Cells, Embryos, and Evolution: Towards a Cellular and Developmental Understanding of Phenotypic Variation and Evolutionary Adaptability

John Gerhart + Marc Kirschner

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Of the major divisions of biology, developmental biology has been least well integrated into the evolutionary synthesis. In *Cells, Embryos, and Evolution*, Gerhart and Kirschner make a major contribution to changing this.

> Strategies of evolutionary change have never before been explored broadly on a cellular level and it is our hope that by examining cellular and developmental mechanisms from the perspective of evolution, and examining evolutionary change from the perspective of cell and developmental biology, we will develop new insights into both.

Their starting point is the conservation of so many cellular processes and structures despite extensive evolutionary diversification. They attempt to do justice to the complexity of the process from genotype to phenotype, with an approach spanning biochemistry and cellular and developmental biology, from the molecular level to the organism. They also reach out to phylogenetics, paleontology, genetics, and other disciplines. The one major limitation is a restriction to the metazoa, with particular attention paid to the arthropods and chordates.

Gerhart and Kirschner begin with the basic idea of contingency, which term they use to refer to regulation and control dependencies, not in the "indeterminate and unpredictable" sense popularised by Gould in paleontology. Some such dependencies are direct and *ad hoc*: examples include basic transcriptional and translational controls, many metabolic pathways, and the cell cycle control system. Others, such as the calmodulin (calcium response) and protein kinase systems, are more general, with a low specificity that makes it easy for evolution to create new contingencies.

Examples of more complex regulatory linkage and control systems include sodium and potassium ion channels and associated membrane potentials, G proteins, and eukaryotic transcriptional controls. Membrane potentials allow linkage over long distances; G proteins couple external signals with intracellular processes (and played an important role in metazoan evolution); and transcription can be activated or inhibited by many different regulatory proteins, often of weak influence individually, acting from long distances. Other important features of these systems are the decoupling of regulation from the underlying metabolism and the ability to "sum" inputs from multiple sources, which allows a form of computation to take place. Selective pressures help explain why such linkage mechanisms are flexible but have highly conserved core structures (such as homeodomain sequences).

Also of key importance are exploratory behaviours: self-assembly, self-organisation, and processes of variation and selection acting at levels other than the genetic. Examples include ant foraging, microtubule organisation in the cellular cytoskeleton (exploration and selective stabilisation), the vertebrate immune system (generation and selection), and the formation of distribution systems in angiogenesis and tracheogenesis (guided exploration). These kinds of exploratory processes are important for evolution because their flexibility provides robustness, protecting systems from changes to other structures. The result is, again, a combination of highly conserved structures (such as the microtubule system) with flexible "behaviour".

Novel proteins can arise in many ways. Where specificity is low, all kinds of proteins can be coopted for use (lens crystallins). Existing proteins can be modified by diversification of new structures (keratin intermediate filaments). And new cell types can create novel possibilities for existing proteins (myelin sheaths). New proteins can also be generated by combination of subunits (lactose synthetase) or by exon shuffling. The ability of such shuffling systems to generate novelty may explain their persistence, if not their origins. Sex has also played a role in creating and maintaining genotype variation.

Increasing conditionality, or control of cellular environments,

accompanied the development of multicellularity: key properties of the stem metazoan included epithelia, extracellular matrix, and intercellular signalling systems. Another opportunity afforded by multicellularity is compartmentalization, or the use of a subset of the genome to produce cell differentiation — cellular, spatial, temporal, and sexual. The example of striated muscle cells illustrates the role of regulatory networks in establishing and maintaining stable differentiated states. The nematode vulva and *Drosophila* eye structure and bristle patterns illustrate the processes of spatial differentiation through local pattern formation. The same signalling "modules" are reused in different contexts within the one organism: developmental stability at one level again accompanies flexibility at others.

Building on the previous material, the second half of *Cells, Embryos, and Evolution* moves on to larger scales, with four chapters surveying metazoan embryology. The first describes the basic body plans, the conserved phylotypic stages, of arthropods (the segmented germ band) and chordates (the pharyngula) and, in less detail, of nematodes, annelids, and molluscs. Hox and other selector genes are central to the creation of this compartmentalisation. Gerhart and Kirschner also reconstruct the Vendian and Cambrian history of the metazoa — as diversification from a stem "roundish flatworm" — and touch on the reasons for the subsequent conservation of basic body plans.

Axis specification in the early embryo relies on a variety of processes for symmetry breaking and self-organisation: case studies include ascidians, amphibians, birds, mammals, insects, molluscs, and nematodes. The diversity found here, even within phyla, is related to reproductive specialisations for protection and nutrient provision. "Intermediate processes" connect this minimal initial organisation to the phylotypic stage. Their flexibility and robustness allow for the decoupling of stages and for greater developmental variability. In *Drosophila* these processes include complex transcription factor cascades and local inductions and morphogenesis; in chordates there is a more complex series of inductions (in which the "organiser" plays a central role), accompanied by extensive morphogenesis.

Post-phylotypic development is linked to evolutionary diversification within phyla. Examples include the vertebrate limb and its organisation and patterning through Hox expression, the manifold diversifications of neural crest in chordates, and the arthropod appendage, diversifications in which account for much of the evolutionary specialisation within the phylum. Once again, the dominant theme is the importance of flexibility, robustness, and compartmentalization in allowing phenotypic variation and evolutionary diversification.

The concluding chapter finally connects this recurring theme, of a mixture of flexibility and variation with stability and conservation, to more abstract, "top-down" evolutionary theory. Central ideas are "evolvability", or the potential for non-lethal phenotypic variation on which selection can act, and the possibility that some lineages may possess developmental flexibility as a result of clade selection. Gerhart and Kirschner also consider notions of directionality in evolution and hint at a vastly more sophisticated form of Haeckel's biogenetic law. They sum up against an externalism that assumes that "all phenotypes are possible" and "is dismissive of the complexity of developmental mechanisms and fails to recognize that there are only some types of change that a given organism can realistically undergo". Though it quite handily refutes claims (for example by Behe in *Darwin's Black Box*) that the evolution of complex biochemical systems is mysterious, *Cells, Embryos, and Evolution* demonstrates a different kind of "irreducible complexity". It shows that there is a basic "messiness" to development which simply will not allow for theories as simple as those in some other areas of biology.

None of these ideas are entirely original, of course, but rarely have they been backed by such a wealth of biochemical and cellular detail. And while the connection of this detail to broader evolutionary theory is still fairly rudimentary, it is a far cry from the vagueness that all too often accompanies appeal to "developmental constraints". Certainly a lot more remains to be done here, but *Cells, Embryos, and Evolution* is a major step forwards.

Diagrams are used to good effect throughout *Cells, Embryos, and Evolution*; it also contains an effective set of colour photographs. The

balance between technical detail and summary is carefully maintained, with maybe one or two exceptions. Gerhart and Kirschner have produced a work which can be followed without a research background in developmental and cellular biology and *Cells, Embryos, and Evolution* deserves a broad, inter-disciplinary audience. It may contain more biochemical, cellular, and embryological detail than paleontologists or population geneticists are accustomed to dealing with, but this is detail which deserves their attention.

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