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Exploring the Design Principle of Emergent Properties in Biological Systems

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Abstract Life sciences are witnessing an interdisciplinary research induced shift in paradigm from the traditional characterization of individual molecules towards an understanding of interactive pathways and networks. Accordingly, it is now becoming widely accepted that an engineering science approach needs to be integrated with wet lab life science research such that the role of genes, proteins, metabolites and cells can be understood and defined through their interactions. The principal goal of systems biology is to understand the design principle of emergent properties in complex biological phenomena. We can think of a cell as made of several superimposed molecular interaction networks such as metabolic networks, signal transduction networks, and gene transcription networks. One good way of understanding such large scale complex networks is to investigate their basic building blocks ('network motifs') and corresponding cellular functioning ('emergent property'). In this presentation, dynamical analysis of network motifs in relation to various biological emergent properties is to be used as a vehicle for discussion on current systems biological challenges.

Keywords emergent property, biological network, network motif, cellular dynamics, feedback loop, feedforward loop, design principle, systems biology

Life sciences witness a shift of paradigm from traditional characterization of individual molecules towards an understanding of interactive pathways and networks. The role of genes, proteins, metabolites and cells can be understood and defined through their interactions and it is this very focus on intra- and inter-cellular dynamics that Systems Biology concerns (Wolkenhauer et al., 2003).

Cellular processes are driven by various types of molecules such as genes, proteins, and metabolites. The regulation networks, of which the molecules form a part, are often highly inter-connected in order to carry out some coordinated cell function, and within them there are frequently observed patterns that are described as 'network motifs'.

One of the interesting network motifs is the incoherent feed-forward loop (FFL) which has two oppositely signed paths from a single input to a single output. At first glance, the structure of this incoherent FFL seems to be very inefficient as the input signal both activates and inhibits the output. However, the incoherent FFL is frequently found in many organisms.

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The behaviour of incoherent FFLs is biphasic and can be further classified into two types: time- and dose-dependent. Time-dependent biphasic behaviour can be thought of as a 'pulse generator', since an input generates an output response that initially increases but subsequently decreases as time evolves, even if the input is sustained. The time-dependent biphasic response is required to achieve a transient, rather than a sustained, activation. This is particularly important to precisely control the cell fate decision. Dose-dependent biphasic behaviours can be thought of as 'band-pass filters' since the steady-state output response initially increases and subsequently decreases with increasing input dose. The dose-dependent biphasic response is required when an output responds only to a certain range of input dose strength.

Although these two different types of biphasic responses are required for different biological purposes, they are implemented by the same incoherent FFL structure. Intriguingly, there are many incoherent FFLs which have different biphasic behaviours. A question then arises whether there is any reason why the structurally identical FFLs perform such different functional roles? To answer this question, we have carried out computational studies based on a simple mathematical model of the incoherent FFL, which captures the essential dynamics. In particular, we have investigated the optimal kinetic parameters that maximize the time- and dose-dependent biphasic behaviours using a genetic algorithm (GA). Through extensive simulation studies, using optimal parameters obtained from the GA, we have found that the dynamics of the two types of incoherent FFLs are mutually exclusive. From these computational results and previous experimental observations, we hypothesize that an incoherent FFL can exhibit different dynamical characteristics depending on whether it has been evolved to have a time- or dose-dependent biphasic response. We further postulate that various types of incoherent FFLs might have been optimally designed to perform their own functions under different cellular contexts (Kim et al., 2008).

Another interesting network motif is a feedback loop. Interestingly, such feedback loops are often found as a coupled structure rather than a single isolated form in various cellular circuits. There have been some studies on the coupled feedback loops (CFLs) for particular cases, but no unified investigation has been reported. The question is about the advantages of such CFLs that must have been evolved to achieve specific regulatory functions in cellular circuits. To answer this question, we first explore the dynamic characteristics of single feedback loops and then study all possible combinations of such single feedback loops. We can classify the coupled structures of feedback loops into three basic modules: PP (a positive feedback loop + a positive feedback loop), PN (a positive feedback loop + a negative feedback loop), and NN (a negative feedback loop + a negative feedback loop). We can consider any coupled feedback circuit as a combination of these basic modules. For simplicity, we consider those CFLs sharing only one node, but the results can be extended to any topology without loss of generality. Through extensive computer simulations and integrative analysis of all scattered previous experimental results, we discovered that the CFLs have their own roles which single feedback loops cannot achieve. In particular, we have found that PP enhances signal amplification and bistability, NN realizes enhanced homeostasis, and PN guarantees reliable decision by properly modulating signal responses and effectively dealing with noises (Shin et al., 2008; Kim et al., 2008b; Kim et al., 2008c; Goh et al, 2008; Kwon and Cho, 2007b; Kim et al., 2007a; Kim et al., 2007b).

Robustness is a key property of biological networks that enables to maintain their functioning against external and internal perturbations. This feature has been ubiquitously observed in various biological examples. Recent studies showed that robustness and fragility of biological networks are correlated with each other, but the underlying design principle for such a phenomenon is still largely unknown. So, we have investigated the robustness and fragility of biological networks through computational experiments on network models with a particular focus on the role of feedback loops. To do this, we considered the robustness of a network defined as the capability of maintaining the stable equilibrium state against perturbations of an initial state. In this regard, the robustness can be measured by a probability with which the equilibrium state is maintained against perturbations in its initial state. Then, we can measure the fragility by a probability with which the robustness can be lost by unexpected mutations.

Through extensive computational experiments, we found that robust networks tend to have a larger number of positive feedback loops and a smaller number of negative feedback loops. Moreover, we found that the nodes of a robust network subject to perturbations are mostly involved with a smaller number of feedback loops compared with the other nodes not subject to such perturbations. This implies that there is a fundamental topological difference among the network nodes depending on their history of perturbations. Such a topological difference results in the fragility against unexpected mutations at the nodes not previously exposed to any perturbation (Kwon and Cho, 2008a; Kwon and Cho, 2008b; Kwon and Cho, 2007a; Kwon et al., 2007).

In summary, I conclude that the topological property of a biomolecular regulatory network characterized by incoherent FFLs and multiple CFLs is crucial in determining the emergent properties of various cellular dynamics.

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