Kinetic insulation as an effective mechanism for achieving pathway specificity in intracellular signaling networks

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Recommended with a Commentary by Martin Howard, The John Innes Centre, UK

In recent years, fundamental questions about how cells first detect stimuli and then process the resulting information have been increasingly studied by physicists and mathematicians. Indeed, without the benefit of systematic theoretical analysis, it would be much harder to make sense of the immense complexity of cellular signaling networks. One particularly troublesome issue in cell signaling is how different signaling pathways are able to maintain high specificity, even though they may often share common components. Limiting “cross-talk” between pathways is clearly vital if the cellular response is to be sufficiently precise.

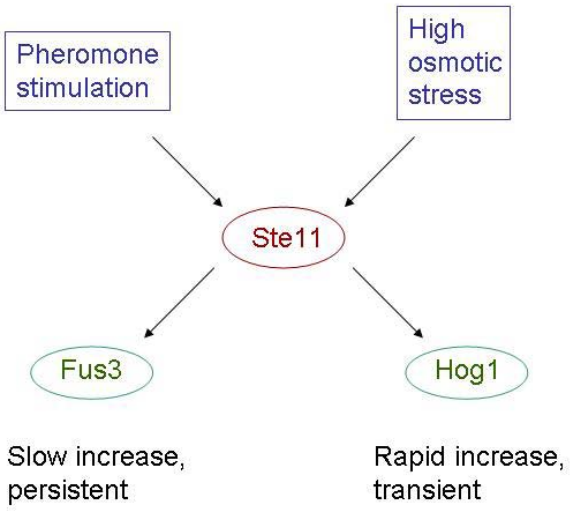
Several mechanisms have previously been proposed to limit such cross-talk. One popular method is by the use of cross-inhibition, where a signaling component present in only one pathway suppresses the activation of other unwanted responses. Spatial localization is also believed to be important as in, for example, the cellular response to different growth factors in higher eukaryotes. The present paper, however, introduces a new idea into cell signaling specificity by considering the distinct temporal behaviour of the network. The key result is that the temporal profile of the signal permits signal specificity: rapid activation of a signaling protein can be distinguished from slow activation of the same protein, and this distinction can lead to different cellular responses without cross-talk. The authors refer to this new mechanism as “kinetic insulation”.

Of course, for this mechanism to work the cell must be able to distinguish between slow and rapid activation kinetics. Slow kinetics can be detected by imposing slow activation kinetics on the detector, which thereby acts as a “low-pass” filter. Fast kinetics can be detected by using adaptive circuits which generate a transient response that returns to pre-stimulus levels even if the input signal persists. Such an adaptive system generates a large amplitude signal only when the input signal increases rapidly relative to the adaption time scale. If the input signal increases more slowly, the system continuously adapts and the output signal remains small. These “high-pass” filter circuits can be built from either feed-forward or negative-feedback loops. By coupling the same signaling protein to both slow and fast kinetic detectors, differing signaling pathways can then be activated depending on the temporal kinetics of this signaling protein. In particular, both pathways can now share this same signaling protein but without compromising signal specificity.

One potential difficulty with such signaling systems is that the shared signaling protein must have radically different temporal behaviours for kinetic

insulation to work. However, the stimuli that originally generated the signal may not possess such convenient properties. In principle, therefore, the cell may have to convert a rapid stimulus into a slowly varying signal and vice-versa in order to ensure proper downstream signaling. Fortunately, as demonstrated in the present paper, inserting appropriate signaling modules upstream between the original stimulus and the shared signaling molecule allows precisely such a modification to be performed. Such modules can be constructed from similar components as before, including slow activation kinetics, adaptive circuits, but sometimes also involving two step signaling circuits.

Of course, these theoretical ideas, even if attractive, must be rigorously tested in experiments. The present paper suggests two pathways with a shared component where kinetic insulation might be at work: the yeast high-osmolarity pathway that regulates the cell's glycerol content, and the yeast pheromone response pathway that regulates cell mating. The protein Ste11 is used in both pathways, yet the output of each pathway is very different: pheromone stimulation produces a slow but persistent increase in output, while high osmotic stress leads to a rapid but transient output. These results clearly satisfy the requirements for kinetic insulation, but much further experimental work will be needed to confirm whether it is truly the key underlying principle.



The idea contained within the present paper is very simple, yet allows for a flexible and robust mechanism for cells to limit cross-talk. Moreover, since components of different signaling pathways can be shared, the total number of signaling elements can be reduced, thereby minimising the biological cost and complexity of the system. Clearly, we still have a long way to go to fully understand the complexities of cell signaling, but the journey towards a better quantitative understanding is well underway.