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2006 J. Phys. A: Math. Gen. 39 2965

(http://iopscience.iop.org/0305-4470/39/12/007)

INSTITUTE OF PHYSICS PUBLISHING JOURNAL OF PHYSICS A: MATHEMATICAL AND GENERAL

J. Phys. A: Math. Gen. **39** (2006) 2965–2971 doi:10.1088/0305-4470/39/12/007

On the dynamics of a gene regulatory network

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Received 19 October 2005, in final form 9 February 2006
Published 8 March 2006
Online at stacks.iop.org/JPhysA/39/2965

Abstract
We examine the dynamics of a network of genes focusing on a periodic chain of genes, of arbitrary length. We show that within a given class of sigmoïds representing the equilibrium probability of the binding of the RNA polymerase to the core promoter, the system possesses a single stable fixed point. By slightly modifying the sigmoïd, introducing 'stiffer' forms, we show that it is possible to find network configurations exhibiting bistable behaviour. Our results do not depend crucially on the length of the chain considered: calculations with finite chains lead to similar results. However, a realistic study of regulatory genetic networks would require the consideration of more complex topologies and interactions.

PACS numbers: 03.70.+k, 11.10.Gh, 03.65.Sq, 11.30.Ly
Mathematics Subject Classification: 34D99, 92D10, 92B05

1. Introduction

Living organisms respond to external signals thanks to a large variety of genetically precoded responses. This is achieved through networks of genes of high connectivity and complexity. The interaction of genes aims at regulating each others' activity and thus leads to the desired response [1, 2]. Typically a gene is subject to the regulatory effect of a few other genes which can act on it in either an activating or a suppressing way, depending on the situation. The predominant focus of many experimental and theoretical studies on genetic circuits thus far has been on the combinatorial control of transcriptional initiation, which to a large extent determines the connectivity of the network [3, 4]. It is thus of the utmost importance to study, and understand, the dynamics of the gene regulatory network.

The activity of a gene is regulated by other genes through the production of transcription factor (TF) proteins. Physically, this is accomplished through the interaction of these transcription factor proteins with the RNA polymerase complex in the regulatory region of the gene. The code segment of the DNA chain (that is the gene) is read by the RNA

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polymerase which binds to DNA and moves along activated by transcription factor proteins and gives rise to the RNA messenger. This transports the respective code to the ribosomal machine and proteins are produced according to it. Among these proteins we also have, of course, constituents of the transcription factor.

In order to build a mathematical model of this process, one must first describe the binding of the RNA polymerase molecule to the DNA promoter, namely a region which is the beginning of the encoded string. In a thermodynamical description [5], the promoter activity is proportional to the equilibrium probability g of the binding of the RNA polymerase to the core promoter. In the case of the simplest processes, namely simple activation or suppression, the dependence of g on the cellular TF concentrations (which we shall denote by p) is described by the Arrhenius form [6]

$$g(p) = \frac{1 + \omega p/K_A}{1 + p/K_A} \quad \text{for activation} \tag{1.1}$$

and

$$g(p) = \frac{1}{1 + p/K_R} + L \quad \text{for suppression,} \tag{1.2}$$

where K_A and K_R are the dissociation constants between p and the respective DNA sequence, ω is the Boltzmann weight of the interaction between the RNA polymerase and L is the promoter leakage. Both expressions have a sigmoïdal form and can be written simply (up to a rescaling of p) as

$$g(p) = \frac{\alpha + \beta p}{1 + p}, \tag{1.3}$$

where $\alpha < \beta$ for activation and $\alpha > \beta$ for suppression.

From these basic ingredients, we can write the dynamical equations for *one* gene. Two steps can be distinguished. First the RNA polymerase produces RNA-messenger acid (m)

$$\frac{\mathrm{d}m}{\mathrm{d}t} = g(p) - \lambda m. \tag{1.4a}$$

Next, the RNA-messenger acid goes to a ribosomal machine and TF proteins are produced with a linear rate (which is just a simplifying assumption at this stage)

$$\frac{\mathrm{d}p}{\mathrm{d}t} = \nu m - \kappa p. \tag{1.4b}$$

Since the kinetics of RNA messenger production are rapid compared to those of the TF proteins, it is not unreasonable to make a steady-state assumption for the reaction leading to their production, and thus we have $m = g(p)/\lambda$. We can then rewrite equation (1.4*b*) as

$$\frac{\mathrm{d}p}{\mathrm{d}t} = g(p) - p, \tag{1.5}$$

where the two parameters have been absorbed into a rescaling of time and a redefinition of the parameters α and β entering the sigmoïd. Equation (1.5) possesses one fixed point. Indeed the equation $p_0 = g(p_0)$ has a single *positive* fixed point. The condition for stability of this fixed point is $g'(p_0) < 1$ and it can be easily verified that it is satisfied by the form of g given by (1.3).

The above considerations form the basis for the construction of the description of a network comprising an arbitrary number of genes in interaction, which we shall present in the following section. In particular, we shall study a genetic network and examine the possibility of existence of a fixed point for the production of TF proteins. As we shall show, when the equilibrium probability g of the binding of the RNA polymerase to the core promoter is given

by a sigmoïd (1.3) a single stable fixed point exists in our networks. However, by slightly modifying the form of the sigmoïdal function, we show that there exist situations where the system possesses *two* stable fixed points and thus exhibits bistability.

Why the bistability is important from the biological point of view? First, cellular regulation is usually achieved through a very complex network of interactions and processes. These networks involve tens of thousands of biochemical reactions. It is, therefore, very important to find procedures of simplifying the description of these networks to facilitate the analysis. One is thus led to the concept of motif [10] which represents some basic subnetwork classifiable on the basis of function, architecture dynamics, etc. At a bigger scale, the motifs can be seen as organized in modules having their specific role. Accordingly, in this approach, the bistability can be seen as a switching motif with a digital-like on/off behaviour. This may be at the level of gene expression, as function of the concentration of transcription factors. Switching behaviour of this type were seen in cascades' ultrasensitivity arising in mitogen-activated protein kynase cascades [13], multi-input cascades found in glycolysis [14], etc.

Second, multistability is useful in the study of storing cellular memory by complex gene and protein networks. For instance in yeast, galactose-signalling network multiple-nested feedback loops create many discrete stable states of network activity. Certain loops can reduce strongly the randomly switching back and forth between expression states [11] preserving thus the cellular memory by reducing stochastic transitions.

Of course the complexity of network, presence of noise, and interaction with other molecular structures can affect strongly the dynamics and thus are very important [12], but our model singles out a certain aspect of the dynamics, namely the bistability for different promoter activities for a linear gene network.

2. A model of a genetic circuit

In this section we shall consider a chain of genes where each gene is in interaction with two others, the effect of which can be either activating or suppressing. From the one-gene model we presented in the introduction, we can write the dynamical equations as

$$p_n' = g(p_{n+1}) + g(p_{n-1}) - p_n, \tag{2.1}$$

where $g(p)$ is given by equation (1.3). The chain under consideration is subject to periodic boundary conditions, but its length is *a priori* arbitrary. (The analysis of finite-length chains has shown that the conclusions concerning fixed points and stability stay qualitatively the same as in the case of an arbitrary-length chain, only the quantitative details do change).

We rewrite (2.1) introducing the variable transformation

$$w = \frac{1}{1+p} \tag{2.2}$$

which means that $g(p) = (\alpha - \beta)w + \beta$ and find

$$w_n' = (\beta - \alpha)w_n^2(w_{n+1} + w_{n-1}) + w_n - (1+2\beta)w_n^2. \tag{2.3}$$

It is straightforward to absorb one of the parameters of (2.3) by the adequate scaling of the dependent variable. We define

$$u = (1+2\beta)w \tag{2.4}$$

and obtain

$$u_n' = \delta u_n^2(u_{n+1} + u_{n-1}) + u_n - u_n^2, \tag{2.5}$$

where $\delta = (\beta - \alpha)/(1 + 2\beta)$. We can readily remark that an activating coupling corresponds to $\delta > 0$, while the opposite sign indicates a suppressing situation. Given that the physical values of p are positive, equation (2.2) implies $0 < w < 1$ and thus from (2.4) we have $0 < u < 1 + 2\beta$.

At this stage it is interesting to look for the general stationary solution of (2.5). Putting $u' = 0$, we find

$$u_{n+1} + u_{n-1} = \frac{1}{\delta}\left(1 - \frac{1}{u_n}\right). \tag{2.6}$$

This relation can be considered as a mapping for u_n and it turns out that it can indeed be solved. It is a special case of the QRT family of mappings, proposed by Quispel, Roberts and Thompson in [7]. The latter is a family of second-order mappings which contain five parameters. They are integrable and possess an invariant which can be expressed as a ratio of two polynomials biquadratic in u_n and u_{n-1}. The solution of the general QRT mapping is just a sampling of an elliptic function on a lattice of equally spaced points. While this solution is interesting mathematically, it is not of particular use in our case since we concentrate on strictly positive definite solutions. Moreover, such solutions are very sensitive to the precise length of the chain, something which is undesirable in the model at hand. We are thus led to the investigation of simpler stationary solutions, which do exist, of course. The obvious one is a constant u independent of n. From (2.6), it is clear that if $\delta < 1/8$ a constant solution $u = u_0$ with positive u_0 does exist for (2.5) (a single one when δ is negative, but two such solutions for positive δ). We have also looked for positive, spatially periodic, stationary solutions of (2.5) of low periodicity, but none was found. If we consider solutions with period 2, i.e. $u_n = u$ and $u_{n+1} = v$, it turns out that the two possible solutions for u are precisely the two solutions obtained for the constant solution $u = u_0$ and moreover, we find that we have $v = u$. For period 3, we find exactly the same situation (provided we discard the spurious, non-positive definite solutions), i.e. only the constant solution survives. The same holds for period 4 solutions which, given the structure of the mapping, are just a copy of the period 2 solutions.

The model of equation (2.5) assumes that both genes which interact with the one under consideration have the same action. The case where the two genes have opposite actions can be treated along similar lines. Moreover, a self-activation (or self-suppression) can be introduced. It suffices to add a term $\pm u_n$ in the parentheses. Thus, the general equation for the genetic network we shall consider is

$$u_n' = \delta u_n^2(u_{n+1} + u_{n-1} + \epsilon u_n) + u_n - u_n^2, \tag{2.7}$$

where ϵ can be 0 or ± 1 depending on the self-interaction. The constant, stationary solution of (2.7) is given by

$$(2 + \epsilon)\delta u_0^2 - u_0 + 1 = 0. \tag{2.8}$$

When the coefficient of the u_0^2 term is negative only one positive root exists, otherwise we have two positive roots provided $\delta < 1/(8 + 4\epsilon)$.

We now turn to the investigation of the stability of the positive solutions. We start by linearizing (2.7) around the solution $u = u_0$ and then we look for a solution of the linearized equation in the form $\mathrm{e}^{\mathrm{i}kn+\lambda t}$ (compatible with periodicity assumption). We find that the eigenvalue λ is given by

$$\lambda = \delta u_0^2(f(k) + \epsilon) + 2\delta u_0^2(2 + \epsilon) + 1 - 2u_0, \tag{2.9}$$

where $f(k) = 2\cos k$ in the case of cooperative interaction. Using condition (2.8) for the fixed point, we can rewrite (2.9) as

$$\lambda = \frac{f(k) + \epsilon}{2 + \epsilon}(u_0 - 1) - 1, \tag{2.10}$$

where again $f(k) = 2\cos k$ and we consider the most unfavourable case namely $\cos k = 1$. We thus obtain

$$\lambda = u_0 - 2 \tag{2.11}$$

and the stability condition $\lambda < 0$ becomes simply

$$u_0 < 2. \tag{2.12}$$

Thus the fixed point $u = u_0$ is stable provided the constraint (2.12) is satisfied. When a single positive solution exists we have one stable equilibrium. However, there exist situations where (2.8) has *two* positive solutions. It would seem *a priori* that it could be possible in this case to have two stable fixed points. This turns out not to be the case. Indeed if we have two positive solutions of (2.8), u_0 and u_1, and assume that $u_0 < 2$ and $u_1 < 2$, we find immediately that $\frac{1}{u_0} + \frac{1}{u_1} > 1$. However from (2.8) we have $u_0 + u_1 = u_0 u_1$ and thus $\frac{1}{u_0} + \frac{1}{u_1} = 1$. This is in contradiction with the existence of two stable points. Thus in this particular model, we have studied in this section no bistability is possible.

3. A generalized linear genetic chain

In the previous section we have analysed a network of genes in interaction and have shown that there exists a single stable steady state. The natural question that can be asked at this point is whether one can obtain a network of genes that will behave as a switch, by possessing two stable steady states [8, 9]. It turns out that this is possible and can be easily realized provided one generalizes slightly expression (1.3) which gives the dependence of the probability that the RNA polymerase binds to the core promoter on the cellular TF concentration. As we have mentioned at the beginning this is related to the simplest activation or suppression. If, for instance there are two operators for the activator then the promoter activity is given by a different expression which is effectively equivalent with a stiffer sigmoïd [6]. For the general case, we can consider the following expression for the promoter activity:

$$2g(p) = \frac{\alpha + \beta p^{\nu}}{1 + p^{\nu}} \qquad \text{with} \quad \nu > 1. \tag{3.1}$$

The case $\nu = 1$ has been analysed in the previous section where it was shown that bistability is impossible. In the case $\nu \neq 1$, we shall concentrate on here, it is not interesting to perform any transformation of the dependent variable and thus we shall deal directly with the dynamical equation

$$p_n' = g(p_{n+1}) + g(p_{n-1}) - p_n. \tag{3.2}$$

The constant fixed points for (3.2) are given by the solutions of the equation

$$2g(p_0) - p_0 = 0. \tag{3.3}$$

Given the form of $g(p)$ it is clear that in the case of suppressing interaction only one fixed point exists and thus no bistability is possible. On the other hand, for activating interactions, $\beta > \alpha$, we may have three fixed points and thus a possibility of bistability. Pursuing the study of this latter case, we expand (3.2) around the fixed point, $p = p_0 + \chi$ and obtain the linearized equation for χ

$$\chi_n' = g'(p_0)(\chi_{n+1} + \chi_{n-1}) - \chi_n. \tag{3.4}$$

We seek a solution of the form $e^{ikn+\lambda t}$ which leads to the equation for λ

$$\lambda = 2g'(p_0)\cos k - 1. \tag{3.5}$$

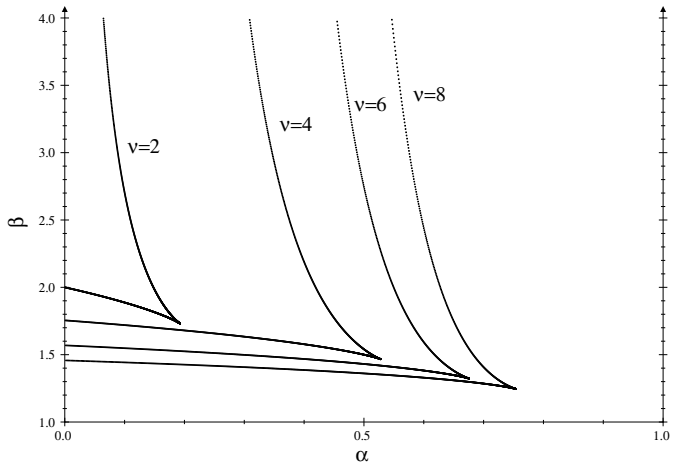

Figure 1. Bistability domain in the (α, β) plane for various values of ν.

Thus the stability condition, in the worst-case scenario $\cos k = 1$, is

$$2g'(p_0) - 1 < 0. \tag{3.6}$$

In order to transcribe the stability domain, we combine (3.3) with $2g'(p_0) - 1 = 0$, i.e. (3.6) with equal sign. This leads to the following expressions for the parameters α and β in terms of p_0:

$$\beta = p_0\left(1 + \frac{1 + p_0^\nu}{\nu p_0^\nu}\right) \tag{3.7a}$$

$$\alpha = p_0\left(1 - \frac{1 + p_0^\nu}{\nu}\right). \tag{3.7b}$$

The form of the (bi)stability domain in the (α, β) plane can easily be obtained from (3.7). First, from (3.7*b*) we see that the maximal-allowed value of p_0 is given by $p_0^\nu = \nu - 1$ in which case $\alpha = 0$ and $\beta = p_0\nu/(\nu - 1)$. The form of the frontier has a cusp at the point where α and β have a maximum and a minimum, respectively. This occurs when $p_0^\nu = (\nu - 1)/(\nu + 1)$ and the corresponding values are $\alpha = p_0(\nu - 1)/(\nu + 1)$ and $\beta = p_0(\nu + 1)/(\nu - 1)$. The upper border of the stability domain has the asymptotic form $\beta\alpha^{\nu-1} = (\nu - 1)^{(\nu-1)}/\nu^\nu$. (One can easily obtain this form by assuming p to be small in (3.7) and keeping only the dominant terms.) In figure 1, we represent graphically the bistability domain for various values of ν.

The typical behaviour of the system is the following. Suppose that we start with a fixed α and increase β continuously. When we are in the region below the bistability domain we have a single solution of (3.3), which is stable, i.e. satisfies (3.6). The same occurs when we exit the bistability domain for large values of β. In the intermediate region, delimited by the two lines, there exists three fixed points. It turns out that the 'middle' fixed point is always unstable, i.e. it violates (3.6). The two other fixed points, on the contrary, do always satisfy these inequalities and thus we are indeed in a bistable situation. It is clear that as $\nu \to \infty$, the bistability domain expands and covers the whole domain $\beta > 1$ and $0 < \alpha < 1$ when the sigmoïd becomes a step function. Still this is compatible with the fact that the middle root of equation (3.3) is always unstable. Indeed when $g(p)$ is a step function, with a discontinuity at $p = 1$, the three fixed points are $\alpha, 1, \beta$. While for $p_0 = \alpha$ or β we have $g'(p_0) = 0$, and thus a stable situation, $g'(p)$ is a delta function centred at 1, $\delta(p - 1)$, and thus the stability condition is violated.

It is easy to extend the above analysis to the case where we have an activating self-interaction. While the quantitative details may change, the overall conclusions on the existence of a bistability region still hold.

4. Conclusion

In this paper we have examined a network of genes in interactions. More precisely, we have analysed the regulatory effect on the RNA polymerase binding (which results to a specific protein production) of the TF proteins produced by other genes. We have constructed a dynamical system which models such an interacting chain and analysed its behaviour under various assumptions concerning the dependence of binding on the TF concentration. We have shown that in a fairly general setting there exists a domain of the parameters for which the system exhibits bistability, possessing two distinct stable steady states. While our results were derived in a specific frame, namely that of a periodic chain of arbitrary length, calculations on short finite chains of genes lead to similar results. Of course regulatory genetic networks have complex topology and interactions which go beyond the scope of the present paper. In this sense, this study is *inspired* from the dynamics of gene networks rather than an exact model thereof. Still the possibility of bistability is a most interesting feature which warrants experimental study.

In a future work we expect to come back to the question of stability of genetic networks in order to investigate, among others, the effect of nonstationarity of the RNA messenger production.

Acknowledgments

A S Carstea is grateful to the University of Paris VII for their hospitality and financial support.

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