of warring city states. Was that because the Khmer area's higher agricultural productivity, domestic animals for transport and abundant fish and other protein sources enabled the Khmer — but not the Maya — to control large domains and feed standing armies of conquest? Related to that political difference, the Khmer practised water management on a scale dwarfing that of the Maya and most other regions of the world. Angkor's surrounds were converted into an artificial landscape criss-crossed with canals, embankments, reservoirs, dams and other massive engineering works to redirect river flows, store water for the dry season and avert floods by disposing of excess water during monsoons. The Khmer struggled for centuries to maintain their hydraulic landscape until it became overwhelmed by climate change, producing floods that broke embankments and canals filled with sediments from eroded terrains[6].

For the third study[3], a success story, we return to the New World. Why did the Inca empire of the Andes expand to become the largest Native American empire, only a few centuries after the Wari and Tiwanaku empires of the same region collapsed? Chepstow-Lusty and colleagues[3] have analysed a mud core from Lake Marcacocha near the Inca capital of Cuzco, representing 4,200 years of accumulated sediments. By sampling every centimetre over the core's top 1.9 metres, they obtained a temporal resolution of about 6 years. They measured the concentrations of pollen and other plant parts, and of charcoal, and $^{13}C/^{12}C$ and C/N ratios, as proxies for local climate, human activity and plant communities.

It turned out that after AD 880 there was increasing drought, which may thus have contributed to the Wari and Tiwanaku collapses, as well as to the earlier and later collapses of the Maya and Khmer. But after AD 1100, during the Northern Hemisphere's Medieval Warm Period, temperatures rose, enabling the Incas to extend agriculture to higher elevations, increase their arable-land area, exploit increased glacial meltwater for irrigation, store more food for their armies, and grow alder trees for nitrogen fixation and timber. Thus, although the Incas' military and administrative organization was essential to their conquests, climate amelioration played a part.

This reminds us that climate can change in either direction, and that in the past such change has variously helped or hurt human societies. But human overexploitation of environmental resources never helps. As Lentz and Hockaday note[1], "Tikal's inhabitants became trapped in a positive feedback loop wherein increasing demands on a shrinking resource base ultimately exceeded the carrying capacity of their immediate environs. The ecological lessons learned from the Late Classic Maya, with their meteoric population increase accompanied by environmental overstretch, serve as a distant mirror for our own cultural trajectory." Amen. ■

Jared Diamond is in the Geography Department, University of California, Los Angeles, California 90095-1524, USA.
e-mail: jdiamond@geog.ucla.edu

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DEVELOPMENTAL BIOLOGY

Rise of the source–sink model

Alexander F. Schier and Daniel Needleman

Gradients of signalling molecules dictate where specific cell types form in developing tissues, but how these gradients are set up is much debated. A model proposed 40 years ago by Francis Crick may provide an answer.

How do the thousands of different cell types in an animal arise time and again at particular locations during embryonic development? The answer lies partly in the distribution of signalling molecules called morphogens[1], which are released from local sources and form concentration gradients in target tissues. Cells that are close to the source of the morphogen are exposed to high signal concentrations and activate developmental programs that differ from those in cells that are farther away and exposed to lower levels of morphogen. This powerful strategy means that the same signalling molecule can be used in the formation of different cell types. But how are morphogen gradients established? On page 533 of this issue, Yu *et al.*[2] describe one mechanism. They propose that, during the development of the zebrafish embryo, the morphogen fibroblast growth factor 8 (FGF8) spreads rapidly by diffusion from a local source and is then taken up by target tissues. This implies that the combination of free random motion and cellular uptake generates a signalling gradient that endows cells with different developmental fates.

Yu and colleagues' findings[2] support a model proposed almost 40 years ago by Francis Crick, dubbed the source–sink model. Crick put forward a mechanism[3] to explain how morphogen gradients could be set up in a developing tissue. He calculated that a stable gradient can be generated by the local production of a signal at one end of a tissue (the source), its spread into surrounding cells, and its local removal at the other end (the sink). Crick argued as part of the source–sink model that the spreading of the morphogen occurs through Brownian motion — the random thermal motion of molecules — akin to the spreading of a drop of ink in a glass of water. If correct, this would imply that simple diffusion was a plausible mechanism for patterning embryonic tissues. But is there evidence for the source–sink mechanism *in vivo*?

The authors[2] used fluorescent correlation spectroscopy (FCS) to analyse the properties of the FGF8 morphogen in zebrafish embryos. FCS is a powerful technology that was introduced in 1972, when it was shown[4] that measuring fluctuations in fluorescence in a small volume can determine the diffusion properties of labelled molecules in solution. In its modern incarnation, FCS is sufficiently sensitive to probe the dynamics of single molecules. The technique is widely used by biophysicists to measure the behaviours and interactions of proteins, but its use has largely been limited to *in vitro* systems, single-celled organisms and cells in tissue culture.

By contrast, Yu and colleagues[2] apply FCS to measure the distribution, diffusion and clearance of FGF8 in zebrafish embryos. These embryos are translucent and are therefore ideal for the visualization of the movements of molecules and cells. Yu *et al.* observed that a stable FGF8 gradient forms within 3 hours after production of fluorescently tagged FGF8 in a local region of the early zebrafish embryo. They obtained a diffusion coefficient for FGF8 in the extracellular space of ~50 $\mu m^2 s^{-1}$, which is strikingly similar to that obtained for molecules of the same size diffusing in water. Therefore, FGF8 seems to move freely and randomly through extracellular space.

But how can such rapidly moving molecules form stable concentration gradients? Yu *et al.* find that extracellular FGF8 has a half-life of only 10–20 minutes. The authors propose that it is the interplay between fast diffusion and the rapid uptake of FGF8 by target-cell endocytosis that creates the gradient. Indeed, green fluorescent protein (GFP), a molecule with similar diffusion properties to FGF8 but much slower clearance, also spreads rapidly but does not form a stable gradient. As predicted by source–sink models, manipulations that increase FGF8 removal, for instance by increasing cellular endocytosis, decrease the range of the FGF8 gradient. By contrast, decreasing endocytosis

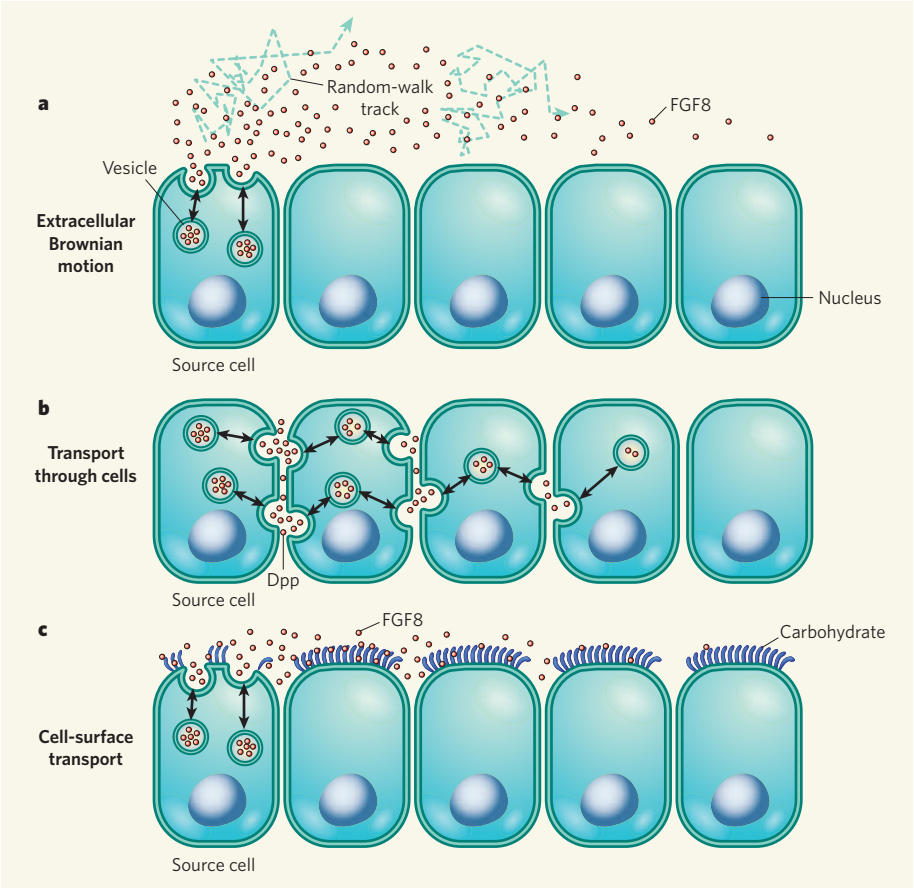

Figure 1 | Models of morphogen dispersal. Source cells harbour vesicles filled with morphogen molecules (red), which fuse with the cell membrane and release their contents. **a**, Yu *et al.*[2] propose that Brownian motion of molecules in the extracellular space leads to dispersal of the FGF8 morphogen. Two tracks of random walk by single FGF8 molecules are shown. **b**, Kicheva and colleagues[5] suggest that repeated release and uptake by cells (transcytosis) leads to dispersal of the morphogen Dpp in the fly wing. **c**, A few slowly diffusing FGF8 molecules are associated with carbohydrates at the cell surface[2]. This cell-surface pool may contribute to long-range dispersal of FGF8.

of FGF8 increases the distance range of the gradient. In this scenario, the sink is not only at one end of the tissue, but is formed by all the target cells that contribute to morphogen removal and gradient formation.

In Yu and colleagues' model[2], the transport of FGF8 is driven by Brownian motion through extracellular space, as Francis Crick proposed (Fig. 1a). But this might not be the only way of establishing morphogen gradients. In their studies of the morphogen Decapentaplegic (Dpp) protein in *Drosophila*, Kicheva *et al.*[5] photobleached a large region of the developing wing of the fly and measured the time it took for fluorescently labelled Dpp molecules to re-enter the bleached region. Their result — an effective diffusion coefficient of only ~0.1 $\mu m^2 s^{-1}$ — means that the typical time taken for Dpp to travel a certain distance would be nearly three orders of magnitude longer than for FGF8. One explanation for this is that the Dpp gradient might be generated by transport through cells[5] (Fig. 1b). In this case, the repeated cellular uptake and release of Dpp (transcytosis) would lead to an effective diffusion coefficient that is much lower than that of the freely diffusing FGF8.

Why are the results for FGF8 and Dpp so different? The simplest explanation is that these systems really are dissimilar. After all, a fly wing is not a zebrafish embryo, and the principles responsible for establishing morphogen gradients in these two structures might not be the same.

It is important to keep in mind, however, that different methods were used to measure morphogen transport in the two studies. The FCS experiments provide data on the motion of FGF8 through a volume of ~0.1 μm^3, whereas the photobleaching experiments measure the recovery of Dpp into a volume of ~10^4 μm^3, a difference of five orders of magnitude. It might be that the small-scale motion measured by FCS and the large-scale motion observed by photobleaching occur by different mechanisms. If that were the case, FGF8 and Dpp might be dispersed in a similar fashion, and the two studies may have simply probed different aspects of morphogen motion. In this context, it is interesting to note that Yu *et al.*[2] identified a second, minor fraction of FGF8 that has a 10-fold lower diffusion coefficient. This fraction of FGF8 seems to be associated with carbohydrates located at the surface of cells. The role of this pool of FGF8 is unclear, but it might contribute to the spread of FGF8 along the cell surface (Fig. 1c).

The studies of FGF8[2] and Dpp[5] have revealed unexpected complexity of morphogen dispersal. They raise the question of what the biophysical properties of other signalling molecules are during development. Do they function like FGF8 or do they resemble Dpp? The further application of quantitative approaches to other systems and organisms will hopefully address these questions. ■

Alexander F. Schier and Daniel Needleman are in the Department of Molecular and Cellular Biology, Harvard University, Cambridge, Massachusetts 0218, USA.
e-mail: schier@mcb.harvard.edu

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CLIMATE CHANGE

The El Niño with a difference

Karumuri Ashok and Toshio Yamagata

Patterns of sea-surface warming and cooling in the tropical Pacific seem to be changing, as do the associated atmospheric effects. Increased global warming is implicated in these shifts in El Niño phenomena.

Through the El Niño events[1,2] that occur every 3–8 years or so, the state of the tropical Pacific Ocean and overlying atmosphere has global effects on climate — sometimes with devastating effects, for example on agriculture in India. El Niños are defined by warmer than normal sea surface temperatures in the eastern tropical Pacific, and are associated with anomalous atmospheric circulation patterns known as the Southern Oscillation. These coupled phenomena, together called ENSO, have been the subject of research since the late nineteenth century. They remain a matter of intense interest today, not least because of a puzzling shift in behaviour over recent years. That shift, and its possible causes, is the