# THE DEVELOPMENTAL SPECIFICITY
## OF PHYSICAL MECHANISMS

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Marta Linde-Medina's historical and analytical essay on theories of organic form shows that the road to our contemporary understanding was bumpy and tortuous, with not everybody arriving at the same place (Linde-Medina 2010). Among modern biologists, some (the inheritors of the mid-twentieth century Modern Synthesis) advocate a view in which the forms of multicellular organisms are generated by hierarchical algorithms, inscribed in the language of nucleotide sequence. These developmental programs are presumed to have emerged through a process of relatively blind search in which individuals whose genomes contained coding changes that led to small, functionally superior anatomies and physiologies were successively enriched in their respective populations. The molding of the forms by functional requirements leads Linde-Medina to term this school of thought "externalist." Other biologists (physicalists) hold that organisms and their organs assume stereotypic morphological motifs by virtue of the material properties of their tissues. The molding forces in this case are largely those of middle-scale (mesoscopic) self-organizing physical processes inherent to these materials, leading the author to term this view "internalist."

It is sometimes claimed that the physicalist framework denies a role for natural selection. But it can be seen from the description above that this paradigm is directed toward explaining the origination of biological forms, not their survival, persistence or abundance. Not every form that is possibly generated by self-organizing processes can find a place in the ecosystems available to it (Batten, et al. 2008). Competition for resources and mates, niche selection and construction, and many other aspects of organism-environment and organism-organism interaction classically considered by the post-Darwin synthesis must therefore enter into the scientific understanding of why the biosphere has the composition it does, even for advocates of the physicalist approach. Of course, nothing in Linde-Medina's essay denies this.

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Where the physicalist approach does come into conflict with the synthesis (and with Charles Darwin and Alfred Russel Wallace's own characterization of their unique contribution to evolutionary theory) is in its rejection of a dogmatic gradualism. As described by Linde-Medina (2010) (who draws as well on the insights of Depew and Weber, 1996), the nineteenth century scientific world was dominated by the inertial mechanics of stationary and moving objects formulated by Galileo and Newton, in which an outside agency is required to make something change its course. Even then, the change is only proportional to the strength of the external influence. It can even be said that the vernacular concept of physical change then (as now) was more like that of Aristotle: changing not only the course of a moving object, but even its position, requires a continual push form outside. Reshaping a ball of clay is an Aristotelian, not a Newtonian project, and it is a regrettable fact that this is the physics implicit in Darwinism.

This stolid view of what physics is capable of doing was overthrown by new concepts of dynamical, qualitative transformations of matter with roots in the late eighteenth and early nineteenth centuries. These would eventually give rise to chemistry, thermodynamics, and electricity and magnetism, and represented a modern turn of thought that ironically (given the contrast of their present-day reputations) the older, physically knowledgeable Lamarck incorporated into his evolutionary theory, but Darwin did not (Newman and Bhat 2011).

Physics was further revolutionized in the twentieth century, not just by the famous quantum and evolutionary theories, which pertained to matter at scales different from most biological phenomena, but by biologically relevant physical theories of the middle scale: nonlinear oscillations and multistable dynamical systems, separation and transitions between fluid phases, viscoelastic flow, reaction-diffusion coupling and the spontaneous breaking of compositional spatial symmetry. By the late 1930s, the anti-vitalist American embryologist E. E. Just (1883-1941), confronted with experimental material that was "self-acting, self-regulating and self-realizing" (Just 1939, p. 237), was calling for "a physics and chemistry in a new dimension superimposed upon the now known physics and chemistry" (Just 1939, p. 3), and by the last third of the century much of this new science was at hand. There was no longer any justification for developmental biologists to adhere to classical mechanical views of how complex materials, such as the soft, chemically and mechanically excitable matter of cell aggregates may become physically reorganized and reshaped. Nor was there any basis for evolutionary biologists to persist in excluding development, with all its multifarious demonstrations of abrupt changes in form resulting from minor alleleic or gene expression alterations, from the canon of their field.

Nonetheless, the physicalist approach continued to be scorned as "anti-genetic." This was partly due to the primitive nature of genetic knowledge available at the time when certain biologists started to think that organisms, being made of matter, were therefore subject to some formative processes in common with nonliving materials. William Bateson (1861-1926), who introduced Mendel's work to the English-speaking world in the first years of the twentieth century, and actually coined the term "genetics," favored a notion of the gene as a component of a complex system of interactions (what we would now term a dynamical system or network), rather than as a particle or corpuscle, as later became the scientific fashion. He proposed a "vibratory theory" of segmentation, in which an underlying physical or chemical oscillation organized the tissue that contained it such that "Divisions between segments, petals, etc. are *internodal lines* like those in sand figures made by sound, i.e., lines of maximum vibratory strain, while the midsegmental lines and the petals, etc. are the *nodal* lines, or places of minimum movement "[1] (Bateson and Bateson 1928, p. 42; discussed in Newman 2007).

But the mischaracterization of physicalist evolutionary-developmental biology has also resulted from scientific turf protection and the impoverished imaginations of some influential evolutionists. According to Ernst Mayr, a founder and long-term enforcer of the synthesis, Bateson's vibratory theory "simply retarded scientific progress" (Mayr 1982, p. 42). This was written fifteen years before that theory was confirmed experimentally in all its essentials (Palmeirim, et al. 1997). D'Arcy W. Thompson (1860-1948), a far-sighted physical theorist of morphology of the pre-gene era (Thompson 1942), though feted in his day, has been similarly relegated to the margins of scientific history, while the contribution of the mathematician Alan Turing (1912-1954) to the dynamics of developmental pattern formation is only now gaining acceptance among mainstream developmental biologists (reviewed in Kondo and Miura 2010).

Perhaps the most deep-seated misunderstanding of physics-grounded evolutionary developmental biology, however, relates to the question of specificity. "We all know embryos are physical entities," the refrain goes, "but physics is the same everywhere. Genes are the only heritable items that make one organism different from another."[2] A moment's reflection, however, reveals that physics does not apply equally to all forms of matter. Billiard balls do not exert a noticeable gravitational pull on each other, nor do they undergo Brownian motion. Light passes freely through glass, is scattered by stone, and gains coherence if pumped through a ruby crystal. Similarly with clusters of cells: certain optional molecular components make them susceptible to different sets of morphogenetic and patterning processes and effects. And if a lineage contains the means to harness a physical effect, that effect is every bit as heritable as the associated gene.

The basis for recognizing the evolutionary sorting of specific physical processes into different phylogenetic lineages, and their changing roles in the generation of form over the history of multicellular life, only emerged over the past two decades. It required major advances in developmental genetics and comparative genomics as well as in mesoscale physics. In the earlier part of this period it began to be clear that "generic" physical effects identified previously in the study of non-living soft, excitable materials pertained to the clusters of cells that constitute the early embryos (and presumably the ancient multicell antecedents) of metazoan organisms (i.e., animals) and their organ primordia (Newman and Comper 1990). As detailed knowledge of the complex, hierarchical nature of present-day developmental mechanisms emerged (e.g., St Johnston and Nüsslein-Volhard 1992; Wilkins 2002), it became equally evident that the self-organizing physical effects active in embryogenesis were not present in "pure" form. Rather, the morphological motifs they generated most likely served as templates and constructional elements upon which canalizing and stabilizing selection (Waddington 1942; Schmalhausen 1949) had operated over time, creating entrenched developmental routines that were profoundly more integrated and *autonomized* (i.e., independent of external conditions and even genetic composition) than any of the originating processes (Newman 1994; Müller and Newman 1999; Newman and Müller 2000).

A few years later, based on accumulating knowledge of a highly conserved metazoan developmental-genetic "toolkit" (reviewed in Carroll, et al. 2001 and Wilkins 2002), the association between specific molecular components expressed in cell aggregates and the key physical effects mediating animal morphogenesis and pattern formation became apparent (Newman, et al. 2006). And then, in light of the newly available genomic sequences of the choanoflagellate *Monosiga brevicollis* and other choanozoans (the present-day single-cell organisms with the greatest genetic similarity to the Metazoa) (King, et al. 2008; Shalchian-Tabrizi, et al. 2008), and comparison of these to the increasingly rich array of genomes of representative of the animal phyla, the surprising fact emerged that many of the toolkit genes, including most of those involved in mediating cell-cell interaction, morphogenesis and pattern formation in present-day animal embryos, actually pre-existed multicellularity.

This suggested that toolkit gene products which had first appeared and evolved in the unicellular world had been co-opted in the primitive cell clusters of the Precambrian era to perform morphogenetic functions. They did so, it appeared, by virtue of physical effects that became newly efficacious in materials of the scale and liquid-like nature of multicellular aggregates. This led to a framework for the origin of metazoan form generation and phylogenetic diversification of morphology in terms of

"dynamical patterning modules" (DPMs), defined as associations of specific gene products (or their derivative or pathways) and a mesoscale physical force, effect or process mobilized by these molecules (Newman and Bhat 2008, 2009).

Linde-Medina has generously discussed this framework in relation to overcoming the theoretical dichotomy she has posed (Linde-Medina 2010). Since the DPM perspective is new and relatively unfamiliar, here I will briefly mention the connection between certain physical effects and certain ancient genes in development, and how they are inextricably tied together in the generation of specific morphological motifs. Additional details can be found in Newman and Bhat 2008, 2009; Newman, et al. 2009; and Newman 2011).

The emergence of the animals depended initially on the formation of multicellular clusters by unicellular ancestors. Although at least one choanoflagellate species attains multicellularity by retention of cellular bridges during cytokinesis (Dayel, et al. 2011), some of these organisms have genes for cadherins and C-type lectins, mediators of cell-cell aggregation and adhesion in modern metazoans. It is therefore likely that the ancient multicellular lineage (deriving from the common ancestor of the metazoans and the choanoflagellates) that led to the animal phyla made use of these functionalities. Since cell clustering results from cell surface molecules (e.g., cadherins) capable of harnessing a physical force, *adhesion*, to generate a novel morphological outcome, this association defined the primary DPM, designated *ADH*.

Following from the step toward multicellularity mediated by *ADH*, other DPMs were set into motion. The physical effect of *lateral inhibition*, almost invariably mediated by the highly conserved Notch signal transduction pathway (forming the *LAT* DPM), ensures that alternative states of differentiation of genetically identical cells can coexist together in a single aggregate. Differential adhesion (*DAD*), employing the physical effect of *phase separation*, leads to the spontaneous sorting out of such subpopulations of cells (if they are adhesively distinct) into separate, non-mixing tissue layers, as seen in gastrulating embryos (Steinberg 2007).

Apico-basal and planar polarization of cells (both mediated by secreted factors of the Wnt family), in addition to the ancient unicellular roles of the intracellular portions of the pathways, mediate *topological change* and *reshaping* of tissue masses. The first (via the DPM termed $POL_a$) does so by mediating the formation of interior spaces (lumens), and the second (via the $POL_p$ DPM) by mediating cell-cell intercalation and the "convergent extension" that results from this (Keller 2002). Both these effects, which are straightforward physical consequences of unicellular functionalities in the multicellular context, are essential for the embryogenesis of many species.

Protein secretion (an ancient cell capability) takes on emergent functions in cell aggregates by virtue of the protein's spatial redistribution via the physical process of *diffusion* or more elaborate processes with similar transport dynamics (Lander 2007). The resulting concentration gradients can act as patterning signals in metazoan embryos by mediating concentration-dependent switching of cells between alternative states. The proteins that mediate such effects are referred to as morphogens (e.g., Wnt, Hedgehog, BMP), and the related DPM, *MOR*. When morphogens are positively autoregulatory, that is, directly or indirectly stimulatory of their own synthesis in target cells, and if the resulting tendency of all cells to become morphogen sources is held in check by *LAT*, a new DPM arises. Formulated in terms of the dynamical interaction of activators and inhibitors by Meinhardt and Gierer (2000), this DPM underlies generation of the vertebrate limb skeleton, the dentition, feather germs, and hair follicles. Since it is related to the mechanism proposed earlier by Turing (Turing 1952), we thus call it *TUR*.

Biochemical oscillations in the concentrations of metabolites and proteins occur within all cells. For cells in aggregates, such oscillations spontaneously come into synchrony (Strogatz 2003), coordinating cell states across broad domains and effectively generating what have classically been termed "morphogenetic fields." This *OSC* DPM, along with *MOR*, underlies somitogenesis, the process by which blocks of tissue form in a spatiotemporal order along the central axis of vertebrate embryos, basically confirming Bateson's vibratory theory of segmentation mentioned above.

This summary does not exhaust the DPMs; several others are described in the cited articles. It is gratifying that Linde-Medina considers the DPM framework to provide a way forward in comprehending the origin and generation of form. Like her position, it does not favor self-organization over genes, but sees the two categories of determinants as intertwined. Where form generation is concerned, the way genes "act" is precisely via the physical processes of self-organization they mobilize. Since DPMs are constituted of molecules *plus* physics in the context of multicellular aggregates, their organization of tissues exhibits all the specificity associated with the commonly held exclusively gene-determinist picture. But because physical processes, unlike gene sequences, are predictably responsive to the world outside the organism, DPM-mediated development is also necessarily plastic.

In relation to Linde-Medina's conundrum, the DPM framework falls decisively on the internalist side, since organismal form is generated from within, in a law-like fashion, not according to a genetic program assembled incrementally and arbitrarily as a result of random mutation and chance encounters. It must be acknowledged, however, that unlike forms gener-

ated by purely physical factors, present-day embryos are, to a certain extent, products of external causation. Not in their shapes and forms, which indeed can largely be predicted from the effects of the DPMs that first molded them more than half a billion years ago. The raw material that was organized by DPMs at the origin of the metazoans, however, consisted of complex gene-containing unicellular organisms with billions of years of evolution behind them, not nonliving matter. The ancient multicellular forms thus continued to evolve, with the means by which they have come to be generated in contemporary species ("developmental programs") bearing the imprint of selection for resistance to derailment and other pathological outcomes. The resulting "overdetermined" and highly integrated forms, though stamped at many levels by the nonliving world from which they arose, have thus achieved a relative autonomy from it.

NOTES

1 Bateson was here using sound as just one example of oscillatory phenomena, as is clear from his other writings on the subject.
2 See Erwin (2011) for a particularly ill-informed statement of this position.

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