Dynamic Motifs of Cellular Networks: Coupled Feedback Loops

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Feedback loops as a network motif

Cellular networks are composed of complicated interactions among biomolecules and complex cellular behaviors can be seen as a result of such interactions. For proper understanding of various cellular behaviors, it is important to figure out the topological and dynamical characteristics of cellular circuits. In this respect, network motifs (1) have been considered. For instance, feedback loops and cascades in signaling networks, and feedforward loops in gene transcriptional networks were studied. Among those, feedback loops have been considered as important motifs (2,3) in maintaining cellular homeostasis and making critical decisions such as differentiation and apoptosis.

Coupled feedback loops as network motifs

We have investigated various types of feedback loops and found that feedback loops often exist as a coupled structure rather than a single isolated form in many cellular circuits (see Fig. 1 for examples of various coupled feedback structures). There have been studies on the coupled feedback loops for some special cases (4-7), but there has been no

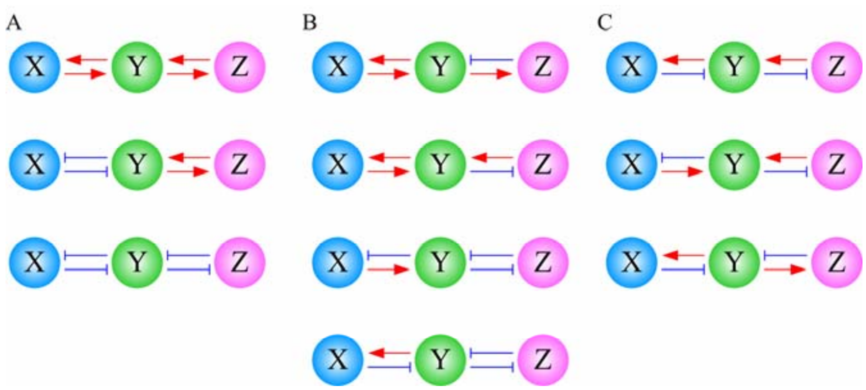

Figure 1 Network motifs of coupled feedback loops. (A) PP (positive feedback loop + positive feedback loop). (B) PN (positive feedback loop + negative feedback loop). (C) NN (negative feedback loop + negative feedback loop).

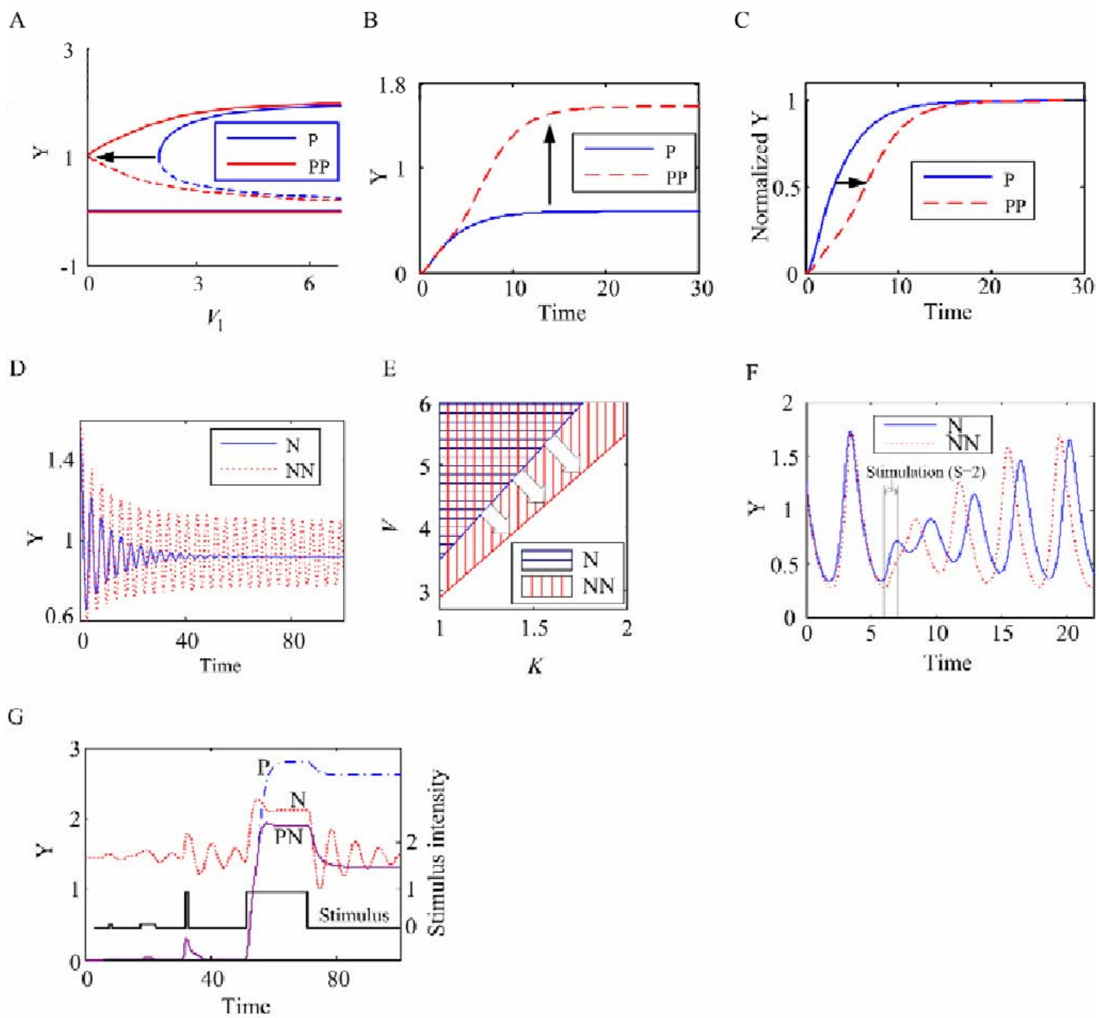

Figure 2 Simulation results illustrating the differences of coupled feedback loops and single feedback loops. (A) Bifurcation diagrams of P and PP. (B) Response curves of P and PP. (C) Normalized response curves of P and PP. (D) Different oscillatory patterns of P and PP for the same parameter values (i.e., a damped oscillation of N and a sustained oscillation of NN). (E) The parameter ranges of N and NN for sustained oscillations. (F) Oscillation profiles of N and NN when a strong stimulation (S=2) is given at time 6. (G) Temporal response curves of P, N, and PN for noisy stimulus.

unified investigation. In particular, we were intrigued by the advantages of coupled feedback loops that must have been evolved to achieve specific regulatory functions in cellular circuits. To address this problem, we first explored the dynamical characteristics of single feedback loops and then studied all possible combinations of such single feedback loops.

Dynamical roles of coupled feedback loops

We have classified the coupled structures of feedback loops into three basic modules: PP (positive feedback loop + positive feedback loop) (Fig. 1A), PN (positive feedback loop + negative feedback loop) (Fig. 1B), and NN (negative feedback loop + negative feedback loop) (Fig. 1C). For simplicity, we have considered the coupled feedback loops sharing only one node, but the results can be extended to any other topologies without loss of generality. From extensive computer simulations and integrative analysis of all the scattered previous experimental results, we found that the coupled feedback loops have distinct roles that cannot be achieved by single feedback loops (8). In particular, we found that PP enhances bistability (Fig. 2A) and induces a slower but amplified signal response (Fig. 2B & C), NN realizes enhanced homeostasis (oscillation) (Fig. 2D, E & F), and PN guarantees reliable decisions by properly modulating signal responses and effectively dealing with noises (Fig. 2G) (these results were verified over wide parameter ranges).

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