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Editorial

Biologists who count*

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The importance of mathematics in biology is a matter of perennial debate. The squabbles of early 20th century geneticists on the value of mathematics to the study of evolution have recently been revisited in *Journal of Biology* [1], and the 21st century has seen an explosion of information from various -omics and imaging techniques that has provided fresh impetus to the arguments urging the need for mathematical competence in the life sciences [2]. While there can be no question about the contribution of mathematics to many fields in biology, there is a curious tendency on the part of numerate biologists (often immigrants from the physical sciences) to insist that it is an essential part of the equipment of a biologist and none should be without it. This seems, on the evidence, extreme.

A more temperate view is taken, if implicitly, by Ferrell [3] in his recent Q&A for *Journal of Biology* on systems biology. (Explicitly, at least in the context of systems biology, he is uncompromising on the math prerequisite.).

Leaving aside the issue of exactly how you define systems biology, one of the objectives of those who would say they are practitioners is to understand the emergent properties of complex systems. Examples of such properties in biological systems are the biochemical switches and oscillators that underlie the cell cycle, and the robustness of biological mechanisms - for example, the morphogenetic gradients that direct early embryonic development - in conditions that are subject to stochastic fluctuation. Ferrell argues that mathematics is required to understand the behavior of an entire system; but acknowledges the value of understanding at a more parochial level the mechanism of parts of it. He gives as a classic example of a switch in biology the gene-regulatory switch [4] that operates the decision between lysis and lysogeny in bacteriophage lambda.

Lambda, which infects *E. coli*, inserts its genome into that of the bacterium and can then either reproduce itself and lyse the bacterial cell (lysis), or remain in a latent state in which it is replicated with the bacterial genes (lysogeny) until an environmental change flips the switch to the lytic program. The basis for the switch is the competitive binding to DNA of two proteins, one of which (repressor) represses the lytic programme and activates its own synthesis, maintaining the lysogenic state, while the other represses the synthesis of the repressor and activates the lytic programme and its own synthesis, maintaining the lytic state. (The switch is operated by an environmentally controlled cellular protein that decreases the affinity of repressor for DNA.) This mechanism was worked out, as far as I know, without recourse to mathematics.

A gene regulatory switch of a somewhat analogous kind is an essential component of the developmental mechanism explored in the review by Lewis, Hanisch and Holder in this issue of *Journal of Biology* on the part played by the receptor protein Notch in the formation of somites in the developing embryo [5]. This process depends on an oscillator known as the segmentation clock, which dictates the formation of regular blocks of tissue (somites) from the embryonic mesoderm. Known components of the clock are the Notch receptor protein and its ligand, Delta, which is also a cell-surface protein; and the products of the *Hes/her* genes, which are gene regulatory proteins that act as transcriptional inhibitors. Notch signaling activates the *Hes/her* genes, whose products feed back to inhibit both their own transcription and that of the Delta gene. Broadly - at least for zebrafish - the *Hes/her* genes are thought to provide a cell-intrinsic oscillator through negative autoregulation, with Notch signaling synchronizing the autonomous oscillators in adjacent cells of the mesoderm

It is not surprising that an understanding of the properties of this oscillating system requires

mathematics; indeed Lewis argues cogently that the behavior of the *Hes/her* oscillator alone is beyond the reach of simple intuition.

Moreover the biological facts, which are almost always beyond the reach of most people's intuition, seem to indicate that an even more complex system operates in mammals (or at least mice, from which it is probably safe to generalize), in which fibroblast growth factor (FGF) and Wnt signaling are also implicated, and in which the *Hes/her* cell-intrinsic oscillator may not be the only one.

So ostensibly significant a difference between vertebrates in so fundamental a process seems surprising, and may dwindle (either in extent or in significance) with the accumulation of more facts.

In any event, if mathematics must be applied to make sense of the facts, at least in so complex a system as a developing embryo, then facts - and indeed understanding - at many levels must be fed into the mathematics. Nor should the value of facts and understanding on their own be dismissed. The case for Darwin's theory of evolution by natural selection would have been strengthened had he been mathematician enough to recognize Mendelian ratios, but this scarcely diminishes his monumental achievement.

There seems no need for the snobbery (it is said) of the highly quantitative founding biologists at the Cold Spring Harbor Laboratories, in whose early history ex-physicists played a crucial part, and who are alleged to have referred to their nearby colleagues at Woods Hole as biologists 'who don't count'.

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*The version of this editorial that appeared from May 22-27 contained some egregious errors that have been corrected in this one.

References

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