Why Building Animals Is Hard: The Logic of Development, Common Descent, and the Origin of Animal Body Plans

7 May 2020

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We stand at a remarkable period in the history of biology, whose features were diagnosed by T.S. Kuhn:

"The proliferation of competing articulations, the willingness to try anything, the expression of explicit discontent, the recourse to philosophy and to debate over fundamentals, all these are symptoms of a transition from normal to extraordinary research."

The Structure of Scientific Revolutions (1970, p. 91)

The Royal Society, London − November 7-10, 2016

New Trends in Evolutionary Biology

Let's begin with Gerd Müller's opening talk at the Royal Society Extended Evolutionary Synthesis meeting...

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Gerd B. Müller

Professor and Head

Department of Theoretical Biology

University of Vienna

Email

Scientific Interest

The relationship between development and evolution in the generation of organismal form and its theoretical conceptualization.

...on 7 November 2016, where he argued that standard evolutionary theory (abbreviated **SET**) failed to explain central phenomena in biology.

These remarks occur starting at the 8:56 point in Müller's presentation.

- He first summarizes the main propositions of neo-Darwinian theory (or what I am abbreviating as SET).
- Müller then moves to his indictment of SET: the theory fails to account for the main phenomena in its domain.

http://downloads.royalsociety.org/events/2016/11/evolutionary-biology/muller.mp3

Using Kuhn's symptomatology of theory crisis, this is unmistakably an "expression of explicit discontent."

"Genetic inheritance *alone* accounts for the transmission of selectable traits, and natural selection actually is the only directional factor that is acting on these incremental and slight differences. *Note* that the majority of these explanations rests on a genetic argument. Really, the Synthesis theory is a theory that is focused on variation in populations, and on its genetic underpinnings. That is really very important, that's the core of the theory, and..."

"And what does it explain? Well, it explains very well what it is *designed* for – to explain – namely, variation, genetic variation in evolving populations, makes very good predict-ions on that. There is – it explains to some extent – the gradual variation of phenotypic characters, explains adaptation of characters, and explains some of the features, genetic features, of speciation."

"However, what it does *not* explain are all these complex levels of evolution that I have mentioned at the beginning, such as the origin of these body plans, but also complex behaviors, complex physiology, development, and the fact that not all of the variation that's been generated is actually equally distributed. There are biases in the variation, there is novel characters..."

"... the standard theory is focused on characters that exist *already* and their variation and maintenance across populations, but not on how they originate, non-gradual forms of transitions, and all the non-genetic factors of evolution that are involved, are not addressed. Actually, the theory is not *designed* for addressing them."

This is explicit discontent.

"Explanatory deficits of the Modern Synthesis"
(bullet points as they appeared on Müller's slide)

- phenotypic complexity
- phenotypic novelty
- non-gradual modes of transition
- non-genetic factors of change
- biases in the generation of variation

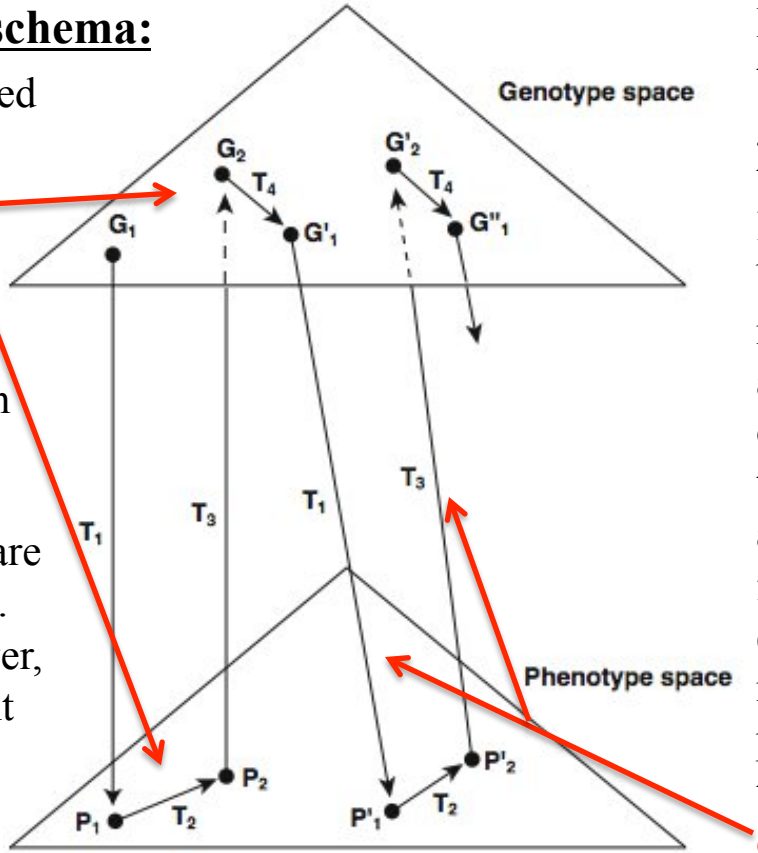
As we shall see, dissent about the adequacy of SET is widespread within evolutionary biology – *and this has been the case for many decades.*

The next slide is atrocious (a textbook example of bad Powerpoint), but I didn't really have a choice. Lewontin's diagram is important, and I needed to say several things about it. Sorry!

Lewontin's 1974 schematic of evolutionary explanation shows the arrow of causation going from genotype (DNA) through development (T_1 and T_3, or the transformation rules) to the phenotype, P. Thus all phenotypic change starts in the genome, by modifying development. **This view of evolutionary change creates observational expectations.**

The importance of this schema:

Neo-Darwinian theory focused almost exclusively on **transmission genetics** (T_4 in genotype space) and **ecological interactions** (T_2 in phenotype space), neglecting the transformation rules, T_1 and T_3, connecting the two spaces. For animal macroevolution, these rules are the province of development. If one does not know, however, what changes in development are *possible*, one cannot explain macroevolution. And focusing on genotype (DNA) similarities misses completely what evolution intends to explain, namely, ***how new forms come to be***.



Caption reads:
"FIGURE 1
Schematic representation of the paths of transformation of population genotype from one generation to the next. *G* and *P* are the spaces of genotypic and phenotypic description. G_1, G'_1, G_2 and G'_2 are genotypic descriptions at various points in time within successive generations. P_1, P'_1, P_2 and P'_2 are phenotypic descriptions. T_1, T_3, and T_4 are laws of transformation. ..." Redrawn from Lewontin 1974.

Lewontin himself worried about this: "To concentrate only on genetic change, without attempting to relate it to the kinds of physiological, morphogenetic, and behavioral evolution that are manifest in the fossil record and in the diversity of extant organisms and communities, is to forget entirely what it is we are trying to explain in the first place" (1974, p. 20). To explain changes in form, one must know what changes are possible, and why. For animals, this entails knowing **the rules of development, T_1 and T_3**.

This schema also creates expectations about homology of developmental processes (see below, slide 66).

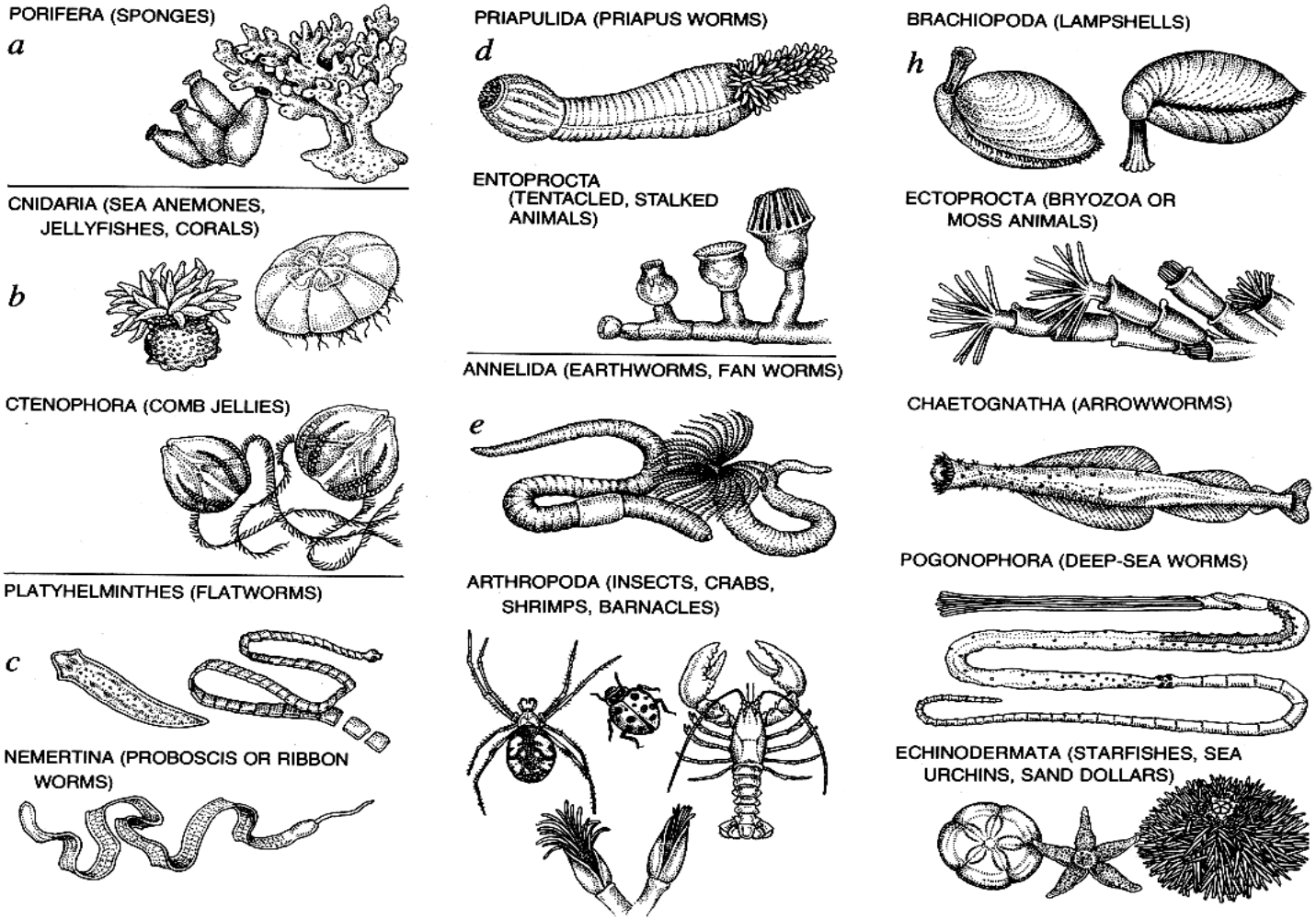
The origin of animal body plans provides a test case about the sufficiency of evolutionary processes − in particular, natural selection − to explain data central to biology.

Caenorhabditis elegans

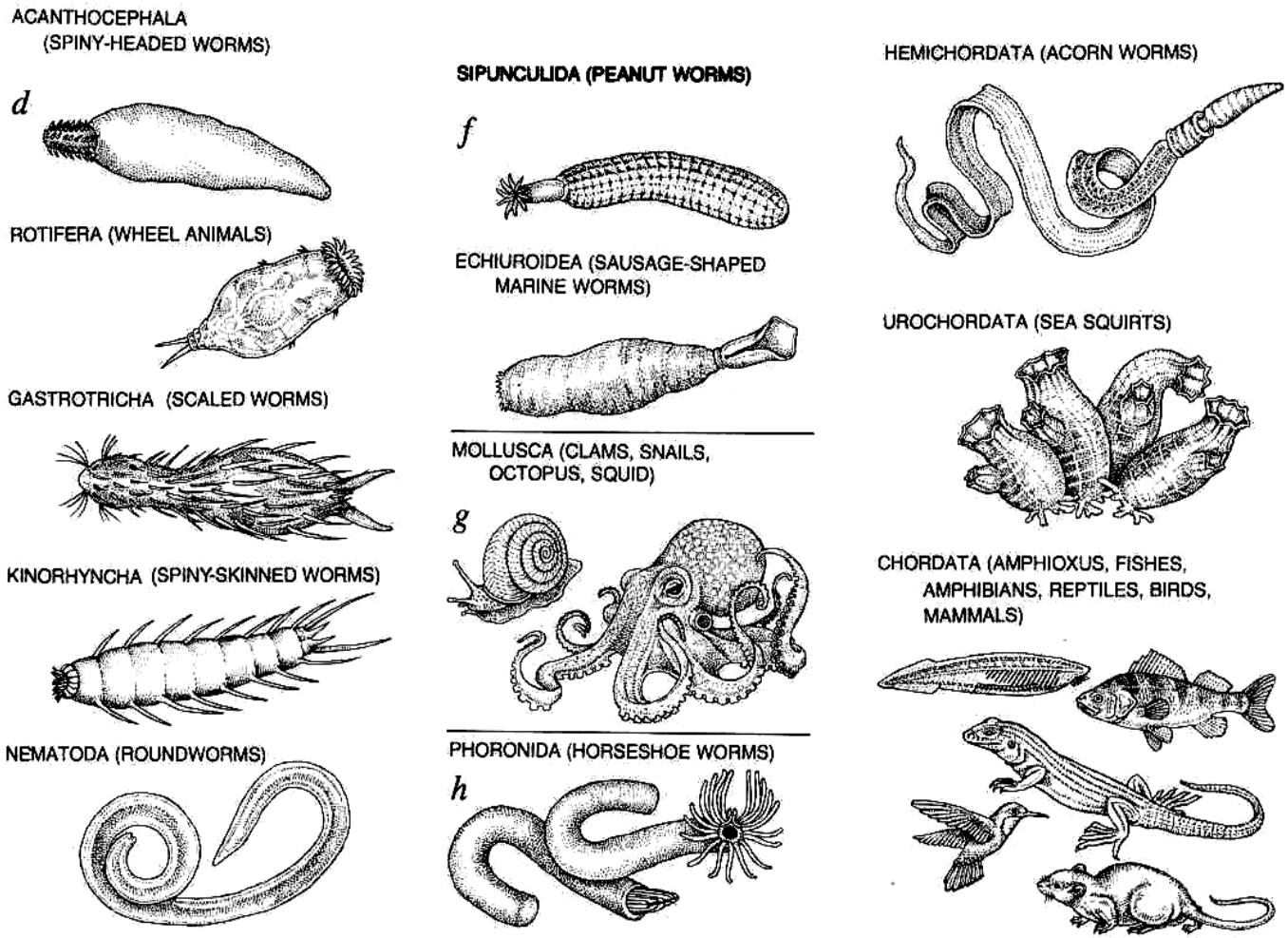
Strongylocentrotus purpuratus

Drosophila melanogaster

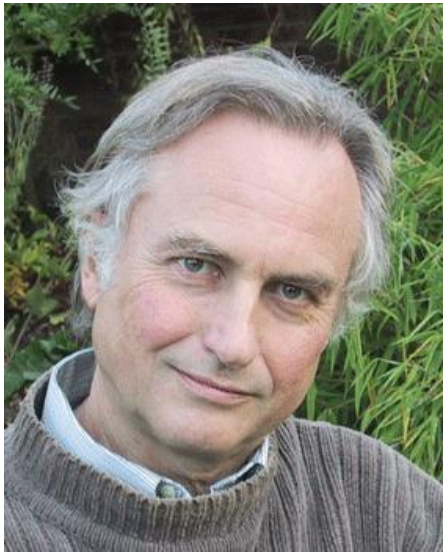
Since Darwin, textbook theory holds that the animals (the Metazoa) share a common multicellular ancestor.



Furthermore, the main complexity-building process to explain body plan differences is natural selection.



Thus, the standard evolutionary view, represented here by Richard Dawkins, claims that natural selection explains the origin of body plans.



"The theory of natural selection provides a mechanistic, causal account of how living things came to look as if they had been designed for a purpose."

(R. Dawkins, "Replicators and vehicles," 1982, p. 45)

This is a proposition we can test.

Deborah Charlesworth

Nicholas Barton

Brian Charlesworth

The causal primacy of natural selection remains the dominant view within evolutionary theory today:

"We have focused our discussion on the sources of the variability used in adaptive evolution...we finish by re-emphasizing the central concept of neo-Darwinism and the MS [Modern Synthesis]: **allele frequency change caused by natural selection is the only credible process underlying the evolution of adaptive organismal traits."**

Charlesworth, Barton, & Charlesworth (2017, 9-10; emphasis added)

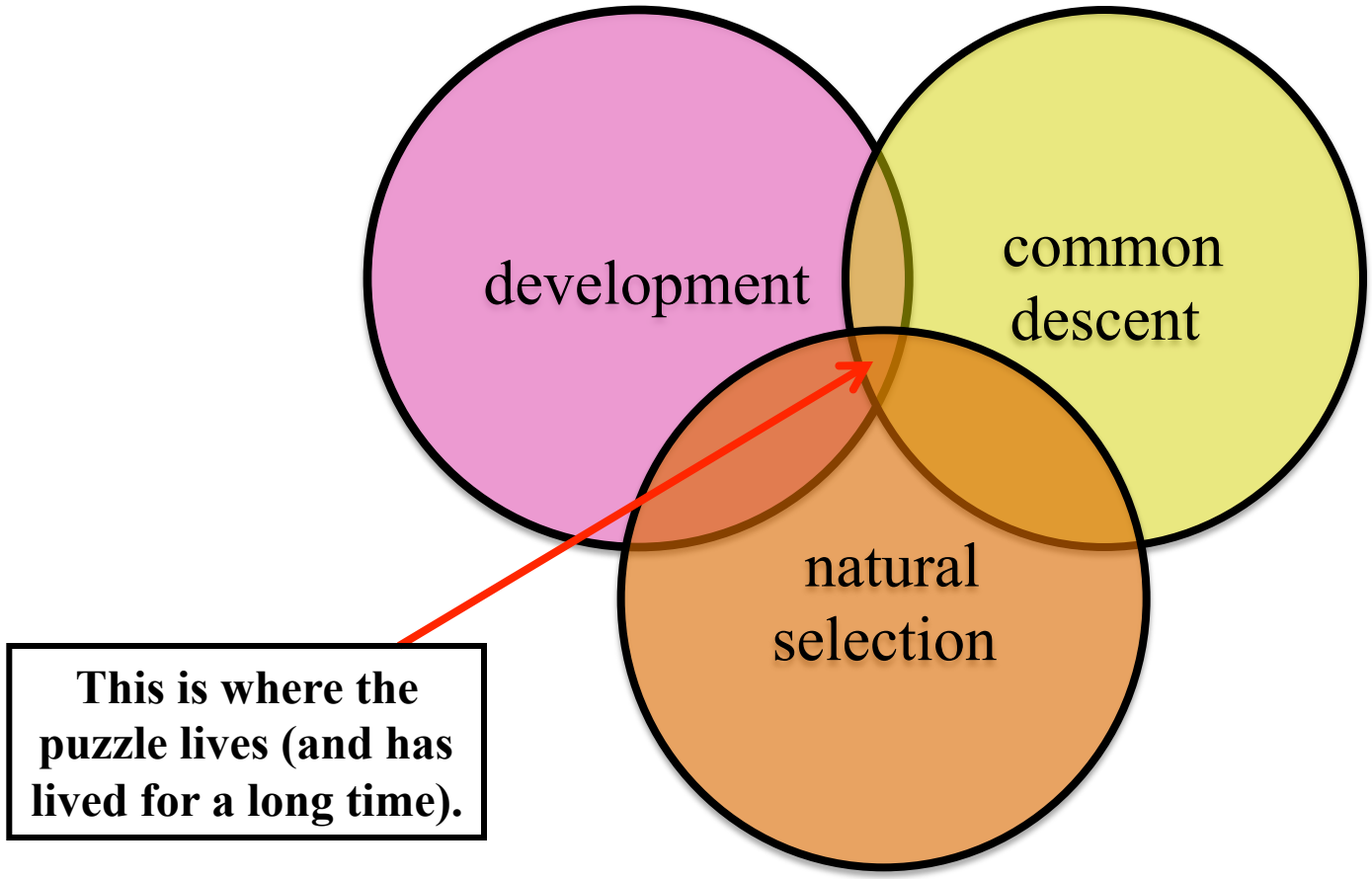
"Can Modern Evolutionary Theory Explain Macroevolution?"

Douglas Futuyma
Ecology & Evolution
SUNY Stony Brook

E. Serrelli and N. Gontier (eds.), *Macroevolution*, Interdisciplinary Evolution Research 2 (Springer, 2015), p. 76.

"Existing theory can provide a plausible account of the history and causes of most or all evolutionary phenomena... I do not know of any macro-evolutionary phenomena that are inconsistent with existing evolutionary theory, any phenomena that would require us to reject one of its principles as simply false."

The problem arises at the intersection of our knowledge of animal development, the theory of common descent, and what the process of natural selection requires:



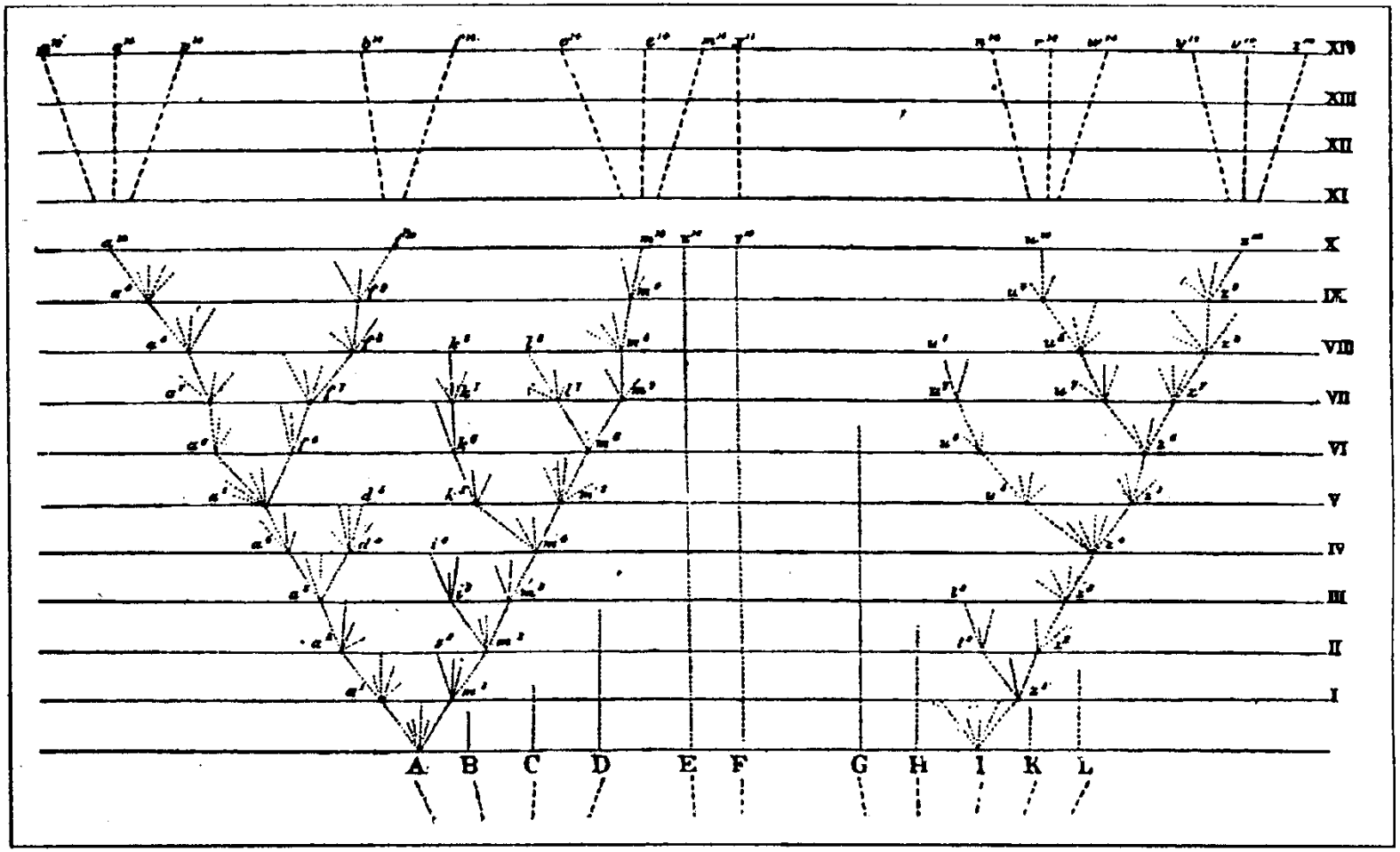
The fundamental puzzle, insoluble within the neo-Darwinian framework, may be expressed as a three-point argument:

1. Animal body plans are built in each generation by a stepwise process, from the fertilized egg to the many differentiated cells of the adult.

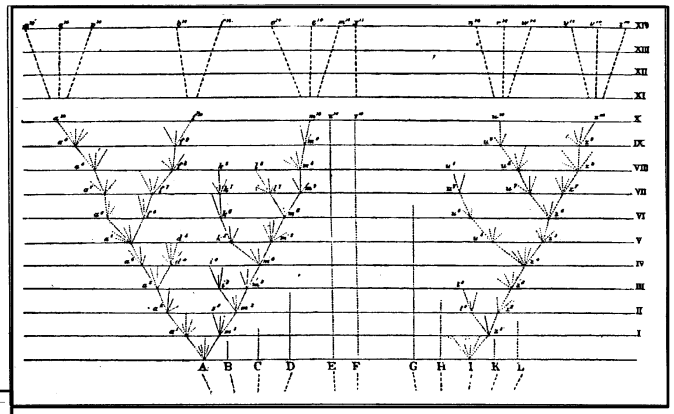
2. The earliest stages of this process determine what follows. Thus, to change any body plan, mutations expressed early in development must occur, be viable, and be stably transmitted to offspring.

3. But such early-acting mutations of global scope, affecting body plan formation, are not tolerated by embryos, as the experimental evidence shows.

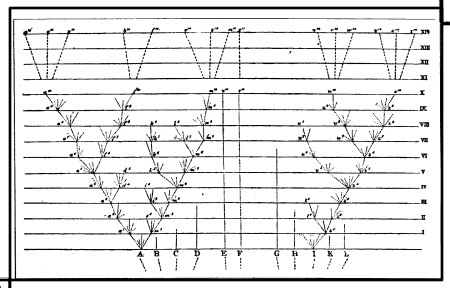
Darwin's (1859, 116) branching diagram − the only figure in the *Origin of Species*, 1st edition − which he deploys as a fractal.

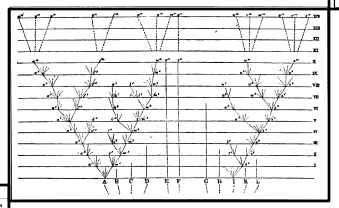


Darwin introduces the figure with a time scale of 10^3 generations between each horizontal line. He then expands the time scale to 10^8 generations, *but the figure itself remains unchanged.* This creates a fractal or self-similar pattern of change on all time scales of descent with modification...

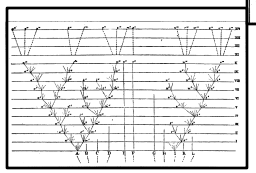


10^8 (p. 124)





10^3 (p. 117)



...with the main theoretical claim being that the variation fueling *macroevolution* (as it was named in the 1920s) occurs in the same size increments at all scales of evolutionary change, with time elapsed increasing the differences in form between groups.

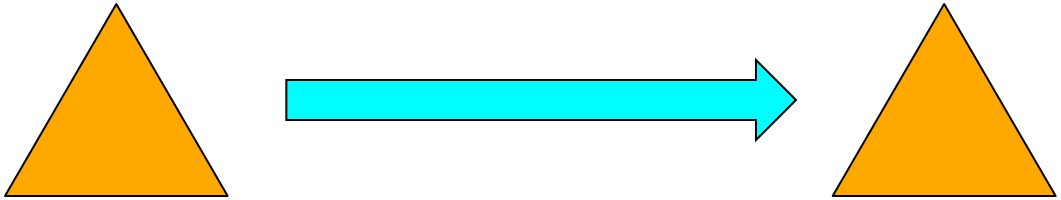
time

disparity

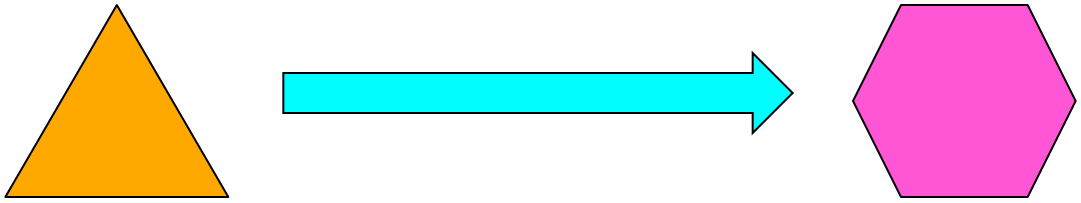
(figures not to scale)

This hypothesis sets up a theoretical tension which persists today in evolutionary theory. Small-scale variation occurs *within* types, but the origin of novel forms requires *deep variation* ***spanning*** *types*.

Evolution is not, primarily, a theory of *similarity*.



Evolution is primarily a theory of *transformation*.

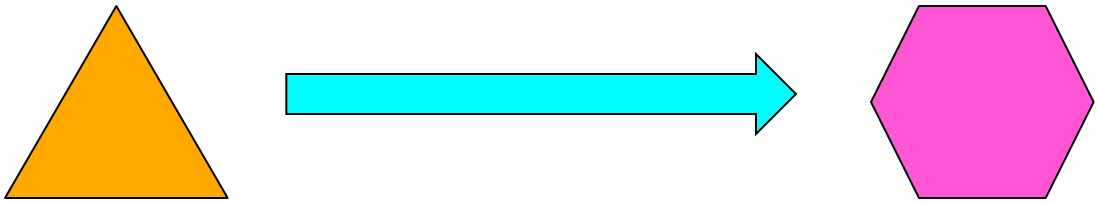


Evolution is primarily a theory of *transformation*, where entities – from gene sequences to proteins to body plans – are connected through space and time by continuous incremental pathways, and where the *origin of differences* are explained (causally) by those pathways.

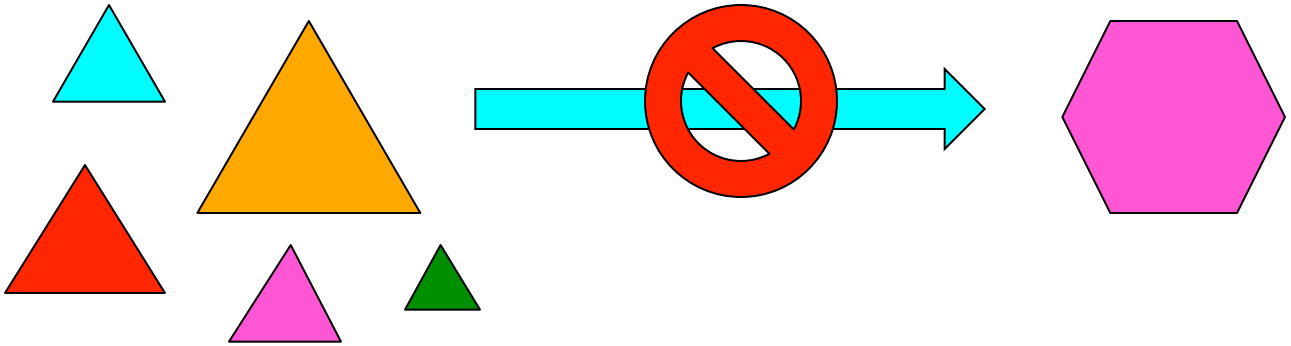
This means searching for the necessary ***deep variation*** required for macroevolution will be inescapable. Either small-scale variations can sum over time to large-scale differences, or they cannot. This debate within evolutionary theory began while Darwin was still alive, and continues today.

Similarities are not sufficient to explain *transformations*.
In fact, similarity is exactly the wrong place to look.

What is needed is *variation* along a continuous pathway, where the endpoints are discernably different, *not* similar.



Without such variation: no transformation.
No transformation means no evolution.



This requirement – to provide evidence of variation at the right scales for macroevolution – was recognized by T.H. Huxley, who urged Darwin to relax his prohibition against "saltations," but especially by younger naturalists such as William Bateson.

Darwin himself either (a) assumed without evidence that the small-scale variation would be sufficient for all evolution, or (b) he postulated the aboriginal existence of the very forms he needed ("grant me a mudfish," he wrote in a letter) as starting points.

Darwin's most capable successors understood that neither (a) or (b) would work as evolutionary explanations.

William Bateson
(1861-1926)

A leading Mendelian, who coined the term "genetics"

"In these discussions we are continually stopped by such phrases as, 'if such and such a variation took place and was favourable,' or, 'we may easily suppose circumstances in which such and such a variation if it occurred might be beneficial,' and the like. The whole argument is based on such assumptions as these – assumptions which, were they found in the arguments of Paley or of Butler, we could not too scornfully ridicule. 'If,' say we with much circumlocution, 'the course of Nature followed the lines we have suggested, then, in short, it did.' That is the sum of our argument."

Materials for the Study of Variation (1894, p. v)

William Bateson
(1861-1926)

A leading Mendelian, who coined the term "genetics"

"That the time has come for some new departure most naturalists are now I believe coming to recognize…I suggest that for this new start the Study of Variation offers the best chance. If we had before us the facts of Variation there would be a body of evidence to which in these matters of doubt we could appeal. We should no longer say '*if* Variation takes place in such a way,' or '*if* such a variation were possible;' we should on the contrary be able to say 'since Variation *does*, or at least *may* take place in such a way,' 'since such and such a Variation *is* possible,' and we should be expected to quote a case or cases of such occurrence as an observed fact."

Materials for the Study of Variation (1894, p. v)

William Bateson
(1861-1926)

A leading Mendelian, who coined the term "genetics"

But Bateson realizes there is a problem. The forms of organisms represent a *discontinuous series:*

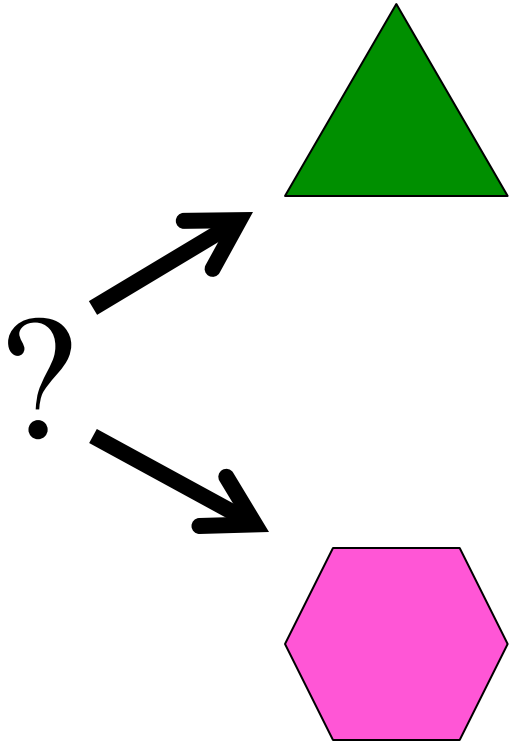
"…the forms of living things, taken at a given moment, do nevertheless most certainly form a discontinuous series and not a continuous series. This is true of the world as we see it now, and there is no good reason for thinking that it has been otherwise. So much is being said of the mutability of species that this, which is the central fact of Natural History, is almost lost sight of, but if ever the problem is to be solved this fact must be boldly faced."

Materials for the Study of Variation (1894, p. 2)

The tension between the need for discontinuous variations and the (relative) improbability of fixing such variants (with their increasing scale) became a major theme within evolutionary theory in the 20th century.

The tension can be seen as a form of destructive dilemma:

Transformation to be explained



Competing Hypotheses

Observed differences require ***discontinuous*** variations (at relative scales, depending on the character in question).

– versus –

Observed differences are ***artifactual***, and pathways exist where small-scale variations suffice to cause the transformations.

But…

As the scale or scope of their effect increases, such variations ***are not tolerated by animals***.

– versus –

Small-scale variations ***cannot*** cause the kinds of transformations required by observed differences among the animals.

Always in the background: Common Descent.

Ronald Fisher
(1890-1962)

The ‘random change of a microscope’ metaphor:

“[The problem of large-scale mutations] will be perceived by comparison with the mechanical adaptation of an instrument, such as the micro-scope, when adjusted for distinct vision. If we imagine a derangement of the system by moving a little each of the lenses…or by twisting through an angle, by altering the refractive index or transparency of the different components…**it is sufficiently obvious that any large derangement will have a very small probability of improving the adjustment…**”

The Genetical Theory of Natural Selection
(1929, 44; emphasis added)

Ronald Fisher
(1890-1962)

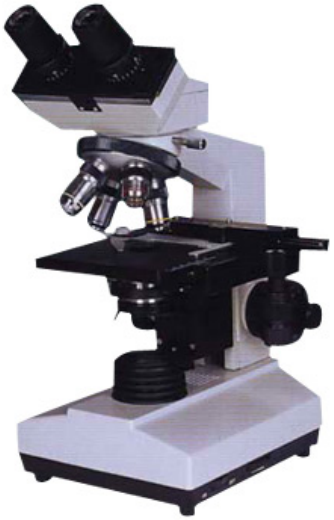
The metaphor fits with the experimental evidence:

"The case of large mutations to the organism may first be considered…A considerable number of such mutations have now been observed, and these are, I believe, **without exception, either definitely pathological (most often lethal) in their effects, or with high probability to be regarded as deleterious in the wild state.** This is merely what would be expected on the view…that organisms in general are, in fact, marvellously and intricately adapted…"

The Genetical Theory of Natural Selection
(1929, 44; emphasis added)

But…microscopes *differ* – often dramatically:

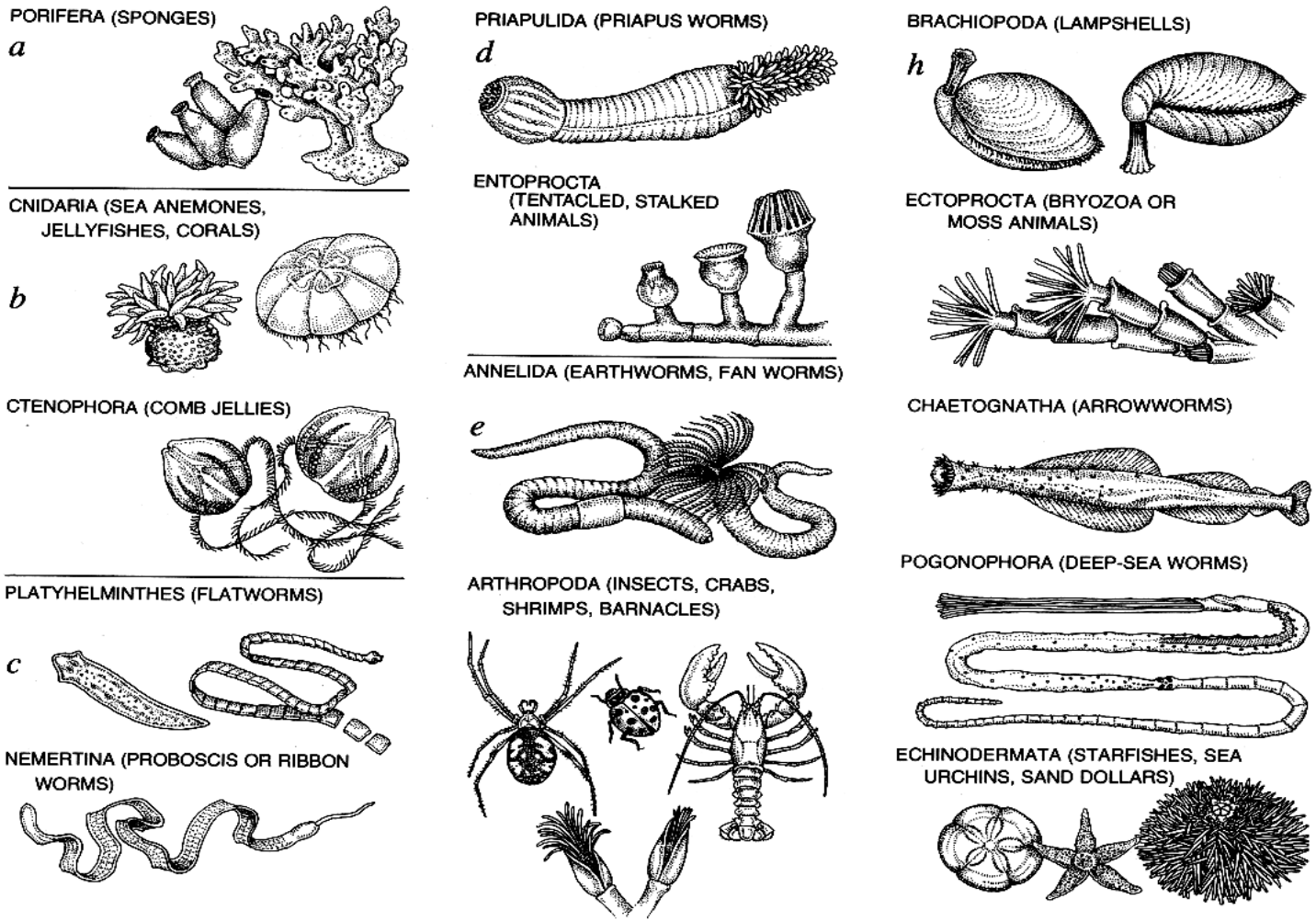
single eyepiece

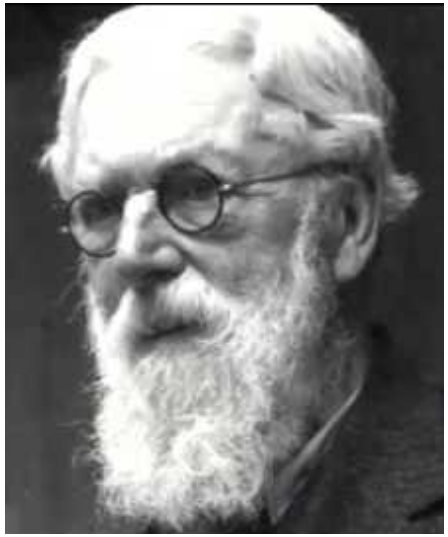


dual eyepiece

transmission electron microscope

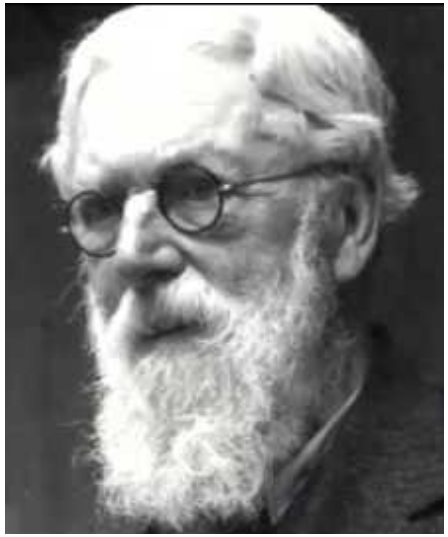
Bodyplan ***disparity*** struck Bateson, and later, Goldschmidt, as an undeniable fact of natural history, which evolution must explain.





D'Arcy Wentworth Thompson (1860-1948)
On Growth and Form
(1917, 1942)

"We cannot transform an invertebrate into a vertebrate, nor a coelenterate into a worm...A 'principle of discontinuity,' then, is inherent in all our classifications, whether mathematical, physical or biological...The lines of the spectrum, the six families of crystals, Dalton's atomic law, the chemical elements themselves, all illustrate this principle of discontinuity. In short, nature proceeds from one type to another among organic as well as inorganic forms..."

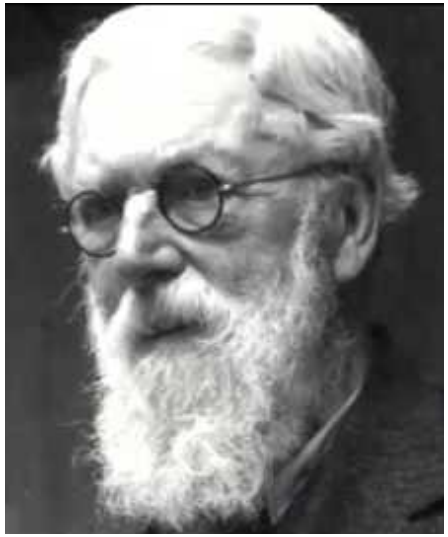


D'Arcy Wentworth Thompson (1860-1948)
On Growth and Form
(1917, 1942)

"In natural history Cuvier's 'types' may not be perfectly chosen nor numerous enough, but types they are; and to seek for stepping-stones across the gaps between is to seek in vain, for ever."

"This is no argument against the theory of evolutionary descent."

"...discontinuous variations are a natural thing...'mutations'... are bound to have taken place, and new 'types' to have arisen, now and then."



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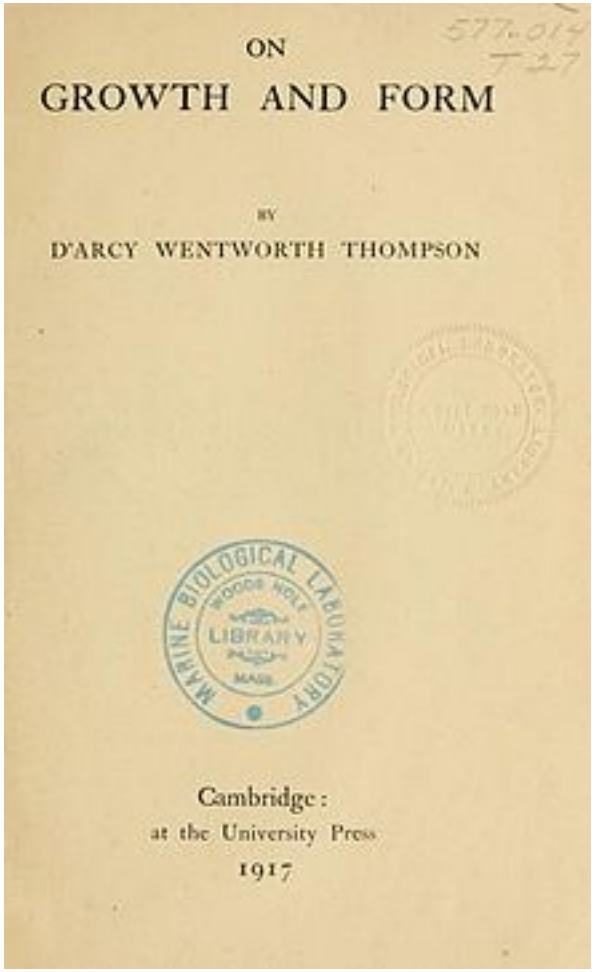
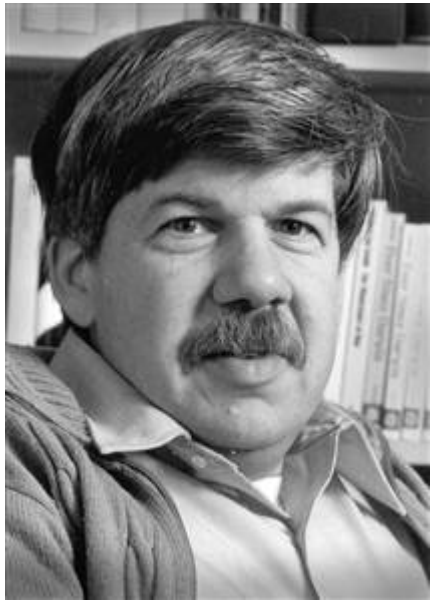




Thompson's views on discontinuity heavily influenced Stephen Jay Gould (1942-2002)

Both Thompson and Gould held that discontinuity existed − and both postulated mechanisms of evolutionary change that might explain discontinuity.

Richard Goldschmidt
(1878-1958)

‘Microscopes differ’ (so to speak): Goldschmidt’s list – which is still unanswered, 80 years later:

“…I may challenge the adherents of the strictly Darwinian view, which we are discussing here, to try to explain the evolution of the following features by accumulation and selection of small mutants: hair in mammals, feathers in birds, segmentation of arthropods and vertebrates, the transformation of the gill arches in phylogeny including the aortic arches, muscles, nerves, etc.; further, teeth, shells of mollusks, ectoskeletons, compound eyes, blood circulation, alternation of generations, statocysts, ambulacral system of echinoderms, pedicellaria of the same…”

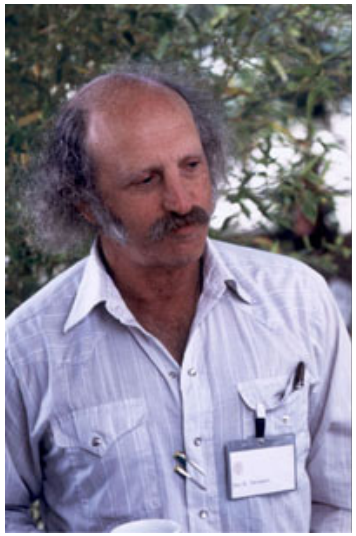
The Material Basis of Evolution (1940, pp. 6-7)

Richard Goldschmidt
(1878-1958)

‘Microscopes differ’ (so to speak): Goldschmidt’s list – which is still unanswered, 80 years later:

“…cnidocysts, poison apparatus of snakes, whalebone, and, finally, primary chemical differences like hemoglobin versus hemocyanin.”

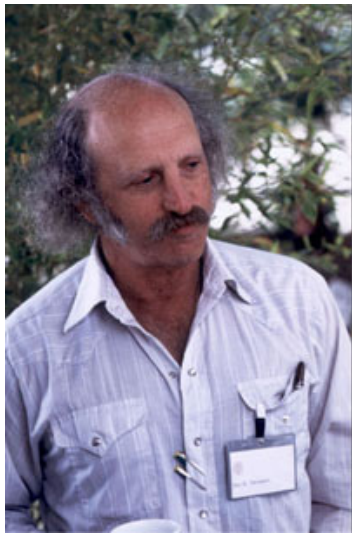
Goldschmidt was never answered – and the tension described earlier (within evolutionary theory) persisted into the 1970s and 80s, with the punctuated equilibria debate, and then into the 1990s and 2000-20, with the evo-devo controversies.



Developmental Biology 412 (2016):S20-S29; p. S25.

Coming down to the past decade, consider the late (d. 2015) Eric Davidson's critical take on textbook neo-Darwinian theory:

"Since the body plans are made by development, when you consider evolution of different kinds of animals, it means their developmental process is different. How else can you think about it? Darwinian evolution was of a completely different kind. It was all about small changes and they felt if you could understand changes in petunia colors, you could understand changes in whether animals have heads or not. And that's just total nonsense."

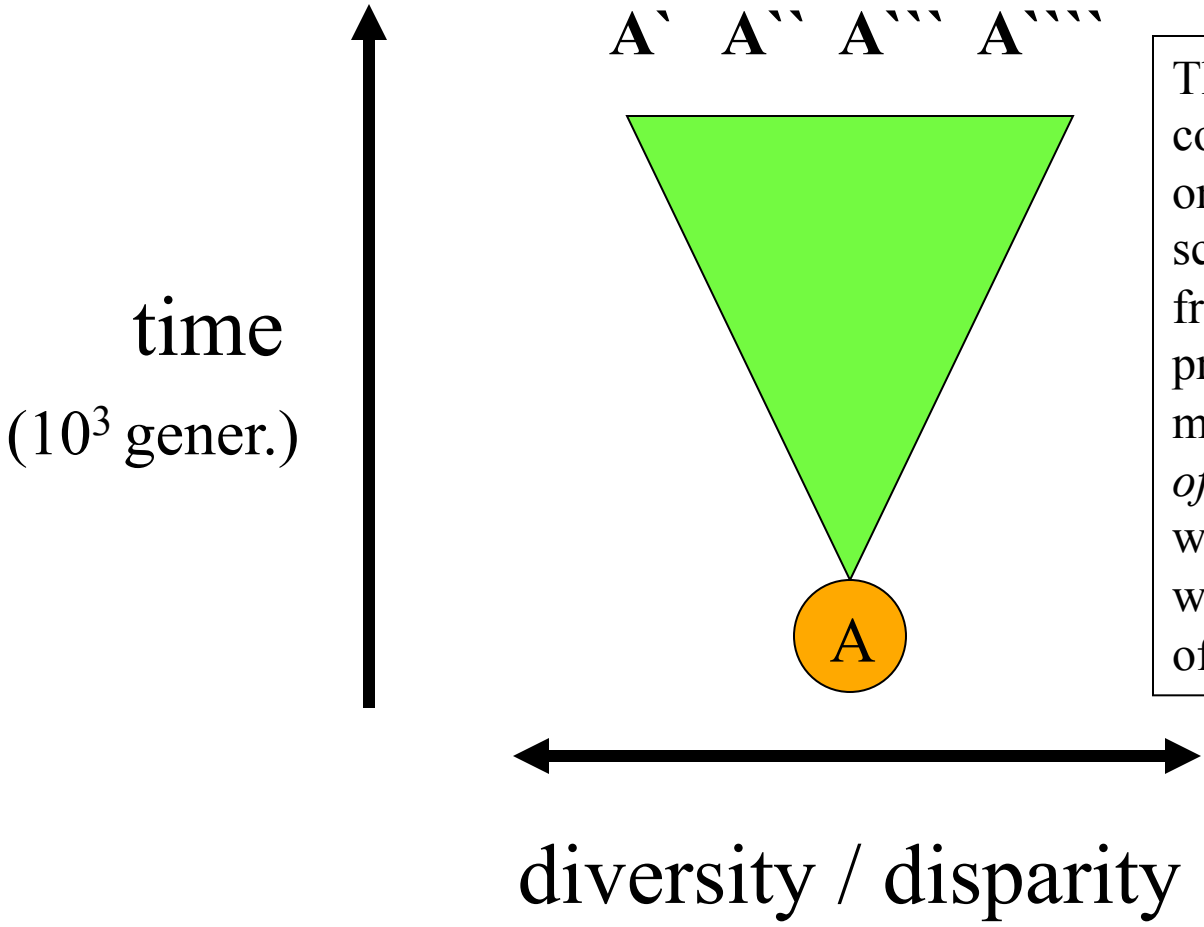


Developmental Biology 412 (2016):S20-S29; p. S25.

Davidson: “So it [i.e., neo-Darwinism] couldn’t possibly have been right, and it wasn’t.”

“But you can't really blame the Darwinians, because all of Darwinian theory, from the Neo-Darwinian synthesis of the 1930s, was built in the absence of, and ignorance of, any knowledge of how development actually works. Other than wrong theoretical ideas. And in the absence of any knowledge about how transcription works and in the absence of any knowledge about anything that has to do with how the processes of life that make animals actually occur. So it couldn't possibly have been right, and it wasn't.”

As is often the case in evolutionary theory, the problem has its roots in Darwin's own reasoning. Motivated by a *vera causa* principle, Darwin sought the "fuel" of all descent with modification only in presently observed scales, or degrees, of variation.



This theoretical commitment comes at a cost, however. If one wants to explain large-scale differences as arising from a common ancestor, presently observed variation may fail to provide *the scale of change* required. More A's will not work if what one wants to explain is the origin of B, C, D, or E.

Following a flirtation with macro-mutationism in the first two decades of the 20th century, the maintream of evolutionary theory returned strongly to Darwin's *vera causa* principle: descent with modification *must* work via presently-observed scales of variation.

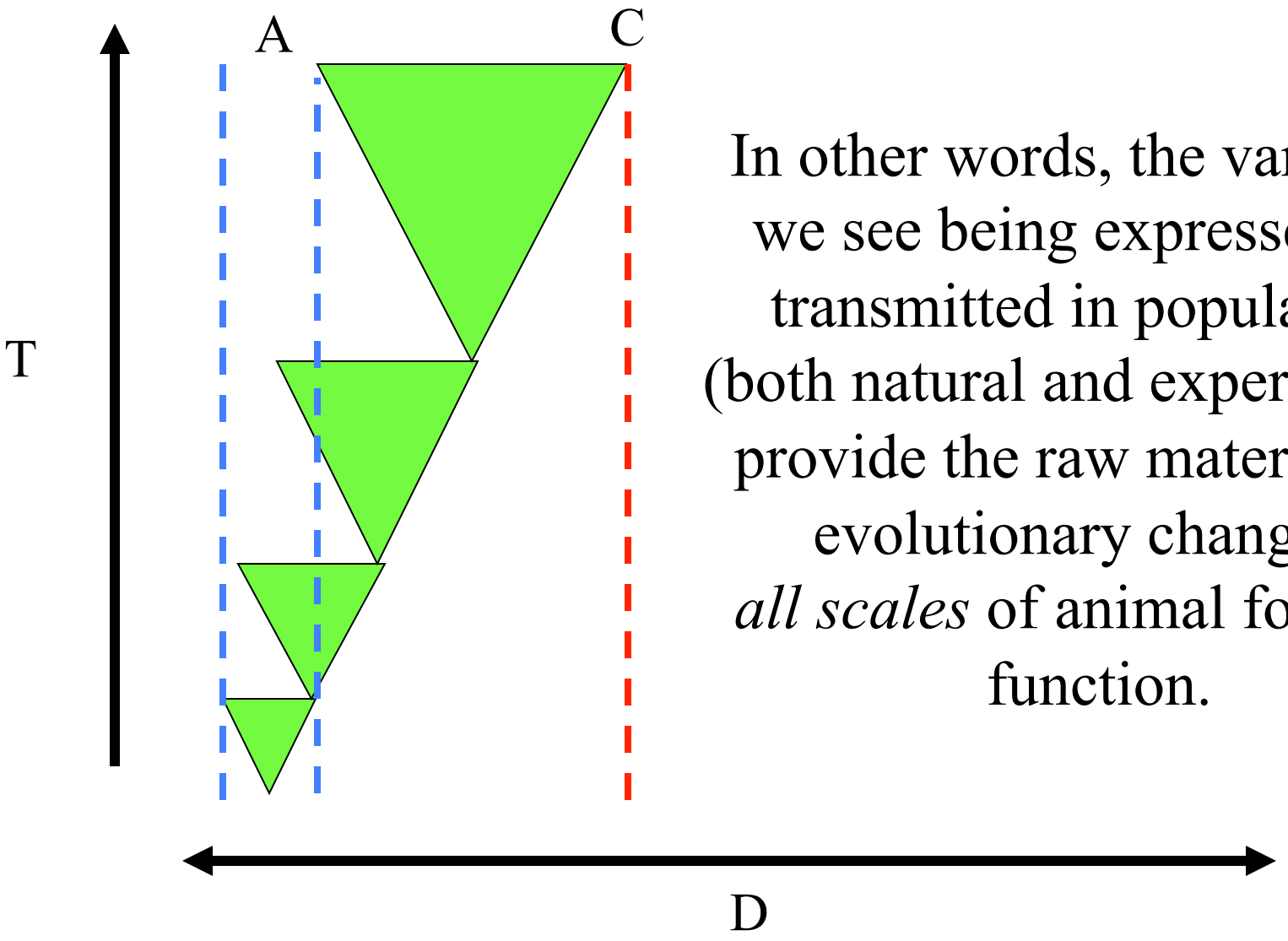
Dobzhansky's dictum: the reluctant "sign of equality" between micro and macro

Theodosius Dobzhansky
(1900-1975)

"Experience seems to show... that there is no way toward an understanding of the mechanisms of macro-evolutionary changes, *which require time on a geological scale*, other than through a full comprehension of the micro-evolutionary processes observable within the span of a human lifetime and often controlled by man's will."

(1937, 12; emphasis added)

Macroevolution is thus microevolution summed (over time, with increasing disparity ∝ time)



In other words, the variations we see being expressed and transmitted in populations (both natural and experimental) provide the raw materials for evolutionary change at *all scales* of animal form and function.

Dobzhansky's dictum: the reluctant "sign of equality" between micro and macro

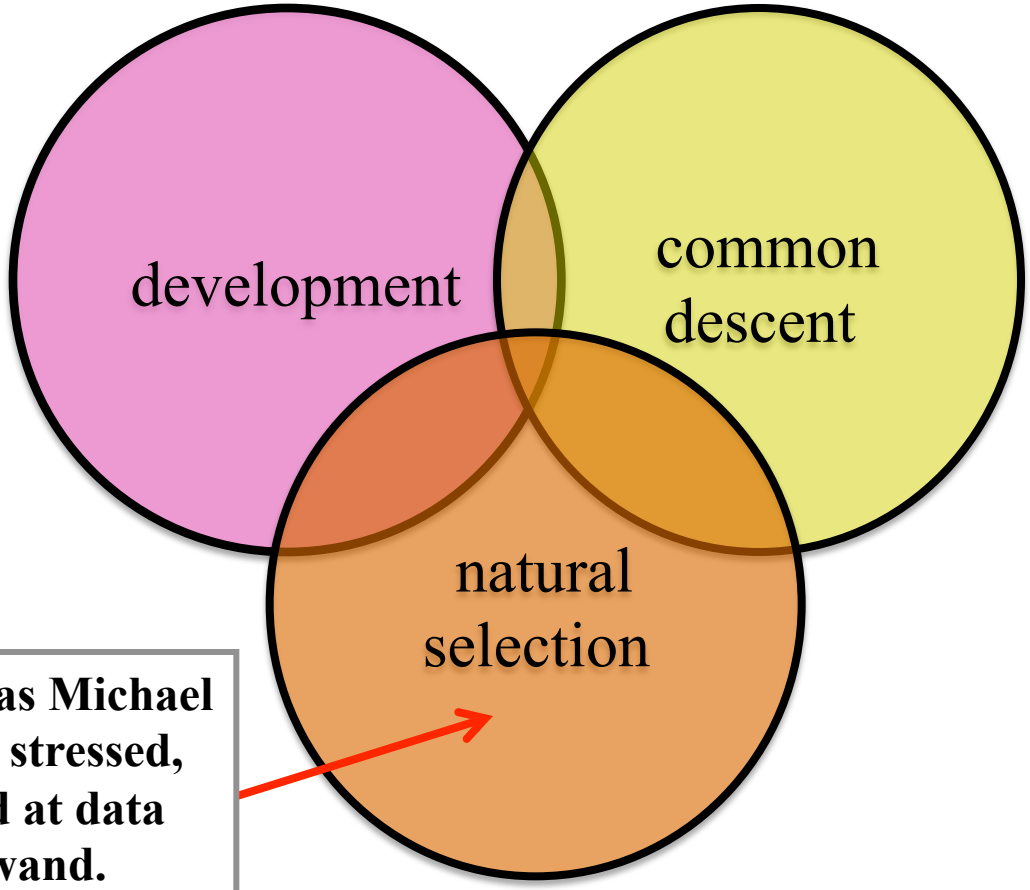
Theodosius Dobzhansky
(1900-1975)

"For this reason we are compelled at the present level of knowledge *reluctantly to put a sign of equality between the mechanisms of macro- and micro-evolution*, and, proceeding on this assumption, to push our investigations as far ahead as this working hypothesis will admit."

(1937, 12; emphasis added)

We may speculate that Dobzhansky's reluctance sprang in part from his association in Russia, in the early 1920s, with leading geneticist Yuri Filipchenko (1882-1930), who coined the terms *microevolution* and *macroevolution*. It is unlikely that Filipchenko would have agreed with the micro-macro "sign of equality."

The second aspect of the neo-Darwinian puzzle is the theory of natural selection, which makes evidential demands on anyone who uses it to explain. ***Variation, reproductive differences, and heritability must all be demonstrated.***



Natural selection, as Michael Lynch (2007) has stressed, cannot be waved at data like a magic wand.

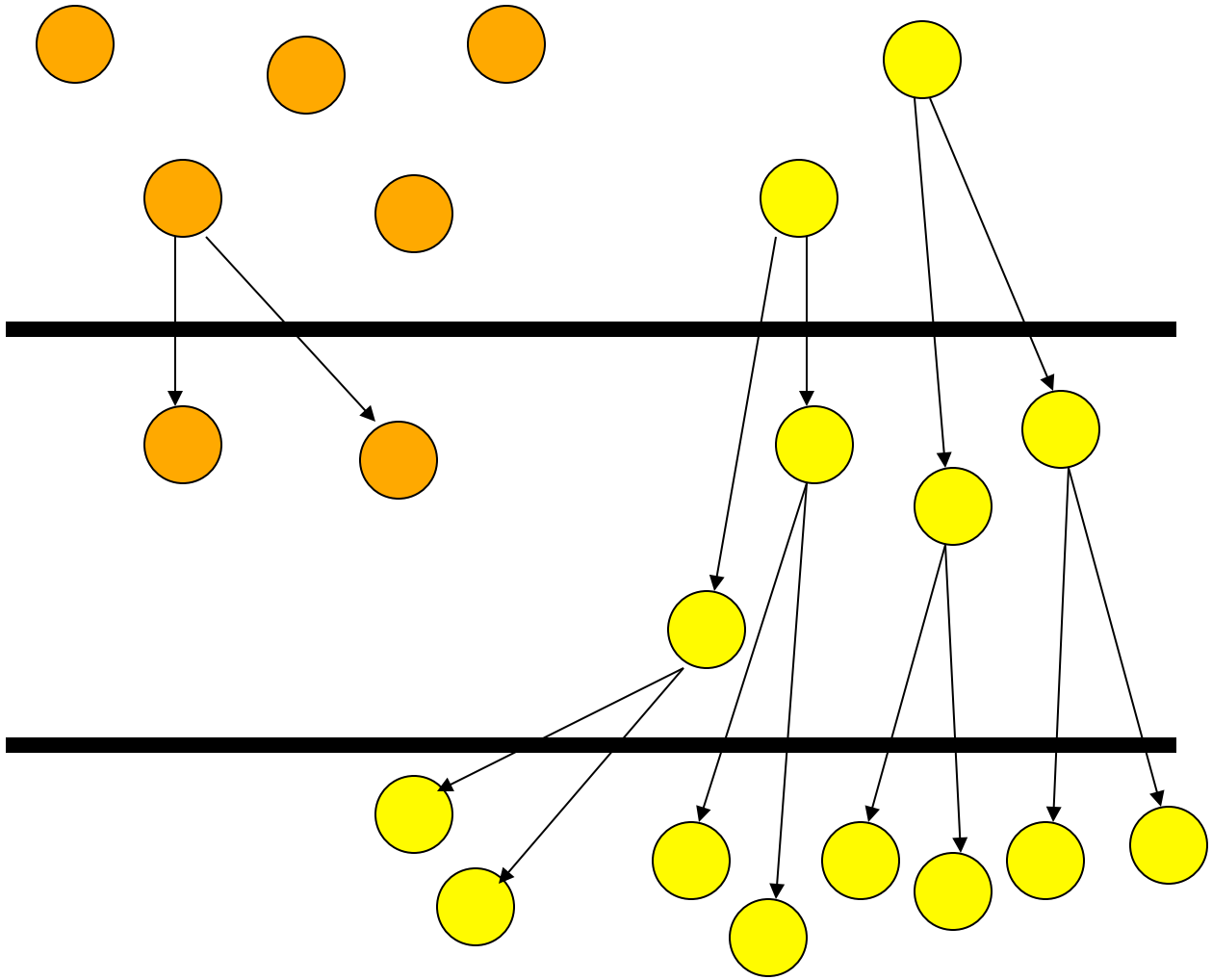
***If*, within a species or population, the individuals**

a. vary in some trait **q** – the condition of **variation**;

***If*, within a species or population, the individuals**

a. vary in some trait **q** – the condition of **variation**;

b. leave different numbers of offspring in consistent relation to the presence or absence of trait **q** – the condition of **selection**;



A population of unicellular eukaryotes (e.g., yeast) subjected to an environmental condition (e.g., heat stress, represented by the black bar) and undergoing selection. The outcome is fixation of the yellow trait.

***If*, within a species or population, the individuals**

a. vary in some trait **q** – the condition of **variation**;

b. leave different numbers of offspring in consistent relation to the presence or absence of trait **q** – the condition of **selection**;

c. transmit trait **q** faithfully between parents and offspring – the condition of **heredity**;

then the frequency of trait **q** will differ predictably between the population of all parents and the population of all offspring. (Lewontin 1978; Endler 1986)

But what characters are varying, *and thus subject to selection*, with respect to the problem of the origin of body plans?

Coat color and pattern

Carapace pigmentation

Stickle number and size

These are not body plan characters.

Even at its zenith, in the 1960s, the Modern Synthesis left many leading evolutionary biologists unsatisfied:

"The whole real guts of evolution – which is, how do you come to have horses and tigers, and things – is outside the mathematical theory."

C.H. Waddington, at the Wistar Symposium (1966)

Geneticist Wallace Arthur, on the unsolved problem of the origin of animal body plans (1987, 180):

"...one can argue that there is no *direct* evidence for a Darwinian origin of a body plan – black *Biston betularia* certainly do not constitute one! Thus in the end we have to admit that we do not really know how body plans originate."

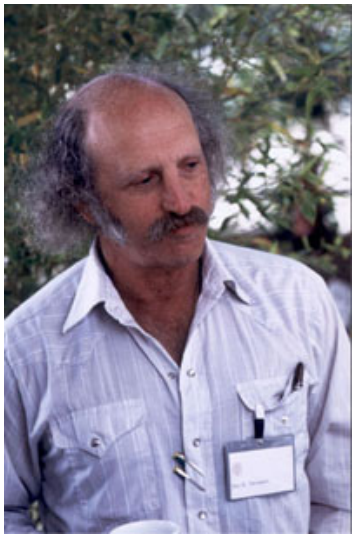
Biston betularia

Quantitative variation in melanin deposition (explained by natural selection, classically) versus the origin of the moth itself.

Massimo Pigliucci (CUNY), an organizer of the "Altenberg 16" meeting:

NSF Workshop on the
Origin of Novel Features,
Indiana University (6-8 Oct 2006)

"The Modern Synthesis doesn't cut it because it's got the conceptual tools to tell us how quantitative variation[s] evolve, but not how qualitatively new traits arise."



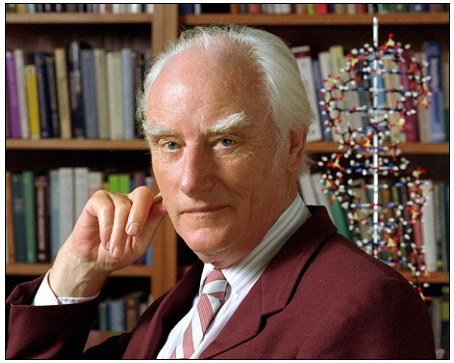
Eric Davidson (1937-2015) evolutionary developmental biologist, Caltech

"*…contrary to classical evolution theory, the processes that drive the small changes observed as species diverge cannot be taken as models for the evolution of the body plans of animals*. These are as apples and oranges, so to speak, and that is why it is necessary to apply new principles that derive from the structure / function relations of gene regulatory networks to approach the mechanisms of body plan evolution." (2006, 195; emphasis added)

The problem of the macroevolution of animal form is unsolved because neo-Darwinian theory has not incorporated the logic of development into its models (T_1 and T_3 in Lewontin's 1974 schema, slide 13, above).

An insightful paper by UK evolutionary geneticist Gabriel Dover provides a jumping-off point for considering this.

Geneticist Gabriel Dover (1992, 281) on Francis Crick's challenge about evolution:



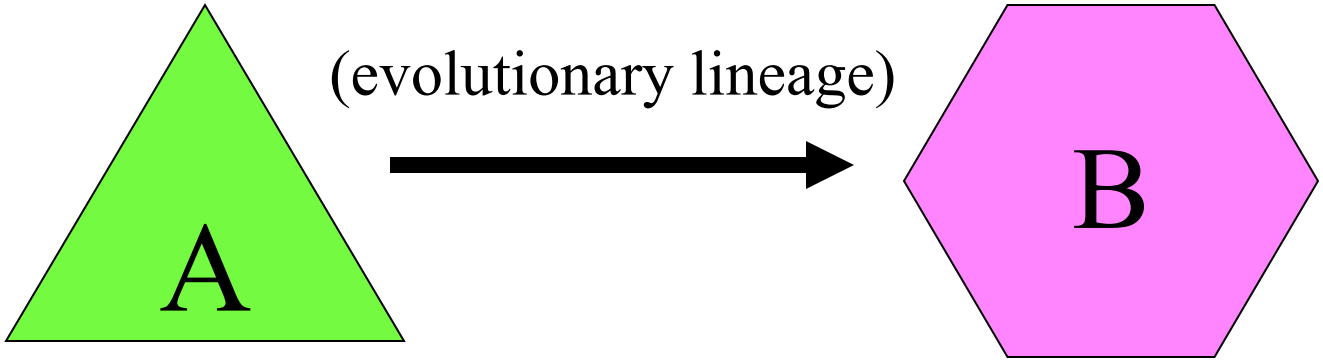
"At the age of 40 (or thereabouts) I was momentarily reduced to feeling like a 10 year-old novice by Francis Crick in Bronowski's old office at the Salk Institute, where I had gone in the early 1980s to discuss selfish DNA..."

As was often the case throughout his scientific life, Crick put his finger precisely on the critical unanswered question.

“Crick challenged me with the statement that nothing can be said about evolution until we understand how organisms are put together.”

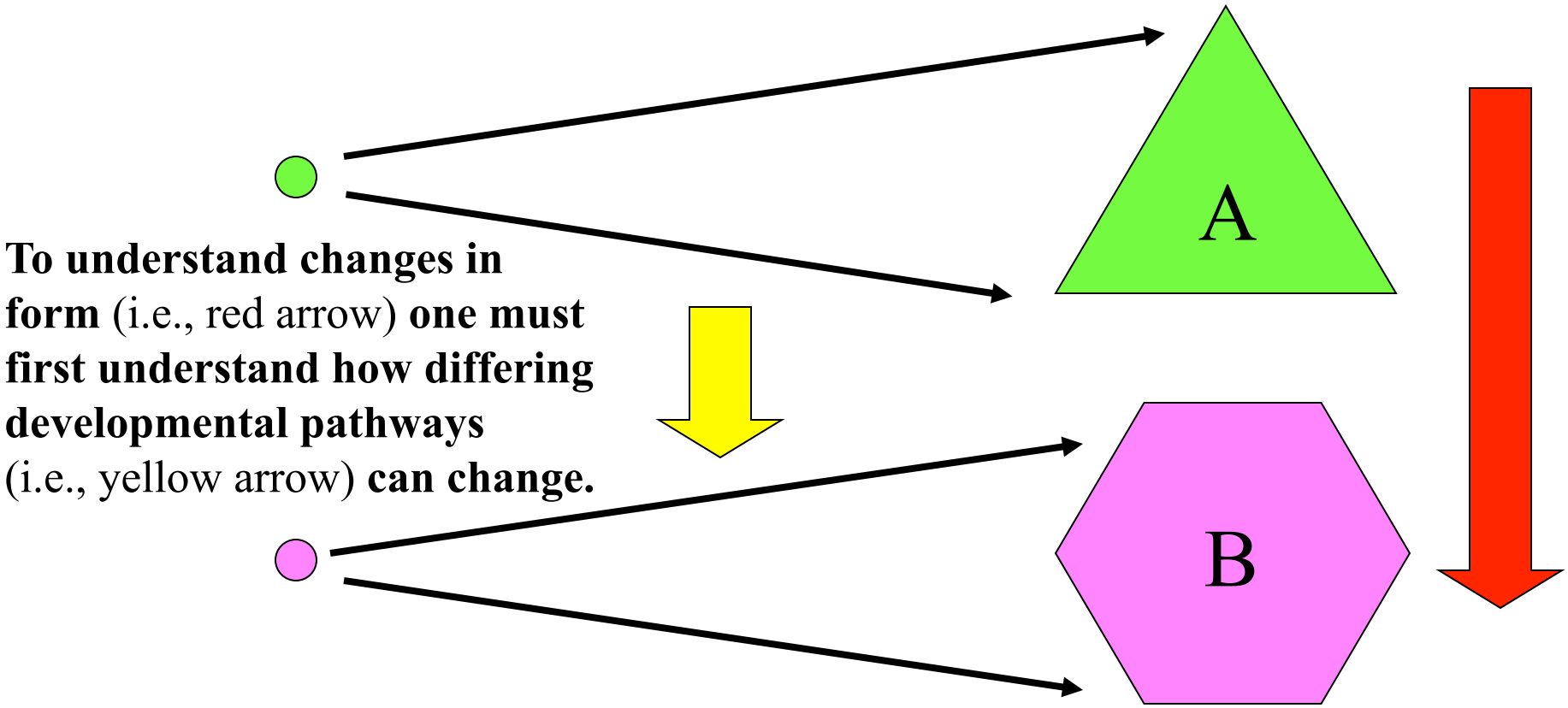
Gabriel Dover (1992, 281)

Why do we need to know, as Crick said, "how organisms are put together" to understand evolution?



If we think of A and B as representing animal taxa, their differences in form would constitute a macroevolutionary transformation. But these are the *adult* forms. They are constructed by developmental pathways, and it is *those pathways which evolution must modify*.

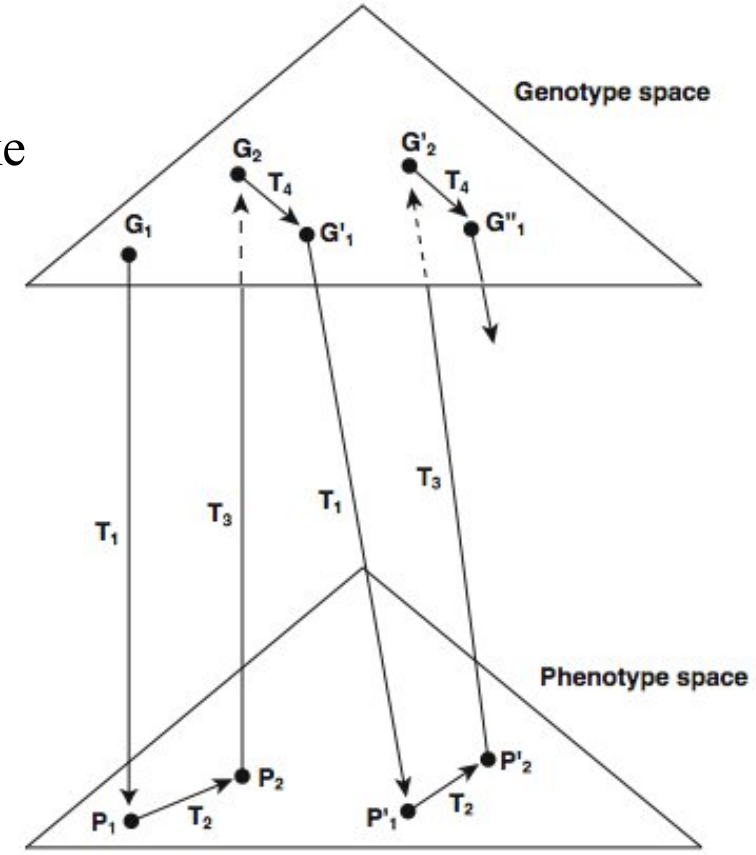
Thus, Crick's challenge to Dover − i.e., that Dover needed to know "how organisms are put together" − means that animal *evolution* lies analytically downstream of understanding the details of animal *development*. Putting development into a black box, as neo-Darwinism did, puts evolution in there as well: not understood.



To understand changes in form (i.e., red arrow) **one must first understand how differing developmental pathways** (i.e., yellow arrow) **can change.**

Two other expectations flow from Lewontin's schema: (1) it is possible that the rules of development (e.g., T_1) will constrain the range of viable variation for any animal. If so, this may imperil hypotheses of common ancestry.

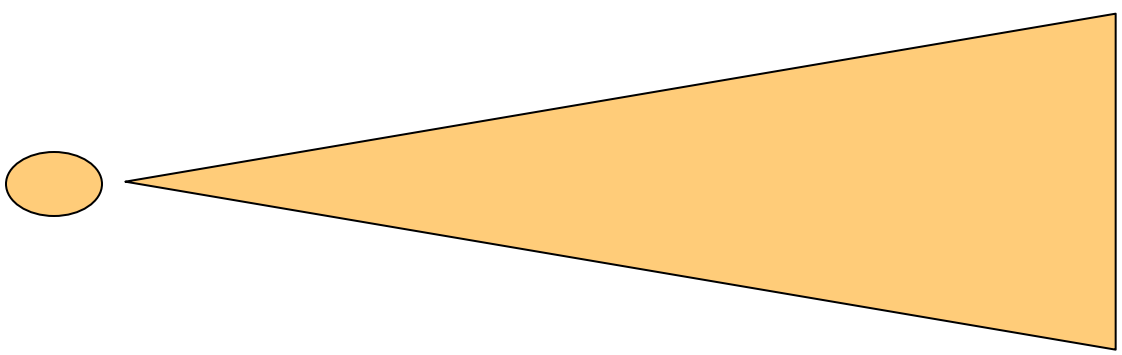
(2) If however we take common ancestry as given, **homologies are expected to exist between genotypic, developmental, and phenotypic spaces.** What follows inferentially if those homologies turn out not to exist?

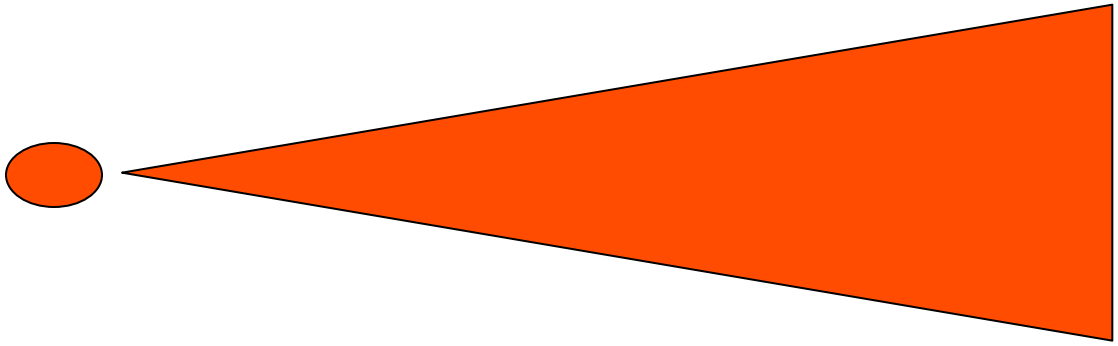


Caption reads:
"FIGURE 1
Schematic representation of the paths of transformation of population genotype from one generation to the next. *G* and *P* are the spaces of genotypic and phenotypic description. G_1, G'_1, G_2 and G'_2 are genotypic descriptions at various points in time within successive generations. P_1, P'_1, P_2 and P'_2 are phenotypic descriptions. T_1, T_2, T_3, and T_4 are laws of transformation. ..." Redrawn from Lewontin 1974.

Let's consider constraints first. Where are body plan differences first established?

Early in development – right at the start.



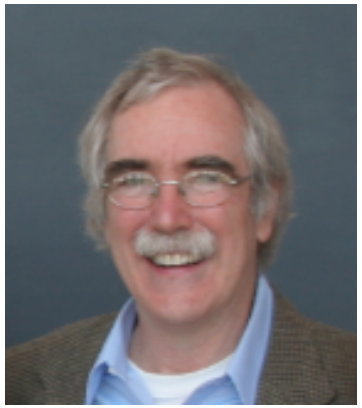


So to modify body plans, we need heritable variation in early development.

But that brings us back to the puzzle *of the missing deep variation*.

Mutations expressed early in development, *affecting body plan formation*, are those *least likely* to be tolerated by embryos.

Christiane Nüsslein-Volhard



Eric Wieschaus

Mutations affecting segment number and polarity in *Drosophila*

Christiane Nüsslein-Volhard & Eric Wieschaus

European Molecular Biology Laboratory, PO Box 10.2209, 69 Heidelberg, FRG

In systematic searches for embryonic lethal mutants of Drosophila melanogaster *we have identified 15 loci which when mutated alter the segmental pattern of the larva. These loci probably represent the majority of such genes in* Drosophila. *The phenotypes of the mutant embryos indicate that the process of segmentation involves at least three levels of spatial organization: the entire egg as developmental unit, a repeat unit with the length of two segments, and the individual segment.*

THE construction of complex form from similar repeating units is a basic feature of spatial organisation in all higher animals. Very little is known for any organism about the genes involved in this process. In *Drosophila*, the metameric nature of the pattern is most obvious in the thoracic and abdominal segments of the larval epidermis and we are attempting to identify all loci required for the establishment of this pattern. The identification of these genes and the description of their phenotypes should lead to a better understanding of the general mechanisms responsible for the formation of metameric patterns.

In *Drosophila*, the anlagen for the individual segments arise as equally sized subdivisions of the blastoderm, each segment represented by a transverse strip of about three or four cell diameters[1]. A cell lineage restriction between neighbouring segments is established at or soon after this stage[2]. Two basic types of mutation have been described which change the segmental pattern of the *Drosophila* larva. Maternal effect mutations like *bicaudal* lead to a global alteration of the embryonic pattern[3]. Bicaudal embryos develop two posterior ends arranged in mirror-image symmetry, and lack head, thorax and anterior abdomen. The *bicaudal* phenotype suggests that the initial spatial organisation of the egg established during oogenesis involves a morphogen gradient that defines antero-posterior coordinates in early embryonic pattern formation[3,4]. The subdivision of the embryo into segments is thought to occur by a differential response of the zygotic genome to the maternal gradient. Homeotic mutations (for example, *bithorax*[5,6]) seem to be involved in a final step of this response process. These mutations change the identity of individual segments; for example, *Ultrabithorax* transforms the metathoracic and first abdominal segments into mesothoracic segments. However, the homeotic loci do not affect the total number, size or polarity of the segments, nor do they point to any other step which might intervene between the maternal gradient and the final pattern of segments.

We have undertaken a systematic search for mutations that affect the segmental pattern depending on the zygotic genome. We describe here mutations at 15 loci which show one of three novel types of pattern alteration: pattern duplication in each segment (segment polarity mutants; six loci), pattern deletion in alternating segments (pair-rule mutants; six loci) and deletion of a group of adjacent segments (gap mutants; three loci) (Table 1, Fig. 1).

The segmental pattern of the normal *Drosophila* larva

Figure 2 shows the cuticular pattern of a normal *Drosophila* larva shortly after hatching. The larval body is comprised of three thoracic and eight abdominal segments. Although differences are observed in different body regions, all segments have certain morphological features in common. The anterior of each segment is marked with a band of denticles, most of which point posteriorly. The posterior part of each segment is naked. The segment borders run along the anterior margins of the denticle bands[7], they have no special morphological features. The polarity of the pattern is indicated by the orientation of the dent cles and, in the abdomen, by the shape of the bands (Fig. 3). In the thoracic segments the bands are narrow with fine denticles whereas those in the abdominal segments are broader and comprised of thick pigmented denticles (for a detailed description of the cuticular pattern see ref. 1).

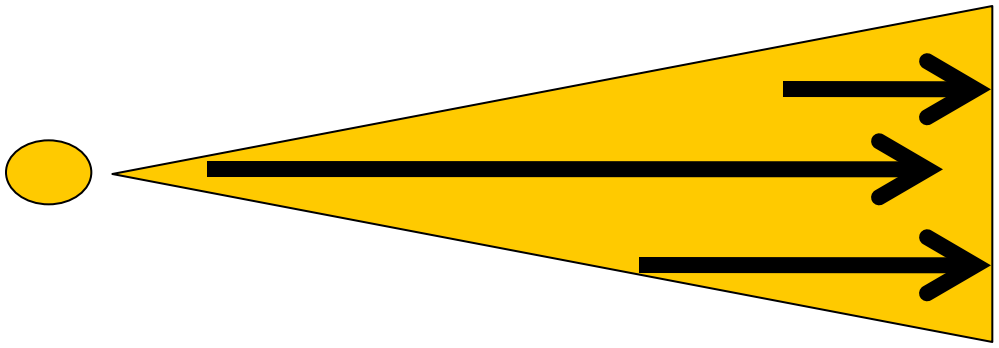
0028-0836/80/440795—07$01.00

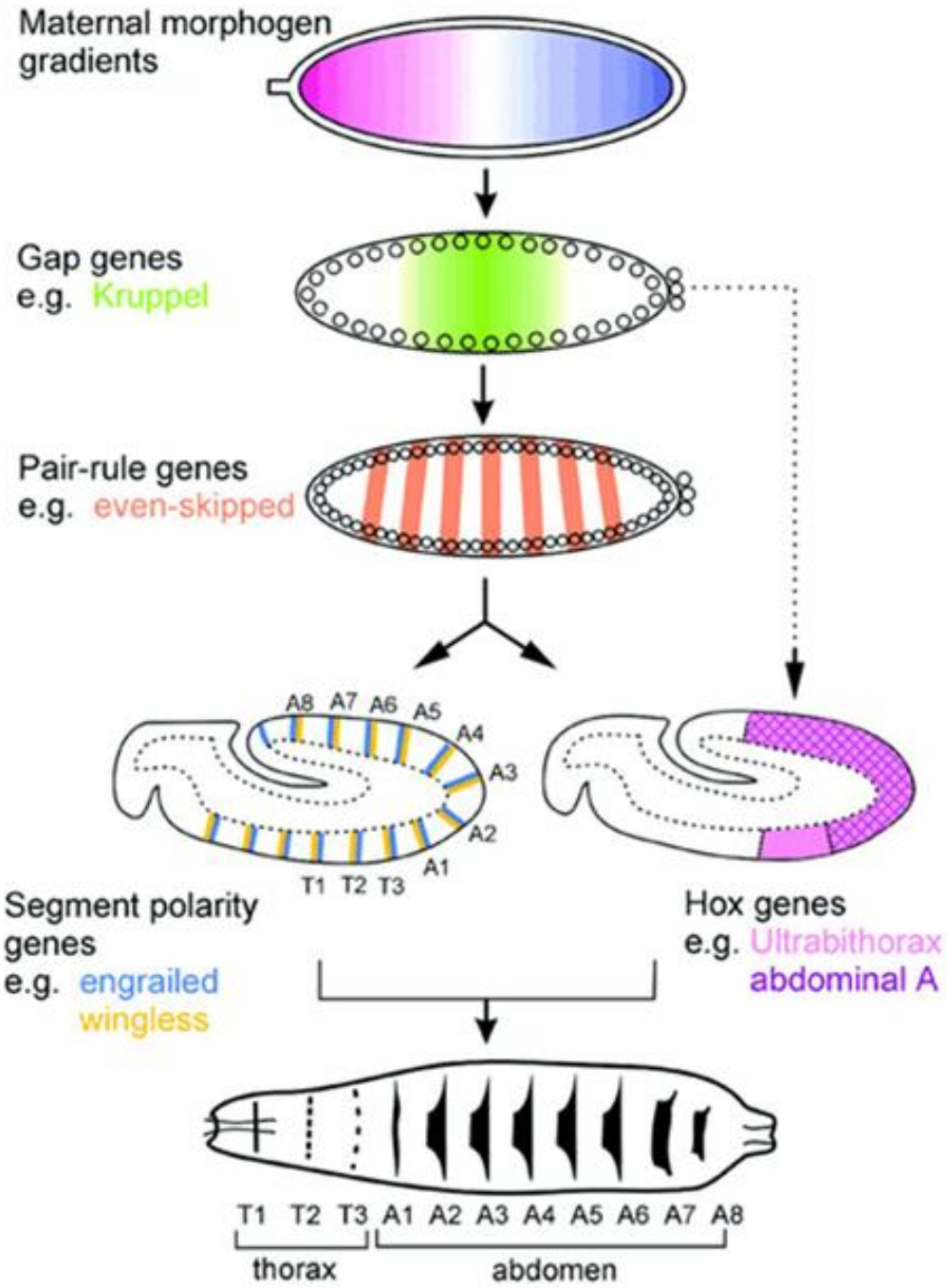
Nature 287:795, 30 October 1980

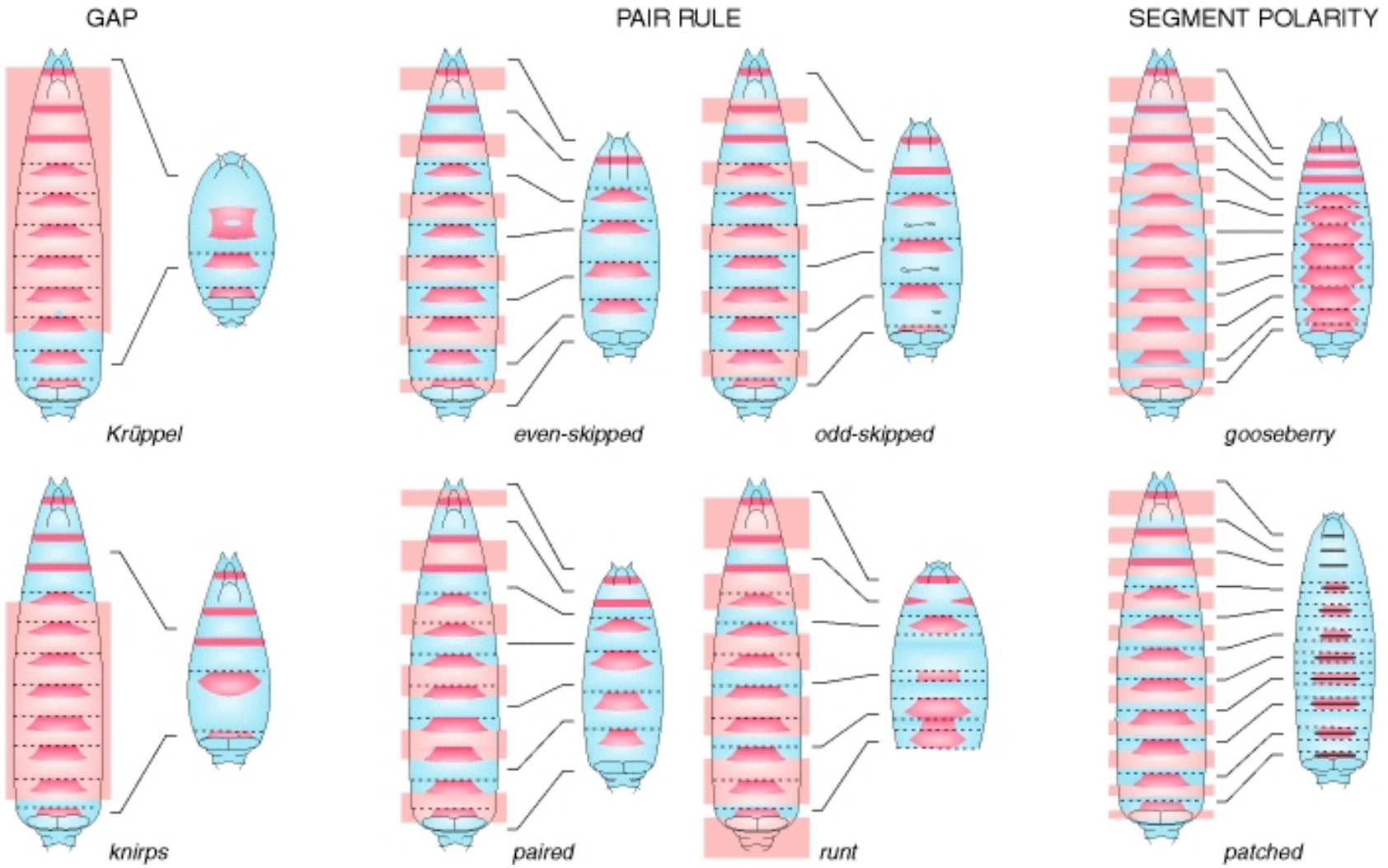
Nobel Prize in Physiology or Medicine, 1995

Nüsslein-Volhard and Wieschaus employed a type of biological reverse engineering:

Disrupt a gene – and thus, its protein product – and observe what happens to the developmental anatomy of *Drosophila*.



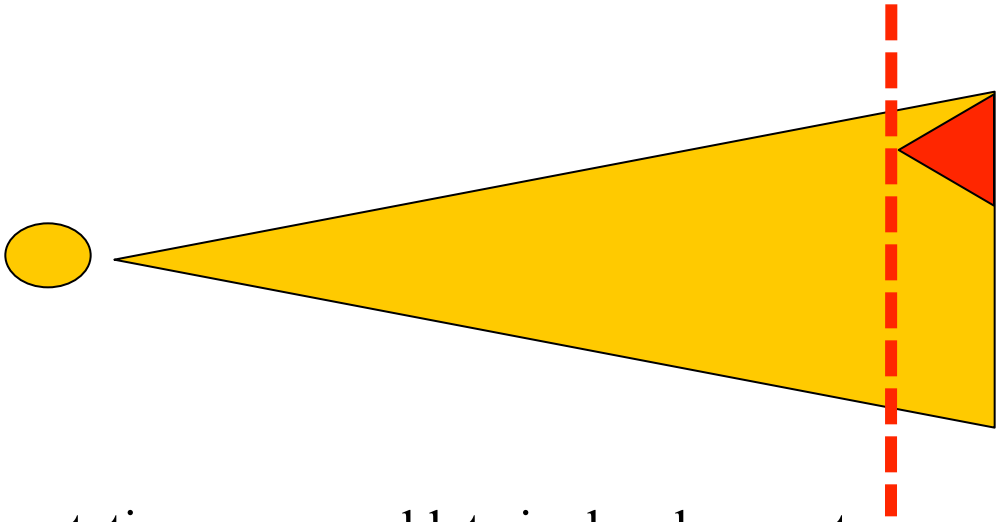

Maternal morphogen gradients
Gap genes
e.g. Kruppel
Pair-rule genes
e.g. even-skipped
A8 A7 A6 A5 A4 A3 A2 A1
T1 T2 T3
Segment polarity genes
e.g. engrailed
wingless
Hox genes
e.g. Ultrabithorax
abdominal A
T1 T2 T3 A1 A2 A3 A4 A5 A6 A7 A8
thorax
abdomen



Mutations affecting body plan formation are embryonic lethals.

Mutations affecting body plan formation are embryonic lethals.

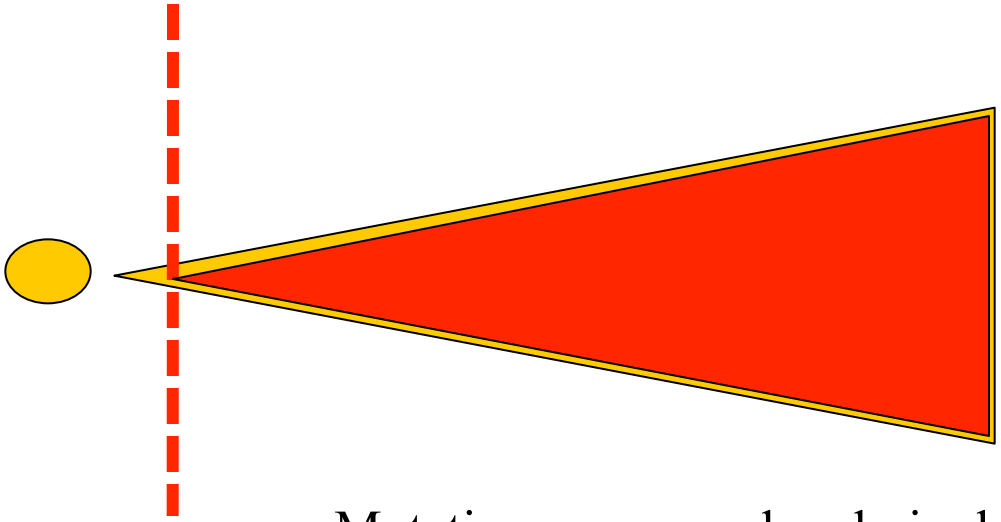
It's not hard to understand why. Indeed, given the causal dependencies of development, *this result is exactly what we should expect*.



A mutation expressed late in development may affect only a relatively small number of cells.

Mutations affecting body plan formation are embryonic lethals.

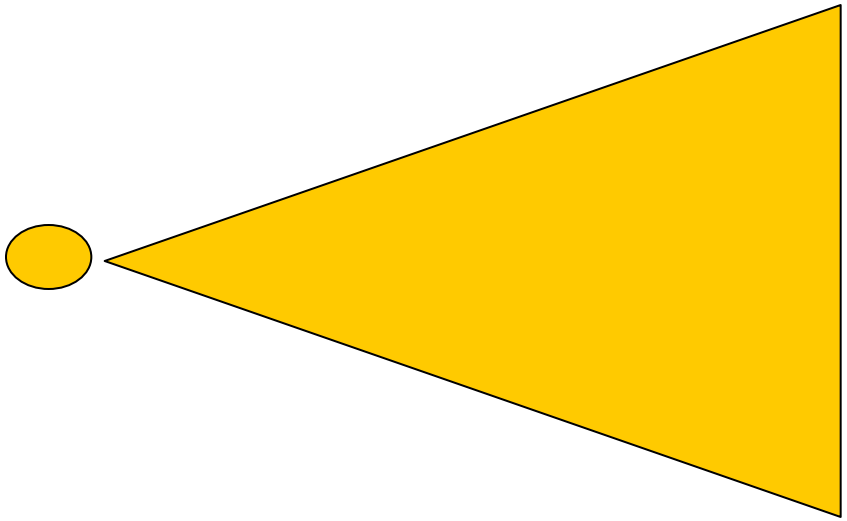
It's not hard to understand why. Indeed, given the causal dependencies of development, *this result is exactly what we should expect*.



Mutations expressed early in development, by contrast, are likely to crash the system, because of pleiotropy and other downstream consequences.

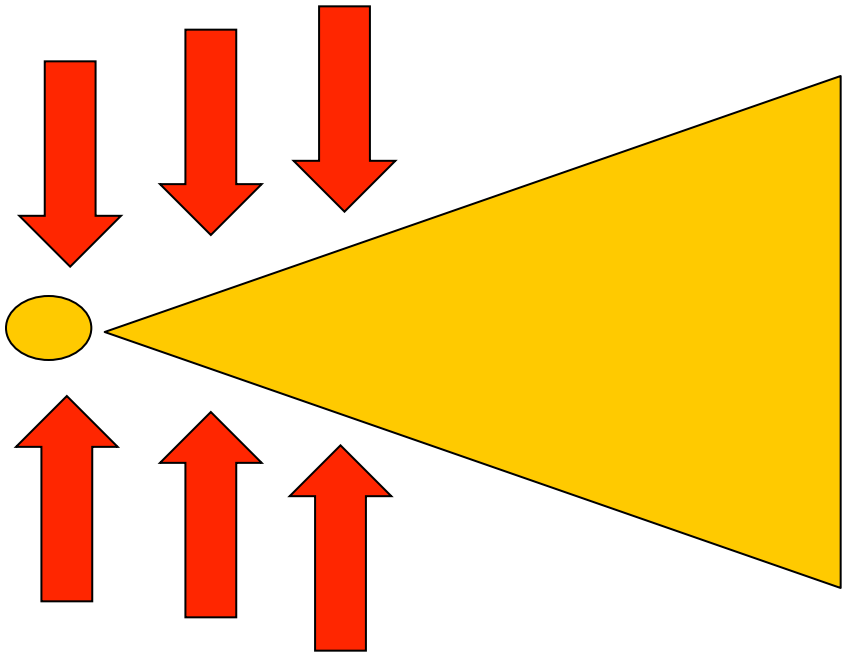
Thus, the insoluble three-point paradox:

1. Animal body plans are built in each generation by a stepwise process, from the fertilized egg to the many cells of the adult. The earliest stages in this process determine what follows.



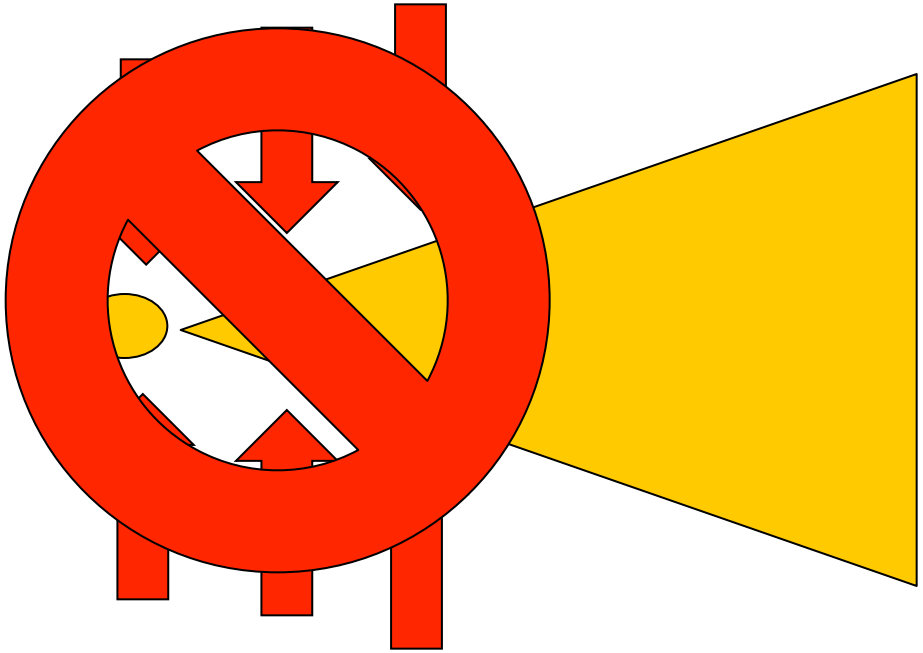
Thus, the insoluble three-point paradox:

2. Thus, to change – that is, to evolve – any body plan, mutations expressed early in development must occur, be viable, and be stably transmitted to offspring.

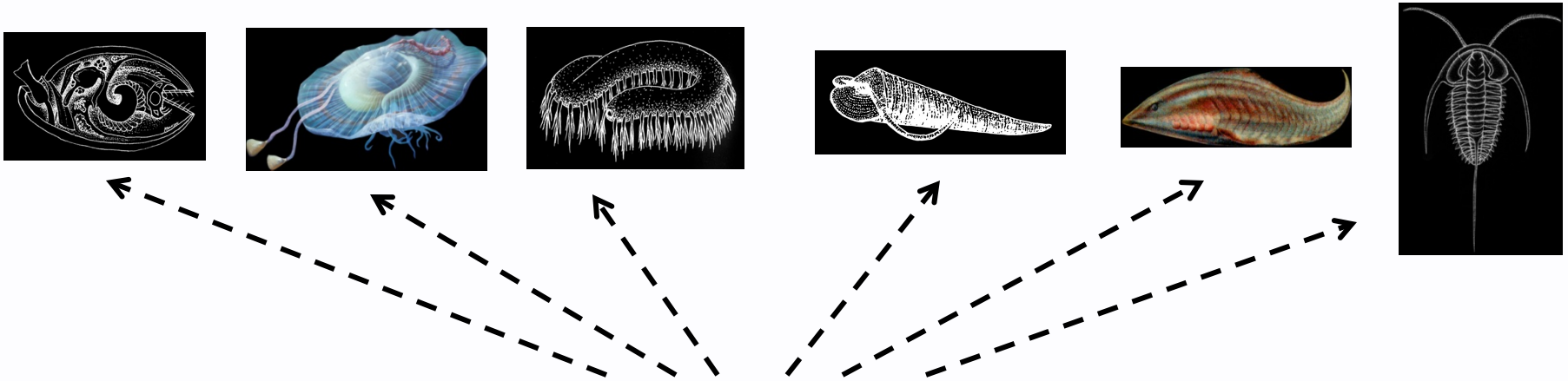


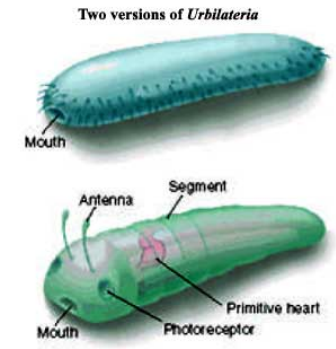
Thus, the insoluble three-point paradox:

3. But such early-acting mutations of global effect on body plans are those *least likely* to be tolerated by the embryo.



What are the consequences of these findings for the neo-Darwinian hypothesis of the common descent of the animal phyla?

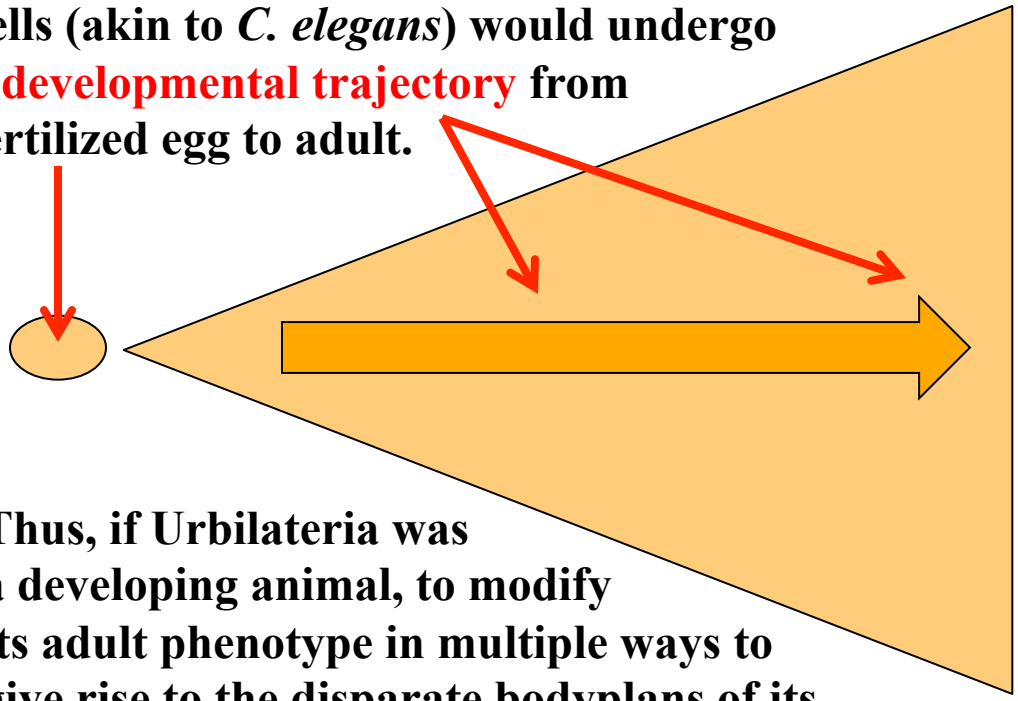


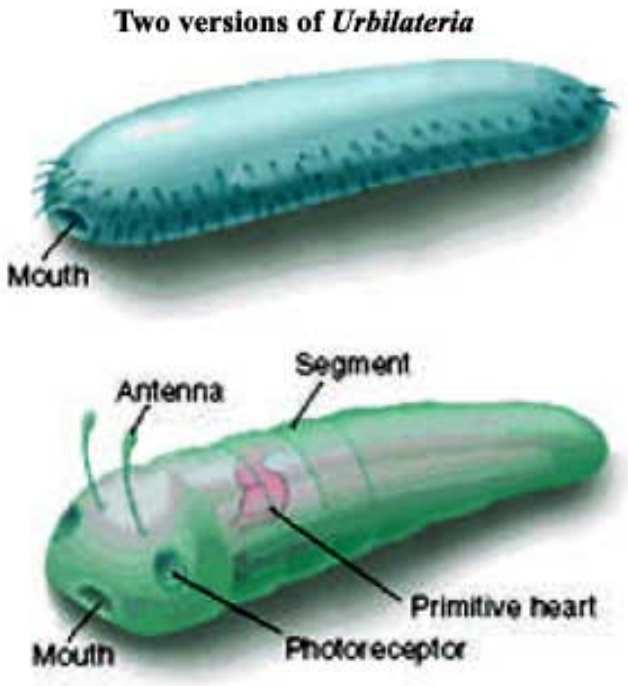


"Urbilateria"

Exactly the same problem obtains: To derive disparate body plans from Urbilateria *would require disrupting its normal development*.

Even a tiny animal, with about 1000 differentiated cells (akin to *C. elegans*) would undergo a developmental trajectory from fertilized egg to adult.





Thus, if Urbilateria was a developing animal, to modify its adult phenotype in multiple ways to give rise to the disparate bodyplans of its descendants, would require (mechanistically) perturbing its normal development, right from the earliest stages. The consequences would likely be lethal. Or we need a reason why not.

It's a little long for a bumper sticker – but you can take this reality to any evo-devo meeting, and it will sustain many hours of fascinating conversation:

Mutations expressed early in development, *affecting body plan formation*, are those *least likely* to be tolerated by animals.

This – in 18 words – is the unsolved problem of animal macroevolution.

Evidence to the present (May 2020): mutations affecting bodyplan formation in animals are inevitably deleterious*, usually catastrophic / lethal. This is a reliable (i.e., universal) finding.

"Ah – Paul, your sample is simply too small. How can you be *certain* that very rare but still viable, heritable, and morphologically novel mutants might not have occurred – *beyond* the boundaries of previous mutagenesis experiments?"

"Remember: *natural selection is a probability amplifier*. The process thrives on the occasional lucky event."

***some losses are viable & stably heritable**


TEN TIMES PAY
10
THIS MACHINE ACCEPTS
$1 $5 $10 $20 BILLS

This represents the gambler's fallacy in evolutionary biology.

This same "reasoning" keeps casinos in business, and explains why I never go into casinos, except to use the bathroom (and then exit the place).

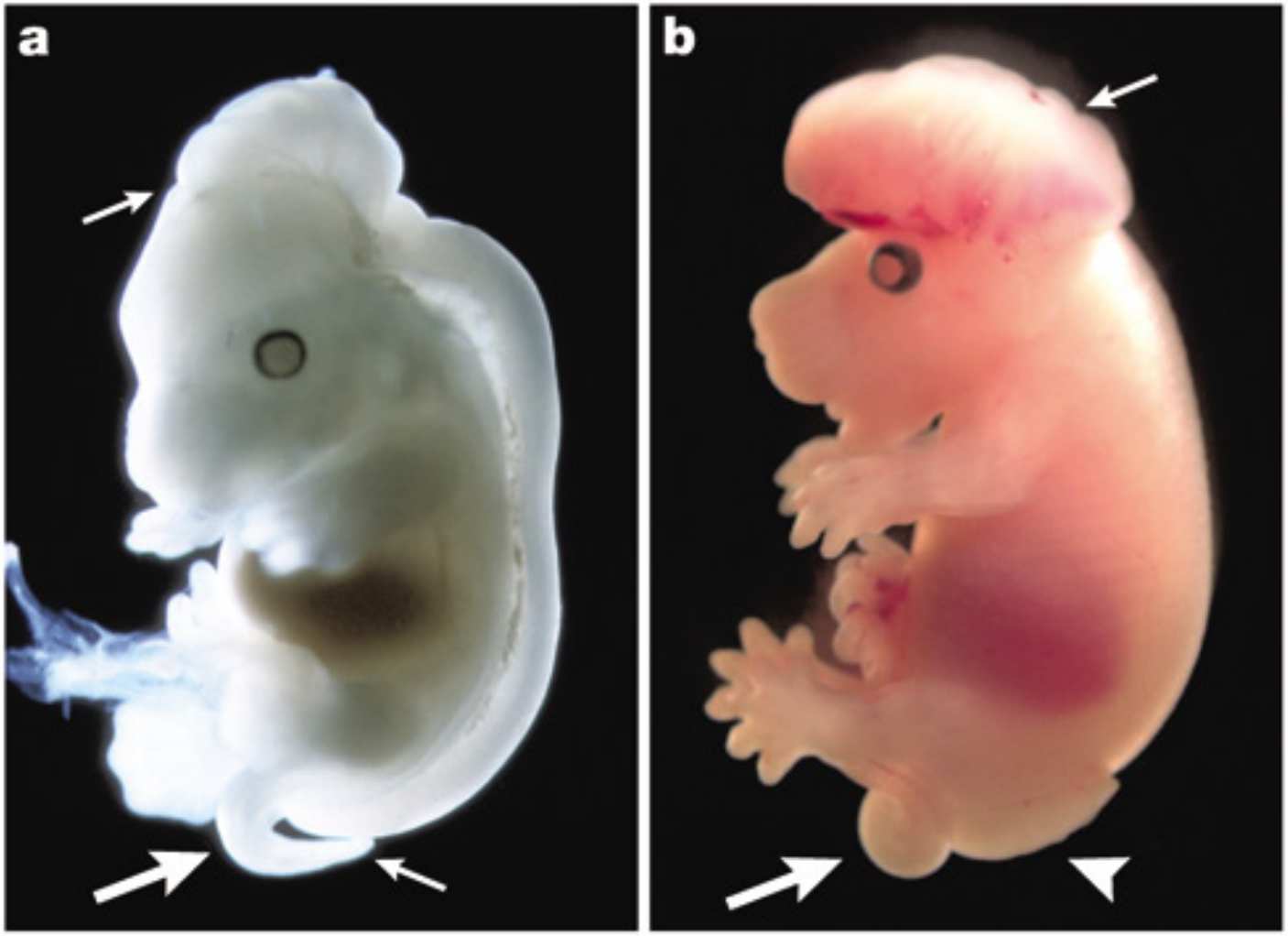
The next slide shows what one will find on examining the results of mutagenesis experiments in the model systems of developmental biology (or evo-devo).

From an ENU-mutagenesis screen in mice (Wansleeben *et al*. 2011):

Table 1. Overview of mutants found in this screen (see Table S2 for additional information).

Line[a]	Phenotype[b]	Chr	Mbp[c]	Affected gene	Mutation	Figure	Ref.
5120-6B	Craniorachischisis	15	71-83.2	Scribble			[12]
5120-6C	Cardiac edema	10	25-29	Unknown		2D	
5120-7	Cardiac edema	17	78–84.5	Ncx1	N874K		[13]
5120-8	Open hindbrain	11	115–120	Unknown		2B	
59458-3	Craniorachischisis	3	121.6–130.8	Sec24b			[12]
59459-2	Situs inversus and short tail	17	5.5–27.5	Dll1	E26G	3	
59468-4	Cardiac edema	10	114–116.5	Ptprb	Y693X	4	
59622-3	Cardiac edema	3	49–76	Unknown		2E	
59780-4	NTD fore- and midbrain	15	8–89.4	PlexinB2	E369G	5	
Amiko	Growth arrest at E9.0	14	24–72	Unknown		2L	
Cerbo	Cardiac and nuchal edema	2	165–166	Unknown		2I	
Flanka	Abnormal head, heart, NTD	6	14.1–32.2	Unknown		2K	
Koro	Cardiac edema	11	3.2–17.6	Unknown		2F	
Pootloos	No limbs	13	-	Fgf10	L91P	6	
Linio	Cardiac edema	11	94–98.7	Unknown		2C	
Nevo	Cardiac and nuchal edema	8	77.4–98	Unknown		2J	
Salsa	Cardiac edema	6	67–71	Unknown		2G	
Staartloos	Posterior truncation	11	55–66	Wnt3a	unknown	7	
Zoef	Cardiac and nuchal edema	19	33.5–33.8	Unknown		2H	

These phenotypes are *bad news* for mice. Bad news going nowhere.



Nature Reviews | Genetics

From Copp *et al.*, 2003

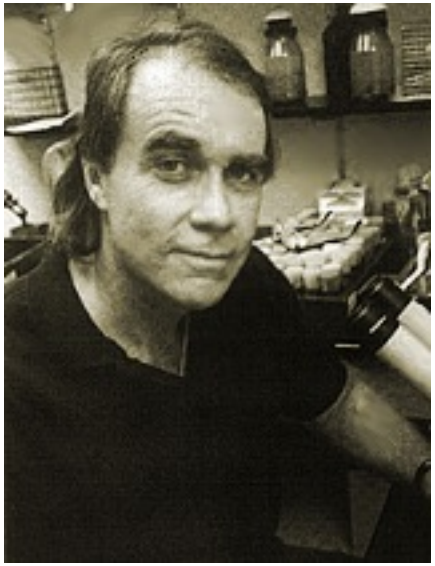
Why think one's "luck" is going to change?

1920 → 2020

The signal from experimental mutagenesis: sick and dead mice (or flies or frogs or worms or fish...)

BUT at last, the **PAYOFF!**

John McDonald (Genetics, GA Tech) cast the puzzle of missing deep variation as follows:

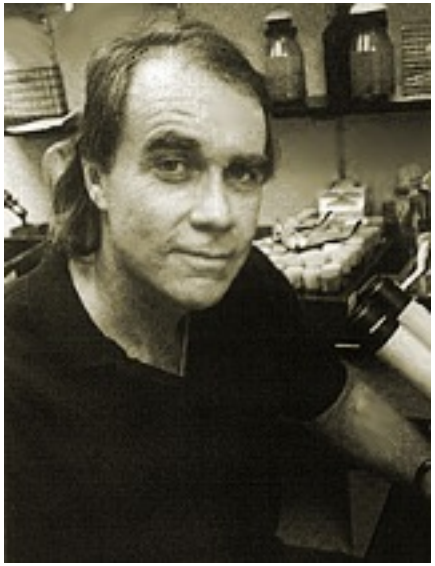


"...the results of the last 20 years of research on the genetic basis of adaptation has led us to a great Darwinian paradox."

(1983, 92-3)

Note the year of this publication: the first Reagan administration. Paul was an unmarried, thin undergraduate with lots of hair.

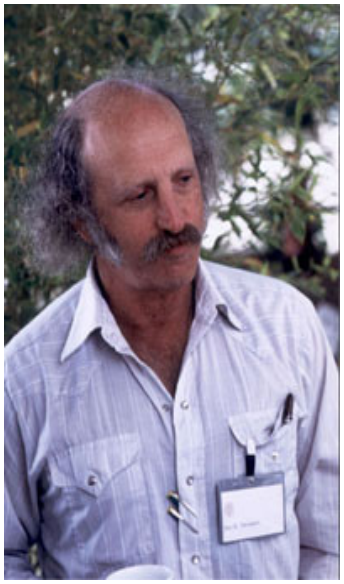
John McDonald (Genetics, GA Tech) cast the puzzle of missing deep variation as follows:



(1983, 92-3; emphasis in original)

"Those loci that are obviously variable within natural populations do not seem to lie at the basis of many major adaptive changes, while those loci that seemingly do constitute the foundation of many, if not most, major adaptive changes, apparently are not variable within natural populations."

Eric Davidson, evolutionary developmental biologist, Caltech (2011): textbook theory "gives rise to lethal errors"



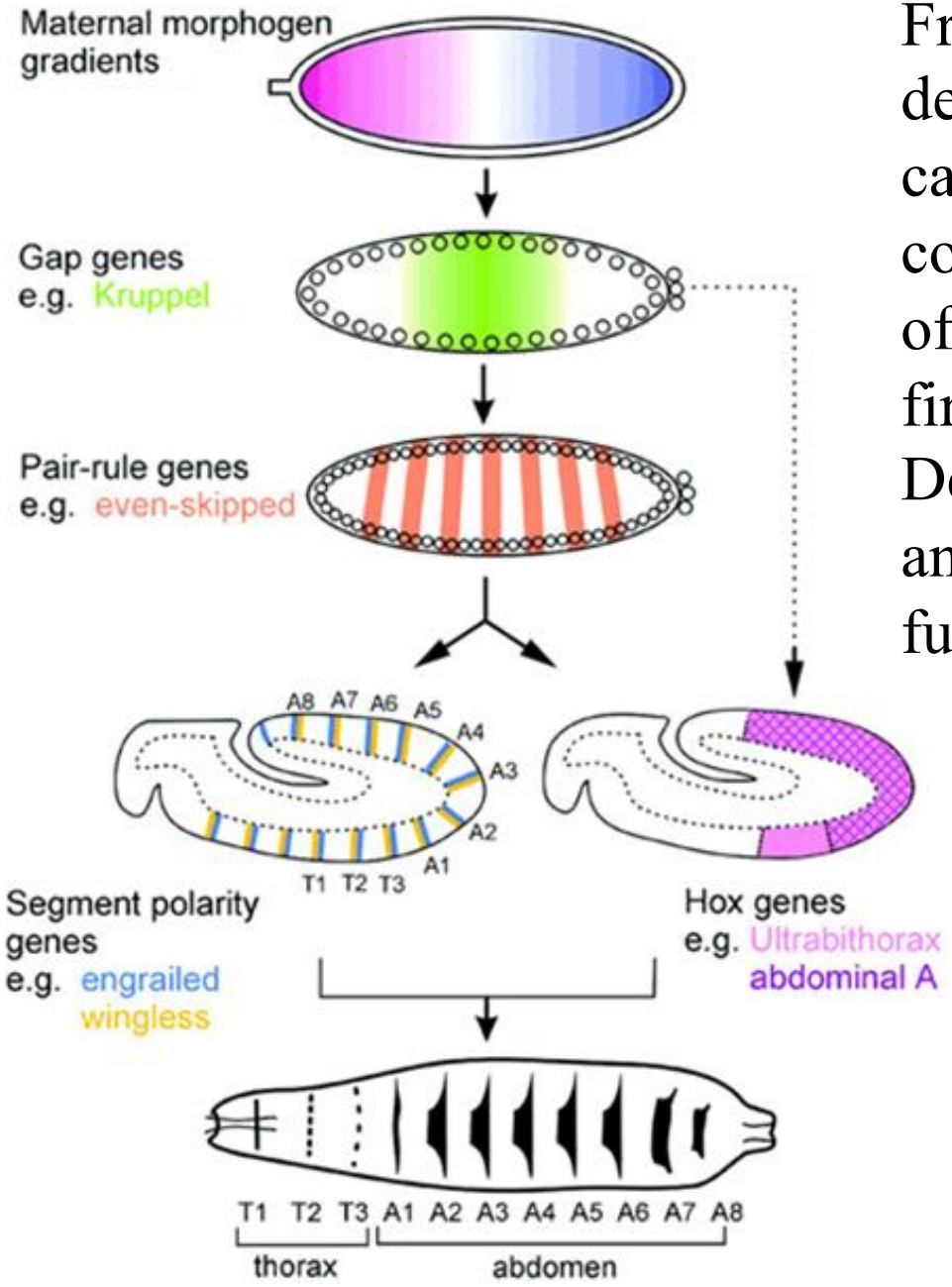
"Neo-Darwinian evolution…assumes that all process works the same way, so that evolution of enzymes or flower colors can be used as current proxies for study of evolution of the body plan. It erroneously assumes that change in protein coding sequence is the basic cause of change in developmental program; and it erroneously assumes that evolutionary change in body plan morphology occurs by a continuous process. All of these assumptions are basically counterfactual."

Andreas Wagner
Univ. of Zurich
Institute of
Evolutionary
Biology

"…we know few of the principles that explain the ability of living things to innovate through a combination of natural selection and random genetic change. Random change by itself is not sufficient, because it does not necessarily bring forth beneficial phenotypes. For example, random change might not be suitable to improve most man-made, technological systems. Similarly, natural selection alone is not sufficient: As the geneticist Hugo de Vries already noted in 1905, 'natural selection may explain the survival of the fittest, but it cannot explain the arrival of the fittest.'"

Trends in Genetics 27 (October 2011): 397-410.

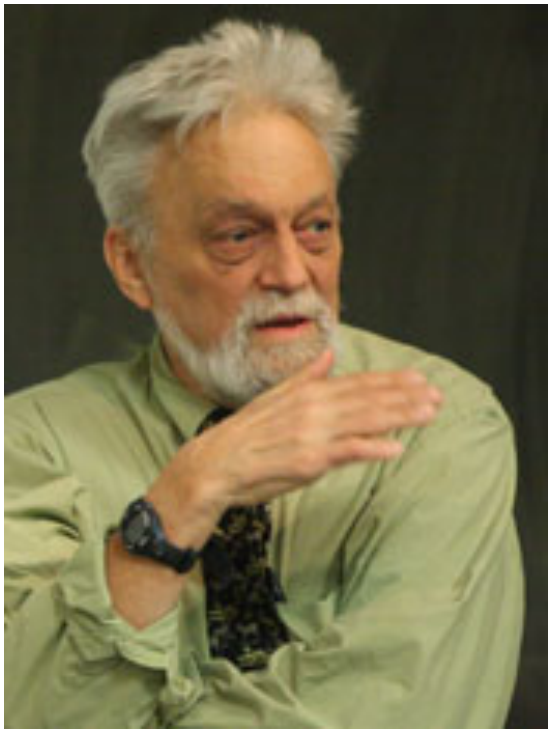
Now we sail into much more controversial waters: asking questions about the *homology expectations* created by Lewontin's schema. You may want to grab onto something secure... common ancestry will be undergoing scrutiny.

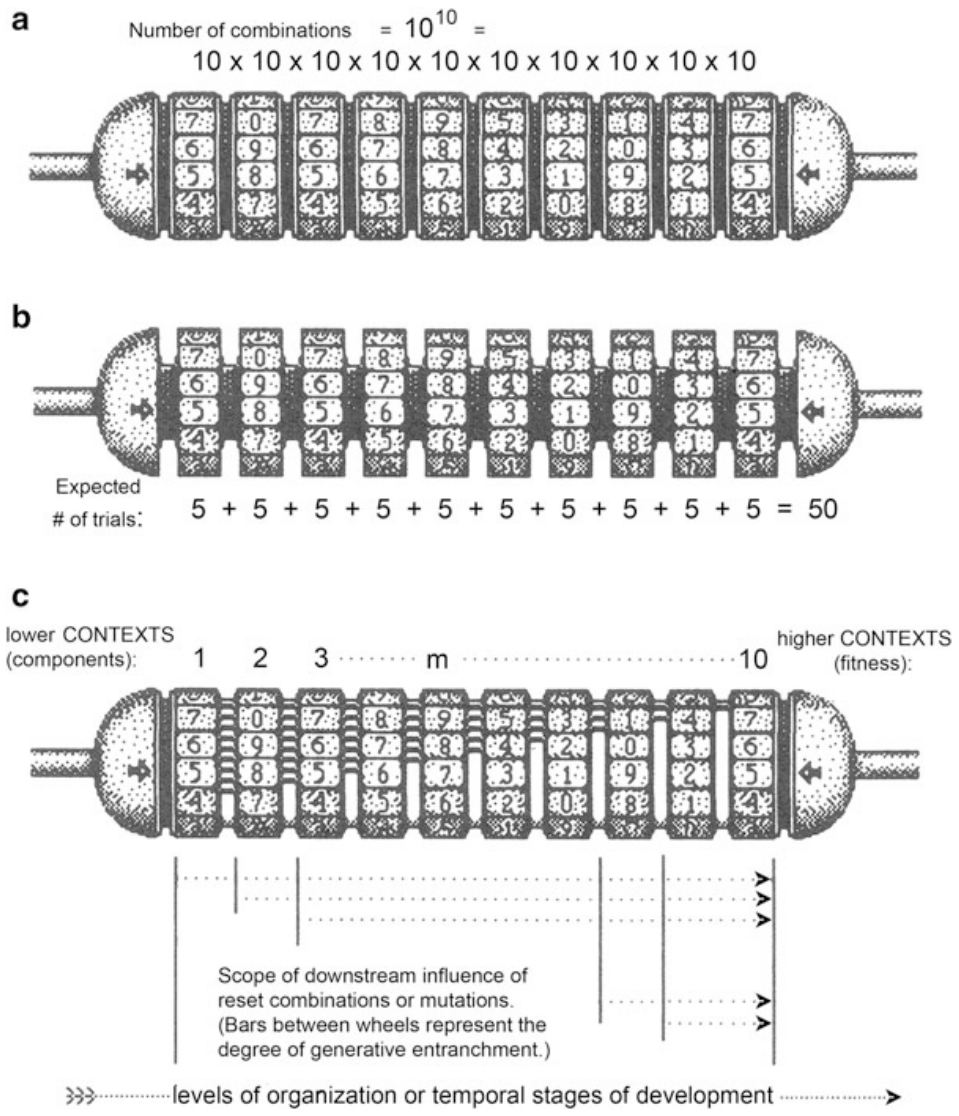


From this and other developmental cascades, Wimsatt constructed a theory of causal relations, first dubbed "the Developmental Lock," and later, in its fully-articulated form,

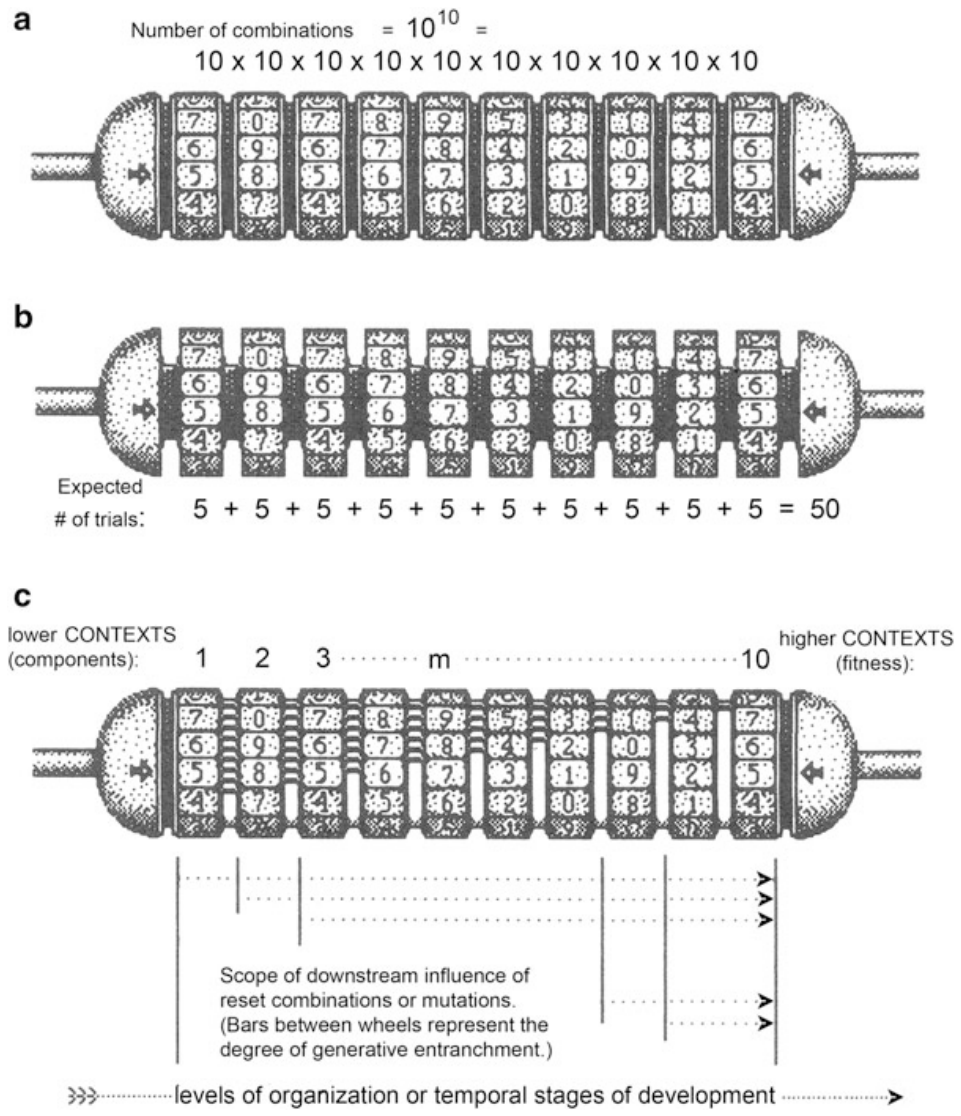
Generative Entrenchment.

William Wimsatt's "developmental lock" model for the causal structure of animal development

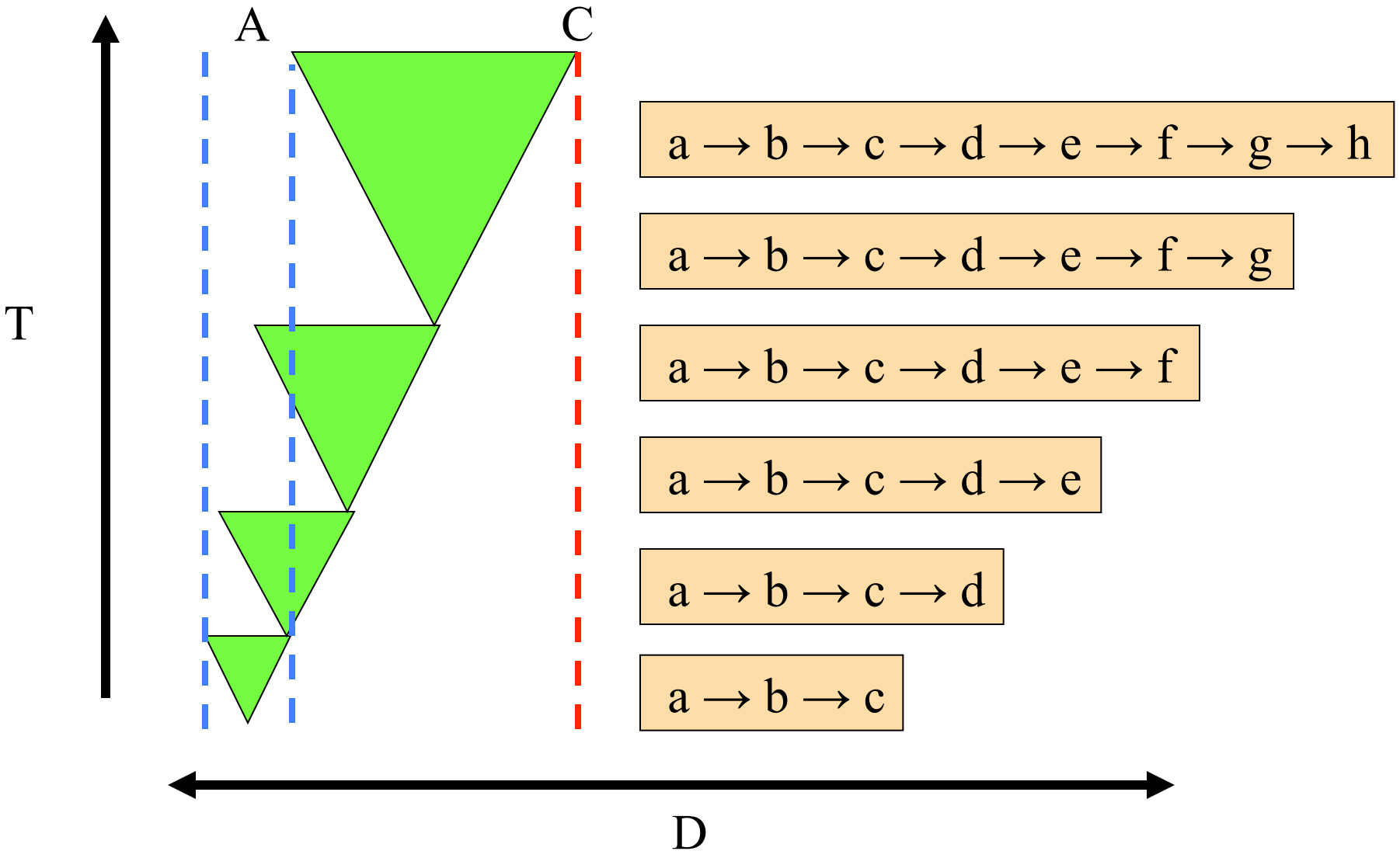




The developmental lock is an illustration within a theory of causal relationships or dependencies characterizing complex systems (including developing embryos). Animal development is a hybrid of “simple” and “complex” locks.



On this picture, how are ontogenies – i.e., novel developmental patterns – likely to be built?



VOL. 46, NO. 2 June, 1971

THE QUARTERLY REVIEW
of BIOLOGY

REPETITIVE AND NON-REPETITIVE DNA SEQUENCES AND A SPECULATION ON THE ORIGINS OF EVOLUTIONARY NOVELTY

BY ROY J. BRITTEN * and ERIC H. DAVIDSON †
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† *Division of Biology, California Institute of Technology, Pasadena, Calif. 91109*

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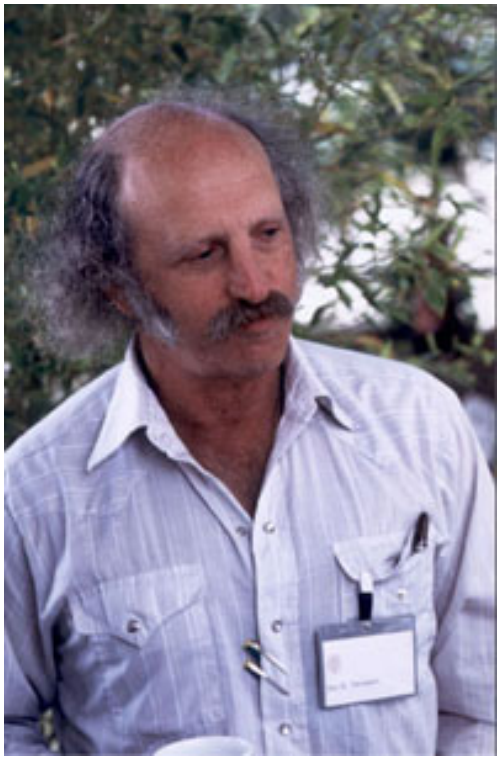

Eric Davidson,
Caltech

The processes of development appear to be sequential, not only in the obvious time course of the events, but in the basic molecular and cellular mechanisms. In other words, the later stages are built on a foundation consisting of the events occuring earlier in development. As a result, changes in the parts of the developmental program operative at a given stage might result in drastic alterations of later developmental events. We expect, therefore, that the regulatory programs active earlier in development would also have been elaborated at early stages of evolution. Clearly, there would be greater freedom for modification and improvement by natural selection of what are now early

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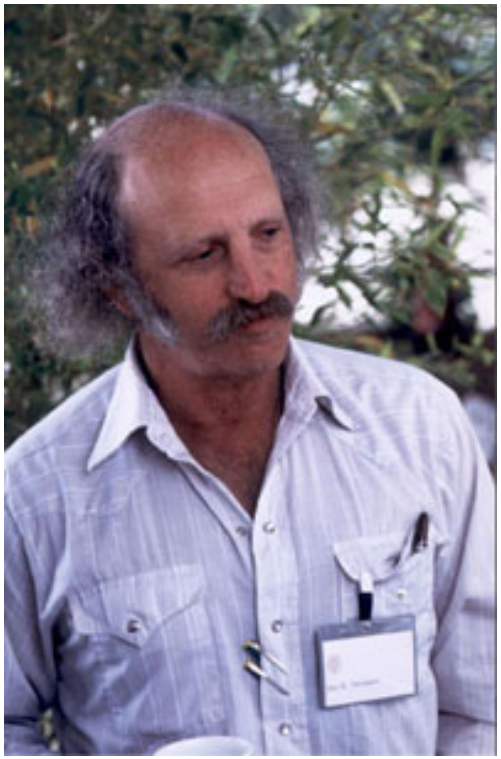
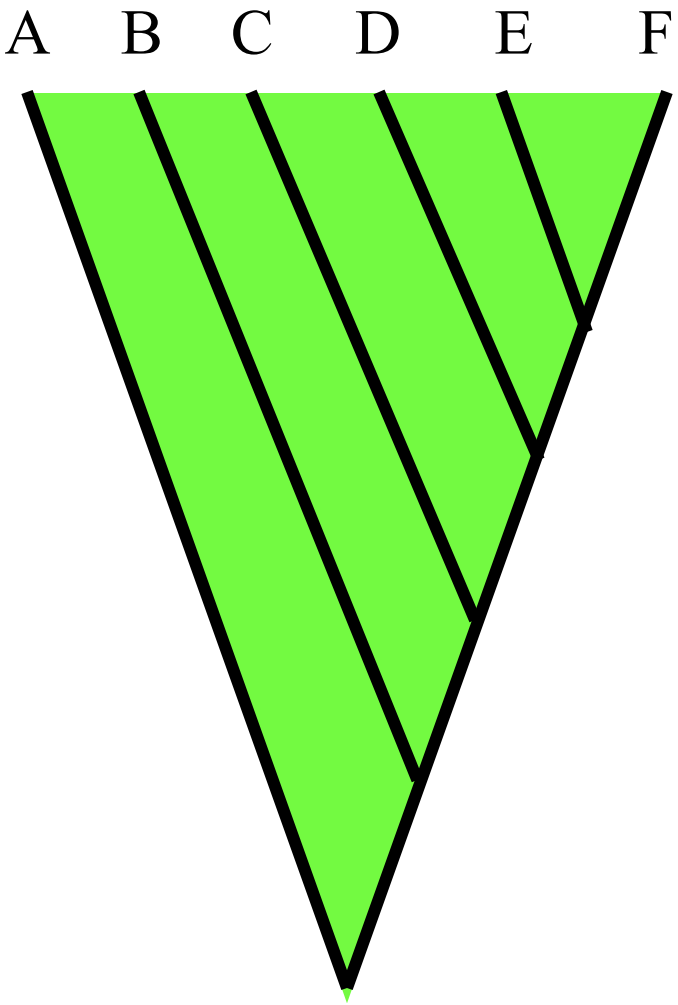


Eric Davidson,
Caltech

developmental stages before the more complex and dependent later stages of development were superimposed on them. As a corollary, we would expect that, once the later stages evolved, the earlier stages of the developmental regulatory program would be more or less fixed. One can imagine modest alterations or additions to the early parts of the developmental program, but it would be very unlikely that such programs could be supplanted. Therefore the basic developmental patterns would be expected to have been elaborated earlier in evolution and be more widespread, phylogenetically.

Given Davidson's argument, what phylogenetic distribution would you expect for these sequences?



F a → b → c → d → e → f → g → h

E a → b → c → d → e → f → g

D a → b → c → d → e → f

C a → b → c → d → e

B a → b → c → d

A a → b → c

(toy phylogeny, illustration purposes only)

Classic model systems of developmental biology

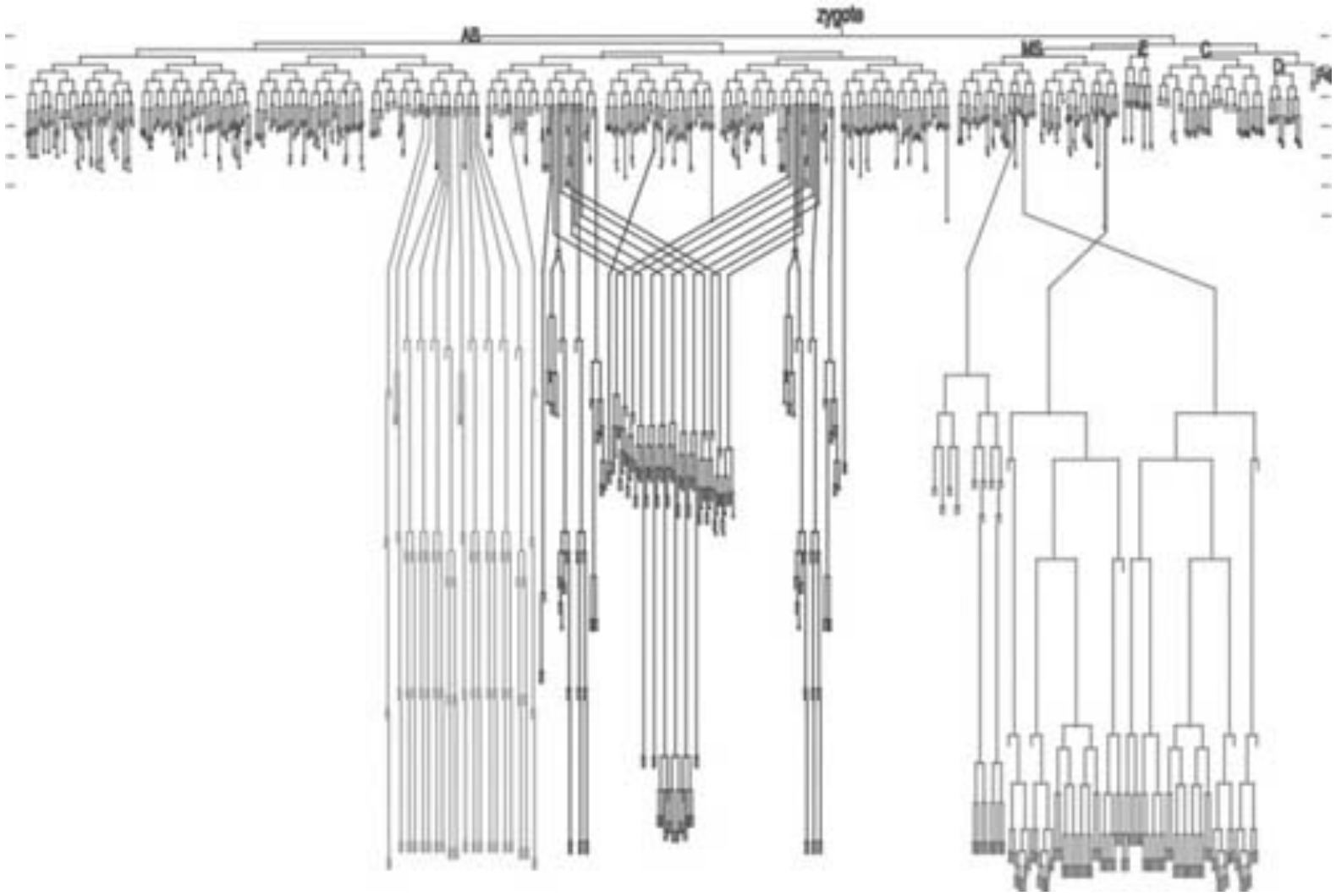


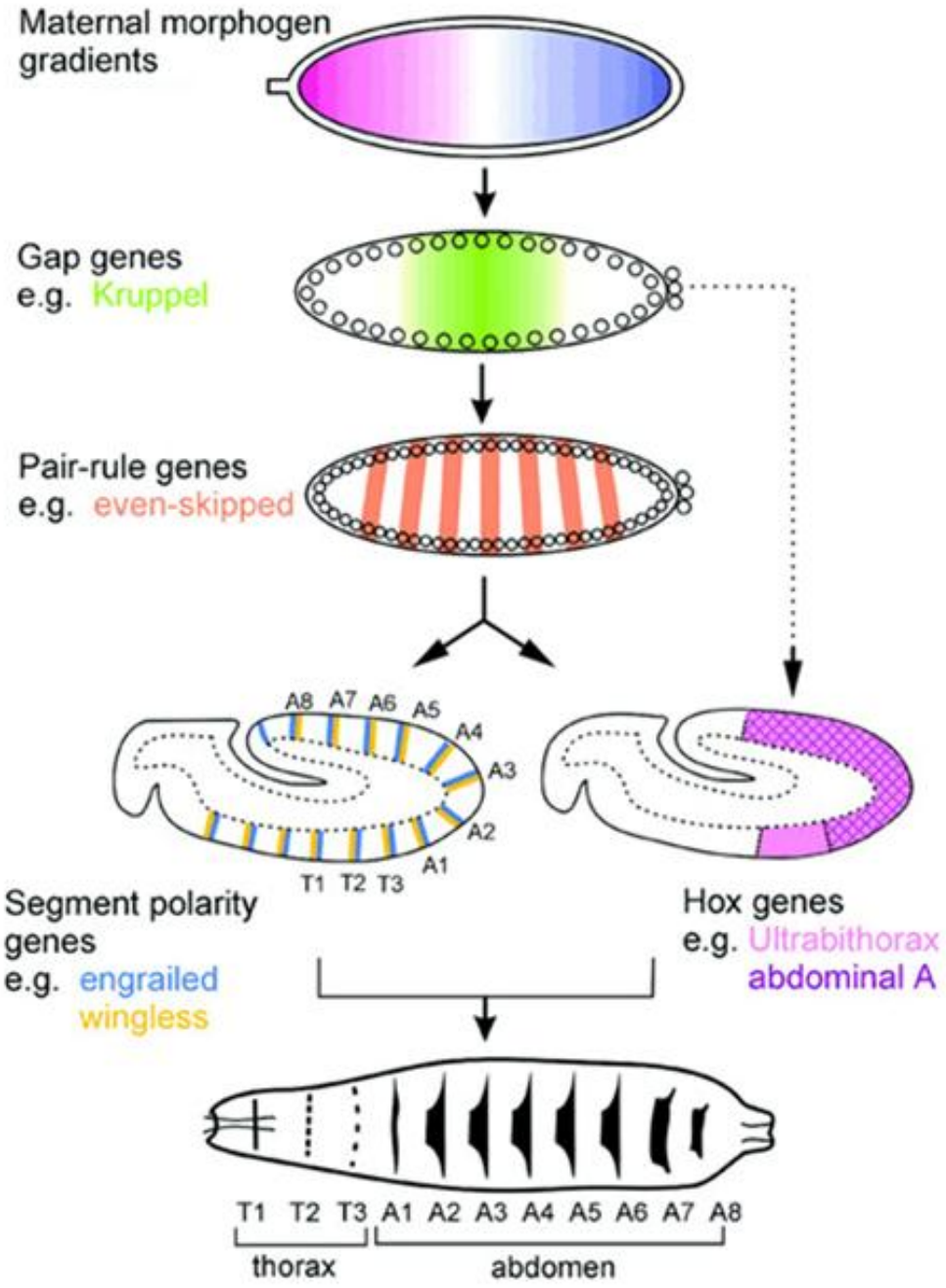



C. elegans *Drosophila* *Danio* *Xenopus* *Gallus* *Mus*

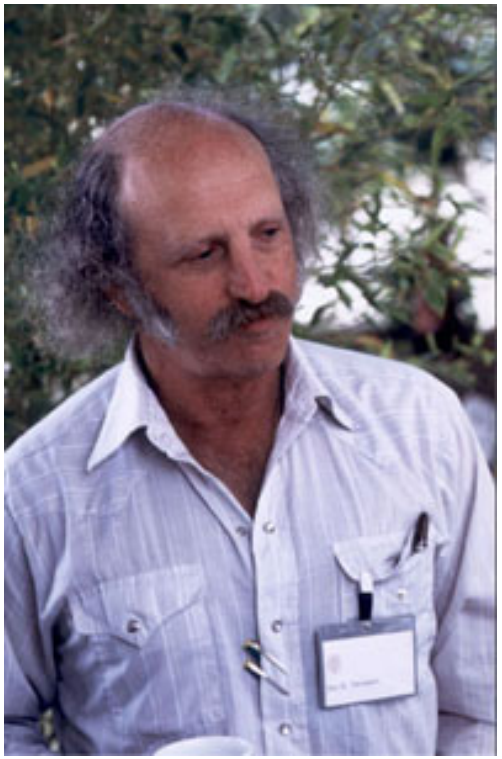
(another toy phylogeny − but C. elegans and Drosophila do nest together in the Ecdysozoa, so not entirely toy)

The cell lineage of *Caenorhabditis elegans,* to hatching




Maternal morphogen gradients
Gap genes
e.g. Kruppel
Pair-rule genes
e.g. even-skipped
A8 A7 A6 A5 A4 A3 A2 A1
T1 T2 T3
Segment polarity genes
e.g. engrailed
wingless
Hox genes
e.g. Ultrabithorax
abdominal A
T1 T2 T3 A1 A2 A3 A4 A5 A6 A7 A8
thorax
abdomen

Early development in the animals is *not conserved*:

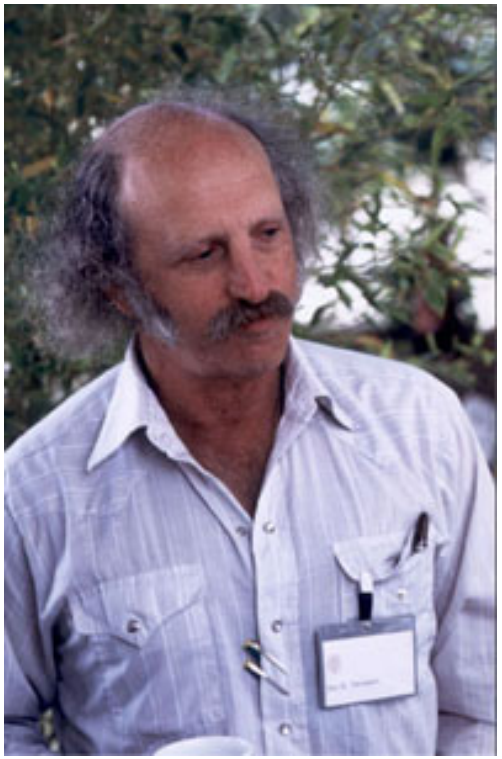


Eric Davidson, Caltech

"Those...who have attempted to deal with more than one embryonic form, have been struck by the amazing variety in the modes of embryonic development in the various phylogenetic reaches of the Animal Kingdom" (1990, 365)

"*Caenorhabditis elegans* embryos have an invariant cell lineage while the cell lineage of a chicken or a mouse or fish embryo is always different from that of another of the same species…" (1991, 1)

Early development in the animals is *not conserved*:



Eric Davidson,
Caltech

"...portions of sea urchin or jellyfish embryos can regulate to generate whole new embryos, while equivalent portions of ascidian or annelid embryos cannot; *Drosophila* embryos specify elegant spatial patterns of gene expression before there any cells to interact, while in *Xenopus* or sea urchin embryos the initial spatial diversification of gene expression depends causally and extensively on intercellular interactions." (1991, 1)

Nicholas Rasmussen, Ph.D. student in evolutionary biology and the Conceptual Foundations of Science, University of Chicago (mid-to-late 1980s, at the same time Paul was there; same Ph.D. advisor)

J. theor. Biol. (1987) **127**, 271–299

A New Model of Developmental Constraints as Applied to the *Drosophila* System

NICOLAS RASMUSSEN†

Department of Philosophy, University of Chicago, U.S.A.

(*Received* 21 *May* 1986, *and in revised form* 19 *November* 1986)

Von Baer's laws of development observe that an embryo, in the course of its ontogeny, progresses through a series of forms which diverge increasingly from the embryonic forms of related species, and in an evolutionary interpretation, from those of its phylogenetic ancestors. This observation on the relation of phylogeny to ontogeny is explained by Wimsatt's (1986) "Developmental Lock" model of complex generative systems, which proposes that evolution is constrained to alter developmental programs in a manner that usually modifies or adds new complexity to pre-existent developmental functions at positions relatively "downstream" in the causal structure. If the Developmental Lock model is correct, (1) evolution should have resulted in hierarchically ordered developmental programs, and (2) the most important developmental functions in the hierarchy should be ancient. Wimsatt also suggests that developmental functions be analyzed according to a degree property called "generative entrenchment", which replaces the temporal analysis in the traditional formulation of von Baer's laws. Herein, a substantial body of data on *Drosophila* ontogeny is analyzed according to generative entrenchment, in order to try the effectiveness of this form of analysis, and also to empirically test these two main predictions of the Developmental Lock model. The novel analytic approach proves to be fruitful, both in generating experimental hypotheses and in ordering existing data. Moreover, data concerning the developmental functions discussed here indicate that the order of the *Drosophila* developmental program conforms to the predictions of Wimsatt's model with few deviations. Explanations of the anomalies are offered, along with proposals for experiments to test some of those explanations.

1. Introduction

Von Baer's laws of development, which describe the sequence of changes observed during embryogenesis, are often summarized in the following manner: "Differentiation proceeds from the general to the particular". Three different interpretations might be given this law, depending on what sort of generality one has in mind (Wimsatt, 1986). In terms of taxonomic generality, the law would hold that features appearing earlier in development are shared with broader taxonomic groups, and with more distant phylogenetic ancestors, than features appearing later. In terms of morphological generality, the forms which a developing embryo passes through should progress from more sketchy to more detailed. In terms of functional generality, the law holds that developmental processes active earlier in embryogenesis

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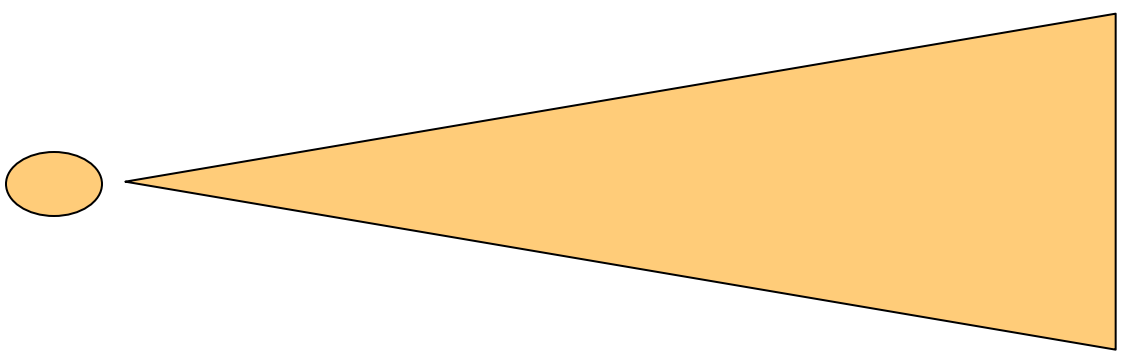
0022-5193/87/150271+28 $03.00/0

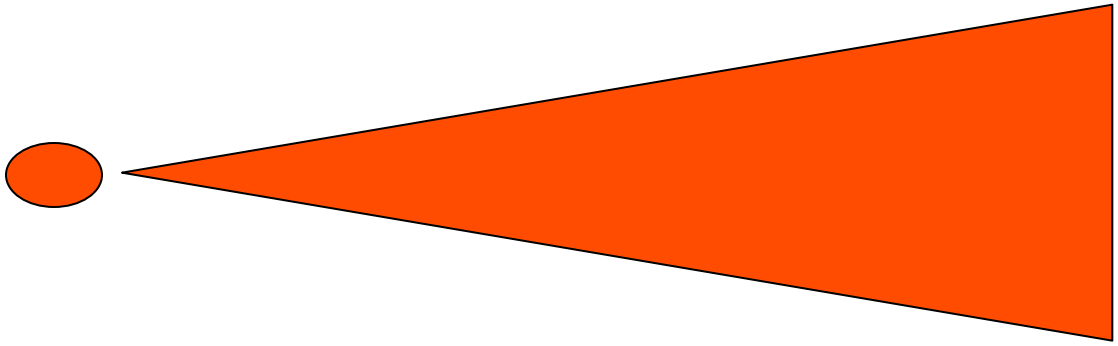
The Developmental Lock model of ontogeny, when coupled with the theory of common descent, makes strong predictions about gene distribution::

"...younger genes are less likely to be highly entrenched than older genes. If the model is accurate, the gene functions in the positions of greatest generative entrenchment in the hierarchy must be among the oldest, since *it should be virtually impossible for a new gene function to appear very far upstream in the causal structure of ontogeny*" (1987, 275; emphasis added).

The downstream consequences of a novel regulatory element are likely to be...?

...either integrated into the already existing system, or catastrophically deleterious.

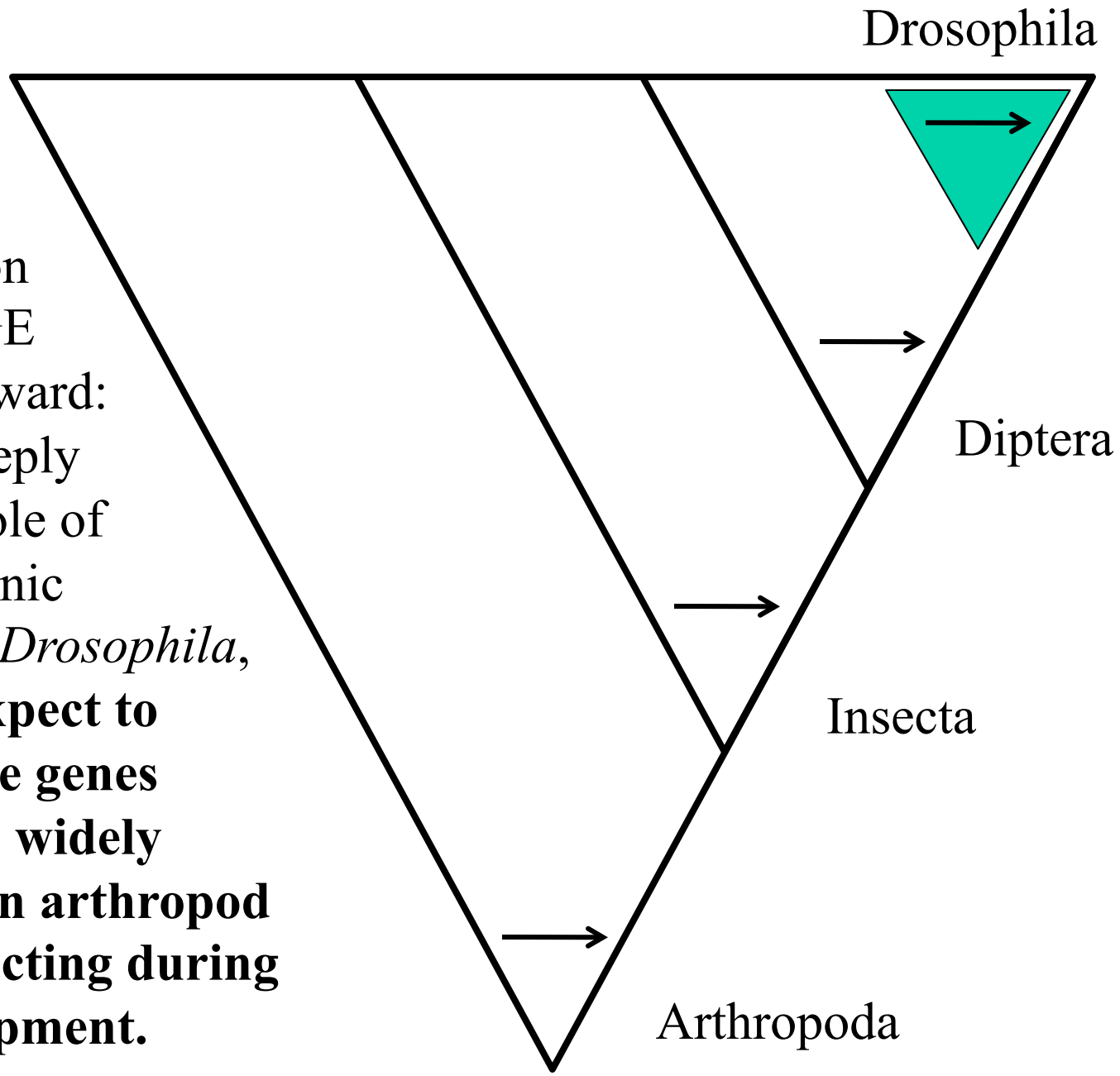




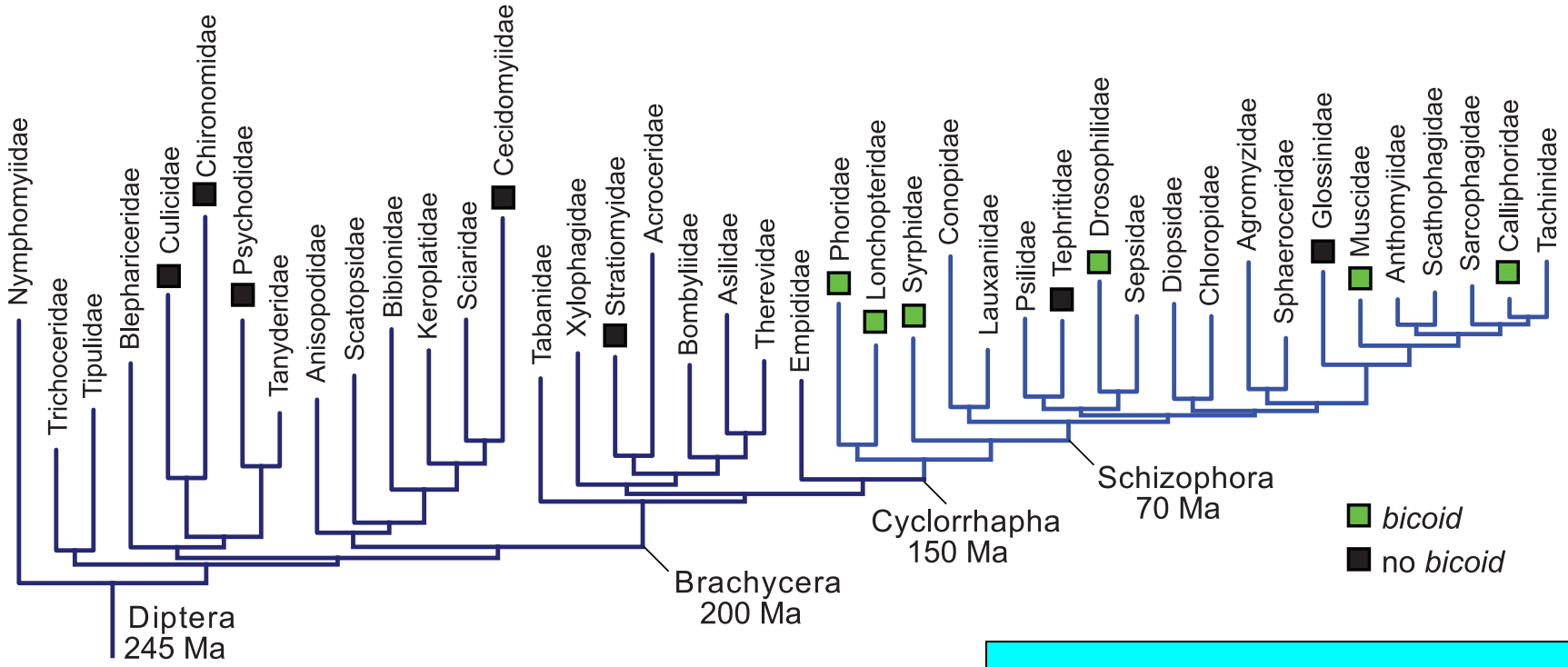
The Developmental Lock model of ontogeny, when coupled with the theory of common descent, makes strong predictions about gene distribution::

"A corollary of the model is that the most deeply entrenched genes in *Drosophila* should be *the most conserved among related species*." (1987, 175; emphasis added)

The prediction from CD + GE is straightforward: Given the deeply entrenched role of early embryonic regulators in *Drosophila*, **we should expect to find the same genes and proteins widely distributed in arthropod phylogeny, acting during early development.**



Any guesses on the distribution of *bicoid* in the Diptera?



(Klomp et al. 2015)

Christmas-tree-ornament pattern: no consistent phylogenetic signal.

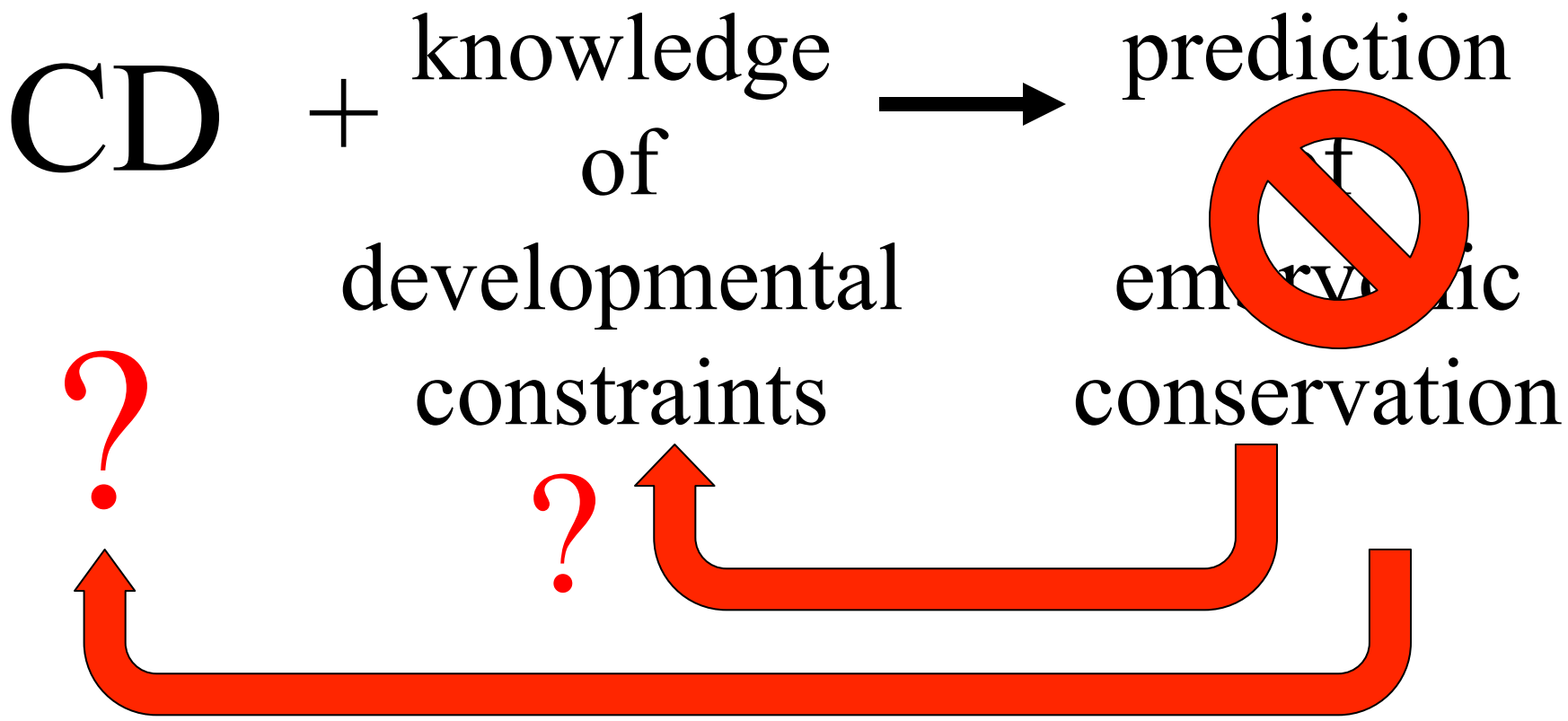
How Common Descent generates observational predictions:

CD + the rest of our biological knowledge → predictions we can check

Throughout most of the 20th century, evolutionary theory predicted the conservation of early embryonic stages in the animals, based on the functional demands of developmental processes:

CD + knowledge of developmental constraints → prediction of embryonic conservation

But what happens if those predictions fail? Who pays then?



Aphidius ervi

What does our biological knowledge lead us to predict?

"Developmental processes have been traditionally viewed to be invariant within higher taxa...Traditionally, changes in early development have been thought to occur rarely because such alterations are lethal…"

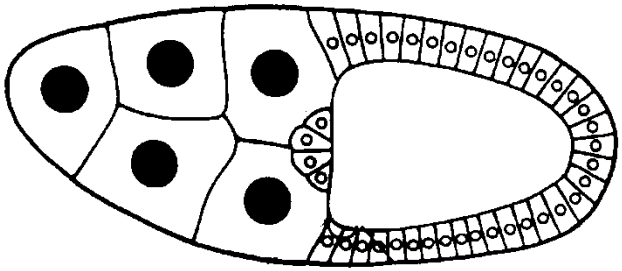
(Grbic and Strand 1998, p. 1097)

The expectation, based on the common ancestry of the Insecta:

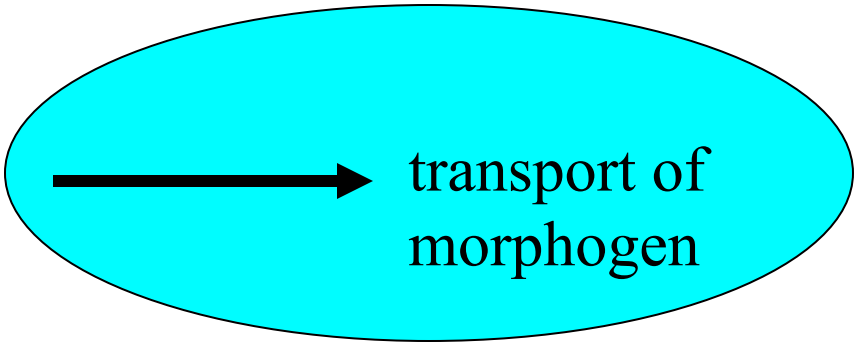
"If ancestry is the primary factor driving patterns of early development, we would expect that most insects in the monophyletic Hymenoptera would look much like the honeybee."

(Grbic and Strand 1998, p. 1097)

Early embryogenesis in flies and bees:

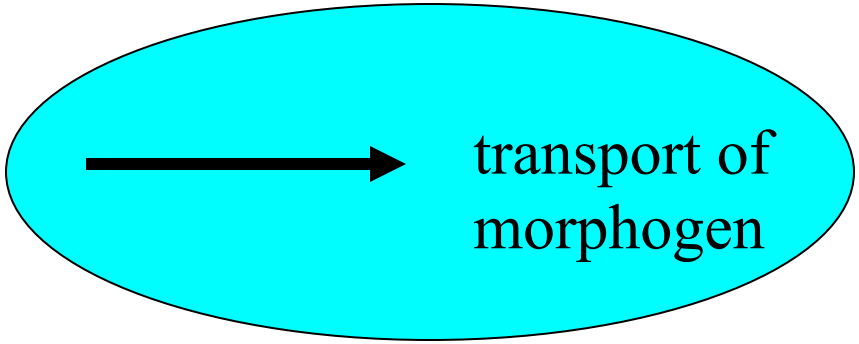


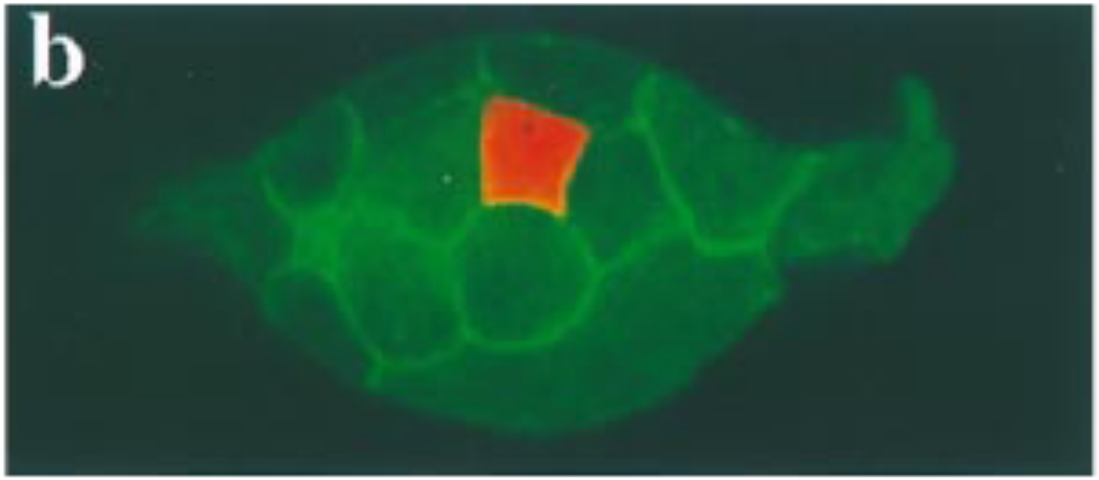
Oocyte



Fertilized Egg

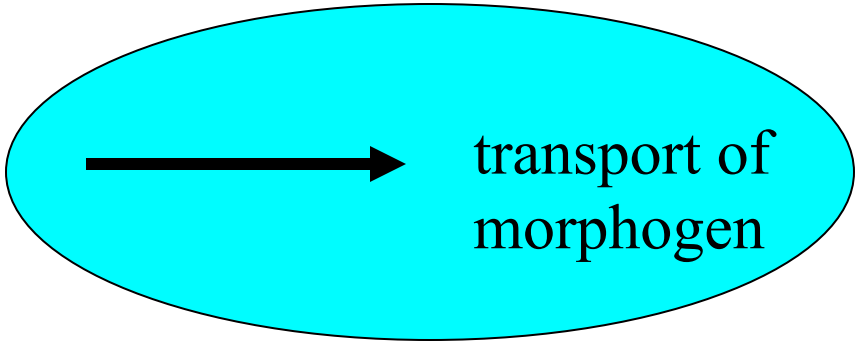
Early embryogenesis in flies and bees, compared to the wasp *Aphidius ervi*

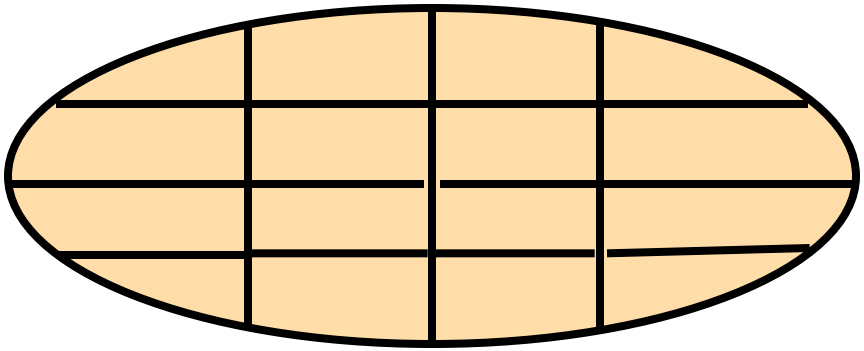




Aphidius exhibits complete cellularization, right from the get-go.

Early embryogenesis in flies and bees, compared to the wasp *Aphidius ervi*





How did complete cellularization arise, given that it would likely disrupt the ancestral pattern of morphogen transport?

How did this radically different developmental architecture evolve?

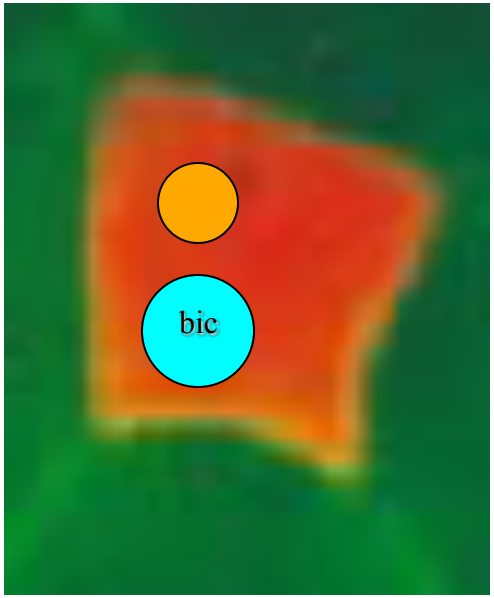
"To determine whether *A. ervi* embryos developed in a completely cellularized environment, we injected individual blastomeres with [a tracer dye]…the tracer remained only in the injected blastomeres."

(Grbic and Strand 1998, p. 1099)

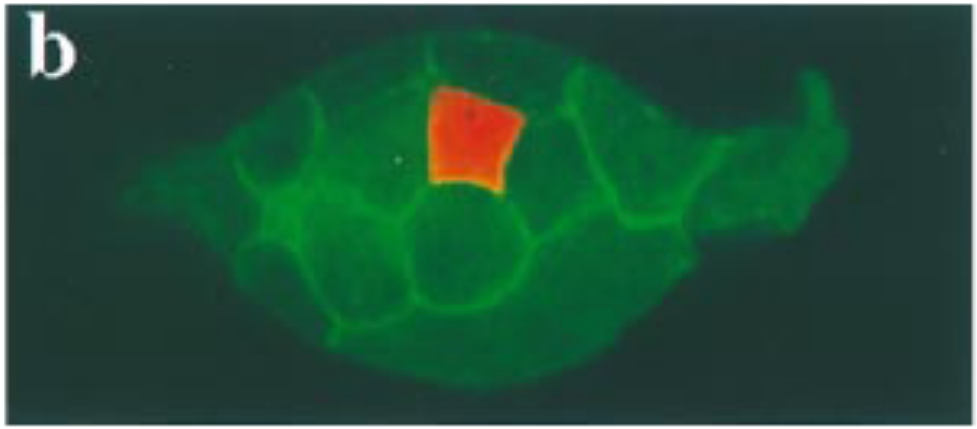
How did this radically different developmental architecture evolve?

"This indicated that early embryonic development of *A. ervi* proceeds in a cellularized environment, and that molecules larger than our tracer dye, such as transcription factors of the *Drosophila* patterning hierarchy, could not freely diffuse between cells."

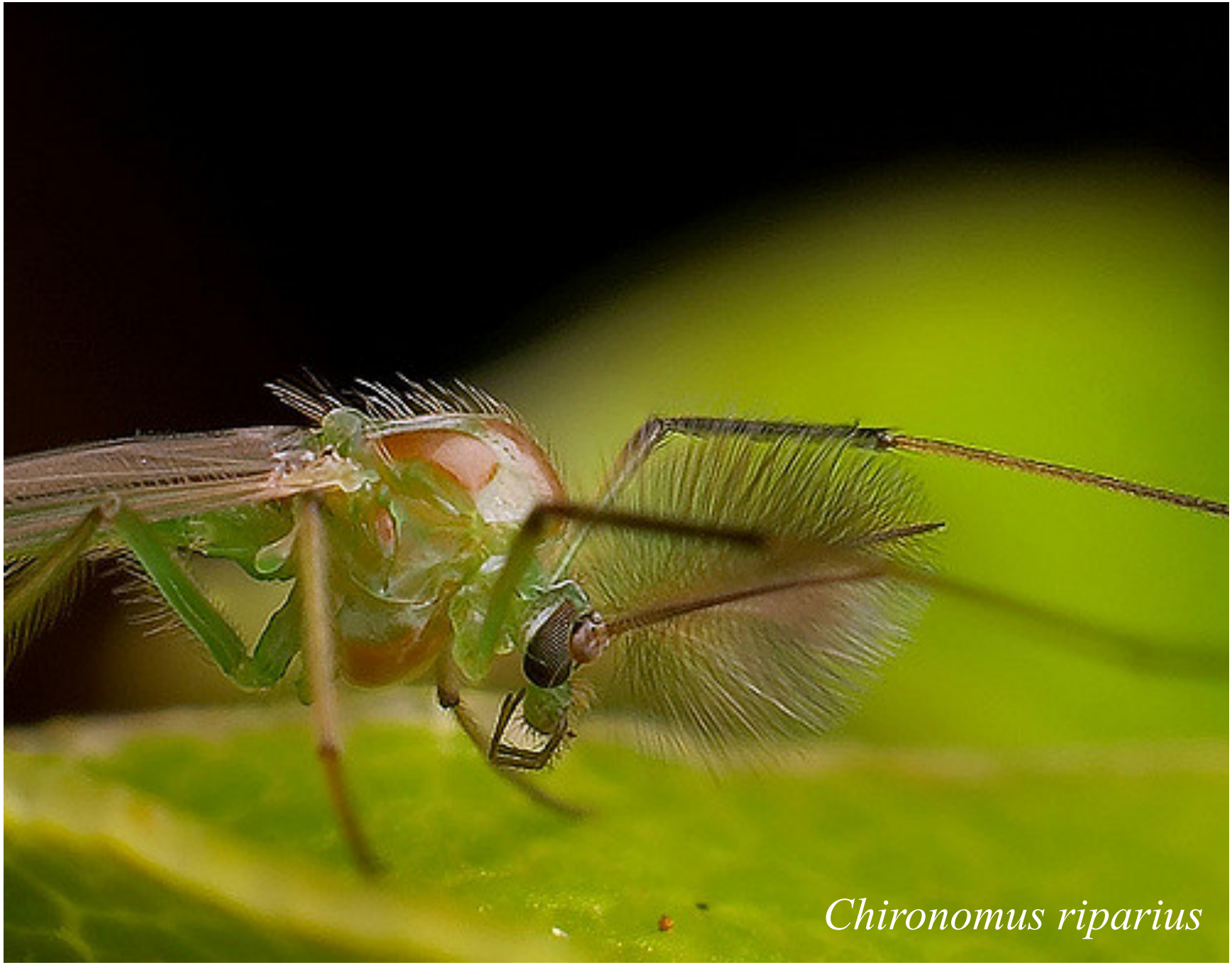
(Grbic and Strand 1998, p. 1099)



If the marker dye can't get out of the blastomere, then bicoid (larger protein) can't get out either.



This developmental architecture is *evidence* that Aphidius and Drosophila do not share a common ancestor.


Chironomus riparius

Urs Schmidt-Ott
University of Chicago

EMBRYO DEVELOPMENT

A cysteine-clamp gene drives embryo polarity in the midge *Chironomus*

Jeff Klomp,[1] Derek Athy,[1] Chun Wai Kwan,[1] Natasha I. Bloch,[1]* Thomas Sandmann,[2]† Steffen Lemke,[1]‡ Urs Schmidt-Ott[1]§

In the fruit fly *Drosophila*, head formation is driven by a single gene, *bicoid*, which generates head-to-tail polarity of the main embryonic axis. Bicoid deficiency results in embryos with tail-to-tail polarity and no head. However, most insects lack *bicoid*, and the molecular mechanism for establishing head-to-tail polarity is poorly understood. We have identified a gene that establishes head-to-tail polarity of the mosquito-like midge, *Chironomus riparius*. This gene, named *panish*, encodes a cysteine-clamp DNA binding domain and operates through a different mechanism than *bicoid.* This finding, combined with the observation that the phylogenetic distributions of *panish* and *bicoid* are limited to specific families of flies, reveals frequent evolutionary changes of body axis determinants and a remarkable opportunity to study gene regulatory network evolution.

"Our results show that *Drosophila bicoid* and *Chironomus panish* encode structurally distinct DNA binding domain proteins that play similar essential roles in establishing AP polarity of the primary axis. In each case, the protein is necessary for breaking the symmetry of the primary axis and, when inactive, results in duplication of the posterior domain. Bicoid is a transcriptional activator of anterior genes. However, Panish appears to be a repressor of posterior patterning genes." (2015, p. 1042)

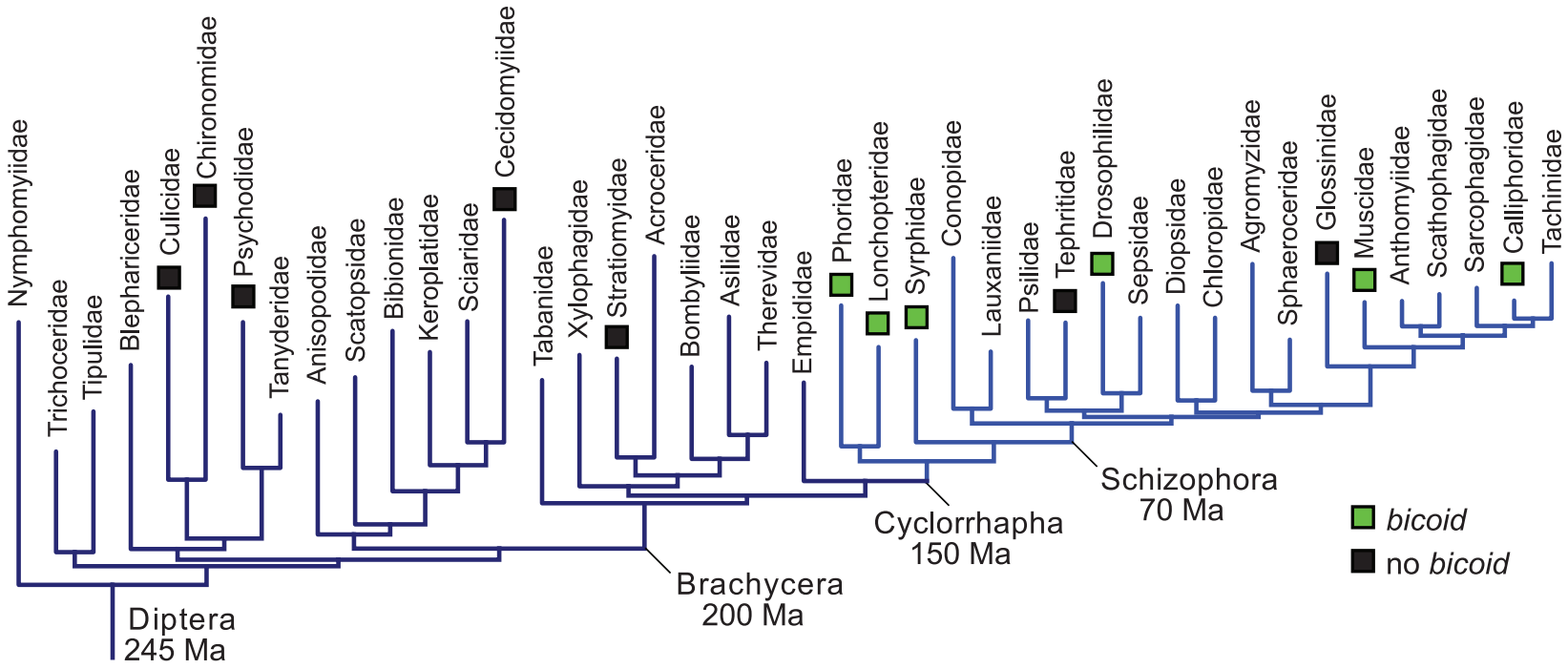


Fig. 1. *Bicoid* in dipteran families. Indicated instances of missing *bicoid* orthologs are based on genome sequences; tree is based on molecular phylogeny [see (*22*) and species list (*23*)], and cyclorrhapha clade, with *bicoid*, is indicated (light blue). Ma, millions of years ago.

Urs Schmidt-Ott
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"We did not find evidence of *panish* in other dipteran genomes, even though the locus is conserved in two closely related chironomid species, *C. tentans* and *C. piger*. This suggests a recent origin of panish."

Urs Schmidt-Ott
University of Chicago

EMBRYO DEVELOPMENT

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"Our study shows that mechanisms of AP patterning in insects are more labile than previously acknowledged."

How Common Descent generates observational predictions:

CD + knowledge of developmental constraints → prediction of embryonic conservation

Ronald Jenner: *No* observed differences can challenge Common Descent.

Natural History Museum, London

"Ever since Darwin, we have understood evolution as descent with modification. *Consequently, no degree of modification can be used as evidence against common descent.*"

(2006, 387; emphasis added)

Ronald Jenner: *No* observed differences can challenge Common Descent.

Natural History Museum, London

"Darwin made it very clear that no amount of difference between organisms due to various degrees of modification could impact our decisions about genealogy.... Unfortunately, this fact has not been internalized by all biologists."

(2006, 387)

How Common Descent generates observational predictions:

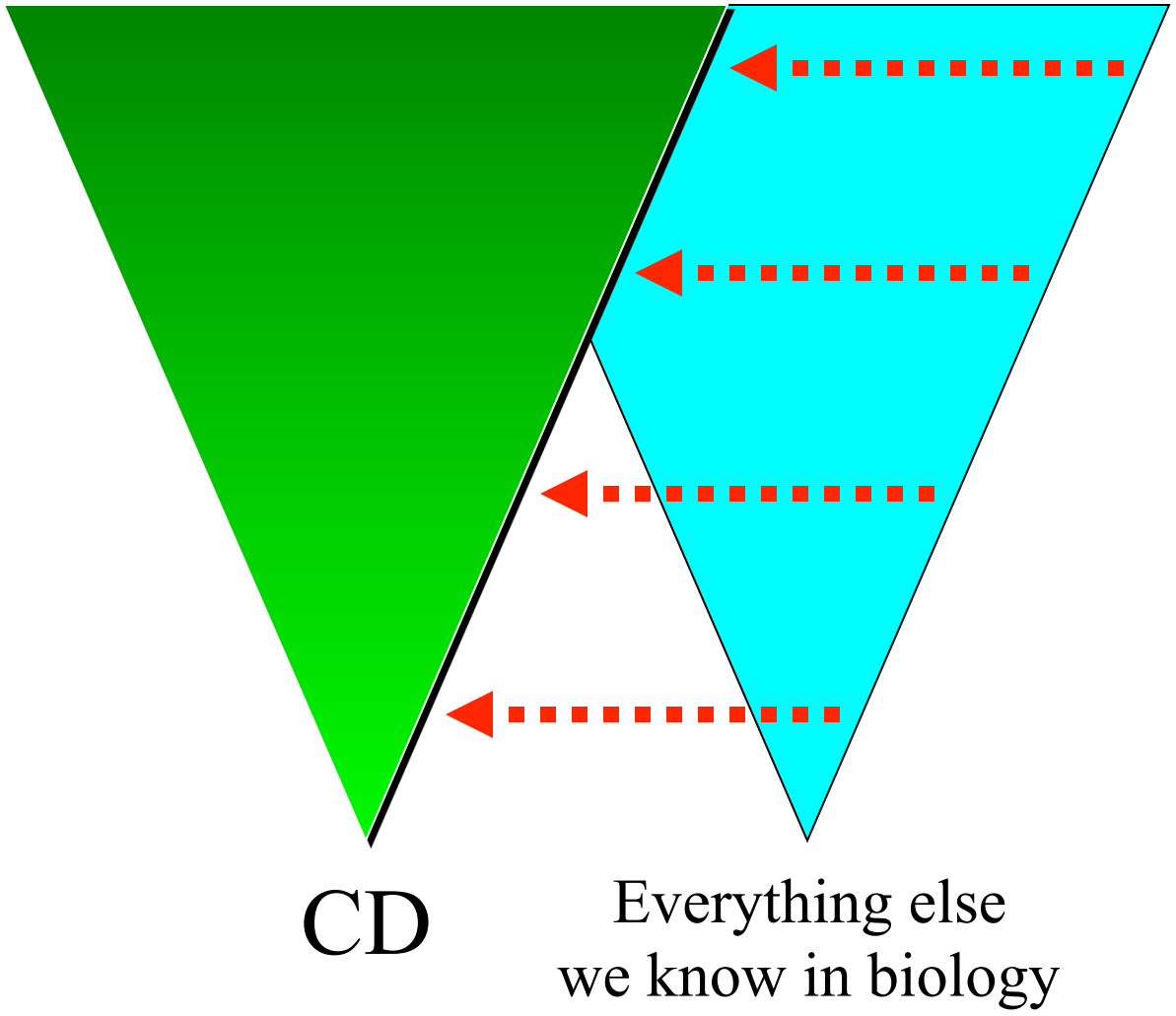
CD + the rest of our biological knowledge → predictions we can check

Let's take some wisdom from Pierre Duhem and Willard van Orman Quine:

When we confront our theories with the world – i.e., with the data – we always bring *very complex bundles* to the task, not just simple propositions.

Thus, if theories fail, it is often unclear *where the problem lies* inside our particular bundle of sub-theories and assumptions.

The problem: in practice, Common Descent is privileged over the rest of our biological knowledge.



What variation is *possible*?

So, the bottom line:

Research on evolution – done within the neo-Darwinian framework over the past 40 years – has discovered that the neo-Darwinian framework is false.

Where do we go from here?

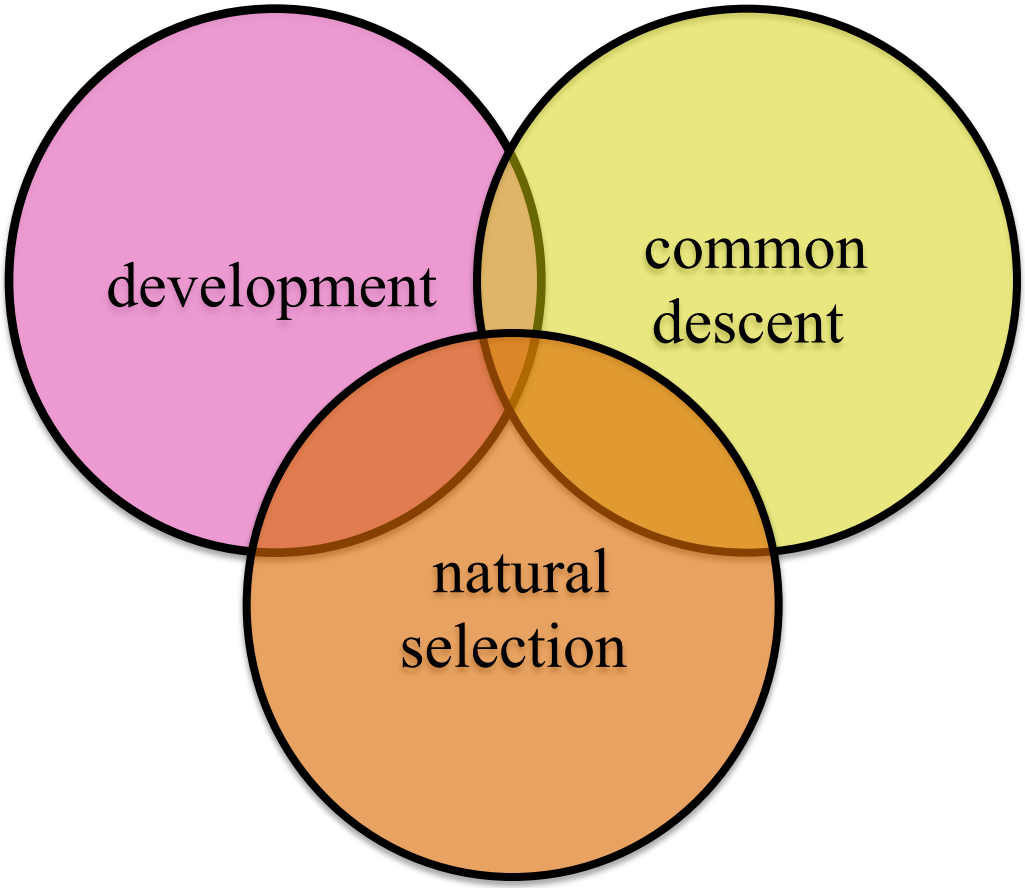
Time to segue to the philosophy of science.

What sort of cause can:

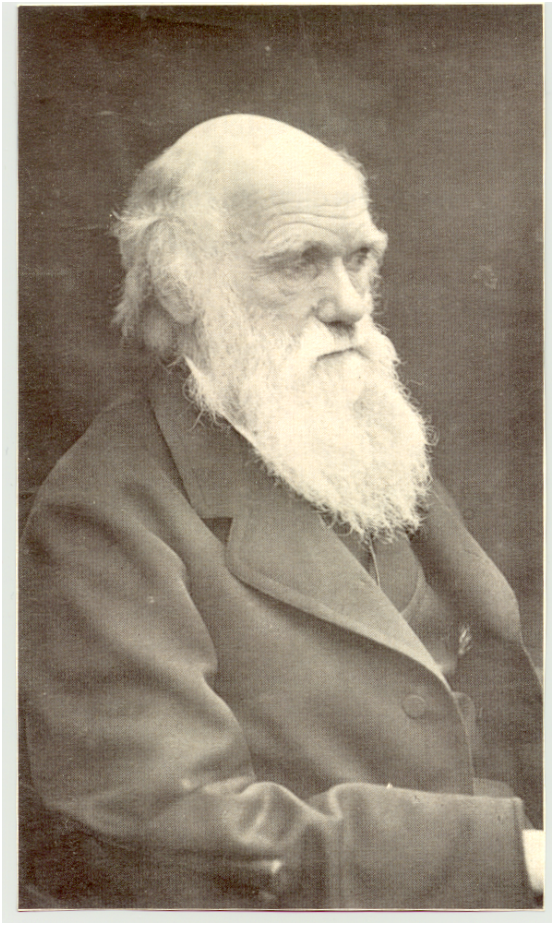
1. Aim at distant functional targets?
2. Reuse lower-level modules?
3. Establish primary discontinuities, top-down (system first, telling its parts what to do)?

Intelligence: a mind.

But here we run into a philosophical barrier from the late 19th century…



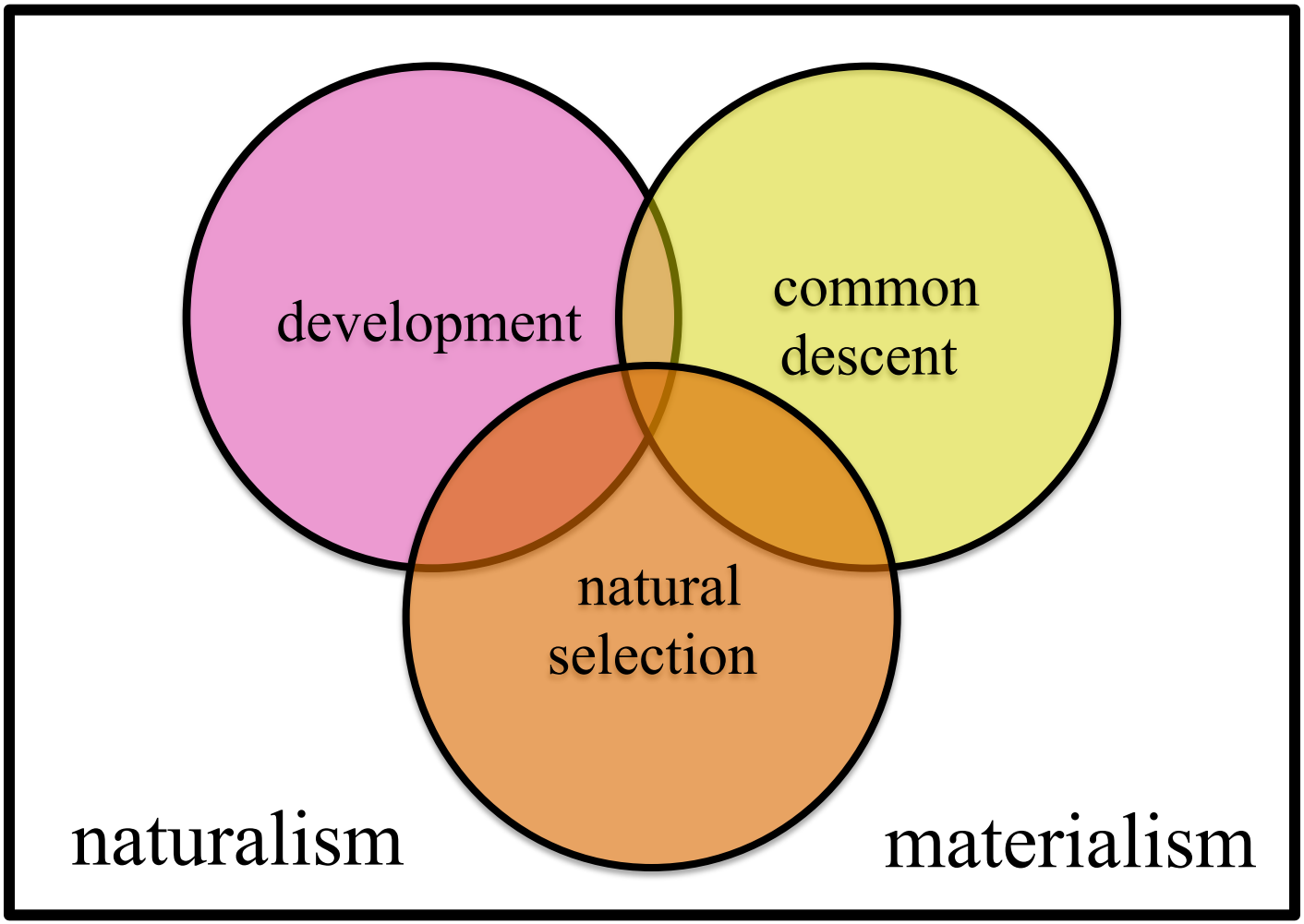
The disappearance of a possible cause



"The Darwinian revolution was as much concerned with *the promotion of a particular view of science* as it was with the introduction of a theory on the transmutation of species."

David Hull, "Darwin and the nature of science" (1983, p. 65; emphasis added)

The range of possible solutions to biological engineering puzzles is philosophically limited.

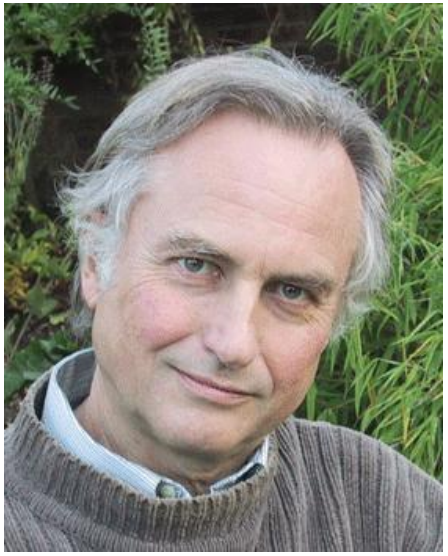


The Rule of Methodological Naturalism

"The statements of science must invoke only natural things and processes."

National Academy of Sciences
(Donald Kennedy *et al*., 1998)

Conclusion: Natural selection explains *almost nothing* about macroevolution, *for reasons having to do with the logic of selection itself*.



"The theory of natural selection provides a mechanistic, causal account of how living things came to look as if they had been designed for a purpose."

No, it doesn't. The "designed purpose" is still there, awaiting causal explanation.