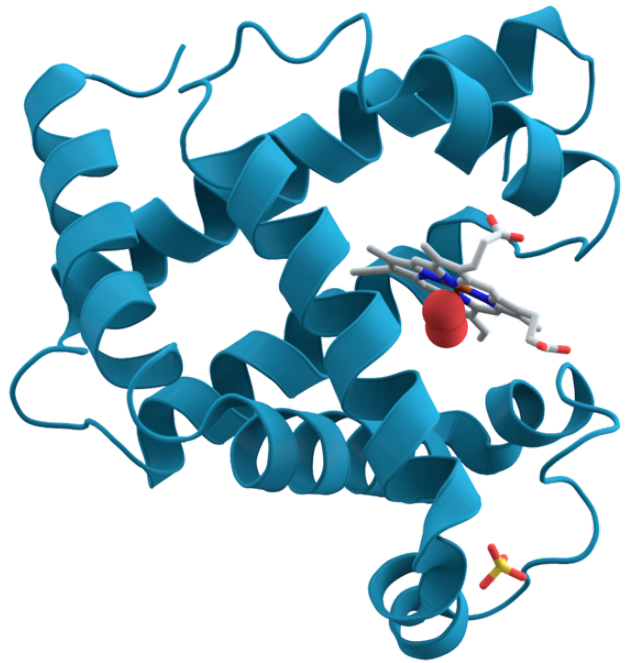
Biological context

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
- $\sim$ 3 million molecules
- $\sim$ 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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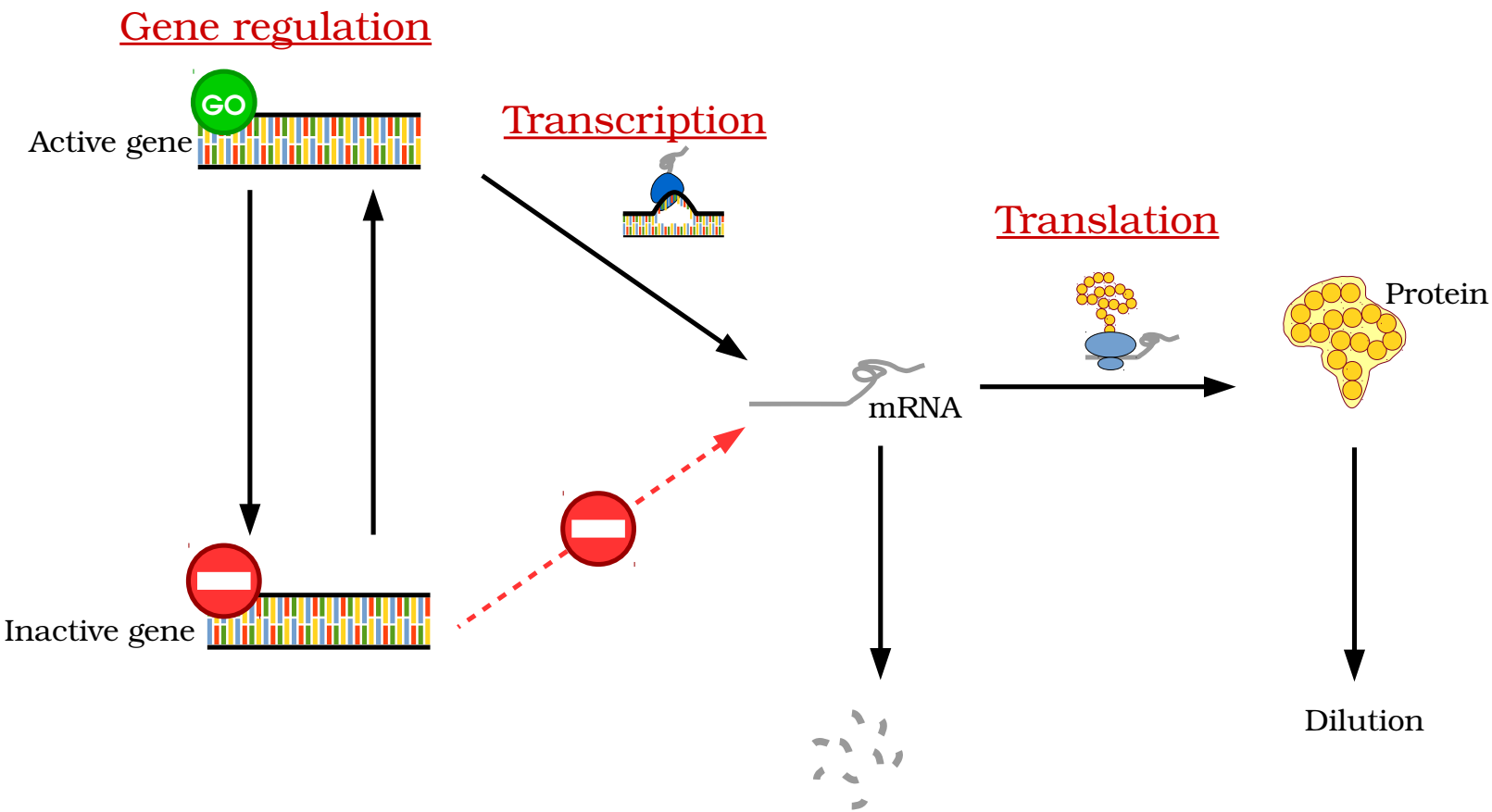
85% of the resources for protein production

Classic protein production mechanism

Protein production in 3 steps:

1. Gene regulation
2. Transcription: to produce mRNA
3. Translation: to produce proteins



Highly variable process

The protein production subject to high variability:

- Interior of bacteria: non-organized medium
- Mobility of compounds: through random diffusion
- Cellular mechanism: random collision between molecules

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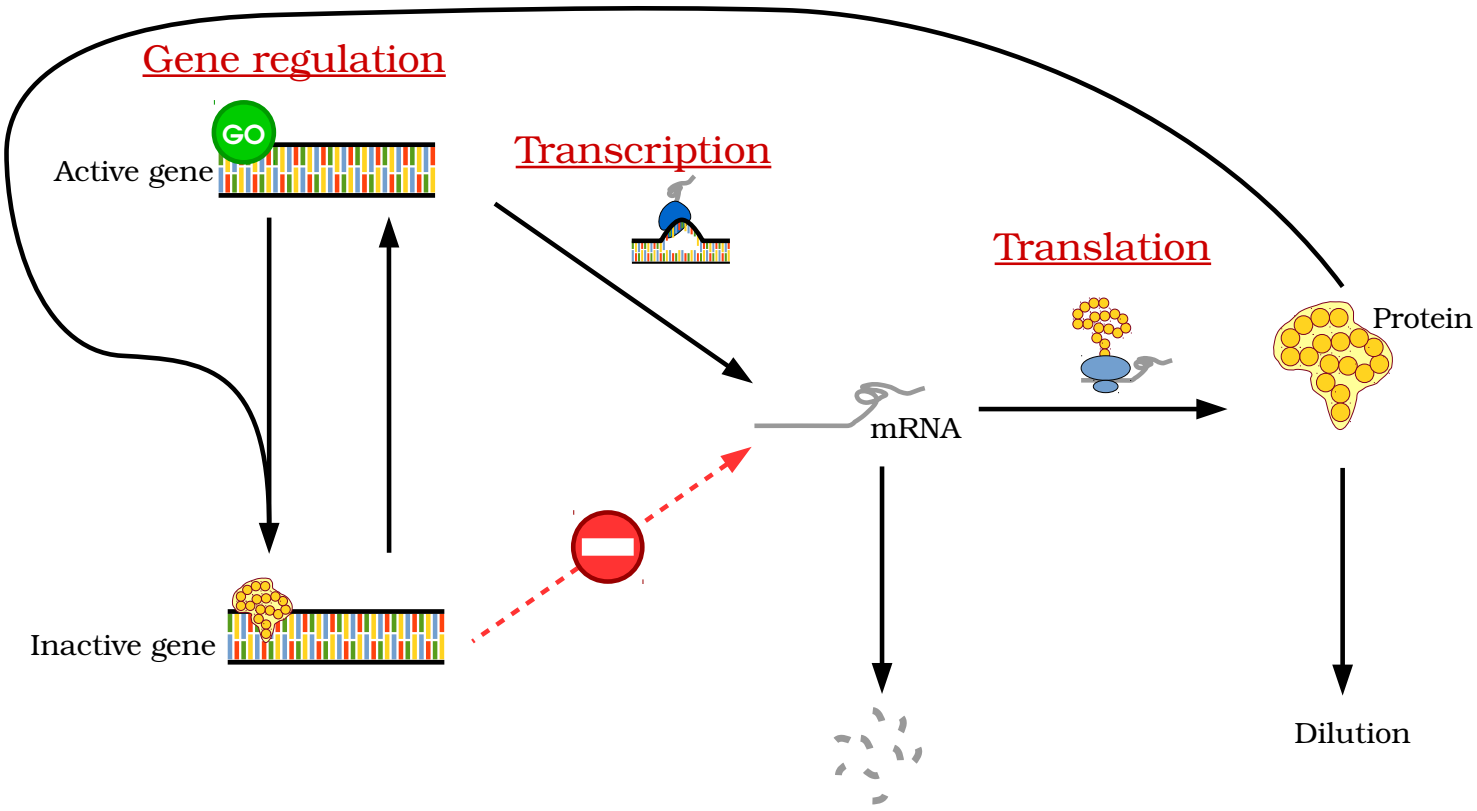
Problem: 85% of the resources for the protein production, impacted by a large variability.

A main issue for the bacteria:
control the variability in protein production.

Protein production mechanism with feedback

Production with feedback: the protein binds to its own gene.



More proteins ⇒ Gene more inactive

A way to reduce variability?

Comparison of models

Classical production vs *Feedback production*

- Conjecture: less variability in proteins with feedback production.

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Classical production vs *Feedback production*

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Our Goal

Comparison of distributions of proteins in the two models.

Part 2

Mathematical framework

Markovian description

Framework for protein production modeling:

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

Three types of events:

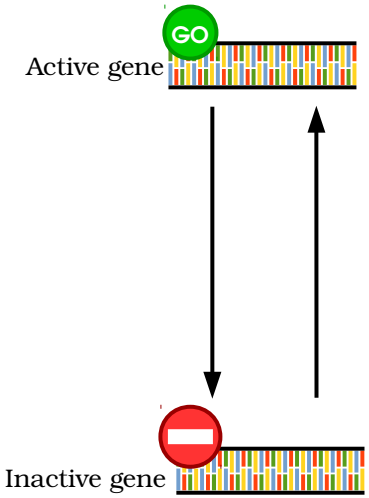
- Encounter between molecules
- Elongation of molecules
- Lifetime of molecules

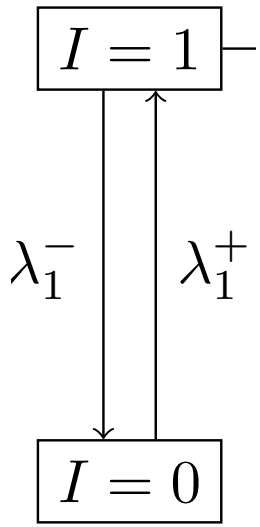
Assumption: Exponential times

Each event occurs at exponential time.

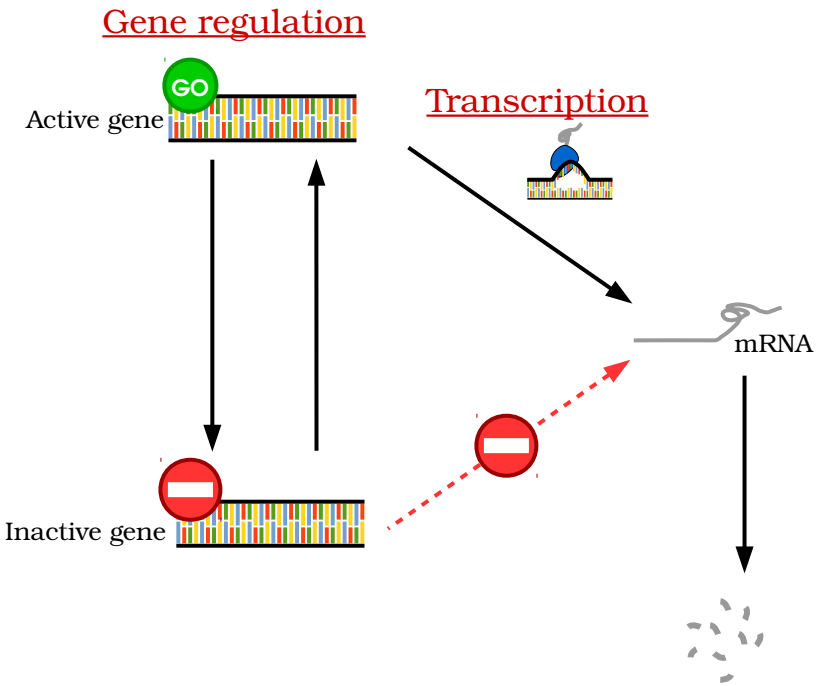
The classical model

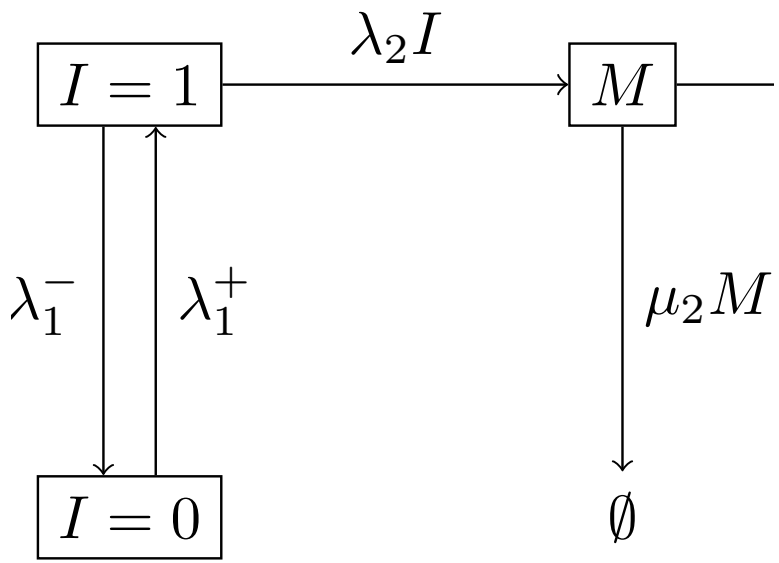
Gene regulation





The classical model





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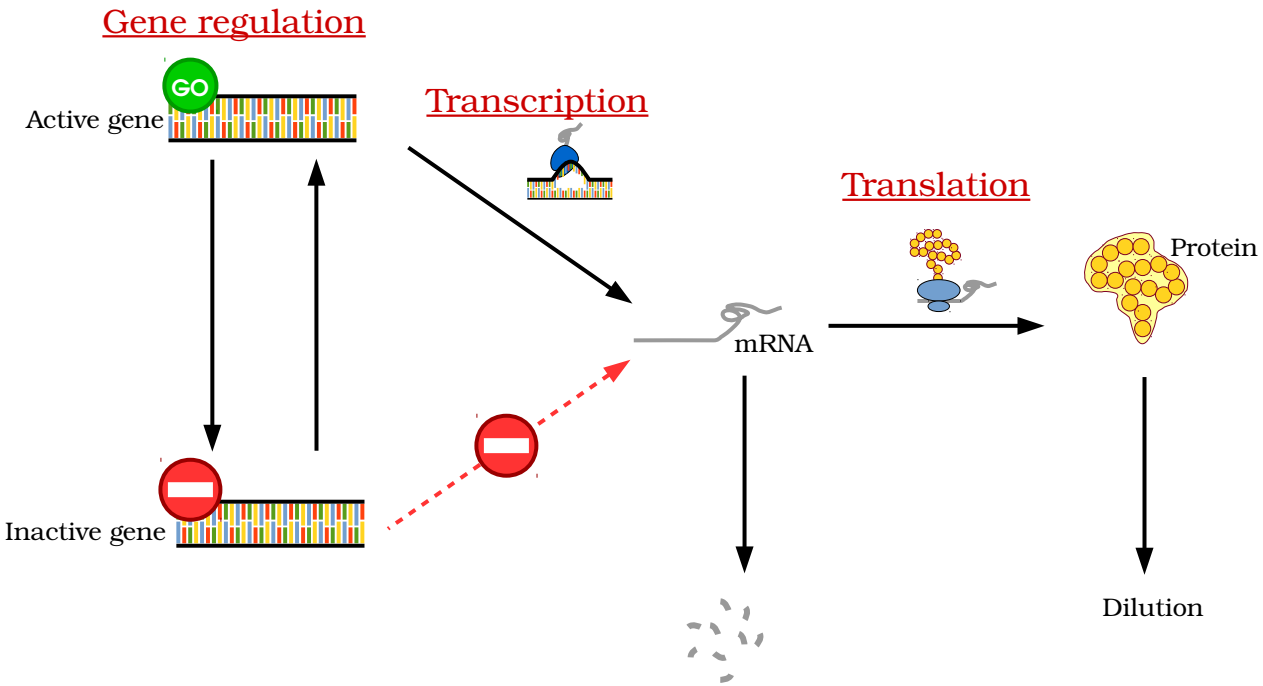
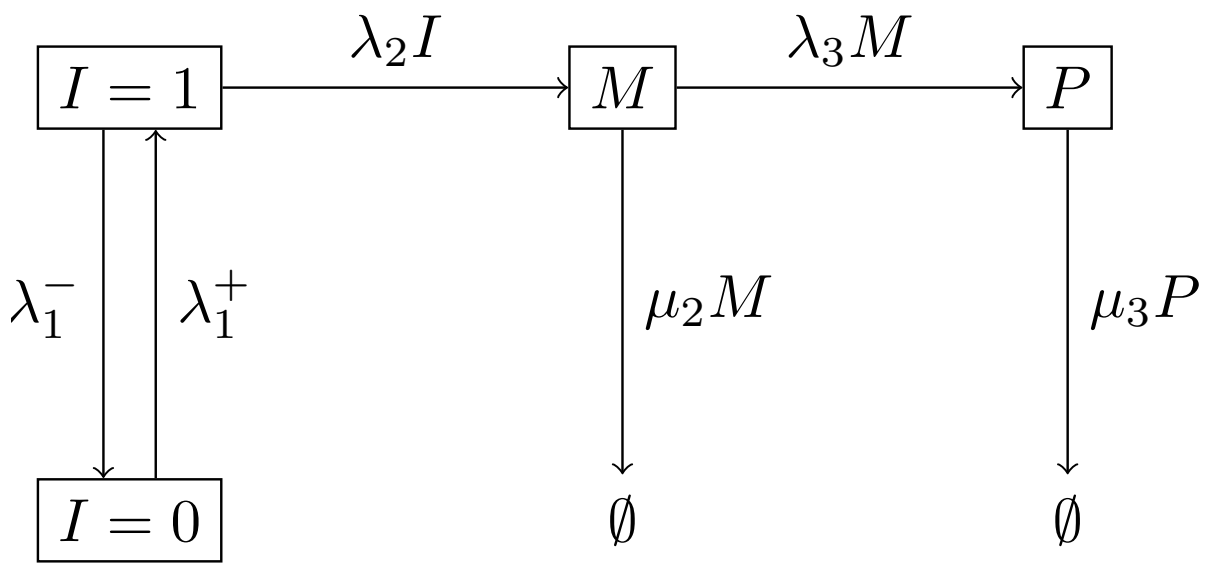




Mean and variance for the classical model

For the classical model, the mean and the variance are known Paulsson (2005):

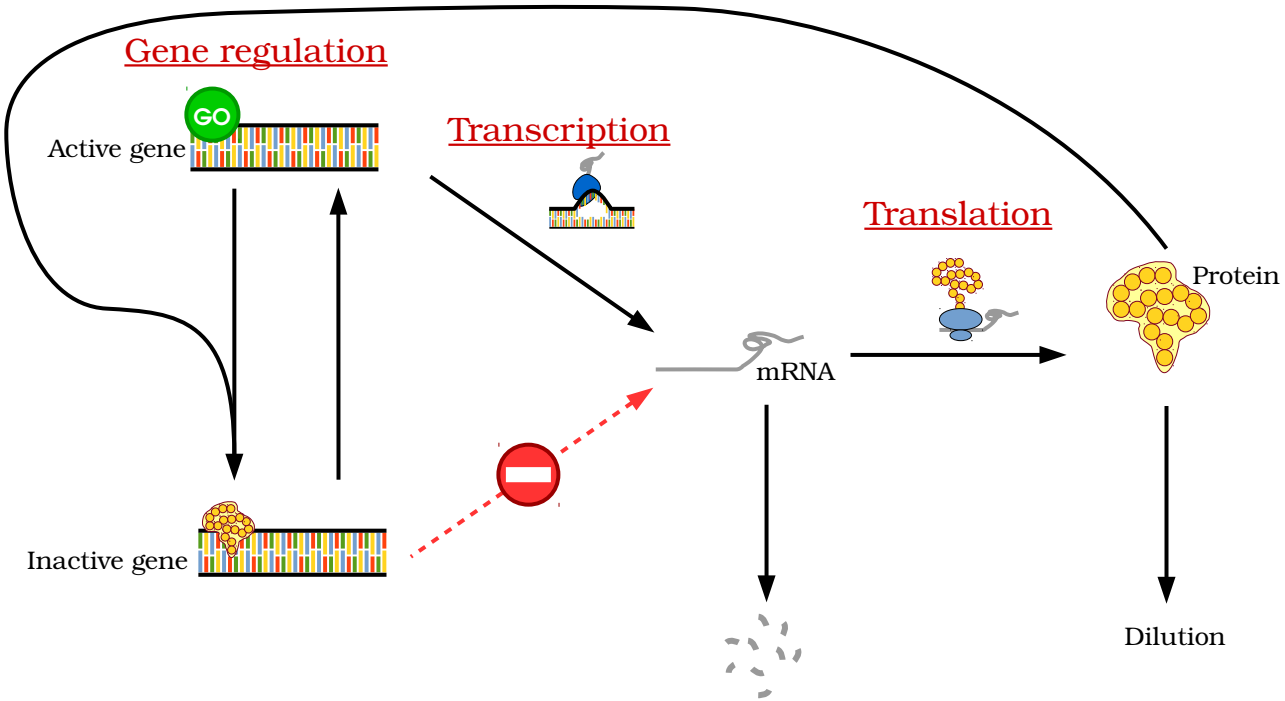
- Equality of flows gives

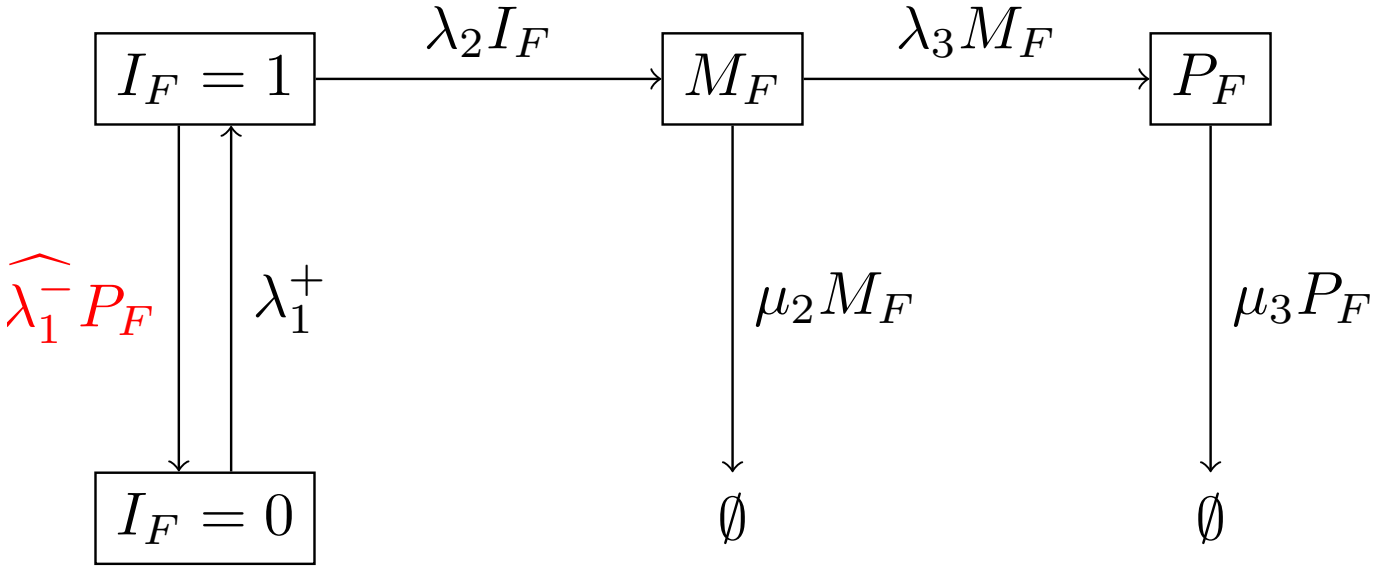
$$\mathbb{E}[P] = \frac{\lambda_1^+}{\lambda_1^+ + \lambda_1^-} \cdot \frac{\lambda_2}{\mu_2} \cdot \frac{\lambda_3}{\mu_3}$$

- Equilibrium equations give:

$$\begin{aligned}\mathbb{V}ar[P] &= \mathbb{E}[P]\left(1 + \frac{\lambda_3}{\mu_2+\mu_3}\right. \\ &\left. + \frac{\lambda_2\lambda_3\left(1-\lambda_1^+/\left(\lambda_1^+ + \lambda_1^-\right)\right)\left(\lambda_1^+ + \lambda_1^- + \mu_2 + \mu_3\right)}{\left(\mu_2+\mu_3\right)\left(\lambda_1^+ + \lambda_1^- + \mu_2\right)\left(\lambda_1^+ + \lambda_1^- + \mu_3\right)}\right).\end{aligned}$$

The feedback model





Mean and variance for the Feedback model

- Equality of flows gives

$$\mathbb{E}[P_C] = \mathbb{E}[I_C] \cdot \frac{\lambda_2}{\mu_2} \cdot \frac{\lambda_3}{\mu_3}.$$

- Problem : no known expression for $\mathbb{E}[I_C]$:
  - the equality of flows on I_C:

$$\widehat{\lambda_1^-}\,\mathbb{E}[I_C P_C] = \lambda_1^+ (1 - \mathbb{E}[I_C]).$$

Difficulties to make comparisons between the two models

Part 3

Equilibrium results

Scaling

- Introduction of a scaling:

$$\left.\begin{array}{l}\text{Gene regulation timescale}\\ \text{Messenger RNA timescale}\end{array}\right\} \text{faster than the protein time scale}$$

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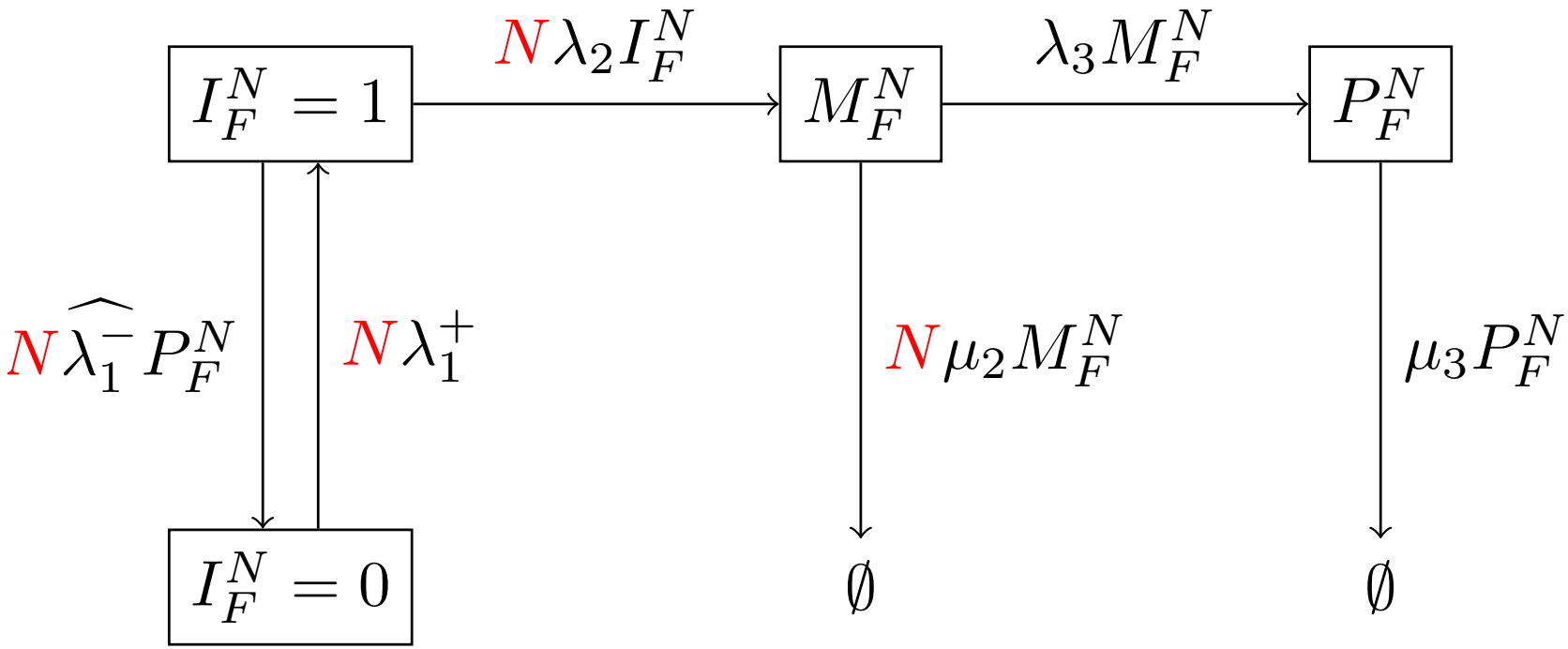

N scaling parameter

Effects of the scaling

Example: Feedback model

- State of the model:

$$\left(I_F^N(t), M_F^N(t), P_F^N(t)\right)$$

  - I_F^N and M_F^N on a quick timescale.
  - P_F^N on a slow timescale.

I_F^N and M_F^N reach some equilibrium depending on the slow current $P_F^N(t)$ state

Convergence of the gene regulation and the messengers

τ_1^N: the first time of jump of P_F^N;
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$$\mathbb{E}\left[I_F^N(t) | 0 < t < \tau_1^N, P_F^N(0) = x\right] \xrightarrow{N\to\infty} \frac{\lambda_1^+}{\lambda_1^+ + \widehat{\lambda_1^-} x}.$$

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- Rate of production of proteins tends to:

$$\lambda_3 \cdot \frac{\lambda_2}{\mu_2} \cdot \frac{\lambda_1^+}{\lambda_1^+ + \widehat{\lambda_1^-}x}.$$

Convergence of the models

Theorem

The process $\left(P_F^N(t)\right)$ *converges in distribution to a birth and death process with (x number of proteins):*

$$\beta_x = \lambda_3 \cdot \frac{\lambda_2}{\mu_2} \cdot \frac{\lambda_1^+}{\lambda_1^+ + \widehat{\lambda_1^-} x} \qquad \textit{and} \qquad \delta_x = \mu_3 x.$$

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Idem for uncontrolled model:

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Feature of the scaled models

- Equilibrium distributions.
  - Classical model: P^{∞} follow a *Poisson distribution*:

$$P^{\infty} \sim \mathcal{P}\left(\frac{\lambda_3}{\mu_3} \cdot \frac{\lambda_2}{\mu_2} \cdot \frac{\lambda_1^+}{\lambda_1^+ + \lambda_1^-}\right)$$

  - Feedback model: P^{∞} follow the limit distribution

$$\pi_F(x) = \frac{1}{Z \cdot x!}\left(\frac{\lambda_3}{\mu_3} \cdot \frac{\lambda_2}{\mu_2}\right)^x \prod_{i=0}^{x-1} \frac{\lambda_1^+}{\lambda_1^+ + \widehat{\lambda_1^-}\, i}$$

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Variance comparison

$$\mathbb{V}ar\left[P^\infty\right] = \mathbb{E}\left[P^\infty\right] \qquad \text{and} \qquad \mathbb{V}ar\left[P_F^\infty\right] \leq \mathbb{E}\left[P_F^\infty\right]$$

Asymptotic behaviour of the Feedback model

Introducing:

$$\rho := \frac{\lambda_1^+}{\lambda_1^-}\frac{\lambda_3}{\mu_3}\cdot\frac{\lambda_2}{\mu_2} \quad \text{and} \quad \eta := \frac{\lambda_1^+}{\lambda_1^-} - 1$$

it comes:

$$\pi_F(x) = \frac{1}{Z\cdot x!}\rho^x \prod_{i=1}^{x}\frac{1}{\eta+i}.$$

Asymptotic behaviour

Increase ρ while keeping η constant:
Increase protein production while keeping the gene regulation constant

Asymptotic behaviour of the Feedback model

With Laplace method:

Theorem

Convergence in distribution:

$$\lim_{\rho\to\infty} \frac{P_F^\infty - a_\rho}{\sqrt{a_\rho}} = \mathcal{N}\left(0, 1/\sqrt{2}\right)$$

with $a_\rho = \left(\sqrt{\eta^2 + 4\rho} - \eta\right)$.

Corollary

$$\lim_{\rho\to\infty} \frac{\mathbb{E}\left[P_F^\infty\right]}{\sqrt{\rho}} = 1 \quad \text{and} \quad \lim_{\rho\to\infty} \frac{\mathbb{V}ar\left[P_F^\infty\right]}{\mathbb{E}\left[P_F^\infty\right]} = \frac{1}{2}$$

Conclusion for the noise control

For the scaled model:

$$\mathbb{V}ar\left[P^{\infty}\right] = \mathbb{E}\left[P^{\infty}\right] \qquad \text{and} \qquad \mathbb{V}ar\left[P_F^{\infty}\right] \leq \mathbb{E}\left[P_F^{\infty}\right]$$

Asymptotic behaviour:

$$\mathbb{V}ar\left[P^{\infty}\right] = \mathbb{E}\left[P^{\infty}\right] \qquad \text{and} \qquad \mathbb{V}ar\left[P_F^{\infty}\right] \underset{\rho\to\infty}{\sim} \frac{1}{2}\mathbb{E}\left[P_F^{\infty}\right]$$

The reduction of variance is limited in feeback model.

Part 4

Other aspects of the controlled model

Dynamical aspects

Equilibrium reaching

Which model go faster to reach the equilibrium?

Biological example: need for a quick activation of the protein production.

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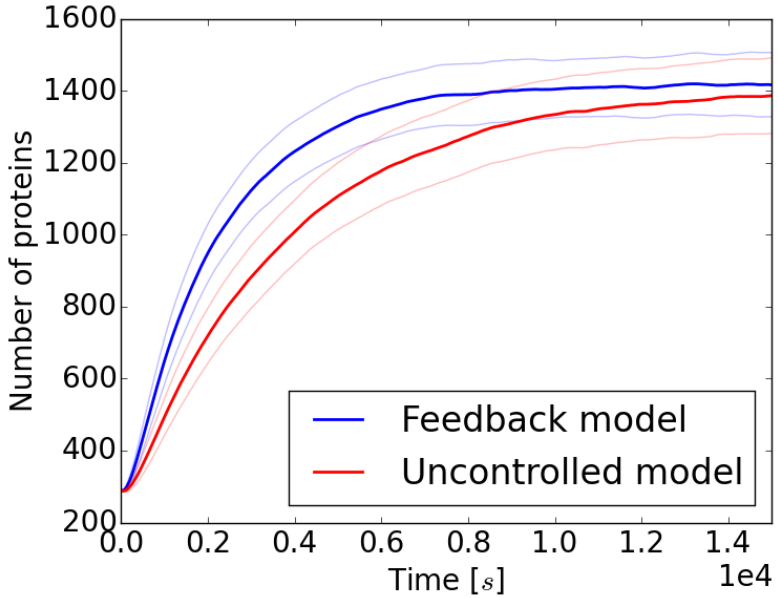
Simulations: comparison for the two models:

- Starting at a low protein production
- Evolution to a high level of protein production

Simulation for dynamical aspects



- 1000 simulations
  - Thick lines: average of trajectories
  - Fine lines: $\pm$ standard deviation
- Here, controlled model is 20% faster

Thank you for you attention

Article:

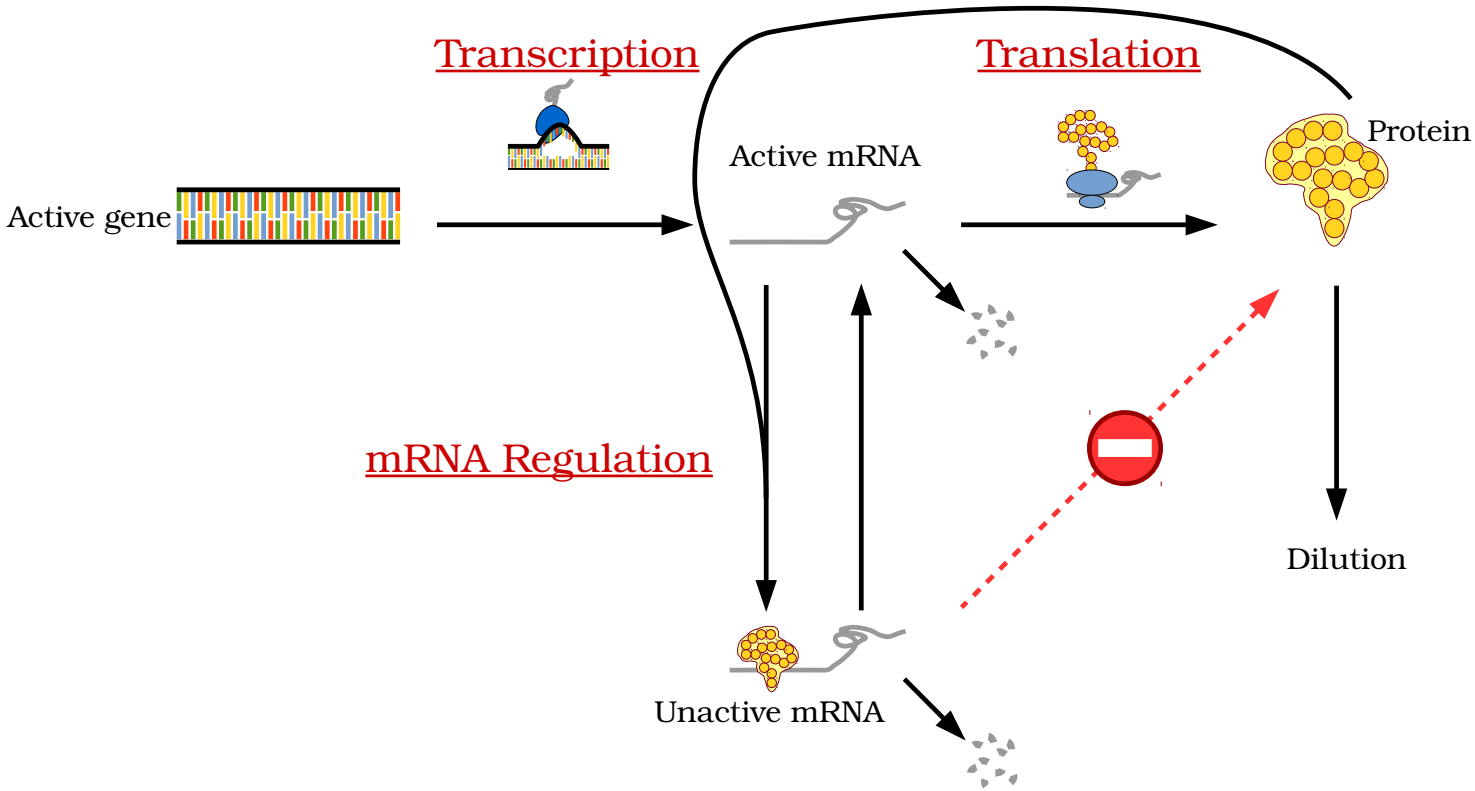
Dessalles, R., Fromion, V., and Robert, P. (2015). arXiv:1509.02045

PhD work supervised by

- Vincent Fromion
- Philippe Robert

Other work

- Regulation on the mRNA rather than on the gene



- Intermediate metabolite step in regulation