Is cell fusion driven by excitation? (Comment on DOI: 10.1002/bies.201100135)

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In many species of filamentous fungi, individual hyphae fuse to form complex interconnected networks (mycelia). The formation of a mycelium is central to an adaptive growth strategy, allowing better utilisation of substrates and robust exploitation of physically complex environments. Fusion processes (anastomosis) start to occur almost immediately after spore germination and continue as the network matures. As detailed in ref. [1], what differentiates fusion in early colony growth of the model species Neurospora crassa is that it is dominated by tip-to-tip events involving special structures called conidial anastomosis tubes (CATs). These appear to auto-locate using chemotactic signalling. The signalling molecule is yet to be identified, but fluorescent labelling has revealed intriguing coupled oscillations in the level of certain tip-localised proteins in partner CATs. The hypothesis is that these oscillations somehow mediate the production of, and response to, the chemo-attractant.

The main obstacle to signalling between isogenic cells is the chemotactic paradox: why is the cell producing the chemo-attractant not ‘blinded’ by its own signal? The answer is that cells have developed mechanisms by which they send and receive signals in different temporal (or spatio-temporal) phases – being insensitive when sending but re-sensitising soon after in preparation for signal receipt and response.

The authors present a mathematical model used to investigate the role of oscillations in tip levels of the MAK-2 MAP kinase in CAT fusion in Neurospora crassa. They take a simplest-first approach: what is important here are the mechanisms. The detailed model formulation is secondary, provided certain core dynamics are preserved.

At the heart of the model are two key processes: excitation and coupling. Essentially, excitable systems have rest states that are stable to small perturbations, but given sufficient impetus, move to a significantly different configuration before returning once more to the rest state. A (non-rigorous) mental image of such behaviour can be formed thus. Consider a bead threaded onto a smooth steel hoop held vertically, then the natural rest state for the bead is to lie at the bottom. Push the bead gently and it simply returns to this (stable) rest state. However, a large push will send the bead up and round the hoop in a large excursion. The final part of the dynamics brings the bead back into the initial state, where it comes to rest again. A basic mathematical representation of excitability is shown in Fig. 3 of ref. [1] – the steady state relates to the bead at the bottom of the hoop; the non-linear structure of the equations (the nullclines) defines the mathematical equivalent of the hoop; gravity acts as inhibitor, bringing the system to rest again. Also key to the model is coupling – the mechanism by which the excited oscillation of one system acts as the driving impulse to activate its partner.

In the full model, the CAT MAK-2 dynamics form two excitable systems, coupled by the chemotactic signal. The authors detail how this simple model neatly explains important features of CAT fusion for example the sudden appearance of synchronised large amplitude oscillations in MAK-2 levels and their role in signal production and response.

Undoubtedly, mathematical models of this signalling process will evolve in tandem with developing biochemical understanding. For example, a more detailed description of the mechanisms by which the signalling molecules traverse the inter-tip distance may reveal further insight. This transit time could be incorporated via a delay term or more completely, by explicitly modelling the spatio-temporal evolution of the signalling molecules. In either case, it is mathematically well-known that such terms can themselves induce oscillations in otherwise simple, non-excitable systems. Hence, the ‘at-tip’ reaction kinetics could be quite different to those proposed. Devising experiments that could discount these more complex alternatives will shine further light on the search for the signalling molecule and its controlling factors. What is clear is that the iterative process of model driven hypothesis and experimental testing as utilised by the authors, is likely to provide an optimal strategy for investigation.

Reference