Biological signaling networks. Robustness and universality in cell decision.

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Signal transduction among different components of the cell is key in the decision-making process of living organisms. Typically, signaling occurs at proteins which change their conformational state in response to the presence of a signaling molecule. These molecules are emitted at a source and transported to the location of the receptor, triggering a sequence of events leading to a cellular response. Using this mechanism, the cell controls signals in space and time in order to regulate its protein make-up and, consequently, its basic functions. A fruitful framework to study the generation-making process in cells is the study of bifurcations in dynamical systems [1], where the system is analyzed in terms of fixed points, limit cycles and their stability. Local or global bifurcations appear given the nonlinear nature of the signalling (in biological terms the cooperativity) where multiple binding events have to occur in order to trigger a response. A cell decsion is understood as the change in the stability of an attractor in the dynamical system upon the arrival of the signaling molecule. This scheme has been used to study protein-protein interaction networks and transcriptional regulation. It explains how the signal transduction systems can perform robust switch like operations similar to that found in electronic systems [2].

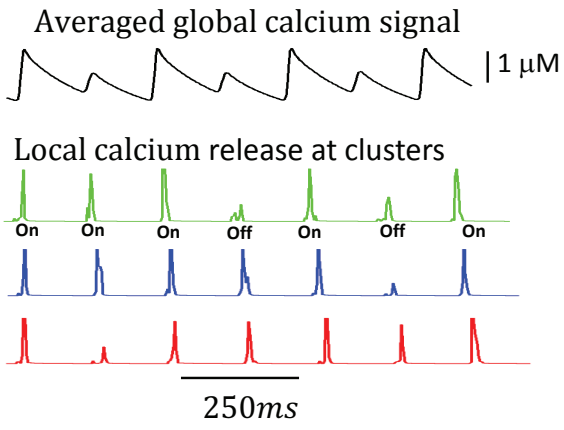

Figure 1: Example where bifurcation analysis is not the proper framework to study cell-decision. The global average of the signalling ion caclium (top) is the result of the ON/OFF activity of around 10000 clusters of RyR2 which control the local release of calcium (bottom).

We have shown that this bifurcation scenario is not correct, at least in one key signalling process: excitation-contraction coupling in cardiac tissue [3]. In this, contraction is the result of the response of a series of receptors (RyR), which control the release of calcium, to external signalling. The response is nonlinear but, more importantly, it is local since it only depends on the local concentration of the signaling molecule (calcium in this case). Receptors are closely packed into clusters so that a response at one receptor influences the behavior of a nearby receptor. This architecture allows the group of receptors to amplify small concentration changes of the signaling molecule and diffuse its effects to the neighbors. Thus, the decision is the result of the coordination of independent units instead of the result of average concentration in cell proteins or ions. Given its local nature and the small number of receptor in each local cluster (around 50), in cell contraction signaling is an inherently stochastic process which is characterized by probability distributions of the various accessible states. Local stochasticity coupled with diffusivity makes the system similar to an Ising-like model with noise playing the role of temperature fluctuations. Our analysis show that changes in the contraction behavior of ventricular cells appear, under some general conditions, as an ordering transition with scaling exponent compatible with Ising universality class and it can not be understood in the standard bifurcation scenario [3].

The simple bifurcation scenario may also fail when cellular signaling transduction involves a complex movement of the molecules in the cell. Given that the intracellular space is filled with organelles and various obstructions, a diffusing molecule has to navigate between complex intracellular structures. Also, the transmission of signals occurs through a hierarchy of intracellular transport mechanisms. Thus, the connections between signaling proteins can be complex and is likely an important component of the biological function making global averages unappropriate to analyze cell decisions. Network theory, where nodes represent local receptors units, becomes a very useful tool in this scenario. A good first general framework is the analysis of general network structures in which nodes are regulated by reaction rates that have a nonlinear dependence on the states of connected nodes. Our main finding is that these networks exhibit bistability where the system can reside either in an active branch, where a large number of nodes are activated, or an inactive branch in which the network is largely quiescent. We analyze the nature of the bistability and show that the onset, and stochastic transitions between the stable branches, are dictated by the community structure of the network [4]. This allows the cell to develop robust responses even outside the standard bifurcation scenario and present a new paradigm for understanding cell decision processes.

[1] J. Keener, J Sneyd, *Mathematical Physiology* Springer

[2] N.I. Markevich, J. B. Hoek, Boris, and N. Kholodenko, The Journal of cell biology, **164** (3): 353, (2004)

[3] E Alvarez-Lacalle, B Echebarria, J Spalding, and Y Shiferaw, PRL **114** (10), 108101 (2015)

[4] G Hernandez-Hernandez, J.Myers, E Alvarez-Lacalle, and Y Shiferaw, accepted in PRE (2016)