sharply in a stripe along the dorsal midline. Eldar *et al.*[3] now offer an explanation for this phenomenon: they propose that Sog coordinates BMP transport with BMP release, and show by modelling that this produces a robust, sharp peak of active BMPs.

The authors began with computer simulations, based on a set of equations, in which they varied both the components and the parameters (protein concentrations and rate constants). To test their findings, they carried out experiments using Dpp. In essence, Eldar *et al.* show that BMPs by themselves probably have a very low diffusion rate. Only when bound to Sog do they become mobile, enabling them to be moved around the embryo. The enzyme Tolloid cleaves Sog, and Eldar and colleagues' models suggest that this happens preferentially when Sog is bound to BMPs, as proposed previously[7]. This releases the BMP molecules, which can act on cells in areas where the concentration of inhibitory Sog is low. That mainly happens at some distance from the ventral source of Sog. In this way, a sharp focus of active BMPs can be built up at a distance from the source of Sog and on a plateau-like source of BMPs (Fig. 1).

Significantly, the authors show that this molecular network is robust to changes in the dosage of the genes involved. They first modelled a simplified system consisting only of Sog, Tolloid and one BMP. In this case, with certain parameters the system was insensitive to the gene dosage of all its components. If both Dpp and Scw were included, the system became unstable. Moderate stability was achieved if molecularly distinct complexes transported the two BMPs, with Sog alone transporting Scw, and both Sog and Twisted gastrulation (Tsg) transporting Dpp. This fits with experimental data[6,8,9]. However, even in the presence of Tsg the system remained sensitive to the Dpp gene dosage, again in agreement with experiments. Whether dealing with the simple or the more complex system, the most remarkable outcome of the simulations is that robustness to variations in system components is always linked to production of a sharp dorsal peak of BMP activity.

A similar mechanism is probably at work in vertebrates, where the same molecular players are involved[10] — although in opposite regions[11]. For instance, the Dpp homologues BMP2 and BMP4 are morphogens; they are produced in a broad ventral region, and are antagonized by the Sog homologue Chordin, localized dorsally in the so-called Spemann organizer. Homologues of Tolloid and Tsg[8,9] are also found in vertebrates.

The puzzle that remains is why such a sophisticated mechanism is needed. At large distances from a localized source or sink, a gradient may be shallow and thus inappropriate for reliable subdivision. In many cases this problem is circumvented by using two gradients with opposite slopes, generated from independent sources at each end of the axis. An example is the fruitfly head-to-tail (anterior–posterior) axis, which is set up by anterior and posterior morphogen gradients that form largely independently of each other[12]. Why isn't dorsal–ventral patterning achieved in a similar way?

The answer may lie in a peculiarity of the dorsal–ventral pattern: the initial peak of Dorsal protein must have the geometry of a long, narrow stripe rather than a small patch. The generation of such a pattern requires a complex set of interactions; otherwise, the stripe would be crooked, or decay into separated patches, or bifurcate. Correct patterning is achieved in vertebrates and insects in different ways — in vertebrates by a sequential elongation of the midline by the organizer, in insects by a repulsive effect from the dorsal side, which orients the Dorsal gradient and localizes the ventral midline[13]. Maybe the effort involved in generating one such midline was so great that the Sog–Tsg–BMP system was developed to use the information contained in that midline to create another at the opposite pole. ■

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Cell biology

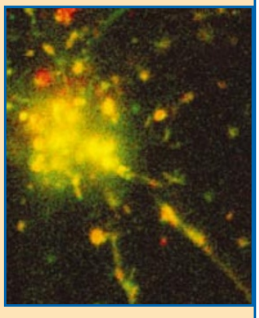
Proteins tracked in a flash

Cell biologists have a lot to thank jellyfish for. The species concerned has provided them with green fluorescent protein (GFP), a tool for monitoring the dynamics of gene expression and following the movement of proteins and even entire cells. Over the years, the usefulness of this 'molecular reporter' has been boosted by the isolation of GFP variants possessing greater fluorescence, altered excitation and emission wavelengths, and greater stability in living cells.

But there was scope for further improvement. In particular, tracking protein movement in real time was difficult if the tagged protein became evenly distributed in the cell under steady-state conditions. Writing in *Science* (**297,** 1873–1877; 2002), George H. Patterson and Jennifer Lippincott-Schwartz now describe a possible solution to this problem. They have produced a GFP variant that shows greatly increased fluorescence if it is activated by light; and it functions in physiological conditions. Using this photoactivatable GFP, tagged proteins in a small area of the cell can be selectively marked by light activation, so that their movement through the cell can be followed against a dark background by fluorescence microscopy.

Normal GFP contains a mixed population of neutral and anionic chromophores — molecules that absorb light then re-emit it. These are respectively associated with a major light-absorption peak at a wavelength of 397 nm and a minor peak at 475 nm. Intense illumination at 400 nm shifts the population to the anionic form, thereby increasing the absorbance of the minor peak. Patterson and Lippincott-Schwartz set out to develop a GFP variant that had a negligible 475-nm peak. They reasoned that illumination at 400 nm would then produce a much greater proportional increase in 475-nm absorbance compared with the normal protein, and therefore increase optical contrast.

One variant, called PA (for 'photoactivatable') GFP, produced a 100-fold increase in fluorescence at 488 nm *in vitro*, and was stable under various conditions. Patterson and Lippincott-Schwartz then tested this variant in living cells. They found that selective



photoactivation of PA-GFP in either the nucleus or cytoplasm of the cell led to a brightly fluorescent population that moved rapidly between the two areas. The authors also attached PA-GFP to a marker protein called lgp 120, found in a cellular compartment, the lysosome, that is responsible for digesting unwanted material. Before photoactivation, little fluorescence of lgp 120 was seen. But after photoactivation, lgp 120 was evident in most of the lysosomes within 20 minutes (see figure), showing that rapid exchange occurs between these organelles.

This new type of GFP should prove valuable for studying the temporal and spatial dynamics of proteins in the living cell. The future for such research literally looks brighter. **Deepa Nath**