➲ **DEVELOPMENT**

Bicoid gradient tried and tested

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How precise and reproducible are morphogen gradients? And how is a gradient 'scaled' in embryos of different sizes? In two papers, Gregor *et al.* addressed these and other long-standing questions in the field by studying the morphogen Bicoid (BCD) in the early *Drosophila melanogaster* embryo.

Using transgenic fly embryos in which endogenous BCD was replaced with a fluorescent BCD fusion protein, the authors quantified BCD in living embryos by two-photon laser scanning microscopy. The anterior-to-posterior BCD gradient was established surprisingly rapidly, within 90 minutes of fertilization, both in the nuclear and cytoplasmic compartments of the embryo.

BCD concentration varied greatly in individual nuclei, with maximal concentrations of BCD occurring during early interphase. This dynamic pattern was reliably reproduced in successive nuclear division

The image shows a 2-hour-old fruit fly embryo that has been colour labelled to reveal Bicoid protein (blue), Hunchback protein (green) and DNA (red) inside the nuclei at its surface. Image provided by T. Gregor, Princeton University, Princeton, New Jersey, USA.

cycles with ~10% accuracy, despite a doubling of the number of nuclei as well as general changes in nuclear volume during each cycle.

Photobleaching studies indicated that the nuclear and cytoplasmic concentrations of BCD are in dynamic equilibrium on a short time-scale. Diffusion of BCD was slow, so how can the gradient be formed so quickly after fertilization? The authors challenged the traditional model for gradient formation, which suggests that a gradient is the result of local protein synthesis, diffusion and spatially uniform degradation. They proposed instead that the BCD gradient is shaped by the intranuclear degradation of protein. This hypothesis could also solve the 'scaling' problem, as the steady-state BCD profile in each embryo only depends on the size of the embryo itself.

In an accompanying paper, Gregor *et al.* attempted to quantify the precision and reproducibility of positional information. They calculated that a 10% concentration measurement is necessary to distinguish individual nuclei from their neighbours reliably (that is, the error bar has to be ≤10%). The absolute concentration of BCD at half-embryo length — that is, where this protein targets Hunchback (HB) — is extremely low: there are only 700 molecules per nucleus, so nuclei would need the ability to distinguish

70 molecules (10%). The authors used this measurement to estimate the physical limit to precision — the limit set by the inherent noise in any physical system — and found that it can only achieve a precision of ~50%, which suggests that mechanisms other than mere noise reduction are needed to achieve 10%.
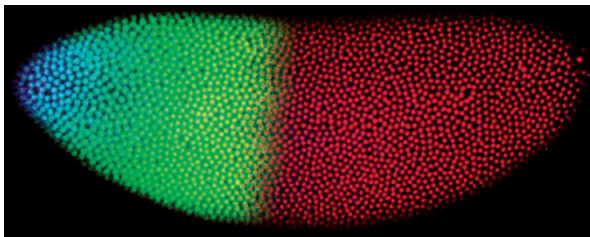
When the authors also measured the input–output relationship between BCD and HB, they found that the precision with which nuclei can measure their concentration at half-embryo length was within 10% accuracy. They also found a 10% reproducibility in the spatial profile of BCD from embryo to embryo, much higher than had been previously reported.

This remarkable agreement in accuracy using different measures and experimental approaches indicates that pattern formation in embryos does not appear to be plagued by noisy input signals and variable readouts, but is instead precisely and reproducibly controlled. The next obvious goal is to understand the mechanisms that control this extreme precision and reproducibility.

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ORIGINAL RESEARCH PAPERS Gregor, T. *et al.* Stability and nuclear dynamics of the bicoid morphogen gradient. *Cell* **130**, 141–152 (2007) | Gregor, T. *et al.* Probing the limits to positional information. *Cell* **130**, 153–164 (2007)