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Analysis and reduction of transcription translation coupled models for gene expression ⋆

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Abstract: The aim of this paper is to analyze and to reduce coupled transcription-translation models developed in (Kremling (2007)), which are a detailed representation of the process describing how the information in DNA turns into proteins in a cell, with polymerase and ribosomes. The full model is of high dimensions, and may be complex to deal with. Under assumptions on the parameters, we can write the full system in the form of a slow fast system. The fast part is a monotone system and we prove its global stability. We put this fast part to its quasi steady state, and show that it is possible to obtain a small reduced model (with three variables) having essentially the same dynamical behavior.

Keywords: Biological systems; Transcription model; Translation model; Gene expression; Nonlinear systems; Stability; Time-scale reduction

1. 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. The first phase of the process is called transcription from DNA to mRNA and is a copy of the information of the gene on the DNA strand into mRNA (messenger RNA), where the polymerase has a key role. The second phase of the process is the translation from RNA to linear amino acid sequences, and folding of these amino acids into functional proteins, via the ribosomal units, see Alon (2007).

Usually, classical models of gene expression only involve concentrations of mRNA and of protein. The 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 (Berthoumieux et al. (2013)), and it is therefore interesting to build detailed models involving the main actors of the transcription translation process, such as polymerase and ribosomes. Some very detailed models of this kind have been developed, see Kremling (2007).

In this paper, in a first step we investigate the dynamical behaviour of the model of gene transcription and the model of translation developed in Kremling (2007). Then we focused on the coupled transcription-translation model which is a part of gene expression machinery (Berthoumieux et al. (2013)). This coupled model can be difficult to handle, therefore in a last step we try to reduce this system into a much simpler system. This simpler system could be included into more general model of gene expression machinery.

We present an approach based on time-scale reduction (quasi-steady-state approximation). This classical approach is already applied to complex dynamics of enzyme-substrate or to models integrating both metabolic and gene regulation. For a discussion of quasi-steady state approximation in biology, see Heinrich and Schuster (1996). We apply this approximation based on time-scale separation and have to check if some conditions on the fast system are satisfied, such as uniqueness of the steady state and its global stability: these conditions are given by the Tikhonov theorem (for a complete description see Khalil (2002)). To show global stability of fast subsystems, we use monotone system theory and compartmental systems theory (see Smith (1995); Jacquez and Simon (1993)). We think that this kind of qualitative tools for proving stability are well adapted to these biological models studies (Sontag (2004)).

The organization of the paper is the following: firstly we study "closed" transcription (section 2) and translation (section 3) models, such as given by Kremling (2007), and show their global stability. Then we combine these two models with some inputs and outputs (section 4); we study some stability properties, then we suppose (based on biological hypotheses) that some parameters are far larger than others; we remark that the fast part of the system is precisely the "closed" models above. We apply reduction theorem, and we numerically compare the two models. Finally we draw some mathematical and biological conclusions.

2. THE CLOSED TRANSCRIPTION MODEL

2.1 Description of the model

In the following we consider the reaction scheme of the transcription model presented in Kremling (2007). A single gene with length l is considered. RNA polymerase P with σ factor binds to the specific DNA binding site D. 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 polymerase which binds to nucleotides along the strand. The completed RNA molecule is subject to degradation (parameter k_m). Nucleotides are supposed to be in excess, and their concentrations are included in the parameters. All vari-

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ables are described by their concentrations. The scheme given in Kremling (2007) is:

$$\begin{aligned} P + D &\underset{k_+}{\overset{k_-}{\leftrightarrows}} PD \\ PD &\xrightarrow{k_c} Y + D + \sigma \\ Y + Nu &\xrightarrow{k_t} Y^1 \\ Y^1 + Nu &\xrightarrow{k_t} Y^2 \\ &\vdots \\ Y^{l-1} + Nu &\xrightarrow{k_t} P + RNA \xrightarrow{k_m} \text{degradation} \end{aligned} \tag{1}$$

We can derive the following system from the reaction scheme (following classical mass-actions kinetics):

$$\begin{aligned} \dot{c} &= k_+ p\, d - k_- c - k_c c \\ \dot{d} &= -k_+ p\, d + k_- c + k_c c \\ \dot{p} &= -k_+ p\, d + k_t y^{l-1} + k_- c \\ \dot{y} &= k_c c - k_t y \\ \dot{y}^1 &= k_t y - k_t y^1 \\ &\vdots \\ \dot{y}^{l-1} &= k_t y^{l-2} - k_t y^{l-1} \\ \dot{m} &= k_t y^{l-1} - k_m m \end{aligned} \tag{2}$$

where p, d, c, y , y^i and m are the concentrations of P, D, PD, Y, Y^i and RNA respectively. The length l of the gene is rather large (until several thousands). Note that the system has to fulfill two mass conservations (because it is closed), describing the total concentration of promoter site d_0 and the total concentration of polymerase M_0:

$$d + c = d_0 \tag{3}$$

$$c + p + y + y^1 + \ldots + y^{l-1} = M_0 \tag{4}$$

Taking into account (3) we can reduce the original system to

$$\begin{aligned} \dot{c} &= k_+ p\,(d_0 - c) - k_- c - k_c c \\ \dot{p} &= -k_+ p\,(d_0 - c) + k_t y^{l-1} + k_- c \\ \dot{y} &= k_c c - k_t y \\ \dot{y}^1 &= k_t y - k_t y^1 \\ \dot{y}^2 &= k_t y^1 - k_t y^2 \\ &\vdots \\ \dot{y}^{l-1} &= k_t y^{l-2} - k_t y^{l-1} \\ \dot{m} &= k_t y^{l-1} - k_m m \end{aligned} \tag{5}$$

2.2 Equilibrium

We obtain the following equations for the steady state:

$$y^{l-1} = \ldots = y^1 = y = \frac{k_c}{k_t} c \tag{6}$$

$$c = \frac{k_+ p\, d_0}{k_+ p + k_- + k_c} \tag{7}$$

$$m = \frac{k_t}{k_m} y^{l-1} \tag{8}$$

We rewrite (7) as

$$c = d_0 \frac{p}{p + K_1} \tag{9}$$

$$K_1 = \frac{k_- + k_c}{k_+} \tag{10}$$

Replacing (9) and (6) in (4) we obtain:

$$l \frac{k_c}{k_t} d_0 \frac{p}{p + K_1} + p + d_0 \frac{p}{p + K_1} = M_0 \tag{11}$$

The left side of (11) is an increasing function of p, which is zero for p equals to zero, and tends to infinity when p tends to infinity; therefore we can deduce that (11) has a unique solution which depends on M_0 and d_0. We define the hyperplane $H_0 = \left\{(c, p, y, y^1, \ldots, y^{l-1}) \in \Re^{l+2} : c + p + y + y^1 + \ldots + y^{l-1} = M_0\right\}$. Therefore system (5) has a unique steady state for each hyperplane H_0. The whole steady state can be obtained after solving (11) for p. We check that the constraint ($c < d_0$) is verified by (9).

2.3 Global stability of the equilibrium

In the following we are going to study the stability of this equilibrium on the invariant hyperplane. We summarize the results of Belgacem and Gouzé (2013). Last variable m has no influence on the other variables of the system, and moreover its equation is linear

$$\dot{m} = k_t y^{l-1} - k_m m \tag{12}$$

Therefore it is easy to show with classical arguments that, if the system with $(c, p, y, \ldots, y^{l-1})$ is globally asymptotically stable (w.r.t. the invariant hyperplane), then the full system (with m) will be such.Therefore we can deal with a reduced system with only $(c, p, y, \ldots, y^{l-1})$.

Notice that this system with $(c, p, y, \ldots, y^{l-1})$: is closed, in the sense that $\dot{c} + \dot{p} + \dot{y} + \dot{y}_1 + \ldots\ldots + \dot{y}_{l-1} = 0$.

It is easy to check that the Jacobian matrix $J(c, p, y, y^1, \ldots, y^{l-1})$ of this system is a compartmental matrix (see Appendix for the definition). To show that, we use the positivity of the variables (included the fact that $(d_0 - c) \geq 0$). Of course we have checked that the nonnegative orthant is positively invariant.

It can also be checked that the graph of the Jacobian matrix is strongly connected, so we can apply Theorem 1 in the appendix to obtain:

Proposition 1. Let $M(c, p, y, y^1, \ldots, y^{l-1}) = c + p + y + y_1 + \ldots + y_{l-1}$ be the (fixed) total polymerase concentration of the closed system. For any $M_0 > 0$, the hyperplane H_0 is forward invariant and the system contains a unique globally stable equilibrium in H_0.

We end our analysis of the complete system (5) by concluding that it is globally stable (with the additional variable m) with respect to the invariant hyperplane H_0.

3. THE CLOSED TRANSLATION MODEL

Now we describe the translation system, using ribosomes to make proteins from mRNA. The process of translation could be initiated from every nascent mRNA as it is shown in (Kremling (2007)); to simplify, in this paper we suppose that the proteins are synthesized from completed mRNA only, with length h; the reaction scheme is the following :

$$\begin{aligned}
R \;+\; RNA' &\overset{k'_-}{\underset{k'_+}{\leftrightarrows}} RRNA \\
RRNA &\overset{k_w}{\to} X \;+\; RNA' \\
X \;+\; tRNA^* &\overset{k'_t}{\to} tRNA \;+\; X^1 \\
X^1 \;+\; tRNA^* &\overset{k'_t}{\to} tRNA \;+\; X^2 \\
&\vdots \\
X^{h-1} \;+\; tRNA^* &\overset{k'_t}{\to} R \;+\; S \overset{k_s}{\to} \text{degradation}
\end{aligned} \tag{13}$$

where RNA$'$ represents a molecule of *mRNA* with length h and with a free ribosome binding site. RRNA represents the ribosome bound to its binding site. X and X^j describe the moving ribosome on the completed *RNA*. R is the free ribosome. S is the protein which is being translated. The system of ODEs associated to the model is:

$$\begin{aligned}
\dot{w} &= k'_+ r m - k'_- w - k_w w \\
\dot{m} &= -k'_+ r m + k'_- w + k_w w \\
\dot{r} &= -k'_+ r m + k'_- w + k'_t x^{h-1} \\
\dot{x} &= k_w w - k'_t x \\
\dot{x}^1 &= k'_t x - k'_t x^1 \\
&\vdots \\
\dot{x}_{h-1} &= k'_t x^{h-2} - k'_t x^{h-1} \\
\dot{s} &= k'_t x^{h-1} - k_s s
\end{aligned} \tag{14}$$

where w, m, r, s, x and x^i are the concentration of RRNA, RNA$'$, R, S, X and X^i respectively. Notice as previously that we have the following equations for the conservation of total amount of mRNA (q_0) and ribosomes (R_0)

$$\begin{aligned}
w + m &= q_0 \\
r + w + x + x^1 + \cdots + x^{h-1} &= R_0
\end{aligned} \tag{15}$$

the reduced system becomes:

$$\begin{aligned}
\dot{w} &= k'_+ r (q_0 - w) - k'_- w - k_w w \\
\dot{r} &= -k'_+ r (q_0 - w) + k'_- w + k'_t x^{h-1} \\
\dot{x} &= k_w w - k'_t x \\
\dot{x}^1 &= k'_t x - k'_t x^1 \\
&\vdots \\
\dot{x}_{h-1} &= k'_t x^{h-2} - k'_t x^{h-1} \\
\dot{s} &= k'_t x^{h-1} - k_s s
\end{aligned} \tag{16}$$

This translation system is quite similar to the system of the transcription system in section 1. The study of the equilibrium and the stability is exactly the same as before, so for the sake of brevity the study will not be given here. We define the hyperplane
$G_0 = \{(w, r, x, x^1, \ldots x^{l-1}) \in \Re^{h+2} : w + r + x + x^1 + \ldots + x^{h-1} = R_0\}$. The final result is that this system (16) has a unique equilibrium on invariant hyperplane G_0 which is globally asymptotically stable on G_0.

4. A COUPLED TRANSCRIPTION-TRANSLATION MODEL

The aim of this section is to analyze a transcription-translation model, which couples the two models above.

4.1 Equations of the model

We can couple both transcription and translation processes, to obtain the following full system (17). The polymerase is made by the cellular global machinery, and also degraded, see Alon (2007). Then for the coupled system we are going to suppose that the free polymerase has a synthesis input term k and a degradation term k_p; these terms are meant to represent the input and output for polymerase, coming from other subsystems of the cell; later, they will be suppose to be small (slow) with respect to the other terms.

$$\begin{aligned}
\dot{c} &= k_+ p (d_0 - c) - k_- c - k_c c \\
\dot{p} &= -k_+ p (d_0 - c) + k_t y^{l-1} + k_- c + \mathbf{k} - \mathbf{k_p p} \\
\dot{y} &= k_c c - k_t y \\
\dot{y}^1 &= k_t y - k_t y^1 \\
\dot{y}^2 &= k_t y^1 - k_t y^2 \\
&\vdots \\
\dot{y}^{l-1} &= k_t y^{l-2} - k_t y^{l-1} \\
\dot{w} &= k'_+ r m - k'_- w - k_w w \\
\dot{m} &= -k'_+ r m + k'_- w + k_w w + k_t y^{l-1} - k_m m \\
\dot{r} &= -k'_+ r m + k'_- w + k'_t x^{h-1} \\
\dot{x} &= k_w w - k'_t x \\
\dot{x}^1 &= k'_t x - k'_t x^1 \\
&\vdots \\
\dot{x}^{h-1} &= k'_t x^{h-2} - k'_t x^{h-1} \\
\dot{s} &= k'_t x^{h-1} - k_s s
\end{aligned} \tag{17}$$

4.2 Stability of the coupled model

We briefly describe the stability properties of the whole model. Because the lack of space, our arguments will be concise.

The model is hierarchically built: the first transcription model is an input to the second translation model, that can be seen by the term $k_t y^{l-1}$ in $\dot{m}$. The first model could be studied by monotone systems technics, as was done in Belgacem and Gouzé (2013), to show its global stability. Unfortunately, the whole system (17) is not monotone anymore, and the same technics cannot be applied.

We can use the global stability property of the first transcription model, and the globally stable equilibrium of this model is used as an input for the second step of the whole model. This kind of argument can be rigorously justified from a mathematical point of view with theorems concerning the stability of hierarchical systems (see Vidyasagar (1993)). In particular, it is valid when all the variables are bounded, which is the case here, as it can be easily checked.

Now if we use the equilibrium $y^{l-1,*}$ to input it in the second model, and introduce the variable $q = m + w$, we obtain

$$\dot{q} = \dot{m} + \dot{w} = k_t y^{l-1,*} - k_m m \tag{18}$$

Unfortunately, this model is not monotone anymore, as the translation model alone (with q constant) is, and we were not able to obtain global stability results for this model. Yet we are more interested in the reduction of the model (17), and, as we see in the next section, if q is a slow variable, it is constant at the fast scale, and we can apply stability results of section 3.

4.3 Time-scale reduction (Fast-Slow Behavior) of the coupled transcription-translation model

Our main interest in this paper is the reduction of the above model (17). We consider the set of parameters listed in Table 1 and 2. This set of parameters for the transcription and the translation process of bulk proteins in table (1) and (2) have been carefully built from the literature by D. Ropers et al, based on classical papers such as Bremer et al. (2003). [1] . The

Table 1. The value of the set of parameters considered for the gene transcription (bulk mRNA) model.

Parameter	values	**Unit**
k_+	1000	$\mu\text{M}^{-1}min^{-1}$
k_-	700	min^{-1}
k_c	1.5	min^{-1}
k_t	245.4	min^{-1}
k_m	0.08	min^{-1}
Gene length l	1000	base pairs
d_0	7.96	μM
p_0	4.5	μM

polymerase is synthesized at a very slow rate (by other genes), and degraded also very slowly. We chose these biologically reasonable constants :

$$k = 0.05\,\mu\text{M}\,\text{min}^{-1},\ k_p = 0.07\,\text{min}^{-1} \tag{19}$$

The ratio $\frac{l}{k_t}$, and $\frac{h}{k_t^{'}}$ is constant see (Kremling (2007)), so if we

Table 2. Parameters for the translation model of bulk protein.

Parameter	values	**Unit**
$k_+^{'}$	1000	$\mu\text{M}^{-1}min^{-1}$
$k_-^{'}$	12380	min^{-1}
k_w	71.63	min^{-1}
$k_t^{'}$	0.96	min^{-1}
k_s	0.006	min^{-1}
mRNA length h	333	base pairs
r_0	20.5	μM

take another gene length l or h, the value of k_t or $k_t^{'}$ will change. For easier simulations we will take $l = 100$ and $h = 30$.

For this set of parameters we can notice that there are two different time scales, so under the assumptions of time scales separation, it is possible to reduce the full model. The main idea is to separate the system into "fast" and "slow" variables, and assume that the fast variables reach a "quasi steady state"; this is valid only if the fast part is globally stable toward his steady state (Tikhonov et al. (1980)).

To write the system with fast and slow variables, we will introduce two new variables z and q which have no real physiological justification but represent the total polymerase and the total mRNA, which were constant in the closed systems before, and are now slowly varying .

$$z = c + p + y + y^1 + \ldots + y^{l-1} \tag{20}$$

z represent the total concentration of polymerase whose slow dynamics is :

$$\dot{z} = k - k_p\, p \tag{21}$$

and

$$q = m + w \tag{22}$$

which implies

$$\dot{q} = \dot{m} + \dot{w} = k_t\, y^{l-1} - k_m\, m \tag{23}$$

where q is the total concentration of mRNA. This equation will also be slow with our choice of parameters.

Replacing variable m by $(q-w)$, and introducing also the variable z the system (17) becomes :

$$\begin{aligned}
\dot{c} &= k_+\, p\,(d_0 - c) - k_-\, c - k_c\, c \\
\dot{p} &= -k_+\, p\,(d_0 - c) + k_t\, y^{l-1} + k_-\, c + k - k_p\, p \\
\dot{y} &= k_c\, c - k_t\, y \\
\dot{y}^1 &= k_t\, y - k_t\, y^1 \\
\dot{y}^2 &= k_t\, y^1 - k_t\, y^2 \\
&\vdots \\
\dot{y}^{l-1} &= k_t\, y^{l-2} - k_t\, y^{l-1} \\
\dot{z} &= k - k_p\, p \\
\dot{w} &= k_+^{'}\, r\,(q-w) - k_-^{'}\, w - k_w\, w \\
\dot{r} &= -k_+^{'}\, r\,(q-w) + k_-^{'}\, w + k_t^{'}\, x^{h-1} \\
\dot{x} &= k_w\, w - k_t^{'}\, x \\
\dot{x}^1 &= k_t^{'}\, x - k_t^{'}\, x^1 \\
&\vdots \\
\dot{x}^{h-1} &= k_t^{'}\, x^{h-2} - k_t^{'}\, x^{h-1} \\
\dot{q} &= k_t\, y^{l-1} - k_m\,(q-w) \\
\dot{s} &= k_t^{'}\, x^{h-1} - k_s\, s
\end{aligned} \tag{24}$$

To obtain the dynamics of the fast part we should notice that the system has a hierarchical structure. The fast system formed with variables c, p, y, y^1, …, y^{l-1} is at the top of the structure and the fast system formed with variables w, r, x, x^1, …, x^{h-1} is at the bottom. The slow variables are z, q, s (these slow variables more clearly appear after some rescaling of the x and y variables; due to the lack of space, we cannot not explain this thoroughly). We also remark that Tikhonov theorem is a limit theorem obtained when some parameter ε goes to zero, but in practice it is used for fixed small values of ε (quasi-steady state approximation).

Then we are going to compute the equilibrium of this top level subsystem

$$y^{l-1} = \ldots = y^1 = y = \frac{k_c}{k_t}\, c \tag{25}$$

$$c = d_0\, \frac{p}{p + K_1} \tag{26}$$

We have proven in section 2 that this equilibrium is globally stable with respect to the invariant hyperplane. The fast system converges toward its quasi-steady state (Tikhonov et al. (1980)). The hyperplane now is slowly varying due to the variation of z and we have the algebraic equation:

[1] Delphine Ropers *et al.*, Edith Grac, personal communication

$$l\frac{k_c}{k_t}d_0\frac{p}{p+K_1}+p+d_0\frac{p}{p+K_1}=z \tag{27}$$

The dynamics of the fast system in the bottom level of the structure has the quasi-equilibrium:

$$x^{h-1}=\ldots=x^1=x=\frac{k_w}{k_t'}w \tag{28}$$

$$w=\frac{qr}{r+K_2} \tag{29}$$

$$K_2=\frac{k_-'+k_w}{k_+'} \tag{30}$$

We have also proven in section 3 that this equilibrium is globally stable with respect to the hyperplane G_0. Taking (28),(29), and (30) into account in equation (15), we can write:

$$r+\frac{qr}{r+K_2}+h\frac{k_w}{k_t'}\frac{qr}{r+K_2}=R_0 \tag{31}$$

where q (slow variable) is fixed; so as previously the left side of (31) is an increasing function of r, which is zero for r equals to zero, and tends to infinity when r tends to infinity; therefore we can deduce that (31) has a unique solution $r(q)$ which depends on R_0 and q.

The analytic solutions of $r(q)$ and $p(z)$ are not very convenient, then we keep equations (31) and (27) as algebraic equations, and the dynamics of the reduced system becomes :

$$\begin{aligned}
z&=l\frac{k_c}{k_t}d_0\frac{p}{p+K_1}+p+d_0\frac{p}{p+K_1}\\
R_0&=h\frac{k_w}{k_t'}\frac{qr}{r+K_2}+r+\frac{qr}{r+K_2}\\
\dot{z}&=k-k_p\,p\\
\dot{q}&=k_t\,y^{l-1}(z)-k_m\,(q-w)\\
\dot{s}&=k_w w-k_s\,s
\end{aligned} \tag{32}$$

If we express y^{l-1} as a function of $p(z)$, and w as a function of $r(q)$ we can write :

$$\begin{aligned}
z&=l\frac{k_c}{k_t}d_0\frac{p(z)}{p(z)+K_1}+p(z)+d_0\frac{p(z)}{p(z)+K_1}\\
R_0&=h\frac{k_w}{k_t'}\frac{qr(q)}{r(q)+K_2}+r(q)+\frac{qr(q)}{r(q)+K_2}\\
\dot{z}&=k-k_p\,p(z)\\
\dot{q}&=k_c d_0\frac{p(z)}{p(z)+K_1}-k_m\,(q-\frac{qr(q)}{r(q)+K_2})\\
\dot{s}&=k_w\frac{qr(q)}{r(q)+K_2}-k_s\,s
\end{aligned} \tag{33}$$

This is the reduced system. To show the similarity between the full system and the reduced system, we performed simulations for the same set of parameters as above, with length $l=100, h=30$; and with the initial conditions $p_0=5, y_0=1, d_0=7.96$, and $r_0=20.5$, the results of simulation are shown in the figures (1), (2) and (3). We see on the simulations that variables z and q are (with our values of parameters) almost the same. Yet, the variable s has a damped oscillatory behaviour in the full model, which is averaged in the reduced model. When h increases, the oscillations increase. We also remark that the reduced model has a chain structure, and it is easy to check that it converges toward a unique equilibrium. Moreover, this model enables us to clearly understand the influence of biological parameters such as d_0 (total promoter) and R_0 (total ribosomes).

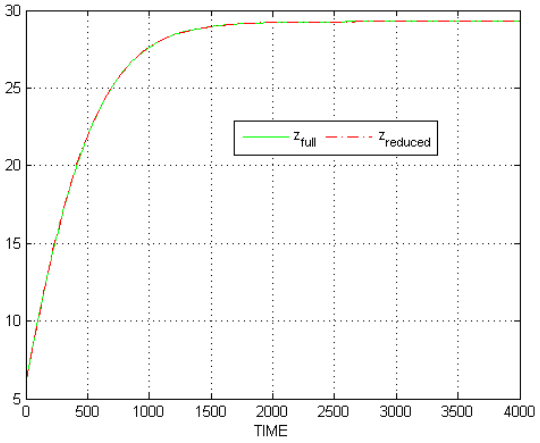

Fig. 1. The dashed line represents the behavior of variable z in the reduced system, the full line shows the evolution of variable z in the complete system (with $l=100$, h=30).

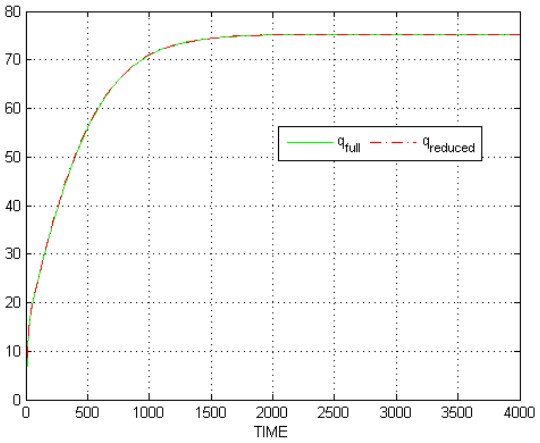

Fig. 2. The dashed line represents the behavior of variable q in the reduced system, the full line shows the evolution of variable q in the complete system (with $l=100$, h=30).

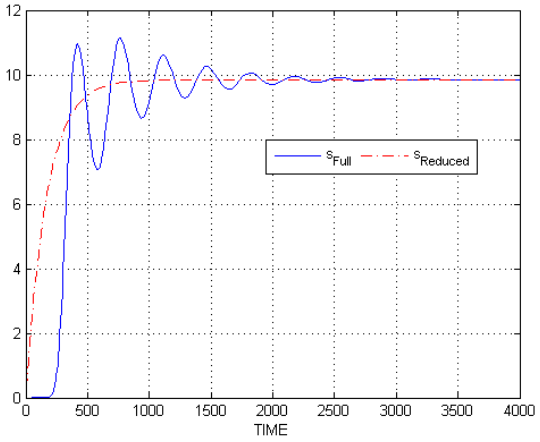

Fig. 3. The dashed line represents the behavior of variable s in the reduced system (with $l=100$, h=30) while the full line shows the evolution of variable s in the complete system.

5. CONCLUSION

The coupled transcription-translation model is of large dimensions and can be difficult to handle; simplifications are necessary, and it was the main interest in this paper. Taking into account the parameters provided by the biology experiments, we wrote the system with two different scales of time: fast and slow. The fast part is a compartmental system, and we used the monotone systems theory to prove the global stability, and therefore the validity of the reduction process. Using these results, we were able to reduce the full system to a new smaller one, with three variables, where the fast system is reduced to two algebraic equations. The behavior of the reduced and the full system is similar but the full system may oscillate with damped oscillations. It is easy to see that this oscillating behavior is generated by the length h of the variables $x, x^1, \ldots, x^{h-1}$, that could be seen as a linear chain or a delay. Moreover, this behaviour appears because the scale of time for this subset of the system is not really fast enough, with our values of parameters. In fact, the whole system could be seen as a three time scale system: a very fast one, which give the variables z and q, a fast one, which gives the variable s, and the slow final scale. If we want to obtain the damped oscillations of s in the reduced system, we have to keep a more important part of the translation system. Such investigations are the subject of further work.

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Appendix A. MONOTONE AND COMPARTMENTAL SYSTEMS

Monotone systems form an important class of dynamical systems, and are particularly well adapted to mathematical models in biology (Sontag (2004)), because they are defined by conditions related to the signs of Jacobian matrix. Such a sign for one element traduces the fact that some variable will contribute positively to the variation of some other variables, and this kind of qualitative dependence is very frequent in biological models. The reader may consult the reference Smith (1995) for a review or an exhaustive presentation of the theory of monotone systems.

In summary, if the system is cooperative, then the flow preserves the partial order in $\Re^n$ (the flow is monotone). Cooperativity is easy to check by looking at the signs of the elements of the Jacobian matrix, that should verify

$$\frac{\partial f_i}{\partial x_j}(t,x) \geq 0 \quad \forall i \neq j$$

These systems have a strong tendency to converge to the set of their equilibria (Smith (1995)). It can be shown that almost any solution converges to the set of equilibria except a set of zero measure. In particular, there are no stable periodic solutions. For more precise theorems, see Smith (1995).

Let us now give a few reminders about compartmental systems (see Jacquez and Simon (1993)), which are strongly linked to monotone systems. This kind of models describes the dynamics of n-compartments interconnected by links with fluxes of matter. The overall equation is written by making a global mass balance between inputs and outputs of each compartment. The definition of a compartmental matrix is the following:

Definition 1. **Compartmental Matrix**
Matrix $f_{(n\times n)}$ is a compartmental matrix if it satisfies the following three properties (Jacquez and Simon (1993)):

$$f_{ii} \leq 0 \quad for \quad all \ \ i, \tag{A.1}$$

$$f_{ij} \geq 0 \quad for \quad all \ \ i \neq j, \tag{A.2}$$

$$-f_{jj} \geq \sum_{i \neq j} f_{ij} \quad for \quad all \quad j \tag{A.3}$$

Note that f_{ij} can in general depend on $x_k, k = 1 \ldots n$ which are the concentrations in each compartment. There are also theorems on the stability of linear and nonlinear compartmental systems (see Jacquez and Simon (1993)). Let the nonlinear system:

$$\dot{x} = f(x) \tag{A.4}$$

Theorem 1. Property 5 in Bastin and Guffens (2006).
Suppose system (A.4) is closed, that is to say $M(x) = \sum_{i=1}^{n} x_i$ is the fixed total concentration.
If the Jacobian matrix of the system is irreducible (the system is strongly connected) and compartmental, then for any $M_0 > 0$, hyperplane $H = \{x \in \Re_+^n : M(x) = M_0 > 0\}$ is invariant and contains a unique globally stable equilibrium in H.