# Journal club

## RECONCILING RANDOMNESS AND PRECISION

One of my research goals has been to combine quantitative experiments and mathematical modelling to address questions of epigenetic regulation *in vivo*.

Why does epigenetics need mathematics? Think of the phenomenon of variegation, which can be seen in plants as green and white patches on leaves, and in the eyes of mutant flies as red and white patches. These random patterns are the result of a switch between two extreme gene expression states that, once established, become epigenetically stable over many cell divisions. This random behaviour seems to be at odds with exquisite developmental precision and quantitative response to signals — both hallmarks of epigenetic regulation during development. A full understanding of epigenetic regulation calls for mathematical models that reconcile these properties of randomness and precision. The papers by Dodd *et al.* and Angel *et al.* are landmarks in this endeavour.

> A full understanding of epigenetic regulation calls for mathematical models

In their theoretical study, Dodd *et al.* were the first to recapitulate bistability using stochastic modelling of chromatin states. This work beautifully describes epigenetic processes in terms that are accessible to non-mathematicians: an array of nucleosomes, a modification state for each one, and a disruption of that state upon DNA replication. Moreover, this very simple model provided insights into some fundamental questions in epigenetics, showing that a system in which individual random nucleosomes change their state rapidly can nevertheless maintain a stable state at the level of the whole array that is robust to the perturbations of replication.

Angel *et al.* adapted and extended the Dodd model to address the quantitative aspect of vernalization (an epigenetic process that confers memory of winter in plants): the longer the cold exposure during winter, the stronger is the epigenetic silencing of a specific gene after the winter is over. This work stands as a landmark for several reasons. First, it is one of very few examples in epigenetics in which mechanistic modelling and rigorous quantitative experimentation are combined. Second, it demonstrated both theoretically and experimentally that the quantitative response to cold is achieved by a digital switch, which is both random and precise. It is random because any cell can switch the gene off or on, but precise because the number of cells in a silenced state is controlled by and directly proportional to the length of cold exposure. Finally, this work has wide consequences beyond vernalization. It established a theoretical framework, within which other questions can be addressed: for example, how does epigenetic regulation adapt to faster acting switches, and is it always digital? Incidentally, the supplemental material in Angel *et al.* is so comprehensive that, with rudimentary programming skills, it is possible to re-implement the entire model from scratch, which is extremely informative for understanding the relationship between randomness and precision.

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The author declares no competing interests.

**ORIGINAL RESEARCH PAPERS** Dodd, I. B. *et al.* Theoretical analysis of epigenetic cell memory by nucleosome modification. *Cell* **129**, 813–822 (2007) | Angel, A. *et al.* A Polycomb-based switch underlying quantitative epigenetic memory. *Nature* **476**, 105–108 (2011)

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**Web summary**
Leonie Ringrose highlights how mathematical modelling can provide insights into fundamental mechanisms underlying epigenetic regulation.