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A coupled transcription-translation mathematical model of RNA polymerase

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Abstract— **The aim of this paper is to analyse the dynamical behaviour of models of gene transcription-translation for the synthesis of RNA polymerase in a cell, with a closed loop from the produced RNA polymerase (end-product) to the transcription step (RNA polymerase is needed to transcribe its own gene). Using monotone system theory we study a reduced version of this model with two variables (mRNA and protein), and show that it has either a single stable trivial equilibrium in $(0, 0)$, or has an unstable zero equilibrium and a stable positive one.**

I. Introduction

One of the central dogma of molecular biology is that "DNA makes RNA and RNA makes proteins", which are the primary components of cells, see [1]. Transcription is the first step of gene expression, in which a fragment of DNA (the gene) is copied into a messenger RNA (mRNA) by the RNA polymerase. The mRNA is translated into proteins by ribosomes in the second step. In prokaryotic cells like bacteria, transcription and translation take place in the same compartment. As a consequence, ribosomes can translate nascent mRNAs being elongated by the RNA polymerase.

Usually, classical models of gene expression only involve concentrations of mRNA and of protein. The RNA polymerase and ribosomes, for example, are always supposed to be in sufficient quantity, and therefore non limiting. Yet, some works emphasize the important role of the global machinery for gene expression (see [2] for an example). It is therefore interesting to build detailed models involving the main actors of the transcription-translation process, such as RNA polymerase and ribosomes. Some partial detailed models of this kind have been developed, see [3].

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In this paper, we focused on a coupled transcription-translation model for the expression of RNA polymerase, which is a small part of the gene expression machinery ([2]). This coupled model being too difficult to handle because of its high dimension, we reduce it into a much simpler system and study the mathematical properties of the reduced model. To show the stability of the reduced system, we use monotone system theory (see [4]). We think that this kind of qualitative tools for proving stability are well adapted to the study of biological models ([5]). This simpler system could be included into more general models of the gene expression machinery.

II. A coupled transcription translation model of RNA polymerase

A. Description of the model

In the following we consider the reaction scheme of the transcription model presented in [3]. For simplicity, we consider that a single gene with length l codes for the RNA polymerase. RNA polymerase P with the transcription-initiation factor σ recognizes and binds to its specific DNA binding site D in the promoter region. After binding, the polymerase clears the promoter (parameter k_c) and moves along the DNA (parameter k_t). Complexes Y and Y^i describe the moving RNA polymerase, which adds nucleotides one by one. Addition of a last nucleotide produces the full length mRNA and releases the RNA polymerase. The completed RNA molecule is subject to degradation (parameter k_m). Nucleotides and amino acids are supposed to be non limiting, as well as sigma factors, and their concentrations are included in the parameters. All variables are described by their concentrations. The scheme given in [3] is:

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$$\sigma + P + D \underset{k_+}{\overset{k_-}{\leftrightarrows}} PD \tag{II.1}$$

$$PD \xrightarrow{k_c} Y + D + \sigma \tag{II.2}$$

$$Y + Nu \xrightarrow{k_t} Y^1 \tag{II.3}$$

$$Y^1 + Nu \xrightarrow{k_t} Y^2 \tag{II.4}$$

$$\vdots \tag{II.5}$$

$$Y^{l-1} + Nu \xrightarrow{k_t} P + RNA \tag{II.6}$$

$$RNA \xrightarrow{k_m} \phi \tag{II.7}$$

$$P \xrightarrow{k_p} \phi \tag{II.8}$$

Now we describe the translation system. The process of translation can be initiated from every nascent mRNA as it is shown in ([3]). For simplicity, we suppose in this paper that proteins are synthesized from completed mRNA only; the reaction scheme is the following:

$$R + RNA' \underset{k'_+}{\overset{k'_-}{\leftrightarrows}} RRNA \tag{II.9}$$

$$RRNA \xrightarrow{k_w} X + RNA' \tag{II.10}$$

$$X + tRNA^* \xrightarrow{k'_t} tRNA + X^1 \tag{II.11}$$

$$X^1 + tRNA^* \xrightarrow{k'_t} tRNA + X^2 \tag{II.12}$$

$$\vdots \tag{II.13}$$

$$X^{h-1} + tRNA^* \xrightarrow{k'_t} R + P \tag{II.14}$$

$$P \xrightarrow{k_p} \phi \tag{II.15}$$

where R is the free ribosome. RNA' represents a free ribosomal binding site on a $mRNA$ with length h. RRNA represents the ribosome bound to its binding site. X and X^j describe the moving ribosome on the completed RNA: a tRNA carrying an amino-acid ($tRNA^*$), the building block of proteins, enters into the ribosome. The amino-acid is transferred to the growing protein. Addition of a last amino-acid completes the RNA polymerase P. This releases both the protein and the ribosome. In addition, the RNA polymerase is subject to degradation (parameter k_p).

B. Full equations

Following the usual mass action kinetics laws, we obtain:

$$\begin{aligned}
\dot{c} &= k_+ p\,(d_0 - c) - k_-\, c - k_c\, c \\
\dot{p} &= -k_+ p\,(d_0 - c) + k_t\, y^{l-1} + k_-\, c + \mathbf{k_t'\, x^{h-1}} - \mathbf{k_p\, p} \\
\dot{y} &= k_c\, c - k_t\, y \\
\dot{y}^1 &= k_t\, y - k_t\, y^1 \\
\dot{y}^2 &= k_t\, y^1 - k_t\, y^2 \\
&\vdots \\
\dot{y}^{l-1} &= k_t\, y^{l-2} - k_t\, y^{l-1} \\
\dot{w} &= k'_+\, r\, m - k'_-\, w - k_w\, w \\
\dot{m} &= -k'_+\, r\, m + k'_-\, w + k_w\, w + k_t\, y^{l-1} - k_m\, m \\
\dot{r} &= -k'_+\, r\, m + k'_-\, w + k'_t\, x^{h-1} \\
\dot{x} &= k_w\, w - k'_t\, x \\
\dot{x}^1 &= k'_t\, x - k'_t\, x^1 \\
&\vdots \\
\dot{x}^{h-1} &= k'_t\, x^{h-2} - k'_t\, x^{h-1}
\end{aligned} \tag{II.16}$$

where p, d, c, y, y^i and m are the concentrations of P, D, PD, Y, Y^i and $mRNA$ respectively, and where w, r , x and x^i are the concentration of RRNA, R, X and X^i respectively.

The loop of the RNA polymerase is indicated by the bold terms.The total number of ribosomes is conserved

$$r + w + x + x^1 + \cdots + x^{h-1} = R_0 \tag{II.17}$$

III. Time-scale reduction (Fast-Slow Behavior)

The value of parameters are given in Table I.

TABLE I – The value of the set of parameters

Parameter	values	**Unit**
k_+	60	μM$^{-1}min^{-1}$
k_-	40	min^{-1}
k_c	15	min^{-1}
k_t	2340	nucleotides.min^{-1}
k_m	0.17	min^{-1}
$Gene\ length$	8253	base pairs
d_0	0.0078	μM
z_0	6	μM
k'_+	11	μM$^{-1}min^{-1}$
k'_-	100	min^{-1}
k_w	80	min^{-1}
k'_t	960	amino acid.min^{-1}
$Protein\ length$	2749	amino acids
R_0	20.5	μM
k_p	0.012	min^{-1}

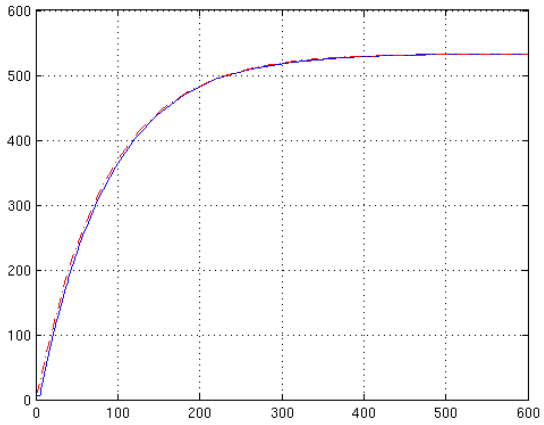

Fig. III.1 – The dashed line represents the behaviour of variable z in the reduced system (with $l = 100$, h=33) while the full line shows the evolution of variable z in the complete system. Units are min^{-1} for x-axis and μM for y-axis.

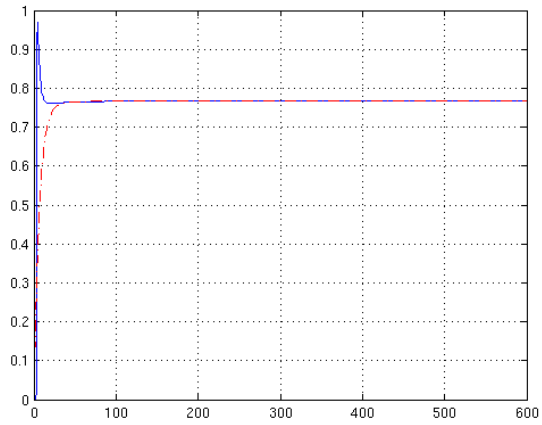

Fig. III.2 – The dashed line represents the behaviour of variable q in the reduced system, the full line shows the evolution of variable q in the complete system, (with $l = 100$, h=33). Units are min^{-1} for x-axis and μM for y-axis.

We have chosen reasonable values for parameters [1]. With these values, the full system can be rather well approximated by a reduced system, using the fact that some variables are faster than others. The slow variables are the classical ones, i.e. the total number of RNA polymerase z and mRNA q.

$$z = c + p + y + y^1 + \ldots + y^{l-1} \tag{III.1}$$

$$q = m + w \tag{III.2}$$

A. The Reduced System

We denote $K_1 = \frac{k_- + k_c}{k_+}, K_2 = \frac{k'_- + k_w}{k'_+}$.
Applying Quasi Steady State Approximation to fast variables and keeping only the slow ones, we write the reduced system:

$$z = l\,\frac{k_c}{k_t}\,d_0\,\frac{p}{p+K_1} + p + d_0\,\frac{p}{p+K_1} \tag{III.3}$$

$$R_0 = h\frac{k_w}{k'_t}\frac{q\,r}{r+K_2} + r + \frac{q\,r}{r+K_2} \tag{III.4}$$

$$\dot{z} = k_w\frac{q\,r(q)}{r(q)+K_2} - k_p\,p(z) \tag{III.5}$$

$$\dot{q} = k_c d_0\,\frac{p(z)}{p(z)+K_1} - k_m\left(q - \frac{q\,r(q)}{r(q)+K_2}\right) \tag{III.6}$$

[1]These values of parameters have been carefully built from the literature based on classical papers such as ([6]).

in this system $p(z)$ and $r(q)$ are given by the two algebraic equations. We prove that they only have one positive solution.

B. Simulations

The behaviour of the full and reduced systems are rather similar after some time, as seen on Figures III.1, III.2. Of course, the reduction depends on the parameters values and will be subject to further investigations to improve the model predictions.

IV. Dynamical study of the Reduced System

A mathematical study of this system gives the following results: the system is monotone [4], with one positive loop, and the solutions are bounded. It has either a single stable equilibrium in $(0, 0)$ or two equilibria, one in zero (unstable) and another stable one (z^*, q^*). The stability or instability of the zero equilibrium depends on the values of the parameters, as shown by computing the eigenvalues of the Jacobian matrix. The global behaviour result is given by monotone systems theory. For the sake of brevity the mathematical details cannot be given here.

V. Conclusion

Many interesting conclusions can be given from the study of this system. For example, computations leads to the fact that, if R_0 is large (many ribosomes), the zero equilibrium is unstable; if R_0 is small, the zero equilibrium is globally stable, and everything goes to zero.

These results are in agreement with several biological observations on the adaptation of living organisms to their environment. For instance, in the case of bacteria, the zero equilibrium corresponds to the situation of cells whose growth is arrested by a deprivation of nutrients in their environment. Translation is halted in these cells, through an arrest of ribosome synthesis and the inactivation of the remaining ribosomes [7], [8]. As a consequence, the intracellular concentration of active ribosomes decreases, which lowers the concentration of RNA polymerase. The essential cell components can no longer be synthesized; cells eventually die if the ribosomes and the RNA polymerase remain at so low concentrations. By contrast, when nutrients are added back to the environment, ribosome synthesis starts immediately and inactivated ribosomes become functional again [7], [8]. The concentration of ribosomes rises in the cell. According to the model, the zero equilibrium becomes unstable in these conditions. The consequence is a rapid accumulation of new pools of RNA polymerase and ribosomes, that are necessary for the cell to synthesize all the precursors needed to grow and divide again. Note that this very simple loop is not isolated from the rest of the cell. The transcription and translation processes are embedded with other regulatory mechanisms, for instance, the competition between different sigma factors for transcriptional initiation in changing environmental conditions. Our simple loop model could be easily extended so as to include these regulatory mechanisms.

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