A Design Principle for an Autonomous Post-translational Pattern Formation

Highlights
- Reversible two-site phosphorylation of a substrate can produce spatial patterns
- This design principle is mass conserved, non-autocatalytic, and non-allosteric
- Cyclic reactions with biased diffusion and enzyme sequestration are design motifs
- Stochastic simulation revealed two reaction-diffusion cycles that shape patterns

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In Brief
Using computer simulations, Sugai et al. showed that a generic Michaelis-Menten scheme of two-site reversible phosphorylation can produce Turing patterns in the spatial distribution of a substrate's modification states. A random parameter search found typical combinations of reaction parameters accounting for the pattern formation and tuning the pattern shapes.
A Design Principle for an Autonomous Post-translational Pattern Formation

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SUMMARY

Previous autonomous pattern-formation models often assumed complex molecular and cellular networks. This theoretical study, however, shows that a system composed of one substrate with multisite phosphorylation and a pair of kinase and phosphatase can generate autonomous spatial information, including complex stripe patterns. All (de-)phosphorylation reactions are described with a generic Michaelis-Menten scheme, and all species freely diffuse without pre-existing gradients. Computational simulation upon >23,000,000 randomly generated parameter sets revealed the design motifs of cyclic reaction and enzyme sequestration by slowly diffusing substrates. These motifs constitute short-range positive and long-range negative feedback loops to induce Turing instability. The width and height of spatial patterns can be controlled independently by distinct reaction-diffusion processes. Therefore, multisite reversible post-translational modification can be a ubiquitous source for various patterns without requiring other complex regulations such as autocatalytic regulation of enzymes and is applicable to molecular mechanisms for inducing subcellular localization of proteins driven by post-translational modifications.

INTRODUCTION

Theoretical modeling has been a powerful tool to analyze the mechanism of autonomous pattern formation in biological systems (Karsenti, 2008; Kondo and Miura, 2010). One of the best-known models is the Turing model deploying reaction-diffusion equations (Turing, 1952). The Turing instability can arise from a system with two components, an activator with a slow diffusion rate and an inhibitor with a fast diffusion rate (Gierer and Meinhardt, 1972). The activator increases the concentrations of both the activator and the inhibitor within a short range of space, while the inhibitor represses the concentration of the activator over a long range. The detailed mechanism to realize the activation/inhibition can be varied; for example, an activator-depleted substrate scheme assumes that the inhibitory pathway is passively mediated by the insufficient supply to produce the activator (Meinhardt, 2008).

The key features underlying the Turing model have been discovered in the molecular and cellular mechanisms of biological pattern formation. At a cellular-circuit level, biological examples of the Turing model were reported in pattern formation of animal skin (Asai et al., 1999; Kondo and Asai, 1995) and in the process of vertebrate morphogenesis (Economou et al., 2012; Müller et al., 2012; Sheth et al., 2012). At a molecular-network level, a system consisting of a group of proteins called MinC, MinD, and MinE is known to show typical spatiotemporal patterns explained based on Turing instability (Raskin and de Boer, 1999; Zieske and Schwille, 2013; Loose et al., 2008). Eukaryotic cells also employ reaction-diffusion systems, including GTPase Cdc42 and kinase-substrate network of PAR proteins and atypical protein kinase C (aPKC) (Etienne-Manneville and Hall, 2002; Hoege and Hyman, 2013) as an underlying mechanism for cellular pattern formation.

Theoretical models to simulate such molecular mechanisms of pattern formation typically employed complex reaction networks (e.g., oligomerization and/or mutual inhibition among PAR proteins [Dawes and Munro, 2011; Tostevin and Howard, 2008] or cell-compartment specific activation of enzymatic activities [Alonso, 2016; Alonso and Bár, 2010, 2014; Halatek and Frey, 2012; Otsuji et al., 2007]). Alternatively, a more generic set of enzymes and substrates might be sufficient for autonomous pattern formation. Analysis using the generic but not too abstractive reaction scheme such as Michaelis-Menten scheme (Michaelis et al., 2011) allows us to compare the model parameters with the biochemically measurable values. A generic set of components to achieve reversible phosphorylation is one substrate and a kinase and a phosphatase (Kholodenko, 2006). Despite its simple setting, it has been found that reversible phosphorylation at a single substrate site can produce an ultrasensitive response in the phosphorylation state of the substrate along with a linear change of kinase/phosphatase activity (Goldbeter and Koshland, 1981). If the number of phosphorylation sites is increased, the phosphorylation status can have two or more distinct steady states (Markevich et al., 2004; Thomson and Gunawardena, 2006). It was also discovered that a traveling wave...
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