that the use of locus-by-locus strategies to analyse interacting loci might be a major contributor to the lack of replication in association studies.

The importance of considering genetic epistasis in the analysis of complex traits is becoming increasingly recognized. By showing here that analytical strategies that explicitly consider interactions between loci are computationally feasible and often yield increased power, Marchini and colleagues offer clear guidance to the community about the design and analysis of future genome-wide association studies.

Kyle Vogan, Associate Editor,
Nature Genetics

References and links

ORIGINAL RESEARCH PAPER Marchini, J., Donnelly, P. & Cardon, L. R. Genome-wide strategies for detecting multiple loci influencing complex diseases. *Nature Genet.* 27 March 2005 (doi: 10.1038/ng1537)

FURTHER READING Hoh, J. & Ott, J. Mathematical multi-locus approaches to localizing complex human trait genes. *Nature Rev. Genet.* **4**, 701–709 (2003) | Zondervan, K. T. & Cardon, L. R. The complex interplay among factors that influence allelic association. *Nature Rev. Genet.* **5**, 89–100 (2004)

DEVELOPMENTAL BIOLOGY

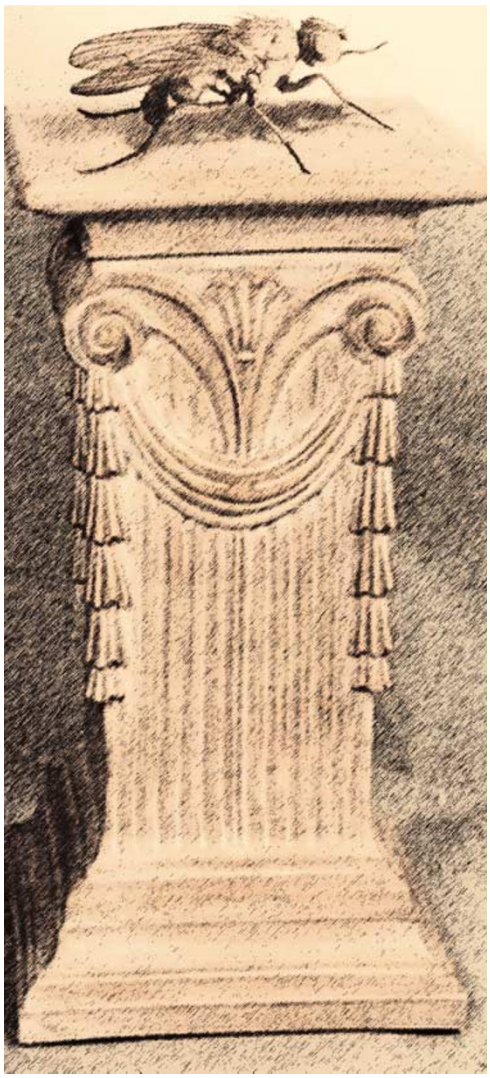
A model model system

In the interdisciplinary spirit that now characterizes much of biology, the hard sciences are increasingly creeping into many aspects of developmental genetics. As two new papers describe, computational methods plus a touch of engineering mean we can model or even build biological systems to refine our understanding of how they work.

Genetic analyses have given us a fairly detailed outline of the signalling hierarchies involved in patterning the nematode vulva and the early development of the fly embryo. However, a more complete view requires tools that can visualize the entire system of cells as well as their dynamic interactions, and that can explore any ramifications the latter might have.

The first study has taken just this approach to studying the vulva of *Caenorhabditis elegans*. This heavily scrutinized part of the anatomy starts out as six multipotent precursor cells (the VPCs), which differentiate to take on one of three fates through the interplay of three signalling events. Modelling what goes on during differentiation involved generating a so-called 'statechart' model for each VPC. This is a visual computational language that describes the behavioural state of a cell at any one time, how it varies depending on the signalling inputs the cell receives and how it interacts with other cells when it is mutated for a signalling component. Although this simulation is still a work in progress, it can analyse VPC specification in some detail — for example, the model highlights the importance of the relative timing of signal reception on the outcome of signalling. The model was built using the bare bones of the vulval network, but adding more recent findings should help to enrich the model and enhance the value of its output.

A second study has applied a creative approach to understanding the elaborate gene network that transforms the maternal morphogen gradient in the fly egg into a neatly patterned embryo. To determine the minimal components required for this process, Mark Isalan and colleagues built an *ex vivo* model of a fly embryo. The syncytium of the early embryo — a pool of nuclei in a common cytoplasm — was recreated by lining a chamber with paramagnetic beads that were coated with DNA encoding different gene constructs, which could then be transcribed, translated and interact with other products as part of a gene network. Tweaking the connectivity of the network yielded different patterns; the system could then be modelled computationally to identify which parameters were compatible with real-life patterns. As for the nematode vulva, this model is simpler than



life, but it suggests several avenues of exploration, such as the realization that diffusion alone cannot bring about the patterns of gene expression seen in real embryos without some sub-localized 'trapping' of the mRNAs or proteins concerned.

Modelling has several advantages over static genetic models; for example, it can easily spot gaps in current knowledge and formulate testable hypotheses. As with all models, it is only as good as the data on which it is based, ensuring that thorough genetic analyses continue to be in high demand.

Tanita Casci

References and links

ORIGINAL RESEARCH PAPERS Fisher, J. *et al*. Computational insights into *Caenorhabditis elegans* vulval development. *Proc. Natl Acad. Sci. USA* **102**, 1951–1956 (2005) | Isalan, M. *et al*. Engineering gene networks to emulate *Drosophila* embryonic pattern formation. *PLoS Biol.* **3**, e64 (2005)

FURTHER READING Isalan, M. *et al*. Localized transfection on arrays of magnetic beads coated with PCR products. *Nature Methods* **2**, 113–118 (2005)

WEB SITES

Jasmin Fisher's web page: www.wisdom.weizmann.ac.il/~jasmin
David Harel's web page: http://www.wisdom.weizmann.ac.il/~dharel
Luis Serrano's laboratory: http://www.embl-heidelberg.de/ExternalInfo/serrano