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Reciprocal enzyme regulation as a source of bistability in covalent modification cycles

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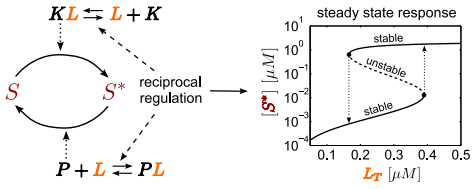
HIGHLIGHTS

- We study covalent modification cycles with reciprocally regulated converter enzymes.
- Reduced models are derived by means of a (total) quasi-steady state approximation.
- The occurrence of bistability is associated with a double negative feedback loop.
- Our results support the view that the PFK1/F1,6BPase cycle can exhibit bistability.
- They provide a novel view on the origin of bistability in the Cdk1–Wee1–Cdc25 system.

GRAPHICAL ABSTRACT



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ABSTRACT

Covalent modification cycles (CMCs) are the building blocks of many regulatory networks in biological systems. Under proper kinetic conditions such mono-cyclic enzyme systems can show a higher sensitivity to effectors than enzymes subject to direct allosteric regulation. Using methods from reaction network theory it has been argued that CMCs can potentially exhibit multiple steady states if the converter enzymes are regulated in a reciprocal manner, but the underlying mechanism as well as the kinetic requirements for the emergence of such a behavior remained unclear. Here, we reinvestigate CMCs with reciprocal regulation of the converter enzymes for two common regulatory mechanisms: allosteric regulation and covalent modification. To analyze the steady state behavior of the corresponding mass-action equations, we derive reduced models by means of a quasi-steady state approximation (QSSA). We also derive reduced models using the total QSSA which often better reproduces the transient dynamics of enzyme-catalyzed reaction systems. Through a steady state analysis of the reduced models we show that the occurrence of bistability can be associated with the presence of a double negative feedback loop. We also derive constraints for the model parameters which might help to evaluate the potential significance of the mechanisms described here for the generation of bistability in natural systems. In particular, our results support the view of a possible bistable response in the metabolic PFK1/F1,6BPase cycle as observed experimentally in rat liver extracts, and it suggests an alternative view on the origin of bistability in the Cdk1–Wee1–Cdc25 system.

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1. Introduction

Covalent modification cycles (CMCs), also known as mono-cyclic enzyme systems, are recurring regulatory structures found

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in many metabolic and signal transduction networks (Fell, 1997; MacDonald, 2004). In such systems, a substrate molecule is interconverted between an inactive and an active state by an antagonistic pair of converter enzymes, e.g. by a kinase and a phosphatase in the case of ubiquitous phosphorylation cycles (Cohen, 2001). It is well-known that CMCs can exhibit highly sigmoidal response behavior, known as zero-order ultrasensitivity, which occurs if the converter enzymes operate in saturation (Goldbeter and Koshland, 1981). Under these conditions, small changes in the activity of either enzyme can lead to large changes in the amount of covalently modified substrate. This sensitivity enhancement, which has been observed in several enzyme systems under in vitro conditions (LaPorte and Koshland, 1983; Meinke et al., 1986; Huang and Ferrell, 1996), is believed to make covalent modification cycles well suited for the regulation of metabolic processes by allosteric effectors or to amplify extracellular stimuli.

However, sensitivity enhancement comes at a cost: in the case of phosphorylation cycles one molecule of ATP is hydrolyzed per substrate cycle. Hence, such CMCs essentially behave as ATPases if their operation is not controlled. To prevent this 'futile' cycling of ATP, the activities of the converter enzymes are often regulated in a reciprocal manner such that when, for example, the kinase is in a high activity state the phosphatase activity is low and vice versa (Fig. 1).

A classical example for such a regulatory pattern is the interconversion between fructose-6-phosphate and fructose-1,6-bisphosphate (Fig. 1A), which is mediated by phosphofructokinase 1 (PFK1) and fructose-1,6-bisphosphatase (F1,6BPase). In liver cells, the reciprocal regulation of the converter enzymes by AMP and fructose-2,6-bisphosphate (F2,6BP) ensures that the enzymatic reaction chain of the central metabolism either generates

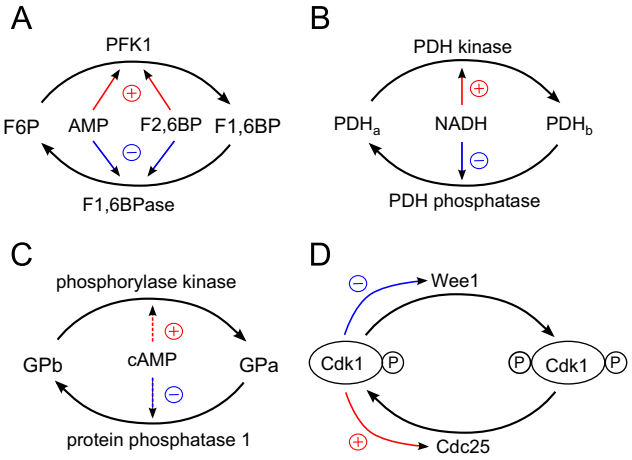

Fig. 1. Reciprocal regulation in covalent modification systems: examples from metabolic (A–C) and cell-cycle regulation (D). (A) Interconversion between fructose-6-phosphate (F6P) and fructose-1,6-bisphosphate (F1,6BP) by phosphofructokinase 1 (PFK1) and fructose-1,6-bisphosphatase (F1,6BPase). Adenosine monophosphate (AMP) and fructose-2,6-bisphosphate (F2,6BP) have opposing effects on the activities of the converter enzymes as indicated by the 'plus' and 'minus' signs (Pilkis et al., 1988). (B) Interconversion between active (PDH_a) and inactive (PDH_b) forms of pyruvate dehydrogenase (PDH) by PDH kinase and PDH phosphatase. NADH acts as an allosteric effector which regulates the activity of the converter enzymes in a reciprocal manner (Pettit et al., 1975). (C) Interconversion between active (GPa) and inactive (GPb) forms of glycogen phosphorylase by phosphorylase kinase and protein phosphatase 1. Dashed lines indicate that the reciprocal effect of cyclic AMP (cAMP) on the activities of the converter enzymes occurs through a series of intermediate steps (Fell, 1997), which have been omitted for clarity. (D) Simplified scheme for the interconversion between active (monophosphorylated) and inactive (double-phosphorylated) cyclin-dependent kinase 1 (Cdk1) by the kinase Wee1 and the phosphatase Cdc25. Cdk1 inactivates its inhibitor Wee1 and it activates its activator Cdc25 both through multiple phosphorylations, which effectively creates two positive feedback loops (Ferrell, 2008).

energy in the form of ATP through glycolytic degradation of glucose into pyruvate (when PFK1 is active) or, under conditions of starvation, pyruvate is reconverted into glucose (gluconeogenesis) through the F1,6BPase catalyzed reaction (Scrutton and Utter, 1968; Pilkis et al., 1988).

Other examples from metabolic regulation include the reciprocal regulation of the converter enzymes in the phosphorylation cycle of the pyruvate dehydrogenase by NADH (Fig. 1B) and the reciprocal effect of cyclic AMP (cAMP) on the converter enzymes of the phosphorylation cycle of the glycogen phosphorylase (Fig. 1C). In the latter case, the reciprocal effect of cAMP is not via direct allosteric interactions with the converter enzymes, but through a series of intermediate steps: rising levels of cAMP first lead to an activation of protein kinase A, which then activates both phosphorylase kinase and the inhibitor of protein phosphatase 1 (Fell, 1997).

An even more intricate regulatory pattern is found in the Cdk1–Wee1–Cdc25 system (Fig. 1D), which governs the transition into M-phase of the cell cycle in eukaryotes (Morgan, 2006). Here, the activities of the converter enzymes (Wee1 kinase and Cdc25 phosphatase) are regulated by the active (mono-phosphorylated) form of the substrate (Cdk1-P) itself (Ferrell, 2008). In contrast to the previous examples regulation does not occur via allosteric interactions, but through (multiple) phosphorylations of the converter enzymes (Kumagai and Dunphy, 1992; Tang et al., 1993).

The theoretical analysis of mono-cyclic enzyme systems has a long history beginning with the work of Stadtman and Chock. They argued that the sensitivity of CMCs with respect to changes in allosteric effector concentrations can, by far, exceed that of single enzymes (Stadtman and Chock, 1977). However, their analysis was based on several simplifying assumptions (e.g. neglecting enzyme–substrate complexes in the conservation relations), which prevented them from recognizing the zero-order effect for the generation of ultrasensitivity, which was later discovered by Goldbeter and Koshland (1981).

Cárdenas and Cornish-Bowden (1989) reinvestigated CMCs by assuming Michaelis–Menten kinetics for the converter enzymes from the outset. They argued that CMCs do not necessarily produce a higher degree of sensitivity to an allosteric effector compared to a system where the effector directly affects the target enzyme. From numerical studies of the corresponding steady state equations they identified several necessary conditions that must be fulfilled for a CMC to generate a high sensitivity to allosteric effectors, among them the requirement for reciprocal regulation of the converter enzymes. Later, Patnaik (1995) noted that CMCs with reciprocal regulation of the converter enzymes should also be able to generate a bistable response, where two stable steady states would coexist for a certain range of effector concentrations. To demonstrate the existence of a bistable regime, he used a graph-theoretical approach based on the reaction network theory of Feinberg (1987, 1988). However, no attempt was made to understand the origin or the kinetic conditions for bistability on a mechanistic level.

Due to the general importance of the regulatory systems shown in Fig. 1 and to gain deeper insights into the regulatory mechanisms that may potentially lead to bistability in covalent modification systems we reinvestigate CMCs with reciprocal regulation of the converter enzymes for two common regulatory schemes: allosteric regulation and covalent modification. In the latter case, two subcases are distinguished: covalent modification by a single auxiliary enzyme and covalent modification by two auxiliary enzymes. In contrast to the previous studies (Cárdenas and Cornish-Bowden, 1989) we do not assume Michaelis–Menten kinetics for the converter enzymes, but instead begin with the full set of mass-action equations. To analyze the steady state behavior of these equations, we derive reduced models by means

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