Supplement A

Attacking the Adequacy of Evo-devo

For an example of how Meyer assesses evo-devo independently as inadequate to account for the macroevolution of new body plans in the Cambrian, consider his treatment of Wallace Arthur's *The Origins of Animal Body Plans* (Cambridge University Press, 1997). In footnote 11 on p. 441 of *Darwin's Doubt*, Meyer reports Arthur as saying "Those genes that control key early developmental processes are involved in the establishment of the basic body plan. Mutations in these genes will usually be extremely disadvantageous, and it is conceivable that they are *always* so." The idea Meyer has in mind is that if even small changes in the developmental gene regulatory networks are almost always harmful to organisms, then evo-devo is unable to account for the appearance of new body plans.

The reader could be forgiven for drawing the conclusion that Arthur's book is arguing against evo-devo as a source of new animal body plans. The actual context for the quote Meyer cites, however, helps us see that Arthur is arguing something different regarding the genes involved in development:

"Those genes that control key early developmental processes are involved in the establishment of the basic body plan. Mutations in these genes will usually be extremely disadvantageous, and it is conceivable that they are *always* so...But it is clear, for example from cross-taxon comparisons of a particular group of such genes–the homobox-containing *Hox* genes...–that homologous 'developmental' genes in different phyla are different. Even where there is an unexpectedly high degree of similarity (e.g., 98 percent between some human and *Drosophila* homoboxes)...there is still a difference. The genes concerned *have evolved*. And comparative embryology shows that early developmental pathways *have* changed in consequence. Does this mean that mutations of these genes are sometimes advantageous? If so, are these in some sense successful macromutations?" (Arthur 1997, pp. 14-16).

The context of discussion is macroevolution via changes in body-plan genes. As Arthur notes, neo-Darwinian approaches have traditionally disregarded any role for macromutations in evolution.[1] For example, he notes that "a point mutation involving a base substitution could have major, moderate, minor or no developmental consequences depending on the nature of the gene, the location within it of the mutation, and exactly what base pairs are involved" (1997, p. 189). The quote Meyer cites is actually from an opening section where Arthur is setting up a context for the questions he explores throughout his book using the *current* complex developmental gene networks as his reference point. This can be seen from the more nuanced view of genetic variations among developmental genes he develops:

[1]See also, Scott F. Gilbert, John M. Opitz, and Rudolf A. Raff, "Resynthesizing Evolutionary and Developmental Biology," *Developmental Biology* 173 (1996): 357-372.

The more complex the organism and/or its developmental system, the harder it is likely to be for individual mutational changes to produce a coordinated overall effect that stands a chance of being beneficial. Thus we can 'predict' that the probability of new animal body plans originating should decline over time from a high point occurring not too long, in evolutionary terms, after the origin of animal multicellularity (1997, p. 207).

Moreover, when discussing mutations within a developmental context, Arthur indicates how the boundary between developmental, coding and terminal target genes "are not clear cut: for example, cadherin genes may in some cases be developmental, in others terminal targets. Also, accumulated mutations can ultimately move a gene from one category to another" (1997, p. 194). He notes that "the probability of a single mutation in a developmental gene being advantageous *varies according to the time of the gene's onset of activity and, in broad terms, the type of effect on development the mutation has*" (1997, p. 204, emphasis added). And in chapters 9 and 11, Arthur argues that there is evidence to support taxonomic bifurcations as involving different genetic processes for change.

Arthur also argues that various forms of genetic variations are responsible for the origin of new genes from pre-existing ones. For instance, he cites several results indicating that many if not most genes arose through gene duplication (cf. 1997, pp. 184-188 and the references therein). And natural selection plays a filtering role grading all variations in their total context (genome, body plan, ecological niche).

Hence, Meyer's strategy of separating evo-devo from genetic variation and natural selection and pitting them against each other as competing theories misrepresents Arthur's work. Arthur (1997) is representative of many evolutionary and developmental biologists in pursuing a grand synthesis among population genetics and developmental biology. Meyer's attempt to assess evo-devo as a standalone failure as an explanation for new body plans suffers from not seeing the work of Arthur and others in context.

Attacking the Adequacy of Developmental Gene Regulatory Networks

Another example of Meyer's divide-and-conquer strategy is a discussion of developmental gene regulatory networks (dGRNs) in chapter 13 of *Darwin's Doubt*: "Another line of research in developmental biology has revealed a related challenge to the creative power of the neo-Darwinian mechanism" (p. 264). Discussing dGRNs is important as Meyer rightly recognizes these lie at the very heart of evo-devo. Having separated evo-devo from neo-Darwinian evolution, he seeks to show that dGRNs on their own cannot explain the new Cambrian body plans.

One of the articles Meyer discusses is Erwin, et al. (2011).[2] These authors combine evidence from the fossil record, molecular clock and diversification data, and developmental biology with an ecological picture to construct a framework for understanding how dGRNs and ecological interactions may have contributed to diversification in the Cryogenian through the Cambrian periods. Erwin et al. (2011) describes an approach where dGRNs met new ecological opportunities through (1) the emergence of predation (carnivorous in particular), (2) ecosystem engineering (e.g., leading to the oxygenation of the waters), and (3) the new complex ecological feedback loops established. The interactions among dGRNs and the ecological conditions *combine* to provide a framework for explaining the Cambrian diversification of body plans. And nowhere do these authors deny that population genetics and natural selection are part of this story.

Similarly, another key reference in *Darwin's Doubt*, Davidson (2011), offers a synthetic account.[3] He proposes an approach for explaining the evolution of body plans that involves the architectures of dGRNs, adaptive variations, population genetics, and selection working as a whole system. In contrast to Meyer, who pits dGRNs against neo-Darwinian evolution, these authors–as we saw with Gilbert et al. and Arthur previously–are working out a synthesis of evolutionary development and neo-Darwinian evolution.

That's the division part of the strategy. What about the conquest part? Meyer argues that the research on dGRNs shows that they are inadequate to explain the appearance of new body plans because they are roughly impervious to changes (pp. 268-270). Building new dGRNs from "a preexisting dGRN by mutations and selection" to build new body plans runs into problems because "Davidson's work has also shown that such alterations inevitably have catastrophic consequences for organisms" (p. 269).

Meyer is partly right, here. Davidson does describe how classic neo-Darwinian evolution, which focuses on changes in protein-coding DNA, has little impact on organism development other than the fact that such changes can produce fatal errors (2011, p. 35). But this is only one approach that Davidson (2011) canvasses. The second approach, variations in *cis*-regulatory genes during development are "less pleiotropically dangerous to the whole [regulatory] system," but the developmental changes involved in the diversification of body plans aren't the accumulation of a series of small changes to these genes (2011, p. 36, square brackets added). For example, structural changes in dGRNs largely are due to redeployment of *cis*-regulatory modules (2011, pp. 36-37). Moreover, the effects of *cis*-regulatory gene changes depend on their locations in dGRNs (2011, p. 37). Davidson (2011) describes several more dGRN changes that go beyond the slow, steady accumulation of small changes.

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[2]Erwin D., Laflamme, M., Tweedt, S., Sperling, E. Pisani, D., and Peterson, K., "The Cambrian Conundrum: Early Divergence and Later Ecological Success in the Early History of Animals," *Science* 334 (2011):1091-1097.

[3]Davidson (2011), "Evolutionary Bioscience as Regulatory Systems Biology," *Developmental Biology* 357 (2011):35-40.

Meyer's argument for the inadequacy of dGRN changes explaining the diversification of body plans in the Cambrian rests on quotes from Davidson (2011) such as this:

there is always an observable consequence if a dGRN subcircuit is interrupted. Since these consequences are always catastrophically bad, flexibility is minimal, and since the subcircuits are all interconnected, the whole network partakes of the quality that there is only one way for things to work. And indeed the embryos of each species develop in only one way (Davidson 2011, p. 40).

So is Davidson (2011) arguing that Cambrian diversification of body plans can't be explained because viable changes in dGRNs can't take place? No. Meyer moves from Davidson's statement about the interruption of current dGRNs to "dGRNs [cannot] be altered by mutation without destroying existing developmental programs" to dGRNs couldn't be developed by any evolutionary processes (Meyer 2013, p. 270). But the inferences don't follow. What Davidson is discussing in the text Meyer quoted is the conservation of *modern* dGRNs in crown groups of animal body plans. Davidson argues that the development of dGRNs and body plans in the Cambrian is different from the situation we see in laboratories today:

Deconstructing the evolutionary process by which stem group body plans were stepwise formulated will require us to traverse the conceptual pathway to dGRN elegance, beginning where *no modern dGRN provides a model*. The basic control features of the initial dGRNs of the Precambrian and early Cambrian *must have differed in fundamental respects from those now being unraveled in our laboratories*. The earliest ones were likely hierarchically shallow rather than deep, so that in the beginning adaptive selection could operate on a larger portion of their linkages. Furthermore, we can deduce that the outputs of their subcircuits must have been polyfunctional rather than finely divided and functionally dedicated, as in modern crown group dGRNs. A general result of these arguments is that considerations of evolutionary change in dGRN structure may at last provide a unified conceptual framework for understanding the stages of crown group evolution, and in the same breath the sequential history of change that has produced the different hierarchical levels of animal dGRNs (2011, p. 40, emphasis added).

So Davidson refers to modern dGRN systems when he's discussing "imperviousness to continuous variation" (2011, p. 38). In contrast, "The early Cambrian was a period of (relatively) rapid evolutionary exploration of diverse developmental pathways as the programs directing the formation of crown group echinoderm characters were stepwise added into the stem group dGRNs" (2011, p. 38). In this way, Davidson seeks to explain how dGRN changes in the Cambrian could produce a diversity of body plans, but then become stable since the Ordovician.

The picture Davidson paints is of regulatory systems with somewhat flexible subunits (e.g., changing their locations within dGRNs, changes in the timing of their function, co-option of existing subunits for new functions). The *cis*-regulatory modules that have been demonstrated to undergo functionally adaptive changes all reside at the periphery of their respective dGRNs. Hence, changes in these modules have fewer adverse effects on dGRN functionality. The changes in these modules are small and continuous as the neo-Darwinian paradigm expects (2011, p. 38). However, as Davidson notes, "the outputs of the upper level pattern formation circuits of dGRNs which specify the overall body plan, and the clade specific organization of individual body parts, *do not display continuous variation in the types of forms they generate*" (2011, p. 38, emphasis added). So although there are small, continuous changes going on in some elements of dGRNs, the overall changes showing up in body plans are larger and more discontinuous. "Therefore the action of selection differs across dGRN structure" (2011, p. 38).

Similarly, Erwin, et al. (2011) infers that dGRNs "are likely to have evolved via intercalary evolution in which developmental genes providing spatial, temporal, and homeostatic control were inserted into preexisting simpler dGRN subcircuits" (2011, p. 1095). Such evolution could have happened through the insertion of micro-RNAs, a known process (2011, p. 1095). And they go on to note that "large expansions in the number of miRNA families correlate to increases in the number of cell types and morphological complexity of animals, as seen, for example, at the base of the bilaterians and at the base of the vertebrates" (2011, p. 1095).

Meyer's strategy of dividing dGRNs from genetic variation and natural selection and pitting them against each other as competing theories misrepresents the work of Davidson, Erwin and colleagues. They are more representative of evolutionary and developmental biologists pursuing a grand synthesis among population genetics and developmental biology than Meyer's picture of the literature communicates. Again, Meyer's attempt to assess dGRNs as a standalone failure as an explanation for new body plans suffers from not treating this work in its actual research context.

Supplement B

Three More Representative Examples of the Question-Shift Strategy

When Meyer discusses self-organization as a possible explanation for the diversification of Cambrian body plans (note the divide-and-conquer strategy!), he critiques the work of Stewart Kaufman and others for failing to explain the advent of the very first body plans. Kaufman is actually discussing how preexisting body plans can change giving rise to new body plans. Yet, Meyer complains that "the self-organizational process that Kauffman cites cannot *explain* the origin of genetic information, because it derives from it, as Kauffman's own description reveals" (p. 297). Meyer shifts the question from diversification to advent, whether it be cells, genes, gene regulatory networks or body plans, and then faults Kaufmann and other self-organization advocates for not answering the first advent of cells, genes, regulatory networks or body plans questions.

As a second example, in a subsection titled "Assume a Toolkit," Meyer complains that

[Stewart] Newman obviously *presupposes* the existence of a "developmental genetic toolkit," that is, a set of genes, including regulatory genes, that help to direct the development of animal body plans. Where does this genetic information come from? He doesn't specify (p. 302).

Again, Meyer shifts the question away from diversification to the advent of the first developmental toolkit and faults Newman for failing to account for the advent of this toolkit. However, Newman is clearly seeking to explain diversification from simple multicellular life to generate various body plans in terms of how those preexisting developmental toolkits could have produced the diversification seen in the Cambrian. Newman's is the Cambrian question rather than the advent of the first gene regulatory networks and first body plan.[4]

In a third representative example, Meyer briefly discusses James Shapiro's natural genetic engineering approach to evolution.[5] Meyer praises Shapiro's work as representing "a promising avenue of new biological research, brining insight into how the cell's information-processing system modifies and directs the expression of its genetic information in real time in response to different signals" (Meyer 2013, p. 334). He then goes on to shift the question of how cells adapt and modify their genetic machinery to the first origin of genetic information: "Could it, then, also provide a solution to the problem of the origin of the information necessary to build an animal body plan? It could, except for one question that Shapiro's otherwise brilliant characterization of how organisms modify themselves doesn't address" (p. 334).

However, Shapiro's work focuses on how pre-existing cells can modify themselves, not on the origin of cells and these self-modification capabilities. Again, the Cambrian question is how, given a few *already existing* body plans did the tremendous diversification of body plans come about. The origin of the machinery to create the first body plan is the origins of life question. Shapiro isn't addressing this latter question.

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[4]Moreover, when he posits some self-organizing principle, such as Kaufman proposed, Newman is laying out a research program, not helping himself to an unspecified mechanism as Meyer charges.

[5]James Shapiro, *Evolution: A View from the 21st Century*. Upper Saddle River, NJ: FT Press Science (2011).