A Density-Dependent Switch Drives Stochastic Clustering and Polarization of Signaling Molecules

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Positive feedback plays a key role in the ability of signaling molecules to form highly localized clusters in the membrane or cytosol of cells in the absence of pre-existing spatial cues or diffusional barriers. However, what prevents positive feedback from amplifying inevitable biological noise when an un-clustered "off" state is desired? And, what limits the spread of clusters when an "on" state is desired? We show that a minimal positive feedback circuit provides a general principle for both suppressing and amplifying noise: below a critical density of signalling molecules, clustering switches off; above this threshold, highly localized clusters are recurrently generated. This behavior occurs only in the stochastic regime, suggesting that finite sizes of molecular populations cannot be ignored in signal transduction networks.

I. Introduction

THE formation of local, high density regions of signaling molecules ("clusters") can switch cells between "off" and "on" states [1]. This transition between may require careful regulation, particularly when an "on" state initiates large-scale cellular changes, such as cell polarization, where the formation of a single, asymmetric accumulation of signaling molecules serves to define a unique cellular axis [2].

Positive feedback can amplify and reinforce spatially asymmetric distributions of signaling molecules in single cells. However, stochastic fluctuations could cause switches between "off" and "on" states to occur at undesired times, and sites of activation to occur in undesired locations. Indeed, for many models of symmetry breaking, such as the classic model proposed by Turing [3], homogeneous steady states are inherently unstable, with small perturbations resulting in the formation of spatial patterns. Here, we consider how positive feedback can enable both the robust repression of noise required to maintain an "off" state, and the reliable establishment and persistence of clusters of signaling molecules required to maintain an "on" state.

II. Results

We previously considered a simple, positive feedback circuit, inspired by the ability of Cdc42 to polarize spontaneously in latrunculin-treated yeast [4]. In our model, molecules stochastically transition between inactive (cytosolic) or active (membrane-bound) states; and activated molecules, diffusing laterally along the membrane, recruited inactive molecules to their membrane locations. It can be shown that polarity emerges from this positive feedback circuit for intermediate ranges of signaling molecule numbers. While stochastic events and diffusion eventually lead to the dispersal of a cluster, at steady state the process is recurrent and a new site of polarity will eventually re-form on the membrane. Here, we investigate the ability of positive feedback in that model to reliably repress the formation of localized signaling domains.

We find that when the density of molecules is below an easily computable threshold, all signaling molecules are expected to be inactive; hence, no clusters of activated signaling molecules form, and cells are buffered against the onset of cluster formation regardless of the constant presence of noise. Above the threshold, increasing densities leads to increasing numbers of activated molecules. This process can be applied to many cell-biological settings, and we investigate clustering of molecules in the case of cell polarity, as well as for 2-D membranes or in 3-D volumes where the inactive and active forms of the signaling molecules are not segregated to spatially distinct compartments.

Taken together, we find seemingly opposing effects for noise in this positive feedback circuit: at low densities of signaling molecules, biochemical noise is ignored in an "off" state; at intermediate densities, biochemical noise drives the formation of single, polarized clusters of signaling molecules to create an "on" state; and at high densities, biochemical noise overwhelms polarization to create a spatially homogeneous "on" state.

III. Conclusion

Regulating the density of signaling molecules provides a simple mechanism for a positive feedback circuit to robustly switch between clustered and un-clustered states [5]. The intrinsic ability of positive feedback both to create and suppress clustering is a general mechanism that could operate within diverse biological networks to create dynamic spatial organization.

References

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