

On the number of steady states in a multisite phosphorylation-dephosphorylation cycle

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Statement of the problem

Multisite phosphorylation-dephosphorylation cycles have attracted much attention in recent years ([3]). The cycle, depicted in Figure 1, consists of two or more inter-convertible forms of one protein. The protein, denoted by S_0 , is ultimately converted into a product, denoted by S_n , through a cascade of “activation” reactions triggered or facilitated by an enzyme E ; conversely, S_n is transformed back (or “deactivated”) into the original S_0 , helped on by a second enzyme F .



Figure 1: A multisite phosphorylation-dephosphorylation cycle of size n .

One very important instance is that of Mitogen-Activated Protein Kinase (“MAPK”) cascades, which consist of three tiers of similar structures with multiple feedbacks. Each individual level of the MAPK cascades is a multisite phosphorylation-dephosphorylation cycle of size two. It was first demonstrated in [2] that multistationarity exists for a single level of MAPK cascades.

To count the number of steady states for a multisite phosphorylation-dephosphorylation cycle of size n , we first write down all elementary chemical reactions, and model them by a set of ordinary differential-algebraic equations according to mass action kinetics:

$$\begin{aligned}
 \frac{ds_0}{dt} &= -k_{\text{on}_0} s_0 e + k_{\text{off}_0} c_0 + l_{\text{cat}_0} d_1 \\
 \frac{ds_i}{dt} &= -k_{\text{on}_i} s_i e + k_{\text{off}_i} c_i + k_{\text{cat}_{i-1}} c_{i-1} - l_{\text{on}_{i-1}} s_i f + l_{\text{off}_{i-1}} d_i + l_{\text{cat}_i} d_{i+1}, \quad i = 1, \dots, n-1 \\
 \frac{dc_j}{dt} &= k_{\text{on}_j} s_j e - (k_{\text{off}_j} + k_{\text{cat}_j}) c_j, \quad j = 0, \dots, n-1 \\
 \frac{dd_k}{dt} &= l_{\text{on}_{k-1}} s_k f - (l_{\text{off}_{k-1}} + l_{\text{cat}_{k-1}}) d_k, \quad k = 1, \dots, n,
 \end{aligned} \tag{1}$$

together with the algebraic “conservation equations”:

$$E_{\text{tot}} = e + \sum_0^{n-1} c_i, \quad F_{\text{tot}} = f + \sum_1^n d_i, \quad S_{\text{tot}} = \sum_0^n s_i + \sum_0^{n-1} c_i + \sum_1^n d_i. \tag{2}$$

The parameters k_{on_0} , etc., are the rates of binding and unbinding. Small letters stand for the corresponding concentration of the proteins in capital letters. The variables c_0 , d_1 , etc.,

denote the concentration of the complex formed by S_0 and E , and the complex formed by S_1 and F , and so forth.

The central question to answer is how many positive steady states (1)-(2) can have. Setting the system at steady state, we obtain $3n + 3$ algebraic equations consisting of (2) and the right hand sides of (1). Following the beautiful observation by Gunawardena in [1], we then reduce them to two polynomial equations with two variables, and study the roots of these two polynomial equations, see [5] for details.

Conclusions

1. A lower bound for the number of steady states: under certain conditions (given precisely in [5]), the system has at least $n + 1$ (n) steady states when n is even (odd).

Currently available results on lower bounds, as in [4], can only handle the case when quasi-steady state assumptions are valid; we substantially extend these results to the fully general case by means of a perturbation argument which allows one to get around these restricted assumptions.

2. An upper bound of $2n - 1$ steady states, valid for all kinetic constants.

A novel feature of this result is that it does not depend on the kinetic parameters, which is crucial for models in biology where the values of parameters are not known in most cases. However, when more information of the parameters are available, sharper upper bounds can be obtained as follows.

3. For parameters near the standard Michaelis-Menten quasi-steady state conditions, there are at most $n + 1$ steady states.
4. For parameters far from the standard Michaelis-Menten quasi-steady state conditions, there is at most one steady state.

References

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