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DEVELOPMENT

Drosophila embryos are doing it for themselves

Canalization — the ability of developing organisms to produce consistent phenotypic outcomes despite biochemical fluctuations — was first described 60 years ago, but a direct mechanistic description of this complex phenomenon has been lacking. A quantitative and experimental approach to analysing embryonic development in *Drosophila melanogaster* now shows that canalization emerges from precise regulatory interactions between genes and is therefore an intrinsic property of this developmental system.

In a canalized system genes should show progressively lower expression variation over the course of development, as indeed is true of the segmentation network of flies. However, the authors sought to examine whether this system also satisfies the second criterion for canalization, namely that the mechanism be explicable solely from internal interactions. By studying gene expression at high temporal and spatial resolution the authors modelled and then experimentally tested the predicted regulatory interactions that give rise to the observed stabilization of gene expression during development.

The authors followed the expression of four zygotic gap genes — *hunchback* (*hb*), *Krüppel* (*Kr*), *knirps* (*kni*) and *giant* (*gt*) — at multiple time points from cycle 13 until gastrulation. This allowed them to construct a computational model that correlated variation in the nuclear concentration, over time, of the encoded transcription factors with the regulatory interactions between these proteins and with their upstream regulators, such as Bicoid (BCD). The resulting 'gene circuits' could then be manipulated *in silico* with respect to initial BCD concentration, and the phenotypic outcomes — in the form of expression boundaries — were compared with their placement *in vivo* (see the figure). Such a model correctly predicts the variance of most (six out of eight) of the boundaries of gap gene expression, which, importantly, are robust to variations in BCD concentration. It also shows that such boundaries scale with variation in egg length, thus excluding the involvement of a hypothetical posterior gradient in regulating expression boundaries.

The gene interactions underlying this reduction in variance over time can be inferred from the model, based on the strength of gene regulation at the gap gene boundary, and from how this regulation is affected by variation in BCD expression. This analysis showed that each boundary is set up by an activator and two repressors. For example, the posterior border of *hb* expression occurs where there is a tipping point between activation by BCD and repression by KR and KNI. This hypothesis was confirmed experimentally in *kni*;*Kr* double mutant embryos, in which the *hb* boundary doubles its variance — this result is particular relevant as it contradicts a previous report that the *hb* boundary is set exclusively by BCD.

In a separate paper, the same group uses a modelling approach to show that the reduction in expression variation over time is caused by the convergence of the developmental trajectory of the system: cross-regulation between gap genes pushes the system towards one of many stable states, or 'attractor states'. Small fluctuations in the starting conditions experienced by each nucleus do not prevent different nuclei from moving towards the same attractor state — the gene network of gap genes ensures that such 'wobble' is ironed out, which is manifest phenotypically as developmental stability.

This work shows that the reduction in variation that occurs during early embryonic patterning is an emergent property of the system — a hypothesis that has been controversial — and highlights the utility of taking a detailed quantitative approach to an age-old developmental question.

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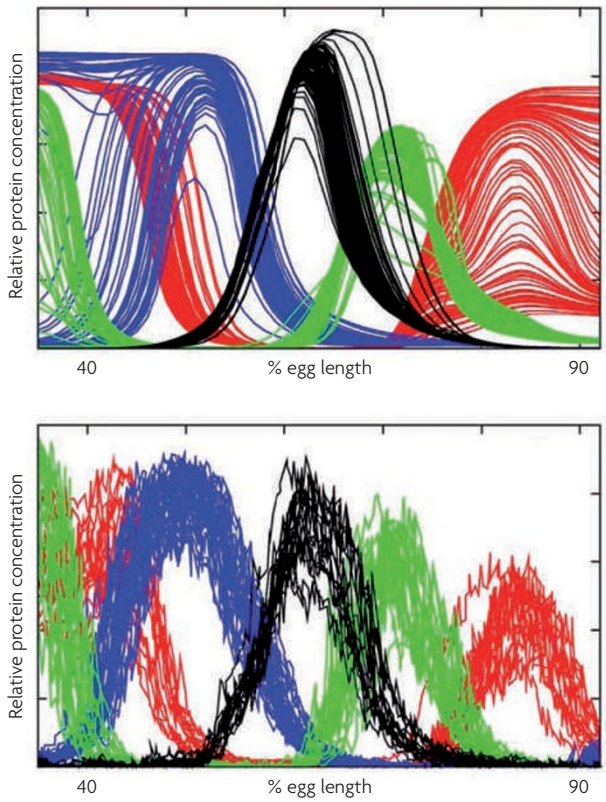

Top. Modelled expression patterns of Hunchback (HB; red), Krüppel (KR; blue), Knirps (KNI; black) and Giant (GT; green) in simulations of the gene circuit using Bicoid profiles from 88 individuals. Bottom. Measured gene expression patterns of HB, KR, KNI and GT from 83 wild-type embryos. Image is modified from Manu & Surkova, S. *et al. PLoS Biol.* **7**, e1000049 (2009).

ORIGINAL RESEARCH PAPERS Manu & Surkova, S. *et al.* Canalization of gene expression in the *Drosophila* blastoderm by gap gene cross regulation. *PLoS Biol.* **7**, e1000049 (2009) | Manu & Surkova, S. *et al.* Canalization of gene expression and domain shifts in the *Drosophila* blastoderm by dynamical attractors. *PLoS Comput. Biol.* **5**, e1000303 (2009)
FURTHER READING Tomlin, C. J. and Axelrod, J. D. Biology by numbers: mathematical modelling in developmental biology. *Nature Rev. Genet.* **8**, 331–340 (2007)