

Monotonicity of Kinetic Proofreading

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Abstract: This manuscript studies the monotonicity of multi-step ligand-receptor signalling motifs. Monotonicity with respect to parameters and state perturbations allow not only to exclude periodic solutions, but also to easily bound the responses in cases of bounded perturbations.

In classical coordinates, multi-step ligand-receptor signalling motifs are known not to be monotone. However, a generic coordinate transform allows for deriving conditions on the kinetic rate constants such that the signal is monotonously affected by perturbations to any one of the kinetic rate constants. The result is illustrated at the hand of a model of kinetic proofreading.

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1. INTRODUCTION

Signalling by ligands binding to their receptors are ubiquitous in cell biology. Examples are T cell activation (McKeithan, 1995), TNF-induced pro- and anti-apoptotic signalling (Schliemann et al., 2011), EPO-signalling (Lucia et al., 2016). Similar, though fully inside the cell are DNA repair of protein synthesis reaction (Hopfield, 1974). Multi-step activation was proposed as a mechanism to achieve high specificity even though the initial receptor-ligand binding step is rather unspecific.

In this paper, we study how the dynamic responses of the receptor-ligand complexes are affected by perturbations of the kinetic parameters. This could for example be achieved directly by targeting the production or degradation of the ligand, e.g. by injecting the drug as in hormone therapies, see e.g. Lucia et al. (2016). Alternatively, a drug could have an indirect effect, for example by modulating the concentration or the activity of phosphatases responsible for an activation step.

We will derive sufficient conditions such that an increase or decrease in a kinetic rate constant leads to a monotonous change of the signal induced by the last step of the signalling cascade. The main advantage of monotone system is that the state trajectories for parameters within a bounded set are bounded by the extreme values of the individual parameters, see Figure 1. This allows for efficient analysis and optimal control design approaches.

1.1 Receptor-ligand signalling

We analyse two variants of the initial signalling. First, the ligand L binds to the receptor R to form a complex C_1 and then this complex is activated in several, possibly reversible steps, e.g. via multiple phosphorylation, see Figure 2. Classical kinetic proofreading models assume this complex activation as being irreversible. However, as

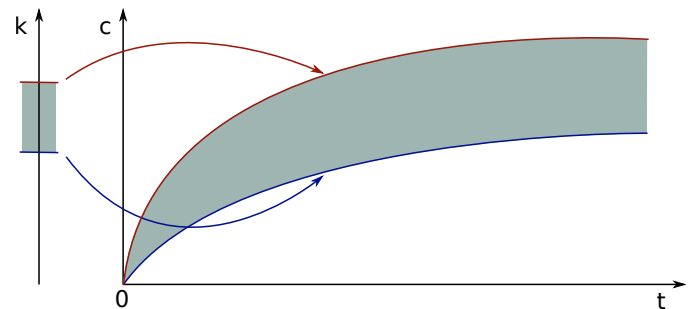


Figure 1. Sketch of a monotone system's response to parameter changes. In a monotone system, a bounded set of parameters is mapped to a bounded set of trajectories, where the extreme parameters correspond to extreme trajectories, see the blue and red cases.

shown below, reversibility has no adverse effect on the here presented analysis. Later, a second messenger will be activated by the last step. Throughout this paper, all reactions are modelled as mass action kinetics.

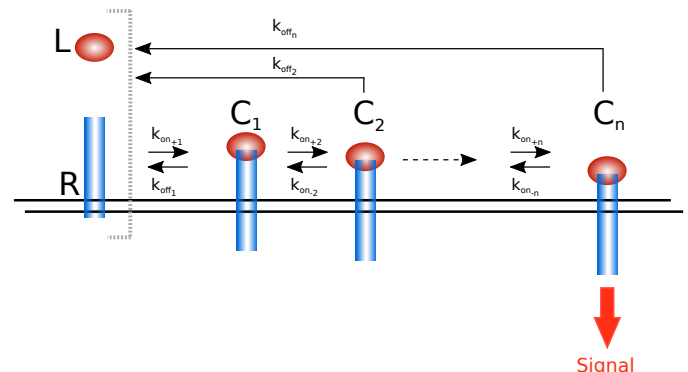


Figure 2. Kinetic proofreading reaction network

1.2 Novelty and structure of the paper

The key novelty of this paper is to uncover monotonic behaviour of multi-step ligand-receptor signalling modules, using a special, though generic coordinate transform. The mathematical tools employed here are graph theoretical approaches that connect the Jacobian of the differential equations with monotonicity.

The paper is structured as follows. First, Section 2 discusses the smallest possible system to illustrate the concept and introduce the terminology and notation. Then, monotonicity conditions are derived for a multi-step signalling system without (Section 3) and with second messenger (Section 4). Finally, the results are applied to a kinetic proofreading example in Section 5.

2. MOTIVATING EXAMPLE

Let us first study the following reaction network of three species R , L and C :



modelled by mass action kinetics. Let the state vector be

$$c = \begin{bmatrix} L \\ R \\ C \end{bmatrix}, \quad (2)$$

where each state (species) is non-negative. The reversible reaction (1) has the rate

$$v_1 = k_{\text{on}_+1}LR - k_{\text{off}_1}C, \quad (3)$$

where the reaction constants k_{on_+1} and k_{off_1} are positive constants. Then, the differential equation model corresponding to (1) is

$$\dot{c} = \frac{dc}{dt} = Nv_1 \quad (4)$$

with v_1 as in (3) and

$$N = \begin{bmatrix} -1 \\ -1 \\ 1 \end{bmatrix}.$$

The Jacobian matrix of the right hand side of (4) is

$$\begin{aligned} J &= \begin{bmatrix} -1 \\ -1 \\ 1 \end{bmatrix} \frac{\partial v_1}{\partial c} = \begin{bmatrix} -k_{\text{on}_+1}R & -k_{\text{on}_+1}L & k_{\text{off}_1} \\ -k_{\text{on}_+1}R & -k_{\text{on}_+1}L & k_{\text{off}_1} \\ k_{\text{on}_+1}R & k_{\text{on}_+1}L & -k_{\text{off}_1} \end{bmatrix} \\ &= \begin{bmatrix} -1 & -1 & 1 \\ -1 & -1 & 1 \\ 1 & 1 & -1 \end{bmatrix} \text{diag} \begin{bmatrix} k_{\text{on}_+1}R \\ k_{\text{on}_+1}L \\ k_{\text{off}_1} \end{bmatrix}. \end{aligned} \quad (5)$$

This Jacobian has the following sign pattern

$$\text{sign}J = \begin{bmatrix} - & - & + \\ - & - & + \\ + & + & - \end{bmatrix}, \quad (6)$$

where the symbol “+” states that the entry is ≥ 0 , a “-” stands for ≤ 0 while a “0” is an entry that is zero.

Following Sontag (2007), we now draw the corresponding species graph G . This has one node per species, and one signed edge per non-vanishing off-diagonal entry of the Jacobian, the sign of each edge is the sign of that entry in the Jacobian. More precisely, an edge from species i to species j corresponds to $J_{j,i}$. For the example (1), the species graph is shown in Figure 3. This graph has three

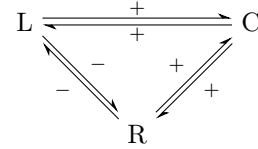


Figure 3. Species graph for Example (1)



Figure 4. Species graph for Example (1) in total coordinates. Arrows stand for an influence, not for a biochemical reaction. Blue arrow denote positive influence.

nodes (L , R and C) and six edges, two of them negative, the ones connecting L and R .

The sign of a path between two nodes is denoted as positive if the path contains an even number of negative edges, and negative for an odd number. If two nodes are connected by negative and positive paths, the graph is inconsistent. However, if a graph is consistent, then the system is monotone. Although graph consistency is only a sufficient condition, it is a condition that is relatively easy to check, thus can quickly give insights as will be seen in this paper.

From the species graph in Figure 3 it follows that a path from L to R has either a negative sign when using the direct connection, or a positive one if passing via C . Thus, this graph is inconsistent. As a consequence, no conclusion can be drawn, whether this system is monotone or not.

Lucia et al. (2016) however showed that the same network is monotone, when transformed into the following coordinates

$$\tilde{c} = \begin{bmatrix} L + C \\ R + C \\ C \end{bmatrix} = \begin{bmatrix} L_{\text{tot}} \\ R_{\text{tot}} \\ C \end{bmatrix} \quad (7)$$

as

$$\dot{\tilde{c}} = \begin{bmatrix} 1 & 0 & 1 \\ 0 & 1 & 1 \\ 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} -1 \\ -1 \\ 1 \end{bmatrix} v_1 = \begin{bmatrix} 0 \\ 0 \\ 1 \end{bmatrix} v_1 \quad (8)$$

with

$$v_1 = k_{\text{on}_+1}(L_{\text{tot}} - C)(R_{\text{tot}} - C) - k_{\text{off}_1}C \quad (9)$$

and the Jacobian

$$\begin{aligned} \tilde{J} &= \frac{\partial \dot{\tilde{c}}}{\partial \tilde{c}} = \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ k_{\text{on}_+1}R & k_{\text{on}_+1}L & -k_{\text{off}_1} \end{bmatrix} \\ &= \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 1 & 1 & -1 \end{bmatrix} \text{diag} [k_{\text{on}_+1}R \ k_{\text{on}_+1}L \ k_{\text{off}_1}]. \end{aligned} \quad (10)$$

As the diagonal matrix has only non-negative entries, the Jacobian \tilde{J} has the sign pattern

$$\text{sign}\tilde{J} = \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ + & + & - \end{bmatrix}. \quad (11)$$

This Jacobian is now sign consistent and the system is monotone, see Figure 4 for the corresponding species graph.

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