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Analysis of transient damped oscillations in gene regulatory networks*

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Abstract— **Existing general purpose software tools for qualitative analysis of gene regulatory networks can handle most types of dynamical behaviour, but one remaining problematic case is that of transient damped oscillations, which certainly can occur. Current methods allow a solution trajectory to be followed by explicit computation of switching points, where the regulation of one or more gene is turned on or off, or more generally, allow parameter ranges to be determined for which a qualitative solution is followed. However, during intervals on which two or more gene products undergo damped oscillations, an arbitrary or even an infinite number of switching points can occur before another switch occurs to disrupt the damped oscillations. Here we resolve the resulting computational difficulties by explicitly calculating the end point of the transient oscillation. For a specific example, we compute regions corresponding to all possible itineraries, which can be used to find periodic solutions with a 'bursting' phase. We assume equal degradation rates, though the method should be generalizable to a wider class of networks.**

I. INTRODUCTION

We investigate the situation where two variables undergo damped oscillations and thus spiral in phase space as a result of a negative feedback loop. Other variables activate or inactivate this spiralling, but are themselves unaffected by the spiralling variables (at least while they are spiralling). Thus, the time during which the spiralling is activated is independant of the spiralling variables, and we can make explicit calculations about their behaviour. It is possible, for example, to have periodic behaviours for the whole system that incorporate phases of damped oscillation in some of the variables, a kind of 'bursting'.

II. THE MODEL

We will deal with simplified class of gene networks

$$\dot{y}_i = F_i(\mathbf{Z}) - y_i\,,\ (i = 1,\dots,n), \quad \text{or} \quad \dot{\mathbf{y}} = \mathbf{F}(Z) - \mathbf{y}\,, \tag{1}$$

where each gene product has a single effective threshold, y_i is the amount by which the concentration of gene product i exceeds its threshold, degradation rates are constant and equal for all gene products, here normalized to 1, each gene product has a single effective threshold, $\mathbf{Z}$ is a vector function and each Z_i is a Heaviside step function with threshold at 0.

Phase space is divided into orthants, separated by boundaries ('*walls*') where '*switchings*' take place. Solution trajectories are calculated directly as maps from one wall to the next [2], [5]. Flow in walls (or more generally, 'singular domains') can be handled by either Fillipov methods [3] or singular perturbation methods [6]. We will not need to dwell here on the possibility of non-uniqueness.

The mapping of a trajectory from the k^{th} wall to the $(k+1)^{st}$, through an orthant, is given by

$$M^{(k)}(\mathbf{y}^{(k)}) = \frac{B^{(k)}\mathbf{y}^{(k)}}{1 + (\psi^{(k)})^\top \mathbf{y}^{(k)}}\,, \tag{2}$$

$$\text{with} \quad B^{(k)} = I - \frac{\mathbf{f}^{(k)}\mathbf{e}_j^\top}{f_j^{(k)}}\,, \quad \psi^{(k)} = \frac{-\mathbf{e}_j}{f_j^{(k)}}\,, \tag{3}$$

where $\mathbf{y}^{(k)}$ is the vector of variables y_i on the k^{th} wall, j is the index of the variable that is switching on the $(k+1)^{st}$ wall, and $\mathbf{f}^{(k)} = \mathbf{F}(\mathbf{Z}^{(k)})$ is the *focal point*, toward which all trajectories in the k^{th} orthant tend. Here, $\mathbf{Z}^{(k)}$ is $\mathbf{Z}(\mathbf{y}^{(k)})$, the value of $\mathbf{Z}$ in the k^{th} orthant. The denominator in Eq. (3) is the exponential of the time taken by the trajectory between $\mathbf{y}^{(k)}$ and $\mathbf{y}^{(k+1)}$. The mapping (3) also describes the flow along singular domains when the variables that are switching in that domain have focal point coordinates at 0, as determined, for example, by Filippov methods.

The composition of maps (3) is again fractional linear, and since $\mathbf{y}^{(k)}$ is always on a wall, one component is always 0, so the map can be reduced to an $(n-1)$-dimensional one. In particular, for a cycle in $\mathbb{R}^2$ that returns to an initial wall where $y_2 = 0$, we have a scalar map in y_1:

$$M(y_1) = \frac{Ay_1}{1 + \phi y_1}\,. \tag{4}$$

If the focal points associated with each quadrant are each located in the adjacent quadrant,

$$\mathbf{F}(1,1) = (-a_1, b_1), \quad \mathbf{F}(0,1) = (-a_2, -b_2),$$

$$\mathbf{F}(0,0) = (a_3, -b_3), \quad \mathbf{F}(1,0) = (a_4, b_4)\,,$$

where $a_k, b_k > 0$, then trajectories follow a counterclockwise circuit of the four quadrants. There is a periodic orbit if $A > 1$. If $A = 1$, then all trajectories spiral in toward the origin asymptotically, so $\lim_{t\to\infty} \mathbf{y}(t) = (0,0)$. If $A < 1$, then all trajectories spiral in to the origin and reach it in finite time [2], [5]. Note that $A = 1$ occurs if focal points are aligned on a rectangle (*i.e.*, $a_1 = a_2, a_3 = a_4, b_2 =$

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$b_3, b_4 = b_1$), which is the case if there is no autoregulation in this network.

Repeated iteration of Eq. (4) gives

$$M^m(y_1^{(0)}) = \frac{A^m y_1^{(0)}}{1+\phi^{(m,0)} y_1^{(0)}}\,, \tag{5}$$

$$\text{where} \quad \phi^{(m,0)} = \sum_{k=0}^{m-1} A^k \phi = \frac{1-A^m}{1-A}\phi\,. \tag{6}$$

III. THE MAPS FOR SPIRALLING

We now consider an n-gene network, and WLOG, suppose y_1 and y_2 are the two variables undergoing the spiralling behaviour. The spiralling is initiated and turned off again when some other variable switches. Let

$$\mathbf{y}_\mu = (y_1, y_2)\,, \quad \mathbf{y}_\gamma = (y_3, \ldots, y_n)\,.$$

Fix the times of activation and disactivation of spiralling as $t = 0$ and $t = t_s$, respectively. We call $\mathbf{y}_\mu(0)$ the *entry point* and $\mathbf{y}_\mu(t_s)$ the *exit point*, and WLOG, we suppose that the entry point is in quadrant $(1, 0)$, *i.e.*, $y_1^{(a)} > 0$, $y_2^{(a)} < 0$, and that the trajectory goes counterclockwise. The signs of the focal point coordinates are determined by this arrangement. We break the spiralling trajectory into three time intervals $t_s = t_i + t_c + t_f$, where t_i is the time taken to reach the first boundary crossing from the entry point, t_c is the time taken to reach the final boundary crossing from the initial boundary crossing, and t_f is the time it takes to reach the exit point from the final boundary crossing.

Let M_i, M_c, and M_f be the maps corresponding to the three respective phases. With entry point $\mathbf{y}_\mu^{(a)} = \mathbf{y}_\mu(0)$, the points arrived at after each of these mappings are given by

$$\begin{aligned}
\mathbf{y}_\mu^{(b)} &= M_i(\mathbf{y}_\mu^{(a)}) = \mathbf{f}^{(a)} + ({\mathbf{y}_\mu}^{(a)} - \mathbf{f}^{(a)})e^{-t_i} \\
&= \frac{B_i \mathbf{y}_\mu^{(a)}}{1+\psi_i^T \mathbf{y}_\mu^{(a)}}\,, && (7)\\
y_1^{(c)} &= M_c(y_1^{(b)}) = \frac{A^{(p,0)} A^m y_1^{(b)}}{1+\phi_m^{(p)} {y_1}^{(b)}}\,, \quad y_2^{(c)} = 0\,, && (8)\\
\mathbf{y}_\mu^{(d)} &= M_f(\mathbf{y}_\mu^{(c)}) = \mathbf{f}^{(c)} + (\mathbf{y}^{(c)} - \mathbf{f}^{(c)})e^{-t_f}\,, && (9)
\end{aligned}$$

where $\mathbf{y}_\mu^{(d)}$ is the exit point. Here,

$$B_i = I - \frac{\mathbf{f}^{(a)}\mathbf{e}_2^T}{f_2^{(a)}}\,, \quad \psi_i = \frac{-\mathbf{e}_2}{f_2^{(a)}}\,,$$

$$A^{(p,0)} = A^{(p-1)} \cdots A^{(0)}, \text{ for } p = 1, 2, 3, \text{ and } A^{(0,0)} = I\,,$$

$$\phi_m^{(p)} = \phi^{(m,0)} + A^m \phi_0^{(p)}\,,$$

$$\phi_0^{(p)} = \sum_{j=0}^{p-1} \phi^{(j)} A^{(j,0)} \quad (p = 1, 2, 3), \quad \text{and} \quad \phi_0^{(0)} = 0\,, \tag{10}$$

with $\phi^{(m,0)}$ from Eq. 6. Note that $\phi_0^{(p)}$ depends on $p \in \{0, 1, 2, 3\}$, the number of additional boundary crossings after the last complete circuit, $A^{(p)}$ and $\phi^{(p)}$ are the values for each of these last mappings.

The times taken by each stage are

$$t_i = \ln\left(1 - \frac{{y_2}^{(a)}}{{f_2}^{(a)}}\right)\,, \quad t_c = \log\left(1 + \phi_m^{(p)} {y_1}^{(b)}\right)\,,$$

$$t_f = t_s - t_i - t_c\,. \tag{11}$$

It is possible, however, that y_1 and y_2 complete spiralling into their threshold intersection within the available time, t_s. If $A < 1$, the time can be obtained by taking the limit of the denominator of M_c in Eq. (8) as $m \to \infty$ (with $p = 0$).

$$\exp(t_c^{(\infty)}) = \lim_{t\to\infty}(1 + \phi^{(m,0)} {y_1}^{(b)}) = 1 + \frac{\phi {y_1}^{(b)}}{1-A}\,. \tag{12}$$

If $t_s > t_{ic}^{(\infty)} = t_i + t_c^{(\infty)}$ then y_1 and y_2 remain at 0 until $t = t_s$, as can be shown by Filippov theory for the singular domain in which y_1 and y_2 are at threshold values. Thus, $\mathbf{y}_\mu^{(c)} = \mathbf{y}_\mu^{(d)} = \mathbf{0}$.

These maps can be formally composed to produce an explicit entry to exit point map, which can then be cast as a full n-dimensional map for the network.

IV. PARTITIONING THE ENTRY QUADRANT

The fate of the trajectory depends on the location of the entry point within the entry quadrant.

Define $t_{ic}^{(p)}$ as the time it takes to reach the final boundary from the entry point, when the final boundary follows the initial boundary by p transitions ($p \in \{0, 1, 2, 3\}$). Then the exit quadrant is p quadrants after the entry quadrant following m complete cycles, if $t_{ic}^{(p)} \leq t_s < t_{ic}^{(p+1)}$, where p is taken mod 4. Using Eqs. (11) and Eq. (7), the left hand bound on t_s gives the condition on the entry point as the linear inequality

$$y_2^{(a)} \geq \frac{f_2^{(a)}\left(1 - e^{t_s} + \phi_m^{(p)} y_1^{(a)}\right)}{1 + f_1^{(a)}\phi_m^{(p)}}\,. \tag{13}$$

The exit point is in quadrant p from the initial boundary following m full cycles if this condition is satisfied but the corresponding one for $p + 1$ is not. Thus, a sequence of lines can be calculated, which determine where in the $(1, 0)$ quadrant each possible itinerary occurs up to the exit point. These lines converge to a limiting line above which entry points lead to convergent spiralling.

Furthermore, the number of full cycles completed can be calculated as

$$m = \left\lfloor \frac{1}{\log A} \log\left(1 - \frac{1-A}{\phi}\phi^*\right)\right\rfloor\,,$$

$$\text{with } \phi^* = \frac{f_2^{(a)}(1 - e^{t_s}) - y_2^{(a)}}{y_2^{(a)} f_1^{(a)} - y_1^{(a)} f_2^{(a)}}\,. \tag{14}$$

Then p, and thus the exit quadrant, can be determined from $\phi_m^{(p)} \leq \phi^* < \phi_m^{(p+1)}$.

V. A FOUR-DIMENSIONAL EXAMPLE

A four-dimensional example serves to illustrate the phenomena described above.

$$\begin{aligned}\dot{y}_1 &= -y_1 + 1 - (1 - Z_3)(2Z_2 + (a_1 - 1)Z_1Z_2)\\ \dot{y}_2 &= -y_2 - 1 + (1 - Z_3)(2Z_1)\\ \dot{y}_3 &= -y_3 + 1 - 2Z_4\\ \dot{y}_4 &= -y_4 + 2Z_3 - 1 + (b_1 - 1)Z_3Z_4\,,\end{aligned}$$

with $a_1 > 1$ and $b_1 > 1$. The state transition diagram for this network is shown in Figure 1.

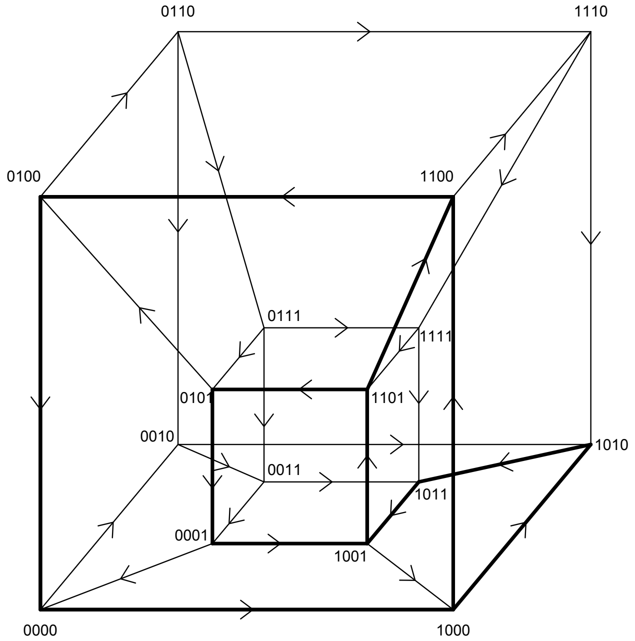

Fig. 1. The state transition diagram for the example network with $a_1 > 1$ and $b_1 > 1$. The bold lines show a possible cyclic trajectory, where the two small loops may be traversed many times in succession within the larger cycle.

Two variables, y_3 and y_4 oscillate periodically, unaffected by y_1 and y_2. When $y_3 < 0$, y_1 and y_2 undergo damped oscillations (spiralling). When $y_3 > 0$, they approach $(1, -1)$. The maps can be calculated as outlined above, and the entry quadrant $(1, 0)$ can be partitioned, as shown in Figure 2 for $a_1 = 1.2, b_1 = 40$.

Suppose a trajectory begins above the $m = \infty$ line, but in the $(1, 0)$ quadrant. Then the exit point is $(0, 0)$ and we can calculate the next entry point as

$$y_1^{(a)} = \frac{b_1 - 1}{2b_1}\,, \quad y_2^{(a)} = \frac{1 - b_1}{2b_1}\,.$$

Using these and Eq. (13) in the limit $m \to \infty$, we find that the trajectory spirals to convergence again if

$$(a_1 - 1)(b_1 - 1) \geq 8$$

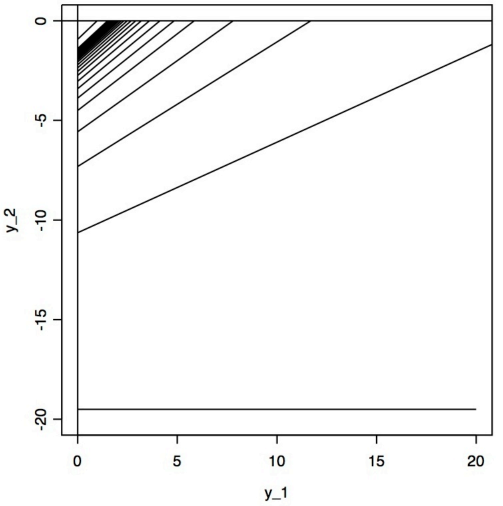

Fig. 2. Lower bounds of regions in the entry quadrant for itineraries with $m = 0, 1, \ldots, 5$ with $p = 0, 1, 2, 3$ in each case. The topmost diagonal line is the lower bound for the region above which spiralling is completed ($m = \infty$). Here, $a_1 = 1.2$, $b_1 = 40$.

and thus continues to do so periodically. This is a stable periodic 'bursting' pattern, with an interval in each period during which y_1 and y_2 are held stationary at their thresholds. Thus, for example, if $a_1 = b_1 = 4$ then there is a stable periodic orbit with convergent spiralling, while if $a_1 = 1.2$ and $b_1 = 40$, then following a convergent spiralling, the next entry point is outside the convergent spiralling region, and in fact the next spiralling event involves 20 full circuits and then exits in the positive quadrant. A fixed point of the full return map in the region for finite m then corresponds to a periodic orbit with an interval of spiralling that is interrupted before convergence.

The above analysis needs to be extended to the more realistic situation where degradation rates are unequal. Although the maps are much more complicated in that case, it may be possible to extract much of the same information as obtained here, especially when only two variables undergo the damped oscillation.

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