Mathematical modeling of the dynamic allocation of resources by a bacterium

Jana Zaherddine

A joint work with:

Vincent Fromion (INRAE) and Philippe Robert (INRIA)

Bacterium

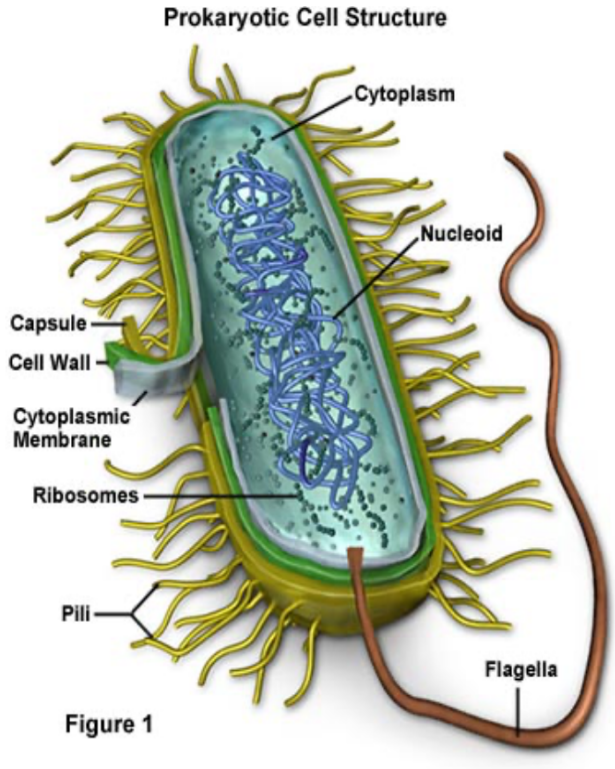

Figure 1

Bacterium

Macromolecules:

- **DNA: no nucleus**
- **proteins, RNAs**
- **ribosomes,polymerases**
- **...**

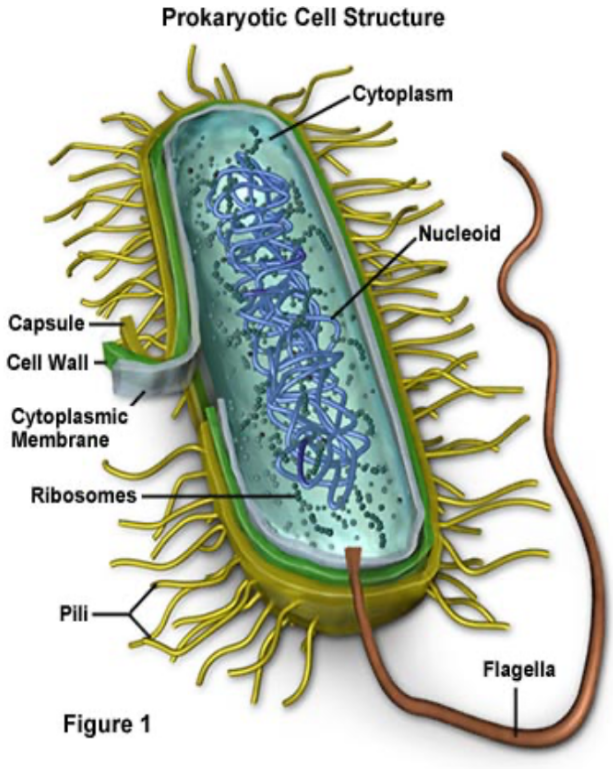

Figure 1

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Disorganized medium:

All macromolecules collide in cytoplasm

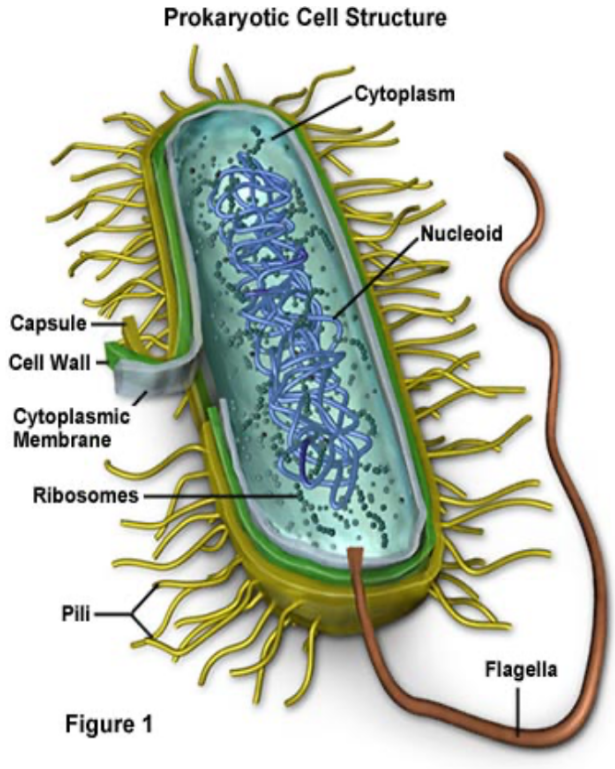
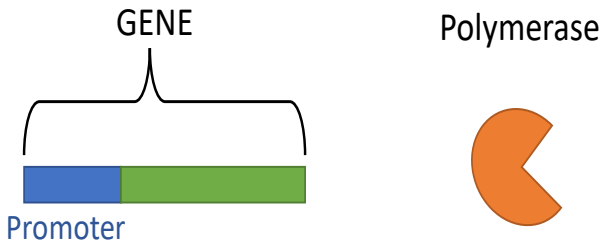


Figure 1

Production of Protein: A multistep process



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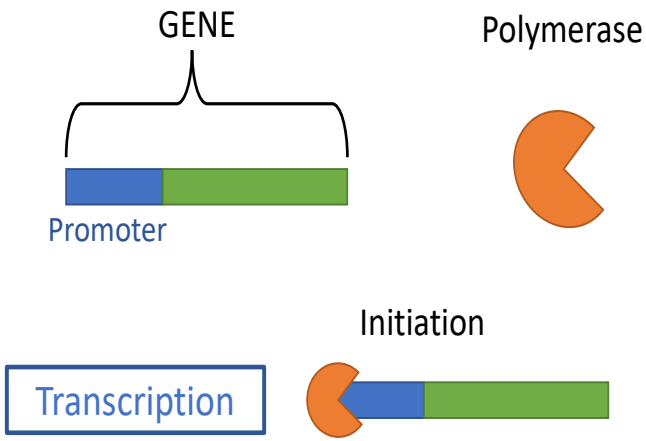

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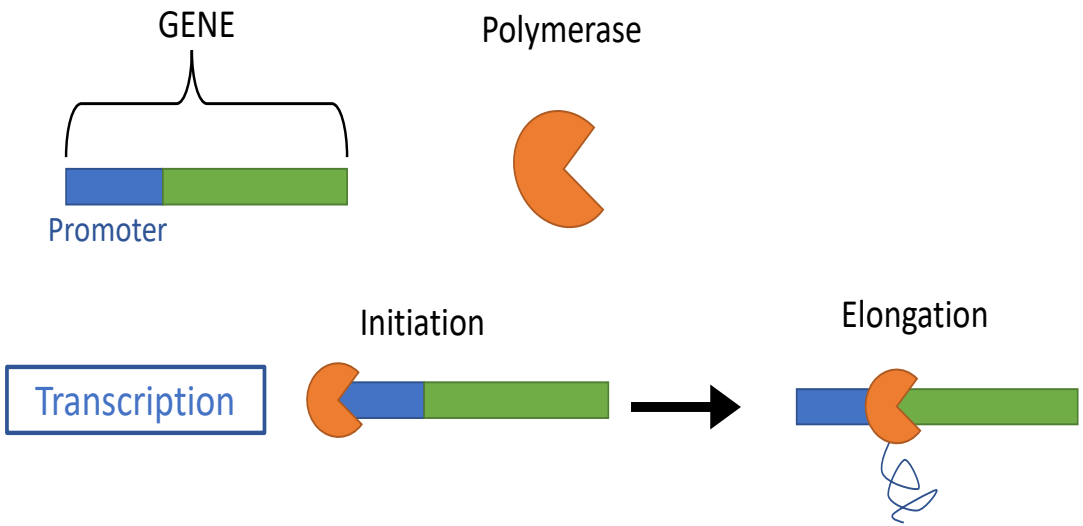

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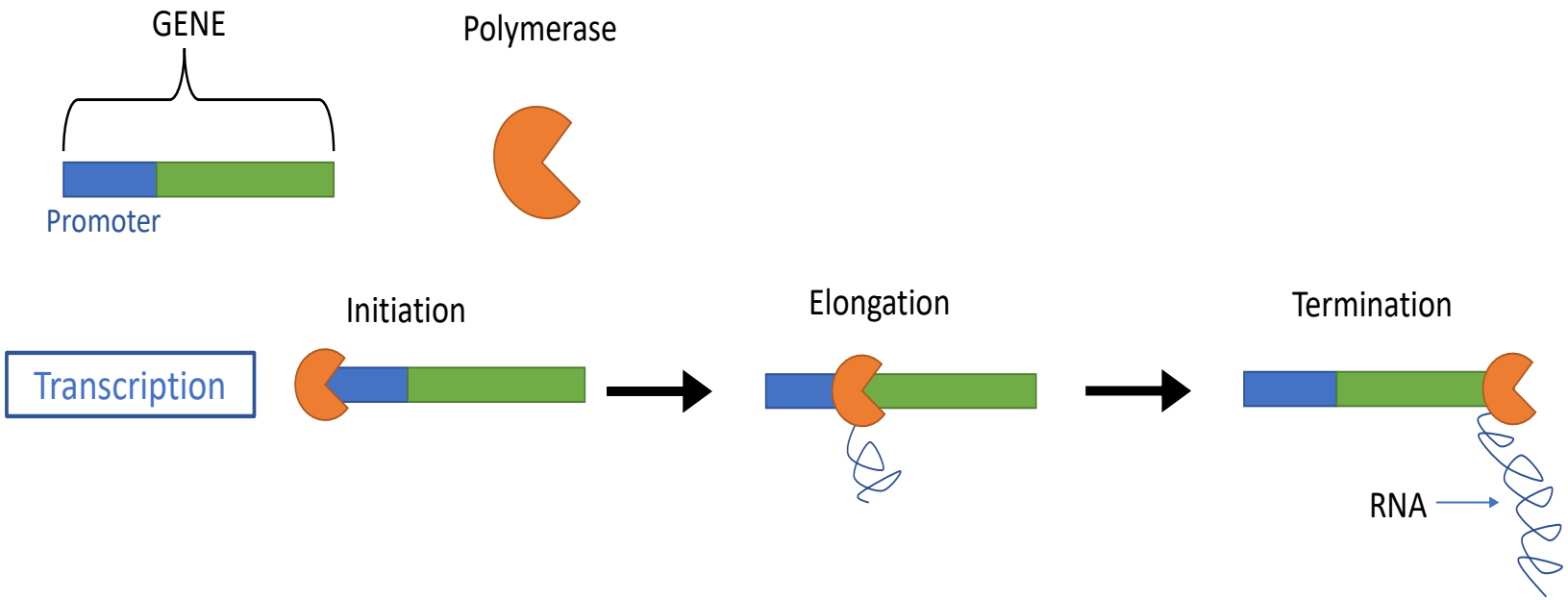

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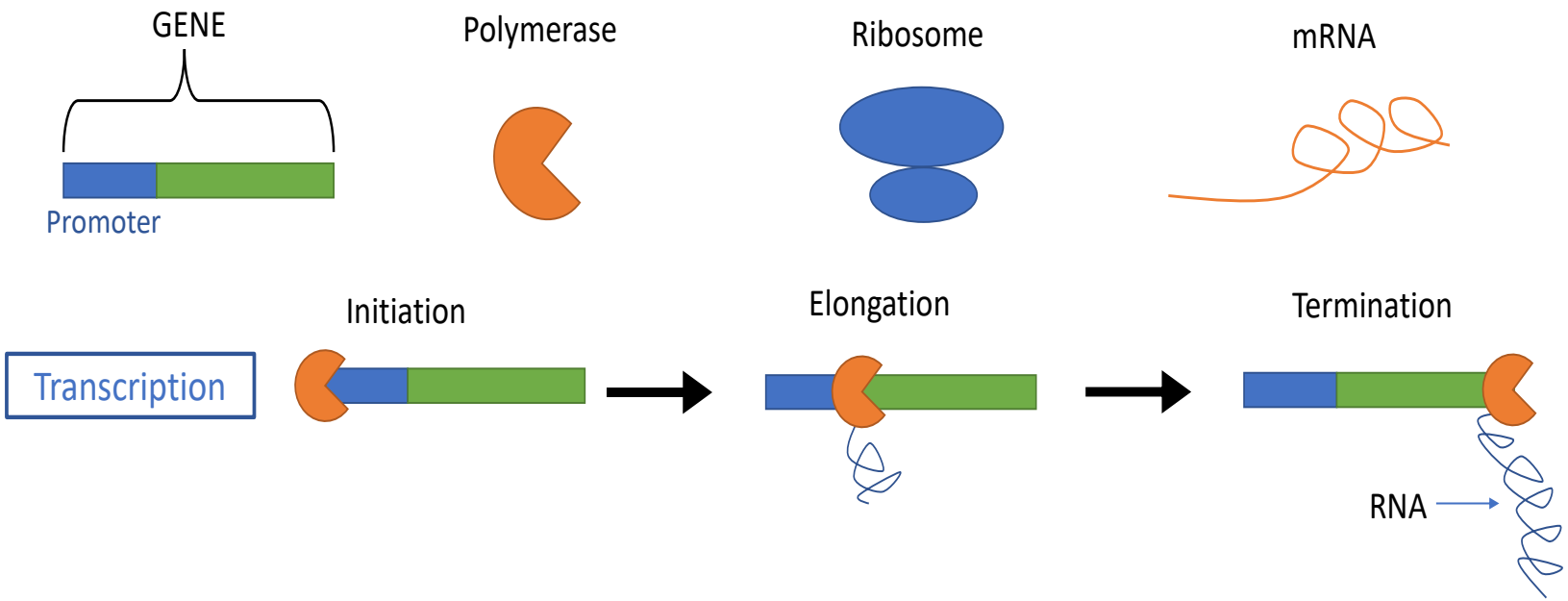

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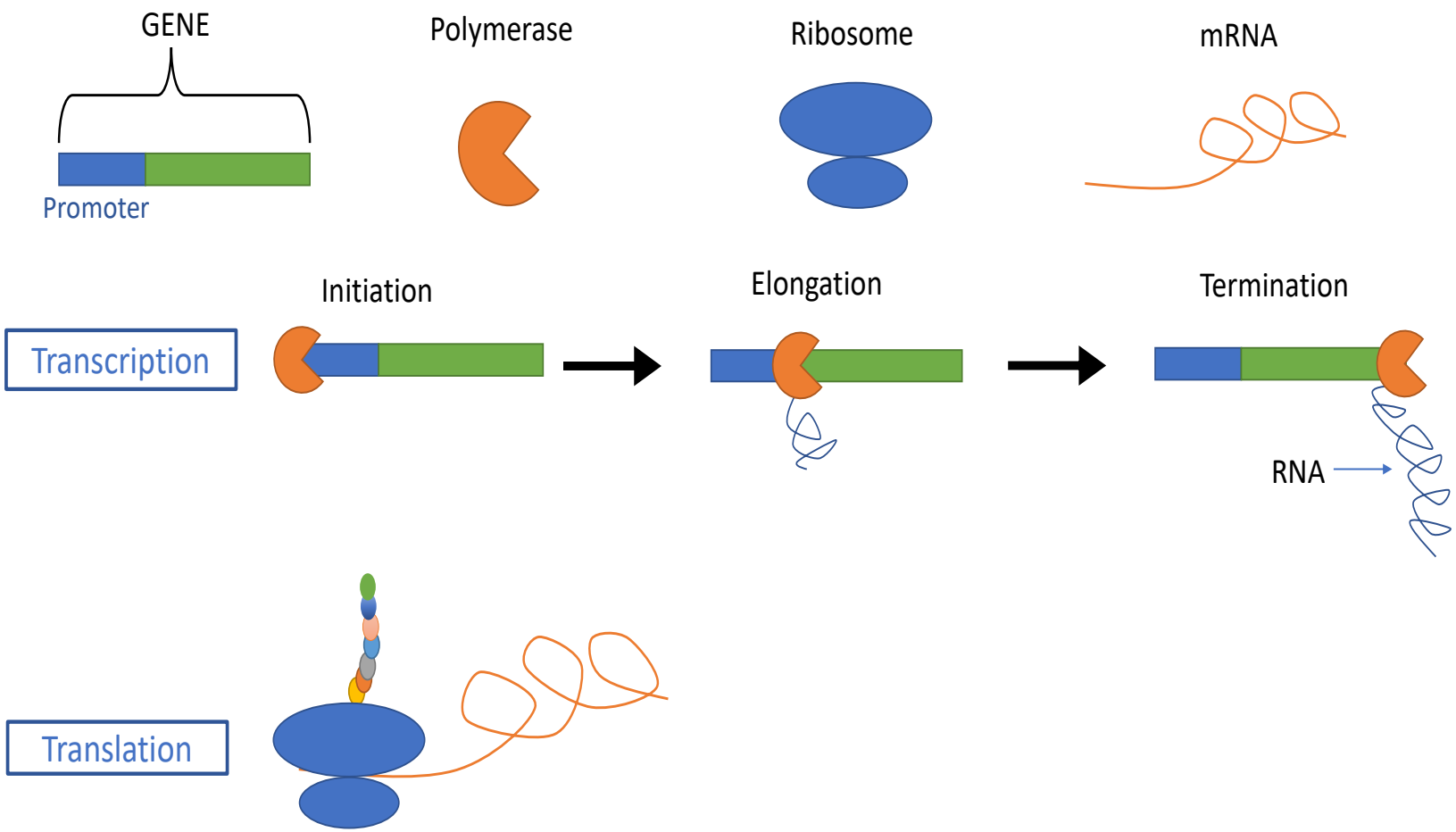

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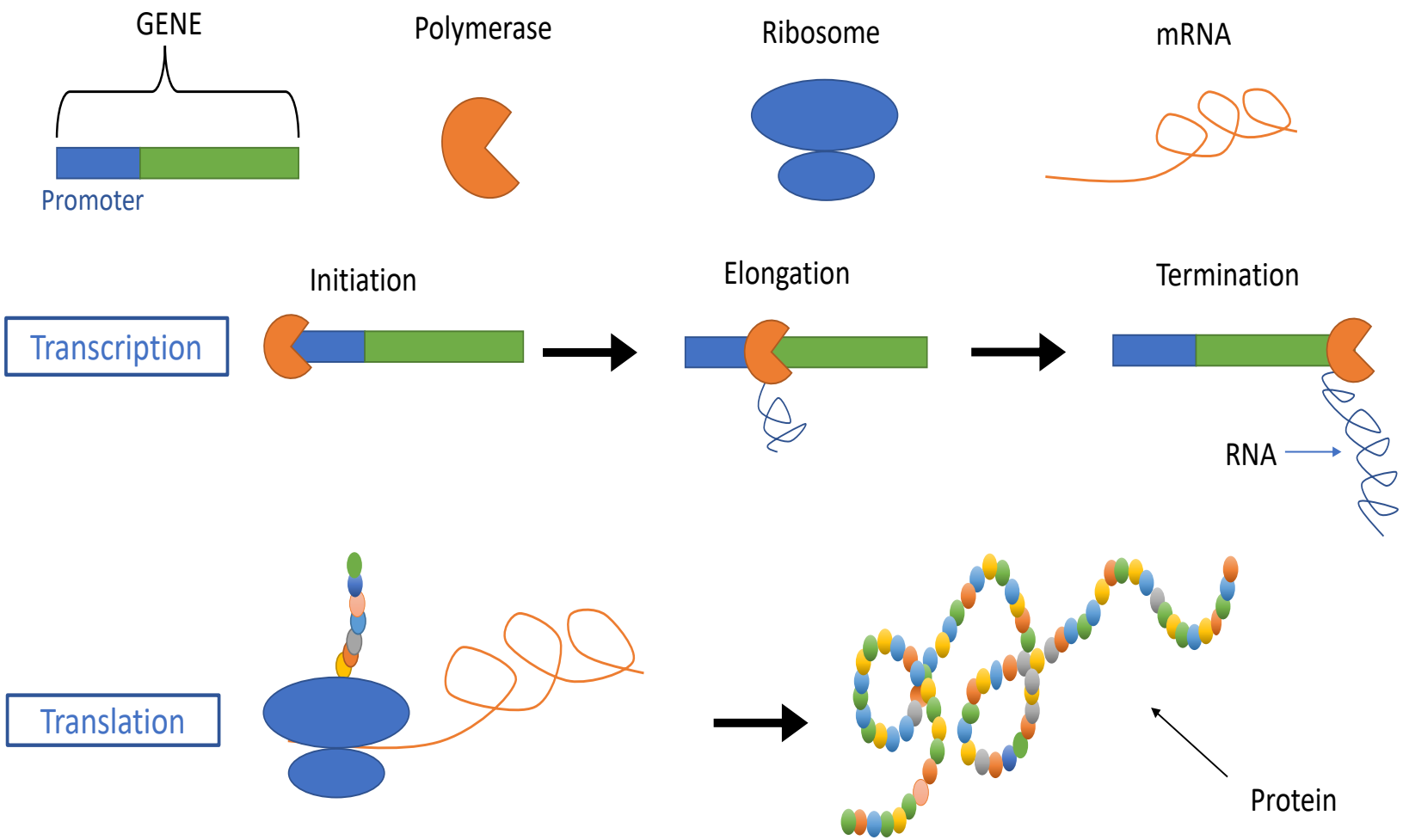

Production of Proteins: A fundamental process of "life"

- **Process consuming most of resources of the cell**

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Production of Proteins: A fundamental process of "life"

- Process consuming most of resources of the cell
- Bacterium capacities:
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  - Adaptation of proteins production to available resources
- Regulatory mechanisms are complex
- **Objective: Investigation of an important global regulatory mechanism**

Different types of RNAs:

- Messenger RNAs (mRNAs): $\simeq$ 600-900 nucleotides
  — Proteins Production
- Ribosomal RNAs (rRNAs): $\simeq$ 5000 nucleotides
  — Ribosomes Composition
- Small RNAs (sRNAs): $\simeq$ 10-200 nucleotides
  — Regulation Mechanisms
- ...

Different Regimes: Exponential Phase with large growth rate

Exponential Phase:

lot of resources in the environment

1. time division of cells $\sim$ 30mn. (E. Coli)
2. Production of a large number of ribosomes
3. Large Transcription rate of rRNAs
4. Large Translation rate of proteins

Figure: Binary fission: Prokaryotic cell division

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$\Rightarrow$ **Most of polymerases are in transcription phase**

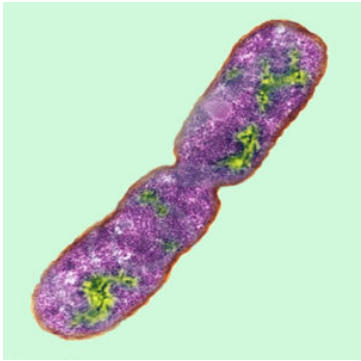


Figure: Binary fission: Prokaryotic cell division

Different Regimes: Stationary Phase

Stationary Phase: Few resources for the cell

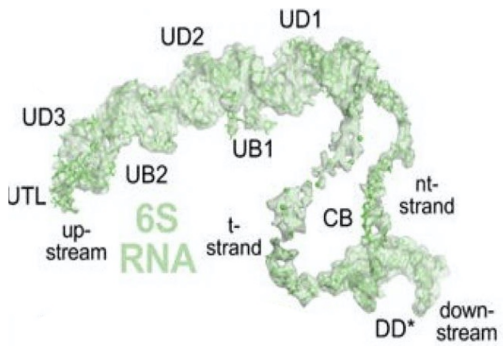
1. Small growth rate
2. No production of proteins
3. No production of rRNA
4. Large number of inactive polymerases

6S RNA: A Global Regulator of Transcription

A small RNA '6S RNA'

In stationary phase:

- Large number of 6S RNAs



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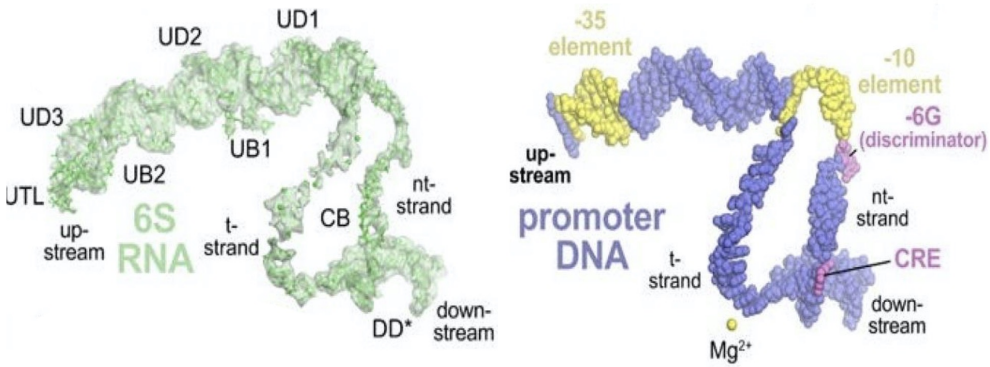
In stationary phase:

- Large number of 6S RNAs
- Similar 3D structure as a promoter of a gene



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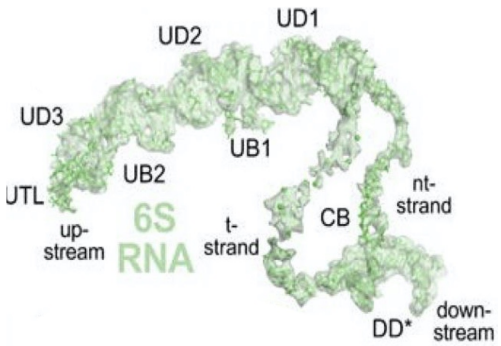
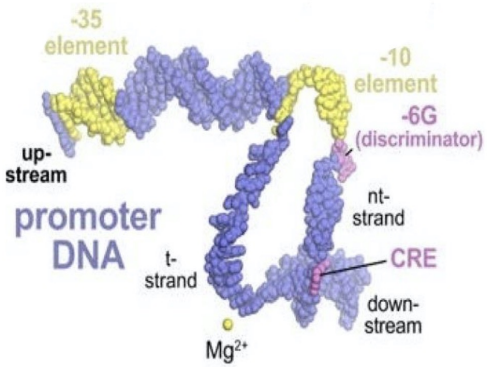
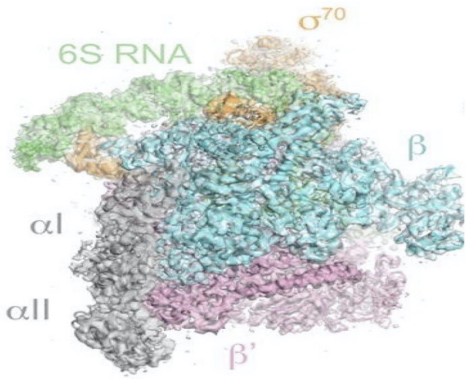




- Sequestration of free polymerases



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$\Longrightarrow$ **Large number of free polymerases**

- **Sequestration of polymerases by 6S RNAs**
- **Number of free polymerases** $\searrow$

Objectives of Mathematical Models

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1. Estimate the efficiency of the 6S RNA regulatory mechanism
2. Study the evolution of the number of free, sequestered and in transcription polymerases
3. Study the impact of sequestration on the production of mRNAs and rRNAs
4. **Describe the transition**
   from exponential phase to stationary phase and vice versa

Mathematical Models

Stochastic Assumptions:

Disorganized medium: **randomness everywhere !**

- Hitting time of two given macromolecules is a random variable
- Repeated failures of binding attempts

  Distribution of binding time is exponential
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- Repeated failures of binding attempts

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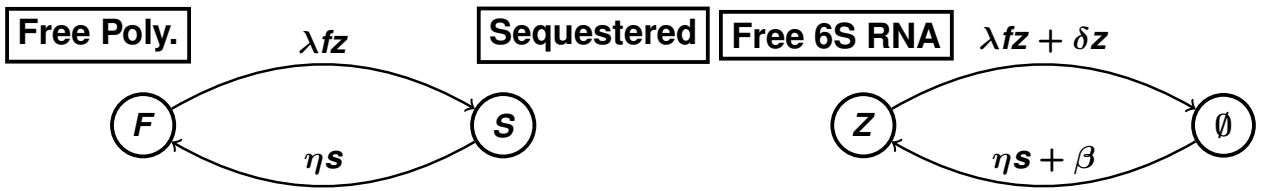
- Distribution of elongation times of RNAs is exponential
- Scaling Model: a large number of polymerases N ($N \sim 10000$)

Model with 6S RNA

Assumption:

- Total number of polymerases = N
- Sequestration rate of a polymerase by a 6SRNA: λ
- Desequestration rate: η
- Production rate of 6S RNAs: β
- Degradation rate of free 6S RNAs: δ



A First Order Theorem

Total number of polymerases $= N$

Theorem 1

$$\left(\frac{F_N(Nt)}{N}\right) \xrightarrow{\mathcal{D}} (f(t)) \qquad \text{as } N \to +\infty$$

such that $f'(t) = -\delta(\rho_0 + \rho_1) + \delta\rho_1 \frac{1}{f(t)}$ *where,*

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Maximal Sequestration rate

$$s_\infty = \frac{\rho_0}{\rho_0+\rho_1}$$

A Functional Central Limit Theorem

Fluctuations of $\left(\frac{F_N(Nt)}{N}\right)$ are of the order of $\frac{1}{\sqrt{N}}$

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Theorem 1

$$\left(\widehat{F}_N(t)\right) \overset{def}{=} \left(\sqrt{N}\left(\frac{F_N(Nt)}{N} - f(t)\right)\right)$$

$$\left(\widehat{F}_N(t)\right) \xrightarrow{\mathcal{D}} \left(\widehat{F}(t)\right) \qquad \text{as } N \to +\infty$$

$\widehat{F}(t)$, *a diffusion, solution of the SDE*

$$d\widehat{F}(t) = -\sqrt{\delta}\sqrt{\rho_0 - \rho_1 + \frac{\rho_1}{f(t)}}\,dB(t) - \frac{\delta\rho_1}{f(t)^2}\widehat{F}(t)dt,$$

with $\widehat{F}(0) = \widehat{F}_0$, *where* $(B(t))$ *is the standard Brownian motion in* $\mathbb{R}$.

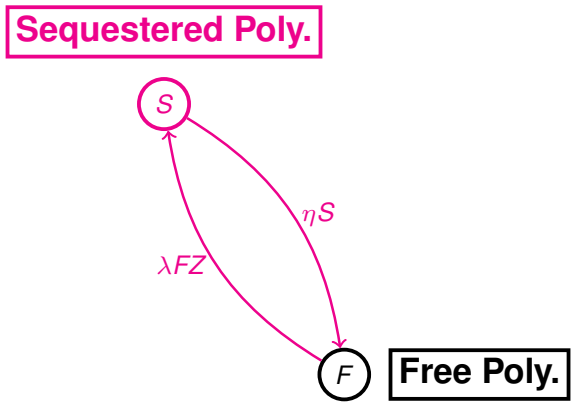
FULL MODEL OF TRANSCRIPTION

Assumptions

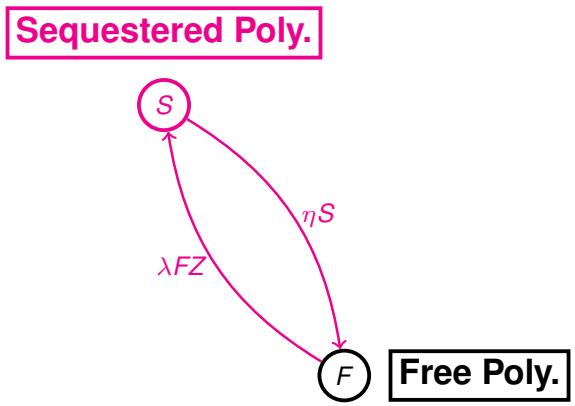
Assumptions:

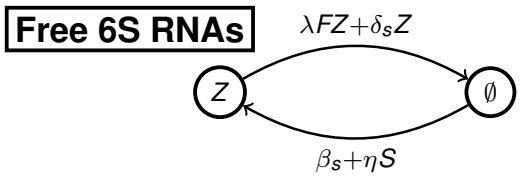
- Sequestration
- Production/Degradation of 6S RNAs
- **Transcription of J types of rRNAs**
- **Transcription of C_m^N types of mRNAs**

Sequestration

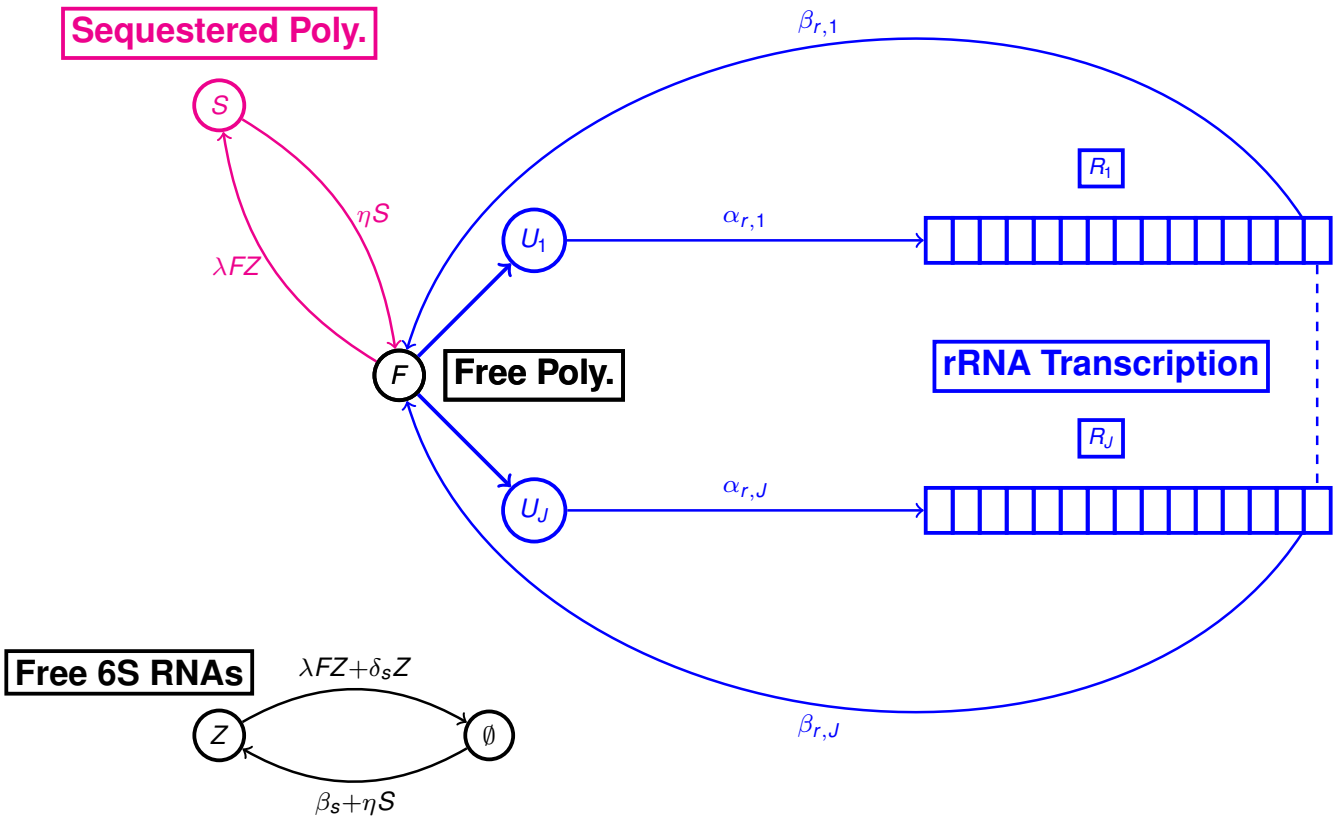


Production and Degradation of 6S RNA

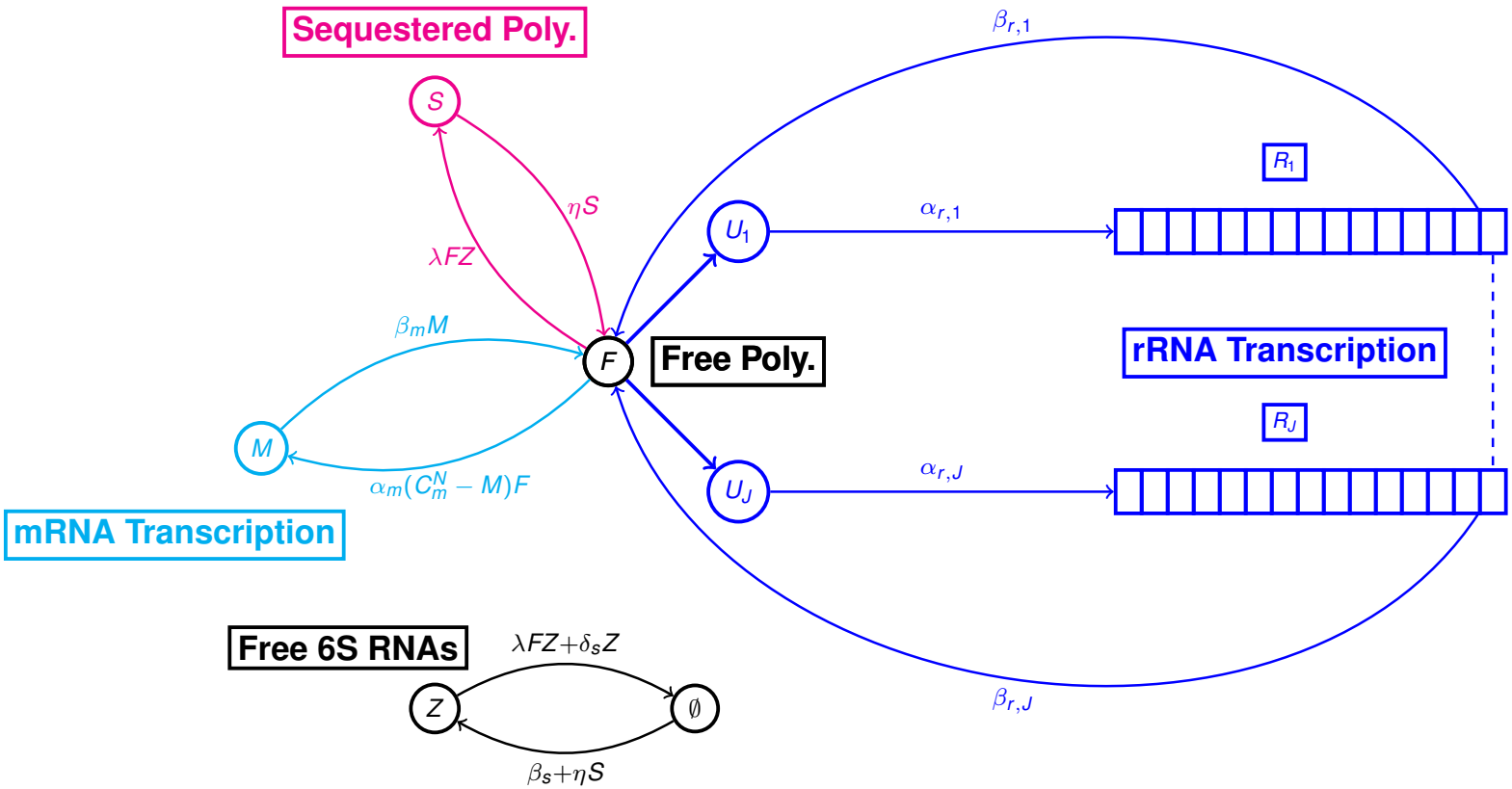




rRNA Transcription

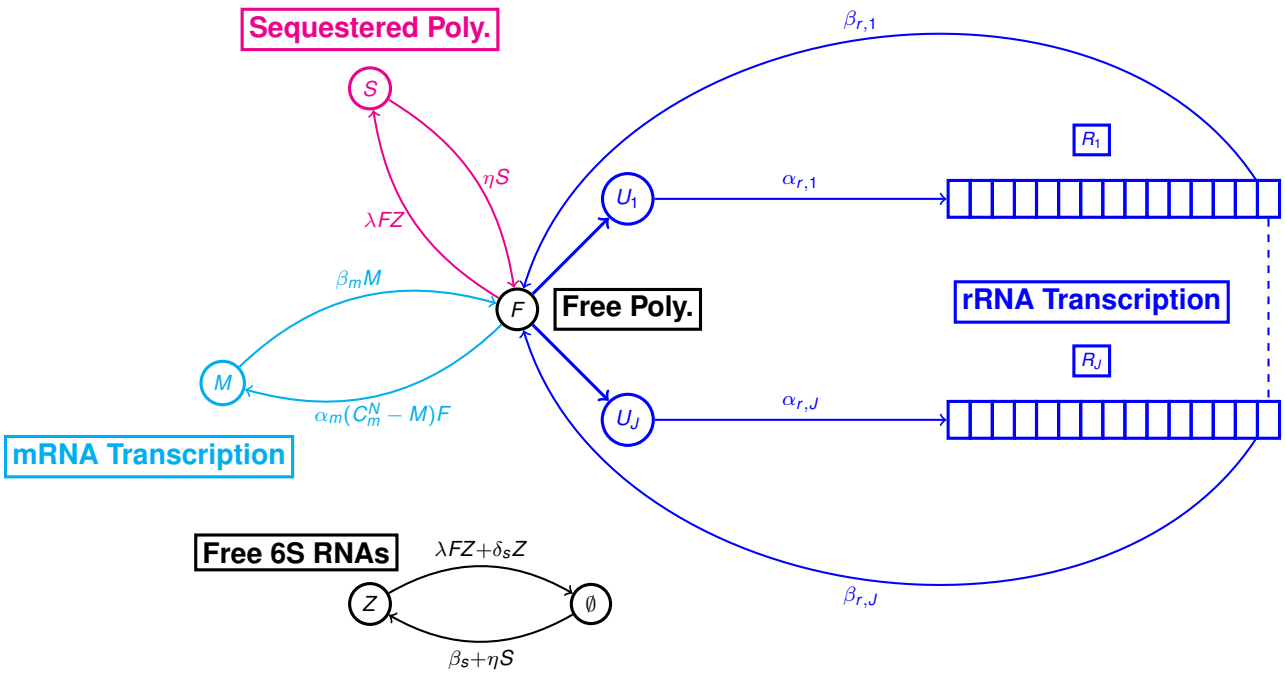


mRNA Transcription



Repartition of polymerases during the Stationary Phase

$$\alpha_{r,j} < \beta_{r,j} \quad \forall j \in \{1, \ldots, J\}$$



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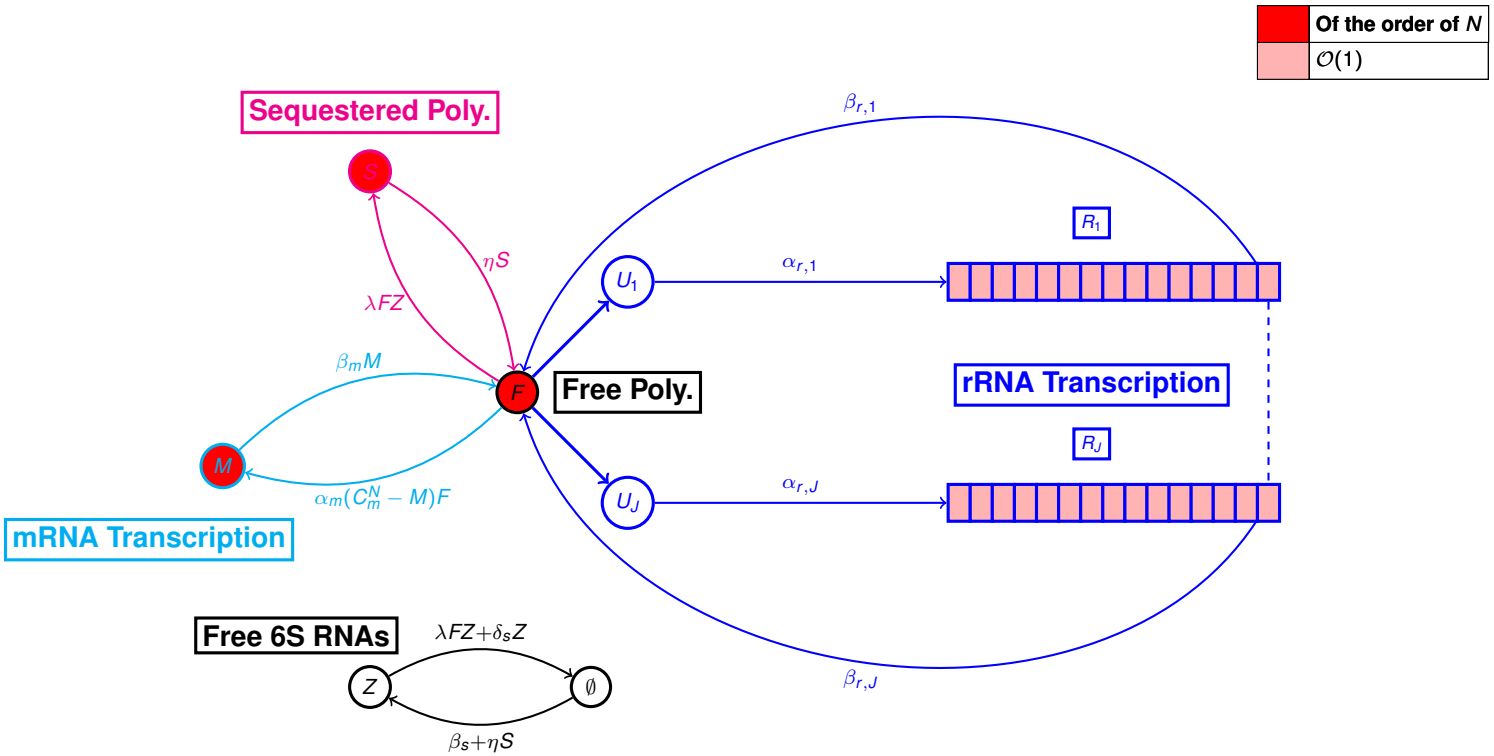

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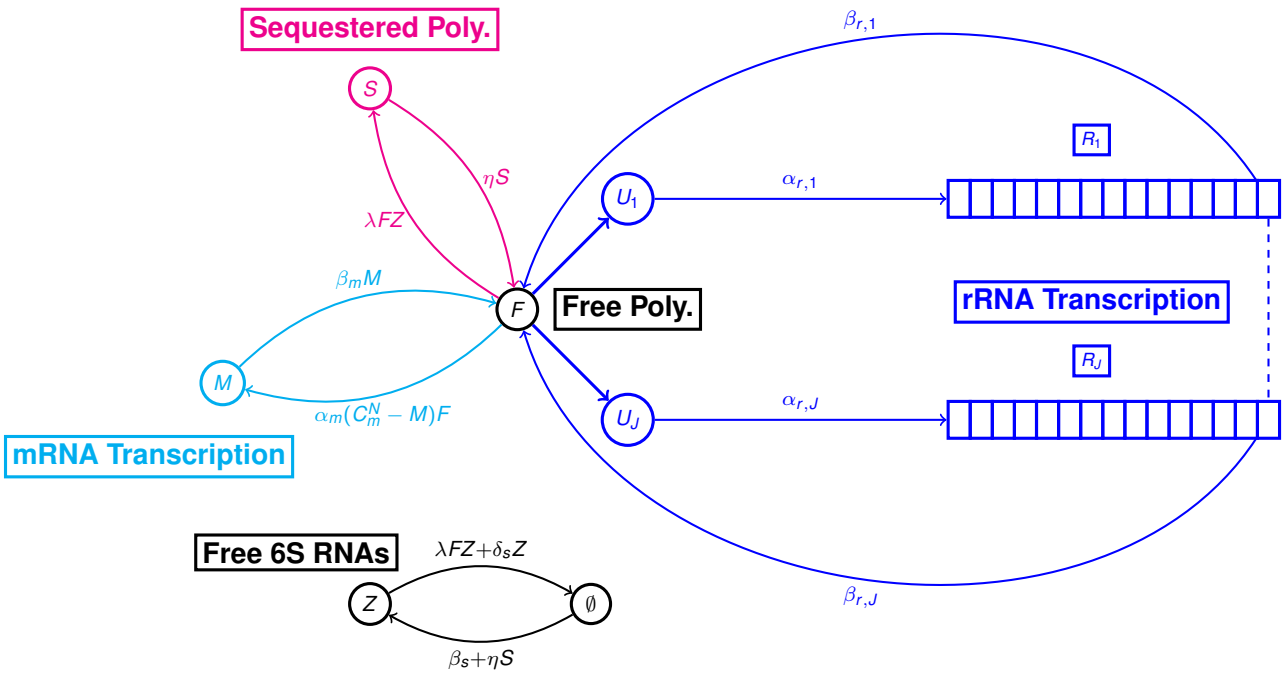

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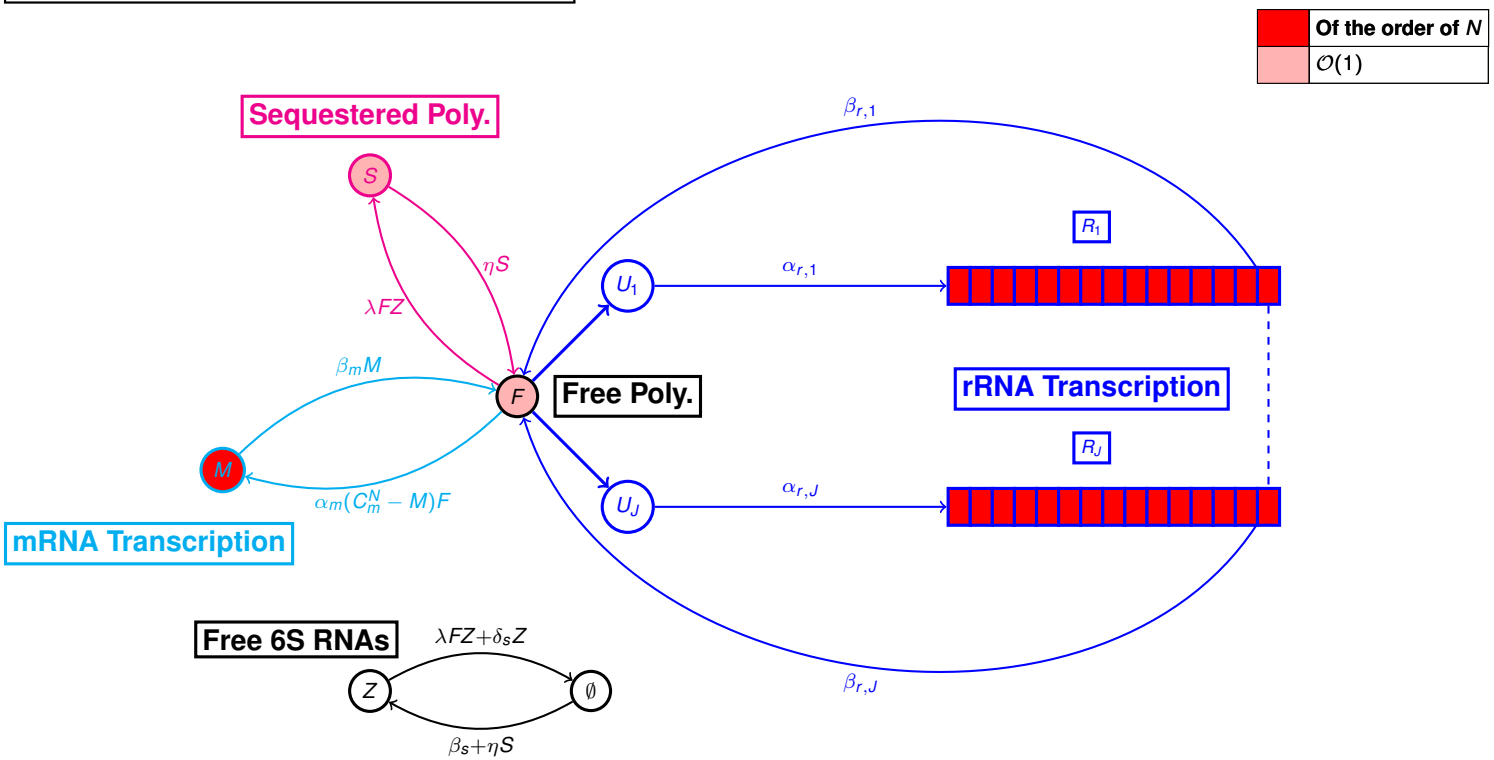

Repartition of polymerases

- **Stationary Phase:**
  - **Free, Sequestered and in mRNA Transcription polymerases : of the order of N**
  - **Polymerases in rRNA Transcription : $\mathcal{O}(1)$**
- Exponential Phase:
  - Polymerases in rRNA and mRNA Transcription : of the order of N
  - Free, Sequestered Polymerases : $\mathcal{O}(1)$

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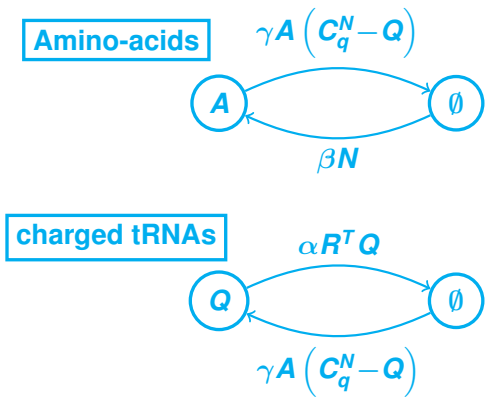
Ongoing Work: The Translation Model with Ribosomes



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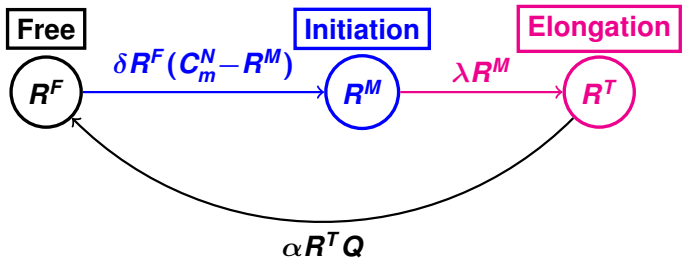

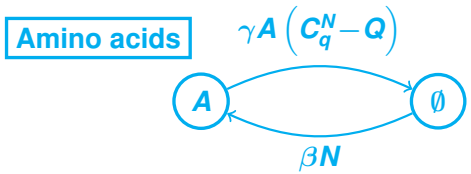

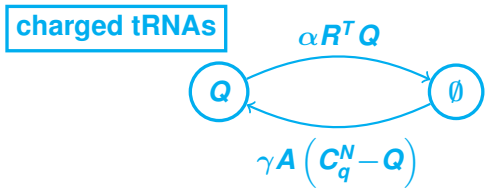

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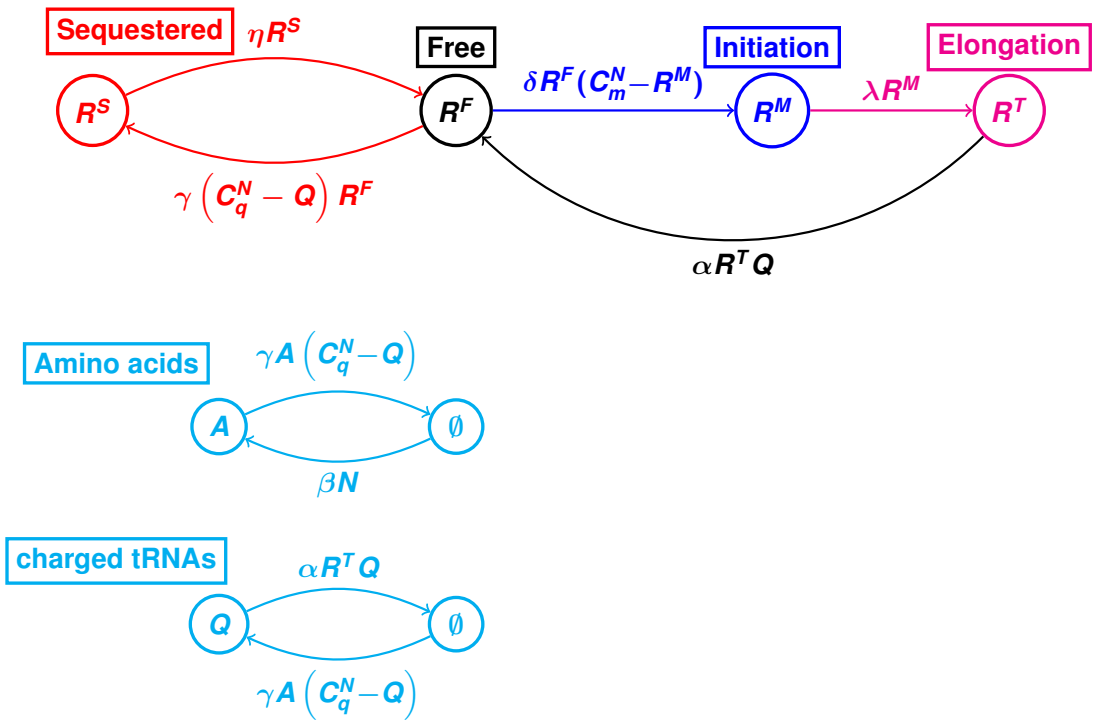

Conclusion

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- Importance of the initiation rate of transcription of rRNA in the transition from exponential to stationary phase
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- **Ongoing work: Study the Translation model with several flows of amino-acids**

Thank You!