

## Dispatches

# Cell Signalling: Changing Shape Changes the Signal

Recent experiments have revealed the existence of subcellular gradients of signalling molecules. A new modelling study shows that changes in cell shape or size allow gradient-controlled pathways to be turned on or off simply by altering the distance between the signal source and targets.

**Martin Howard**

Spatial gradients of signalling molecules are now believed to exist in a wide range of key cellular processes, such as cell division and cell motility. Such gradients can form when signalling molecules are activated and deactivated in different locations. For example, signalling molecules could be activated by phosphorylation at the cell membrane and be deactivated by dephosphorylation in the cytoplasm. In combination with diffusion, these processes can give rise to a concentration gradient of the active molecules, with a high density close to the site of activation at the cell membrane and a decreasing density away from it. Crucially the locations of activation/deactivation must be separate for such a gradient to be formed. Depending on the local density of the active molecule, downstream processes can then be turned on or off, defining, for example, regions of the cell where specific reactions are permitted. A computational analysis of these gradients, reported in this issue of *Current Biology*, has added an exciting new twist to this mechanism. Meyers *et al.* [1] show that, by changing the overall size or shape of a cell, a gradient-controlled signalling pathway can be switched on or off simply by changing the distance between the source of the signal and its targets.

Previous modelling of subcellular concentration gradients has firmly established that such gradients can exist over subcellular dimensions [2]. This is a critical feature: if the length scale for the decay of the gradient was too long, then the concentration

would be almost uniform over the entire cell, making such a gradient useless for differentiated signalling. Assuming typical diffusion constants of  $D = 1\text{--}10 \mu\text{m}^2\text{s}^{-1}$  and (first order) deactivation rates of  $k = 0.1\text{--}100 \text{s}^{-1}$ , gives a length scale of decay for the gradient of  $l = \sqrt{(D/k)}$ , or about 0.1 to 10  $\mu\text{m}$  [2]. In other words, the change in density across a cell is easily large enough for the gradient to impart useful positional information in essentially all cell types. Of course these gradients are nothing other than the subcellular cousins of morphogen gradients, long familiar from developmental biology for their control of gene expression and cell differentiation.

The key idea of Meyers *et al.* [1] is to control the gradient by changing the cell size and/or shape. Suppose we again have a molecule activated at the membrane and deactivated in the cytoplasm forming a concentration gradient as described above. The activation/deactivation could, for example, be mediated by kinases/phosphatases, or alternatively by guanine nucleotide exchange factors/GTPase-activating proteins; the fundamental mechanism remains the same. Now imagine that the cell adopts a flattened shape as illustrated in Figure 1A. In this case, all parts of the cell are in close proximity to the membrane. The concentration of the active molecules will therefore be high in all regions of the cytoplasm. Assuming that the target of the activated signalling molecules is located in the cytoplasm, then this gradient-controlled signalling

pathway will be switched on. If, on the other hand, the cell adopts a more spherical or cuboidal configuration, then much of the cytoplasm is now far from the membrane. In these regions the density of active molecules will be low, leading any gradient-controlled signalling pathway to be switched off in most of the cell, as shown in Figure 1B. Hence, simply by changing shape, the cell can switch on or off a gradient-controlled signalling pathway. Importantly, the localization of the activation/deactivation processes to the membrane/cytoplasm does *not* have to be altered: changing shape alone suffices to change the signal. Meyers *et al.* [1] suggest that a similar mechanism might be at work more locally within a thin protrusion such as a filopodium, whose cytoplasm would again be close to the membrane. In fact the cell could easily compartmentalize itself into two biochemically distinct regions simply by sending out a thin protrusion (activated), while retaining most of the cell in a more spherical or cuboidal geometry (deactivated away from the membrane), as in Figure 1C. Clearly, however, for such a difference to be robust, the cell must adopt radically different geometries in the two regions.

Meyers *et al.* [1] apply their ideas to recent experiments on Cdc42 activation by Nalbant *et al.* [3]. Cdc42 is a member of the Rho-family of small GTPases, and regulates multiple functions in the cell, including apoptosis, motility, proliferation, and cell morphology. Using a fluorescent probe, Nalbant *et al.* [3] measured the localization of Cdc42 activation, finding it to be greatest close to the cell perimeter, but did not propose a specific mechanism for this variation. Meyers *et al.* [1] analyse this situation using the above model of membrane activation/cytoplasmic deactivation with the original cell

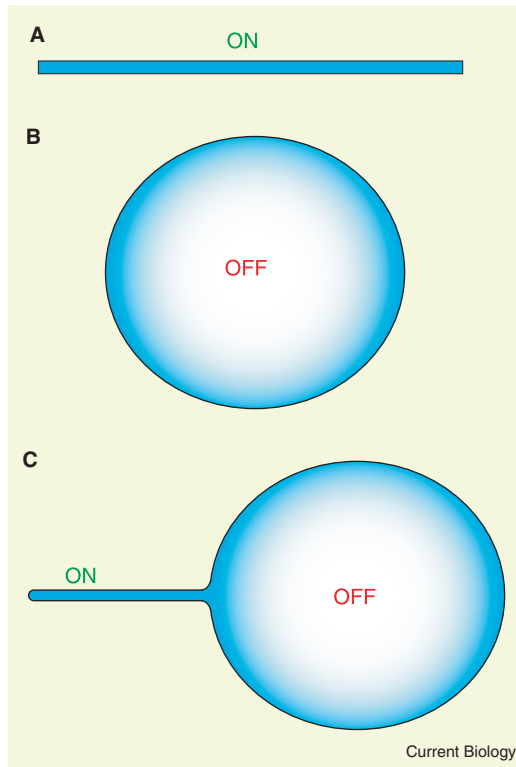


Figure 1. Schematic illustration of how changes in cell size or shape can switch on or off a gradient-controlled signalling pathway.

We assume that activation of the signalling molecules occurs in the membrane with deactivation occurring in the cytoplasm. The spatial separation of activation/deactivation together with diffusive transport ensures that a concentration gradient of the activated species is formed. Dark cyan shading represents a high concentration of the activated molecules, with white representing a low concentration. (A) The cell adopts a flattened configuration: all areas of the cytoplasm are close to the membrane, ensuring high concentrations of the activated molecules everywhere. The resulting signal is therefore turned on. (B) The cell adopts a spherical configuration: most regions in the cytoplasm are far from the membrane. By the time signalling molecules have diffused into

these regions from the membrane, they have been almost entirely deactivated. Hence the concentration of activated molecules is very low in most of the cytoplasm. In most of the cell, away from the membrane, the signal is therefore turned off. (C) The cell can also compartmentalize itself into biochemically distinct regions simply by altering its geometry. Here the cell sends out a thin protrusion: the cytoplasm inside the protrusion is close to the membrane, leading to a positive signal in this region. However most of the rest of the cytoplasm in other parts of the cell is still located far from the membrane, leading to a negative signal in the main body of the cell, away from the membrane.

thicknesses from [3] as model inputs. The model then generated a fair agreement with the experimental data: Cdc42 activation was predicted to be greatest at the cell periphery where the cell was thinnest, with the lowest activity where the cell was at its thickest, close to the nucleus. The agreement was not entirely perfect, and there are certainly other ways in which such a distribution might be generated (the availability of microtubule plus ends is a likely candidate). However, the analysis does indicate that an appealingly simple and general mechanism could be an important factor in generating the observed Cdc42 distribution.

Subcellular concentration gradients are now known to exist in an ever-increasing number of important situations, ranging from bacterial cell division to microtubule dynamics [4–9].

Strong experimental evidence for such gradients comes from the spatial distribution of the phosphostate of stathmin [4], a regulator of microtubule dynamics. Other computational modelling work has demonstrated that efficient chromosome capture during mitotic spindle assembly may require a gradient-based mechanism [5]. In this case, a spatial gradient biases microtubule dynamics towards the chromosomes. This prediction has received support from recent experiments on gradients of RanGTP [6] and also HURP [7]. Gradients are also well established both theoretically and experimentally in bacterial cell division placement [8,9]. Clearly it is important to see how widely the ideas of Meyers *et al.* [1] might be employed in these and other cell signalling systems. Nevertheless, one important theme emerging

from all these studies is that spatial effects are absolutely critical for a proper understanding of subcellular signalling dynamics. Unfortunately many modelling analyses completely neglect spatial aspects, and instead assume that the cell is a perfectly well-mixed reactor. The work of Meyers *et al.* [1] underlines once again that this assumption rests on decidedly shaky foundations and is unlikely to withstand more detailed scrutiny.

A further little-explored aspect of subcellular concentration gradients is the issue of fluctuations. The cell is a remarkably noisy environment where gradients are subject to a variety of perturbations that can arise from both extrinsic cell-to-cell variations in, for example, protein copy numbers, as well as from intrinsic stochasticity generated by the inherent randomness of biochemical reactions. These effects have been analysed in the context of stochastic gene expression [10], but not in their effect on spatial concentration gradients. Quite how precise positioning and reliable gradient-controlled cell signalling are maintained in the face of these considerable obstacles will be a fascinating topic for future research.

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DOI: 10.1016/j.cub.2006.08.014

## Parenting Behaviour: Babbling Bird Teachers?

One of humankind's most distinctive characteristics is our extended and complex period of child dependency. New research on a noisy African bird may help to shed light on how our unusual parenting behavior evolved.

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We humans are extraordinarily solicitous parents. This is not to say that intensive infant-care duties, like feeding and keeping watch over baby, are so remarkable. Other primates do the same for their infants, and many other vertebrate species do, too. What makes us stand out as parents are both the duration (relative to lifespan) and complexity of our caretaking behavior. New research from an unexpected source, reported in this issue of *Current Biology* [1], may help to shed light on how our unusual parenting behavior evolved.

Unlike most other animals, human parents continue to invest in their offspring well into adulthood. For example, in rural Ethiopia, mothers regularly visit their married daughters' households, helping with heavy domestic chores, and in so doing increase the survival prospects of their grandchildren [2]. In industrialized nations, parents often invest extensively in their children's education to help them succeed in a competitive environment. Many of the readers of this article undoubtedly know families who have even welcomed back into the parental nest offspring who have finished college but just have not yet been able to land that lucrative job.

Human parental care is complex because it is characterized by changes in the type of care offered as the child matures; emphasis shifts during development from

providing for nutritional and other basic physical needs to training and encouragement. This lengthy period of dependency is integral to who we are as a species. Anthropologists have argued that in subsidizing the diets of young group members, provisioning supported a prolonged learning period, and was the lynchpin that permitted our ancestors to specialize on increasingly varied and difficult-to-acquire resources, and the technological advances used to exploit them [3].

Given such importance to the human life history strategy, one might expect to find an extended period of provisioning as well as adult instruction or encouragement of offspring learning among our primate relatives, at least in nascent form. But provisioning of weaned young generally is infrequent and active support of skill development is virtually nonexistent. When a human child takes on a new skill, his or her caregiver often plays a facilitating role. Among nonhuman primates, in contrast, learning is a much more exclusively self-motivated proposition [4]. A young wild chimpanzee must learn to recognize and process hundreds of different kinds of food by paying close attention to what the mother and other adults eat. A mother usually tolerates her juvenile feeding in the same area and taking an occasional scrap of food, but even complex foraging techniques such as termite-fishing (in which a tool, designed from nearby vegetation, is inserted into

a mound to extract termites) and other types of tool use are learned without active guidance from adults [5,6].

In this issue, Radford and Ridley [1] report how wild adult pied babblers modify their caretaking behavior in a way that may favor learning by juveniles. Pied babblers (*Turdoides bicolor*) are medium-sized passerine birds of southern Africa, noted for their steady chattering contact calls — hence the name. They inhabit scrubby acacia woodlands and savanna, and spend much of their time foraging on the ground for invertebrates [7]. Groups typically consist of one breeding pair and several non-reproductive adults, all of whom help to care for the group's altricial young, a type of social system called cooperative breeding [8,9]. The study's most remarkable observation is not that pied babblers provision their group's young: all birds who have helpless, relatively immobile hatchlings must provision their young. Nor is it that adults preferentially allow fledglings to share their foraging sites with them: tolerance for immatures while foraging is known in a variety of bird species [10–12]. The striking finding is that adults appear to take an active and variable role in the development of their fledglings' foraging abilities.

Radford and Ridley [1] observed that, a few days before young pied babblers fledge, adults begin to emit a soft 'purr' vocalization when they bring food to the nest. Upon fledging, the young follow foraging adults and solicit food from them (Figure 1), while adults, for their part, continue to use the purr vocalization during provisioning interactions. It is at this point that adults begin to purr-call from time to time in a new context: while foraging. Using playbacks of calls, experiments with supplemental