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Landscape and Flux Framework for Networks[1]

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We developed a global framework to robustness of networks applied to biological oscillation by directly exploring the probabilistic distribution in the whole protein concentration space (therefore global) for oscillations with a stochastic approach. We uncovered two distinct natures essential for characterizing the global probabilistic dynamics of biological oscillations: the underlying potential landscape directly (logarithmically) related to the steady state probability distribution and the corresponding flux related to the speed of the protein concentration changes. We found that the underlying potential landscape for the oscillation has a distinct closed ring valley shape when the fluctuations are small. This global landscape structure leads to attractions of the system to the ring valley. On the ring, we found that the non-equilibrium flux is the driving force for oscillations. Therefore, both structured landscape and flux are needed to guarantee a global robust oscillation. The barrier height separating the oscillation ring and other areas derived from the landscape topography, is shown to be correlated with the escaping time from the limit cycle attractor, and therefore provides a quantitative measure of the robustness for the network. The landscape becomes shallower and the closed ring valley shape structure becomes weaker (lower barrier height) with larger fluctuations. We observe that the period and the amplitude of the oscillations are more dispersed and oscillations become less coherent when the fluctuations increase. When the fluctuations become very large, the landscape is flattened out and coherence of the oscillations is destroyed. Robustness decreases. When the fluctuations are small, changing the inherent parameters of the system such as chemical rates, equilibrium constants and concentrations can lead to different robust behaviors such as multi-stability. By exploring the sensitivity of barrier height on the parameters of the system, we can identify critical kinetic parameters important for robust oscillations. This provides a basis for reengineering and design.

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