Physica D 331 (2016) 102–113

Contents lists available at ScienceDirect

Physica D

journal homepage: www.elsevier.com/locate/physd

Dynamics of transcription–translation networks

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ARTICLE INFO

Article history:
Received 15 January 2016
Received in revised form
24 May 2016
Accepted 25 May 2016
Available online 2 June 2016
Communicated by K. Josic

Keywords:
Gene regulatory networks
Piecewise-linear
Singular perturbation
Transcription–translation

ABSTRACT

A theory for qualitative models of gene regulatory networks has been developed over several decades, generally considering transcription factors to regulate directly the expression of other transcription factors, without any intermediate variables. Here we explore a class of models that explicitly includes both transcription and translation, keeping track of both mRNA and protein concentrations. We mainly deal with transcription regulation functions that are steep sigmoids or step functions, as is often done in protein-only models, though translation is governed by a linear term. We extend many aspects of the protein-only theory to this new context, including properties of fixed points, description of trajectories by mappings between switching points, qualitative analysis via a state-transition diagram, and a result on periodic orbits for negative feedback loops. We find that while singular behaviour in switching domains is largely avoided, non-uniqueness of solutions can still occur in the step-function limit.

1. Introduction

Models of gene regulatory networks often omit many biochemical details, partly because parameters in specific systems are often not well known, but also because it is argued that qualitative behaviour, at least, will be similar in simplified models. For example, a good deal of work on developing general-purpose tools for analysis of the behaviour of gene networks has modelled only concentrations of proteins that act as transcription factors, as if these proteins directly regulated production of other proteins. We know that this is not really the case—proteins regulate the transcription of mRNA's that in turn produce proteins by translation. There may also be post-translational modifications to a protein before it is effective as a regulator. It is often argued that the time scales of the dynamics of mRNA and protein are vastly different, so that it is not unreasonable to consider mRNA dynamics to be infinitely fast, so that only the protein variables need be retained in a model.

Typically, mRNA decay rates are significantly higher than those of proteins, or equivalently, protein half life tends to be longer. However, these time scales may not always be so different and the range of ratios of these decay rates is highly variable across genes and organisms (see, for example, [1–5]). In previous work, it has been shown that behaviour of transcription–translation networks and the corresponding protein-only networks can differ qualitatively, even in some cases when time scales of the two types of variable are very different (but not infinitely different) [3,6].

This observation makes it desirable to develop a method of analysis for transcription–translation networks. One can still use the simplifying assumption that the regulation (promotion or repression) becomes effective sharply at a particular threshold, so that the regulatory effect as a function of protein concentration is a very steep sigmoid, or even infinitely steep. A start to an analysis of such systems was made in a previous paper [6], but the focus there was on a comparison of the transcription–translation system to its protein-only counterpart. One of the main advantages of a transcription–translation model, from the point of view of analysis, is that there is no self-input of any variable as a regulator of its own production. If, biochemically, a gene is autoregulating, the process is now modelled as a feedback loop between the gene's mRNA transcript, and the corresponding translated protein. Thus, the difficulties that arise in protein-only networks with 'black walls' (trajectories approach a threshold hyperplane from both sides), 'white walls' (trajectories move away from a threshold hyperplane on both sides) and sliding in walls (trajectories confined to a threshold hyperplane for a nonzero time interval, while moving in other variables) no longer arise. There are still sensitive behaviours at intersections of walls that require careful analysis, but the problems of singular flow seem to be avoided in typical solution trajectories.

On the other hand, even in the case of infinitely steep switching, maps between threshold transitions are no longer as easy to calculate, and contrary to the protein-only case, trajectories can reverse direction without crossing a threshold. These issues are

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http://dx.doi.org/10.1016/j.physd.2016.05.013
0167-2789/

explored in more detail here, and we show that, in fact, the direction reversal leads to particular trajectories that graze a threshold hyperplane tangentially, leading once again to non-uniqueness of some solutions in the infinitely steep switching case (Section 4.3). It is possible, however, to divide phase space up into regions (which will here be called *pseudo-state domains*) in such a way that flows are logically captured by a directed graph in which nodes represent regions, in a similar way to what is done for protein-only networks, even though here, only half the variables have thresholds (Section 6). Negative feedback loops still correspond to cycles on such a state-transition graph, and with appropriate parameter values, these have a corresponding unique locally stable periodic solution that is also qualitatively stable with respect to the (adjacent) boxes through which it passes.

We investigate a number of other properties of trajectories of the transcription–translation model, in a way that parallels the theory for protein-only networks. For example, we show that a fixed point in a regular domain (we use this term also in the limit of infinitely-steep switching, where it becomes a region of phase space bounded by threshold hyperplanes) is still necessarily asymptotically stable, but not globally with respect to that regular domain, unlike the protein-only case (Section 4.2). In Sections 4.1 and 5, we determine how to calculate the map from one threshold transition to the next, though in practice this requires numerically finding a root of a transcendental equation in most situations (this was partially done in [6], but not every case was covered there). We finish with a summary of what has been achieved and discussion of implications.

2. The protein only model

In this work, we are interested in qualitative descriptions of gene regulatory networks. A class of simplified models, proposed by Glass [7], and elaborated by others (for example [8–10]), describes n-gene networks by an n-dimensional system of differential equations with either a step function or a sigmoidal interaction term. Using the notation of Plahte and Kjøglum, the equations are

$$\dot{y}_i = F_i(Z) - \beta_i y_i, \quad i = 1, \ldots, n, \tag{1}$$

where $\beta_i > 0$ is constant and $Z = (Z_{11}, \ldots, Z_{np_n})$ is a vector of sigmoid functions $Z_{ij} = \mathcal{S}(y_i, \theta_{ij}, q)$ satisfying a number of conditions laid out in their paper [10]. Here y_i denotes the concentration of the ith protein, θ_{ij} is the switching threshold of Z_{ij}, $j \in \{0, 1, \ldots, p_i\}$, and q is a steepness parameter. The functions $F_i(Z) \geq 0$ are multilinear polynomials, i.e., affine with respect to each Z_{ij}. Inherently, production rates are bounded, so there exist positive constants $\bar{F}_i$ such that $0 \leq F_i(Z) \leq \bar{F}_i$ for each $i \in \{1, \ldots, n\}$. We define $\theta_{i0} = 0$ and $\theta_{i,p_i+1} = y_{i,\max} := \frac{\bar{F}_i}{\beta_i}$.

As in [8], we take $\mathcal{S}(y_i, \theta_{ij}, q)$ to be the Hill function $H(y_i, \theta_{ij}, q)$,

$$H(y_i, \theta_{ij}, q) = \frac{y_i^{\frac{1}{q}}}{y_i^{\frac{1}{q}} + \theta_{ij}^{\frac{1}{q}}}. \tag{2}$$

Note that

$$\lim_{q \to 0} H(y_i, \theta_{ij}, q) = \begin{cases} 0 & \text{if} \quad y_i < \theta_{ij} \\ 1 & \text{if} \quad y_i > \theta_{ij}. \end{cases}$$

Since for each gene i we assign one equation, we refer to (1) as Model 1.

In the limit as $q \to 0$, phase space can be divided into boxes,

$$\mathcal{B}_{j_1, \ldots, j_n} = \prod_{i=1}^{n} (\theta_{ij_i}, \theta_{i,j_i+1}), \quad j_i \in \{0, 1, \ldots, p_i\},$$

separated by threshold hyperplanes. Flow in each box is directed towards a focal point $\Phi_i = \frac{F_i(Z)}{\beta_i}$, for the value of the binary vector Z appropriate to the box ($Z_{ij} = 0$ if $y_i < \theta_{ij}$ and $Z_{ij} = 1$ if $y_i > \theta_{ij}$). If a fixed point lies inside its own box, then no switching occurs and the trajectory converges asymptotically to the focal point, which is then an asymptotically stable fixed point (this straightforward result has been observed many times; see, for example, [11–14]). Otherwise, mappings from threshold to threshold can be calculated. One can apply these maps iteratively to get a long term mapping that one can use to give conditions for existence and stability of periodic solutions. See, for instance, [15] or [9].

3. The transcription–translation model

A $2n$-dimensional model explicitly describing both the transcription and translation steps has been proposed in [3,6]:

$$\begin{aligned} \dot{x}_i &= F_i(Z) - \beta_i x_i \\ \dot{y}_i &= \kappa_i x_i - \gamma_i y_i \end{aligned} \quad i = 1, \ldots, n, \tag{3}$$

which we refer to as Model 2 henceforth. In Model 2, x_i represents the concentration of the ith mRNA and y_i represents the concentration of the protein product for gene i. We take $Z = (Z_{1j}, \ldots, Z_{np_n})$, where each Z_{ij} is as before. Again, we take $\mathcal{S}(y_i, \theta_{ij}, q) = H(y_i, \theta_{ij}, q)$ to be the Hill function defined in (2). We take each F_i and β_i to be defined as before, and add that $\gamma_i > 0$, and $\kappa_i > 0$. All the examples we present will deal with the limit case $q \to 0$, but the main results will be shown for both $q \to 0$ and for $q > 0$.

We first note that since $\dot{y}_i$ is independent of Z_{ij}, all threshold hyperplanes $y_i = \theta_{ij}$ are *transparent*, i.e. solution trajectories pass through them.

The threshold hyperplanes $y_i = \theta_{ij}$ divide $\mathbb{R}^{2n}$ into regions that we call regular domains. To be more precise, we adapt some notation from [9]: let $\mathbb{N}_{p_i} = \{0, 1, \ldots, p_i\}$ and let $\mathcal{H} = \prod_{i=1}^{n} \mathbb{N}_{p_i}$. For consistency, we declare that $\theta_{i,0} = 0$ and $\theta_{i,p_i+1} = y_{i,\max}$. It follows that y_i has p_i thresholds. Let $h \in \mathcal{H}$. We define a *Regular Domain*, $\mathcal{D}_h$, in the limit $q \to 0$, to be

$$\mathcal{D}_h = \mathcal{D}_{h_1, \ldots, h_n} = \mathbb{R}^n_+ \times \prod_{i=1}^{n} (\theta_{i,h_i}, \theta_{i,h_i+1}), \quad h_i \in \mathbb{N}_{p_i}. \tag{4}$$

Note that for $q > 0$, the intervals $(\theta_{i,h_i}, \theta_{i,h_i+1})$ have to be replaced by $(\theta_{i,h_i} + \delta(q), \theta_{i,h_i+1} - \delta(q))$, where $\delta(q) \to 0$ as $q \to 0$, and the switching regions have thickness that vanishes as $q \to 0$. Inside a regular domain none of the y_i are at threshold value. For $0 < q \ll 1$, the sigmoid vector Z can be approximated by a binary vector B, and it converges to B as $q \to 0$. Thus, inside regular domains in the limit as $q \to 0$, each $F_i(Z)$ is a constant, α_i (which implicitly still depends on Z, of course). Consequently, in a regular domain $\mathcal{D}_h$, Eqs. (3) can be solved uniquely in the limit as $q \to 0$ and these solutions will hold until one of the y_i hits a threshold. Solutions must be directed towards a focal point,

$$\begin{aligned} &\Phi = (x^*, y^*) = (x_1^*, \ldots, x_n^*, y_1^*, \ldots, y_n^*) \\ &\text{where } (x_i^*, y_i^*) = \left(\frac{\alpha_i}{\beta_i}, \frac{\kappa_i \alpha_i}{\gamma_i \beta_i} \right), \end{aligned} \tag{5}$$

monotonically in each x_i, but not necessarily in each y_i.

4. Local dynamics in a regular domain

In this section we talk about local dynamics in regular domains, and compare with local dynamics in Model 1. For what follows, we make the following assumption:

Assumption 1. No focal point, $\Phi = (x^*, y^*)$, from (5), for any binary vector Z, lies on a threshold, i.e. $\frac{\kappa_i \alpha_i}{\gamma_i \beta_i} = \frac{\kappa_i}{\gamma_i \beta_i} F_i(Z) \neq \theta_{i,h_i}$ for any $i > 0$ and $h_i \in \mathbb{N}_{p_i}$.