

Topology of biological networks and reliability of information processing

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Survival of living cells and organisms is largely based on highly reliable function of their regulatory networks. However, the elements of biological networks, e.g., regulatory genes in genetic networks or neurons in the nervous system, are far from being reliable dynamical elements. How can networks of unreliable elements perform reliably? We here address this question in networks of autonomous noisy elements with fluctuating timing and study the conditions for an overall system behavior being reproducible in the presence of such noise. We find a clear distinction between reliable and unreliable dynamical attractors. In the reliable case, synchrony is sustained in the network, whereas in the unreliable scenario, fluctuating timing of single elements can gradually desynchronize the system, leading to nonreproducible behavior. The likelihood of reliable dynamical attractors strongly depends on the underlying topology of a network. Comparing with the observed architectures of gene regulation networks, we find that those 3-node subgraphs that allow for reliable dynamics are also those that are more abundant in nature, suggesting that specific topologies of regulatory networks may provide a selective advantage in evolution through their resistance against noise.

genetic networks | biological computation | robustness | stability | computer model

The processes of life in cells and organisms rely on highly reproducible information processing. It has been a long-standing question how reliability in biological circuits is accomplished even though these involve elements with nonreproducible, noisy dynamics (1). In nerve cells, for example, firing of spikes is not fully determined by synaptic input (2). Similarly, in gene regulation, protein concentrations evolve in a quite irreproducible manner under given promoter levels (3–6). In the steady state of a system, such fluctuations can easily be dampened, even solely on the basis of properties of the single elements. In genetic transcription, for example, autoregulation of single genes successfully attenuates noise (7). In dynamical situations with rising and falling levels of activation, however, intrinsic noise of the interacting elements causes nonlocal effects, e.g., through fluctuations of switching delays (3, 8). In larger systems of interacting elements, such fluctuating delays can cause stability problems because, e.g., timing and coordination between the elements may fail. Such system failures may be incurable on the single-element level (e.g., single gene level) because, eventually, the entire circuit can be involved. In this work we study this problem in detail. We ask under which conditions a complex network of fluctuating dynamical elements can be stabilized by a suitable circuit design, maintaining an overall reproducible system dynamics. Our study is motivated by the extraordinary reliability of gene regulation networks as observed in living organisms and as exemplified by the dramatic consequences of rare system failures, e.g., at the origin of complex diseases.

The question of when a circuit is robust and the implications of desired reliability for circuit design are well known in electrical engineering. There, reliable design of electronic circuits is achieved by specific circuit architectures and has become a field

of its own since the early days of electrical switching circuit design (9). In the study of biological circuits, the question of reliable circuit design, although being equally important, has not yet gained as much attention, mostly because of lack of detailed knowledge of the circuitry so far. However, during recent years, biochemical interactions involved in the information processing within or between cells of an organism have been characterized systematically, up to an emerging systemwide picture. Such networks have been obtained for gene regulation (10–13), including regulatory networks of entire cells as of yeast *Saccharomyces cerevisiae* (14, 15), as well as for signal transduction (16) and neuronal information processing (17). Such systemwide perspectives allow one to take a closer look at biological circuit design. Do biological networks show structural signatures that point to reliable design, similarly to the specific structures used in designed circuits?

Architectural features of biological signaling networks have been analyzed recently, drawing a surprisingly coherent picture for networks of different origins. Gene regulation networks, for example, when reduced to their graph representation (i.e., drawn as nodes and links), show strong mutual similarities despite their different origin and even when compared with networks of different function as hard-wired neural networks (18). When comparing each biological network with a randomized version of itself (19), some subgraphs are seen to be relatively abundant whereas others are strongly suppressed (20). This pattern is not shared by other, mostly nonsignaling networks, such as the World Wide Web, social acquaintance networks, and the graphs of word adjacency in various languages. Although this observation points at possible universal features in the wiring of signaling networks, its origin is a major open question at present.

We ask here whether architectural features of biological networks are related to the ability of reliable information processing. For this purpose we study reproducibility of dynamics in model networks of information-processing units in the presence of noise, here implemented as fluctuating response times of the nodes. Starting with the simplest system of two mutually coupled nodes, we observe that there are two distinct classes of dynamical circuit behavior. In the class of reliable dynamics the nodes regain synchronization after random perturbations, whereas for the class of unreliable dynamics the system does not self-synchronize. This distinction appears in a formulation as differential equations for continuous variables (as, e.g., protein concentrations), as well as in models with discrete binary state variables, both exhibiting the same synchronization properties. Turning to networks with three nodes, we find that the occurrence of reliable dynamics strongly depends on the underlying topology. One observes that reliable dynamics is more likely to appear on those triads that have been found as building blocks (motifs) in real biological networks. Further insight into the relationship between topology and reliability is gained by the analysis of cyclic behavior (attractors). Dynamics

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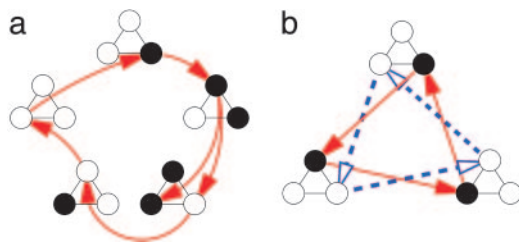


Fig. 6. Causal structure of attractors. (a) The attractor shown in Fig. 5 has one causal chain of flipping events triggering each other. (b) A different attractor (on the same wiring diagram) with two independent causal chains of flipping events. The attractor in b is obtained after replacing the NOR in Fig. 5 with the Boolean function that gives 1 if and only if it receives 0 from the top node and 1 from the left node.

time t_{ret} simply retards all subsequent events by the same amount of time. Event (i, t) in the unperturbed scenario becomes event $(i, t + t_{\text{ret}})$, but the sequence of states encountered by the system remains the same. This built-in compensation of fluctuations renders the dynamics reliable.

An example of an unreliable dynamical attractor is shown in Fig. 6b. In this case there are two separate chains of flipping events, one connecting the on-events and the other connecting the off-events. Retarding an event in one of the chains does not influence the timing of the events in the other chain. By repeatedly retarded on-events, the time span that a node spends in the on-state is gradually reduced and eventually reaches zero. Then the system is caught in a fixed point and does not follow the attractor any longer. In general, the dynamics is reliable if and only if the attractor contains exactly one causal chain.

Feedback Loops of Arbitrary Length

The relation between topology and reproducibility is particularly obvious in isolated feedback loops. Such loops are rare in biological contexts [short oscillating loops occur in the gene networks controlling the cell cycle (34)], however, are tractable and therefore useful in theoretical models. Consider $N \geq 2$ nodes connected in a directed cycle, i.e., each node receives input only from its (clockwise) predecessor. If node $i - 1$ changes state (“flips”) at time t , node i will change state at time $t + \tau_i$, node $i + 1$ will change state at time $t + \tau_i + \tau_{i+1}$ and so forth. The dynamics can be interpreted as “wave fronts” of flipping events traveling at constant speed on a ring. The nodes are located on this ring at distances given by the transmission delays τ_i , as illustrated in Fig. 7. For constant transmission delays, the dynamics is periodic (with period $\tau_1 + \dots + \tau_N$). However, when a transmission delay τ_i fluctuates, consecutive passages of wave fronts from node $i - 1$ to node i take different times. Eventually wave fronts encounter and annihilate: Flipping from 0 to 1 and back to 0 at the same time results in no flipping at all.

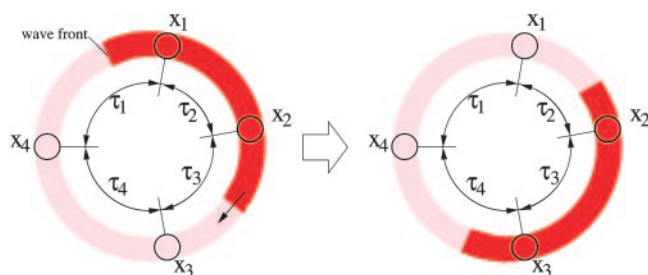


Fig. 7. The wave front picture of dynamics in a feedback loop with $N = 4$ nodes all performing the Boolean function Identity.

Annihilations of wave fronts happen stochastically because they are driven by the random fluctuations of transmission delays.

Consequently, the dynamics is reproducible only if wave fronts cannot annihilate. This condition is fulfilled in the cases of a single wave front or no wave fronts at all. In the latter case the state of the system is a fixed point. When all nodes perform the function Identity, as in the example of Fig. 7, the number of wave fronts is even. Two or more wave fronts can annihilate, eventually leading to irreproducible dynamics. The only reproducible dynamics in this case is a system that stays on a fixed point, corresponding to zero wave fronts. However, if one of the nodes performs the function Negation then this node acts as a resting wave front, because states on the two sides are always different. The total number of wave fronts (including the resting one) is still even, but now the number of traveling wave fronts is odd. Initial conditions exist such that there is a single traveling wave front, giving reproducible dynamics. The two cases generalize easily. For an even number of inhibitory couplings (i.e., an even number of nodes performing Inversion) the dynamics is reliable if and only if one of the two fixed points is chosen as initial condition. Then the fraction of initial conditions with reproducible dynamics is

$$q_{\text{even}} = 2/2^N = 2^{N-1}, \quad [11]$$

for a feedback loop of N nodes. Analogously we find for the feedback loop with an odd number of inhibitory couplings

$$q_{\text{odd}} = 2N/2^N = N2^{N-1}, \quad [12]$$

where $2N$ initial conditions generate a singular wave front. Note that the only feedback loop that yields reproducible dynamics for all initial conditions has $N = 2$ nodes, one performing Inversion and the other Identity. This is the system studied as case (i) given by Eqs. 1 and 2.

Summary and Conclusions

Biological information processing systems as circuits of intrinsically noisy elements are constrained by the need for reproducible output. Effects of fluctuations on the system level can be suppressed through a suitable circuit design. This finding is a main result of our study of the influence of network topology on the reliability of information processing in networks of switches with fluctuating response times. In the reliable scenario, the elements cooperatively suppress fluctuations and tend to synchronize their operations. In the unreliable scenario, in contrast, networks desynchronize and show irreproducible behavior when response times fluctuate.

The occurrence of the two dynamical classes is strongly biased by the topology. Whether or not the system shows reliable dynamics can to a large degree be deduced from the unlabeled wiring diagram without information on the type of couplings and functions of switches.

When comparing our findings with empirical networks of genetic transcription, signal transduction, and the nervous system, we observe that the statistics of their local wiring structure is closely related to our reliability measure. Reliable triads tend to occur significantly more frequently in natural networks than in randomized versions of the networks, whereas unreliable triads are typically suppressed.

Our study suggests that biological signaling networks (as gene or neural networks) are shaped by the selective advantage of the ability to robust signal processing. This finding adds to the earlier evidence that the dynamical attractor of the yeast cell cycle is already robustly designed against switching errors as well as mutations of single genes (35). We suggest here that a second mechanism secures the standard operation mode against noise, even before any switching errors occur.

