

exaggeration in all populations. There is no direct and necessary relationship between the ecological intensity of an interaction — for example, proportion of plants or seeds attacked — and the strength of natural selection on that interaction. The strength of selection imposed by an enemy on a plant population depends on the degree to which that enemy differentially reduces the fitness of some plant genotypes more than others. At the extreme, a high level of random attack would impose no selection on a host or prey population, whereas a moderate level of differential attack could exert strong selection.

Hence, even when coevolution is focused on the same few traits in a pair of interacting species, selection is likely to vary geographically. Some local interactions will be coevolutionary hotspots, exhibiting strong reciprocal selection on the interacting species. Other local interactions will be coevolutionary coldspots, with selection acting on only one species or neither species. In many interactions, there will often also be regions where one species occurs without the other. These different forms of coevolutionary coldspots will lead to relaxed selection on the traits that are escalating to varying degrees in the hotspots. In addition, gene flow among these regions, random genetic drift, metapopulation dynamics, and selection for novel traits rather than exaggeration of current traits can all further mitigate relentless escalation of coevolving traits across the geographic range of an antagonistic interaction [6].

Geographic mosaics of antagonistic coevolution have now been demonstrated over the past decade in an increasingly wide range of interspecific interactions, including those between vertebrates and their prey [1,7], insects and plants [8–10], fungi and plants [11], and slave-making ants and their victims [12]. Toju and Sota's [3] study, however, is the first to suggest how the steepness of geographic clines in coevolving traits may shape geographic patterns in the strength of coevolutionary selection.

Collectively, these studies suggest that coevolution is a pervasive process that continually reshapes interspecific interactions across broad geographic areas. And that has important implications for our understanding of the role of coevolution in fields ranging from epidemiology to conservation biology. Many diseases, for example malaria, vary geographically both in parasite virulence and host resistance, potentially creating regions of coevolutionary hotspots and coldspots. The spread of introduced species seems to be creating new geographic mosaics of coevolution as some species become invasive and coevolve with native species in different ways in different regions or drive rapid evolution in native species, sometimes in less than a hundred years or so [8,13,14]. The results for Japanese camellia and camellia weevils reinforce the developing view that interactions coevolve as a geographic mosaic across landscapes, and it is often difficult for one partner to get ahead of the other (or others) everywhere.

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Yeast Polarity: Negative Feedback Shifts the Focus

A new study of Cdc42p polarization in yeast suggests that the actin cytoskeleton can destabilize the polarity axis, causing Cdc42p foci to wander aimlessly around the cell cortex.

Daniel J. Lew

Most cells know which way to polarize. Concentration gradients of attractants, repellents,

nutrients, or pheromones reveal the optimal directions for successful attack, escape, feeding, or mating. Some cells also carry internal landmarks

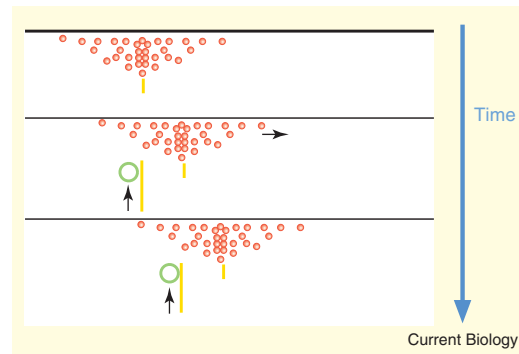
inherited from their parents that guide polarization without environmental input. Polarization might therefore be viewed as a response to specific external or internal cues. However, many cells polarize even when deprived of directional cues, choosing a random axis and committing to it as if they knew where they were going. This 'symmetry breaking' is thought to reflect the action of positive feedback loops that reinforce inequalities in the local concentrations of polarity factors, so that stochastic fluctuations are amplified into a single dominating asymmetry [1]. A new study combines experiment with mathematical modeling and proposes that polarization in yeast also involves unexpected negative feedback loops, destabilizing the polarity axis so that the axis migrates around the cell [2].

Budding yeast cells are born carrying within them localized cortical landmark proteins [3]. After a period of uniform growth during G1, all growth becomes polarized towards one and only one site, targeting new secretion and cell wall synthesis to build a bud. Current models posit that the landmark causes localized activation of the Ras-family GTPase Rsr1p, which then recruits components of the polarization machinery, including the key Rho-family GTPase Cdc42p. When *RSR1* is deleted, however, polarization still occurs with normal timing in the cell cycle and with normal efficiency. The only difference is that the chosen site is now random with respect to the landmarks [4,5].

In this recent study, Ozbudak *et al.* [2] used a green fluorescent protein (GFP) reporter for activated Cdc42p to monitor polarization in living cells containing or lacking Rsr1p. In the presence of Rsr1p, a focus of active Cdc42p appeared in early G1 and remained stable until bud emergence about an hour later. However, in the absence of Rsr1p the focus of active Cdc42p moved around the cortex, only settling down to a stable location a few minutes before bud emergence. In a particularly striking movie, the Cdc42p focus moved consistently

Figure 1. Modeling a travelling wave of GTP-Cdc42p.

Each panel depicts the spatial distribution of GTP-Cdc42p (red dots) at different times. Actin cable assembly (yellow line) is nucleated at the site of maximal GTP-Cdc42p concentration, and the actin cable then grows and delivers secretory vesicles (green) carrying GAPs to that site at the next time point. By



then, the center of the focus has shifted slightly towards the right and the arriving GAPs trigger GTP hydrolysis by the Cdc42p on the left (trailing) side of the focus. This shifts the GTP-Cdc42p distribution further to the right, perpetuating the travelling wave.

in one direction for eight minutes before reversing and moving at a similar rate in the other direction for over twenty minutes. What kind of molecular processes would create such sustained motion, reminiscent of travelling waves?

Prior studies on symmetry breaking in yeast had emphasized the expected contributions of positive feedback loops, concluding that a rapid feedback loop mediated by the scaffold protein Bem1p was critical for polarity establishment, while a slower actin-mediated loop was important for the maintenance of polarity [6–8]. The recent work shows that in *rsr1Δ* cells depolymerization of actin did not affect polarity establishment, but abolished the wave-like motion of the polarization site, implying a key role for filamentous actin in this movement. Moreover, deletion of individual GTPase-activating proteins (GAPs) for Cdc42p dramatically reduced migration of the polarization site. Thus, GAPs and actin filaments are both needed for wave-like motion, leading the authors to suggest that actin-mediated delivery of GAP proteins to the polarization site could destabilize its position, causing it to migrate [2].

To assess the plausibility of their hypothesis, the authors turned to mathematical modeling. In their model, the concentration of active Cdc42p at any point on a one-dimensional 'cell surface' depends on several factors. A fast-acting positive feedback loop allows GTP-Cdc42p to recruit

Bem1p from the cytosol, generating more local GTP-Cdc42p, thereby building up a local focus. (Bem1p is assumed to diffuse rapidly in the cytosol and is present in finite amounts, limiting this positive feedback.) Slow diffusion of Cdc42p in the plane of the membrane combined with GTP hydrolysis act to dissipate the focus, and with these components alone the model maintains a stable focus at a stationary site. Incorporation of a second feedback loop, representing the contributions of the actin cytoskeleton, makes things more interesting.

GTP-Cdc42p is thought to induce nucleation of actin cables in its vicinity, which then deliver secretory vesicles to the nucleation site [9]. Actin assembly and vesicle delivery take time, and in the model two minutes elapse between the initiation of cable formation by GTP-Cdc42p and the effects of the ensuing vesicle delivery. The vesicles may deliver cargo that promotes (e.g., Cdc42p itself) or antagonizes (e.g., GAPs) the accumulation of GTP-Cdc42p, yielding a net positive or negative effect denoted by the sign of a coefficient in the model. If the coefficient is negative, then this loop destabilizes the GTP-Cdc42p focus, potentially causing it to migrate in a persistent direction (Figure 1).

The idea that GAPs are delivered on actin cables is reasonable but lacks experimental support. Moreover, the idea that actin cables have a net negative

effect is at odds with recent findings suggesting that the net effect of cables is to reinforce, not dissipate, polarity [6,8]. The authors acknowledge that their mathematical formalism could equally well represent alternative physical manifestations of the negative feedback loop. One attractive possibility is that GTP-Cdc42p stimulates endocytic retrieval of proteins from the polarization site. Endocytosis is dependent on polymerized actin (in cortical patches, not cables [10,11]) and will dismantle the polarization site unless its effects are counteracted by cables [6]. Thus, it may be the balance between endocytosis and cable-directed delivery that determines whether the net effect of actin favors wandering of the polarization site.

Why do the wandering Cdc42p foci abruptly change direction? This is not addressed by the model, in which migration continues in the same direction forever. Unlike the model, in which actin-mediated feedback acts in a continuous and perfectly noise-free manner, in the cell actin's effects are quantal, with integral numbers of cables or patches leading to discrete vesicle fusion or retrieval events. Stochastic noise from off-center events (or clusters of events) might therefore derail the direction of the motion, leading to the sudden changes in direction observed experimentally. The observed net movement of

foci over the long term is diffusive, for which the direction of migration is randomized about every 10 min (A. van Oudenaarden, personal communication).

So what benefit might cells derive from wandering foci, and why does wandering cease several minutes before bud emergence? The stabilization appears to coincide with the time (called 'start') when cells commit to the cell cycle, suggesting that a cell-cycle signal changes the ground rules so that wandering is no longer allowed. The septin ring assembles around the polarization site at this time [3], potentially corralling the polarized Cdc42p to make it commit to a specific budding site. Previous studies did not detect Cdc42p polarization in proliferating cells prior to start [6–8,10]. However, a wandering polarization site has been reported in *rsr1Δ* cells arrested before start by exposure to mating pheromone [12]. The directional plasticity that allows wandering may be an advantage for cells that polarize to follow a shallow pheromone gradient in search of a mating partner. Once cells commit to building a bud, on the other hand, such wandering would be a severe liability.

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Olfactory Coding: Inhibition Reshapes Odor Responses

Olfactory information is dramatically restructured as it makes its way through the brain. Recent work using a remarkable experimental preparation has revealed how this transformation is achieved.

Mark Stopfer

How is information transmitted from the outside world to the inside of the brain? In recent work [1,2], Rachel Wilson, Glenn Turner and Gilles Laurent have addressed this big question by focusing on a small neural circuit:

the olfactory system of the fruit fly, *Drosophila melanogaster*. Why the fly? The animal's relatively small number of neurons and its amenability to sophisticated genetic tricks allow unprecedented insight into the design and function of its olfactory apparatus.

In form and function, the insect olfactory system appears remarkably analogous to that of other, larger animals [3]. Peripheral olfactory receptor neurons, each expressing a single functional receptor gene, send fibers centrally to an interneuronal relay station — the vertebrate version is the olfactory bulb, the insect version is the antennal lobe. There, the incoming fibers collate by receptor type and converge into spherical structures called glomeruli. Within the glomeruli, receptor fibers mingle with those of inhibitory local neurons (LNs), and the excitatory