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The Hegemony of Molecular Biology

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I

Dick Lewontin has probably had more influence on contemporary philosophy of biology than any other living biologist – partly because of his brilliant and wide-ranging contributions to genetics and evolutionary theory, partly because of the warmth and kindness he has extended to philosophers, and especially because of his own major philosophical contributions. For nearly two decades, my own writings have been substantially indebted to Dick's insights, and I've found myself fighting on the same side in many of the same battles. But there have been important differences. As Dick has often noted, his own opposition to various popular doctrines, especially in sociobiology and other forms of genetic determinism, has been more radical than my own. Where I have accepted the ground rules of a particular enterprise and argued that the alleged conclusions don't follow, Dick has often wanted to sweep away the enterprise as misguided. In effect, we've replayed the relationship between early twentieth century British socialists and their more revolutionary counterparts in continental Europe – my Keir Hardie to Dick's Lenin. I can think of no better way to honor his legacy to philosophy of biology than to play it again.

Although his principal concern about the contemporary practice of molecular biology has centered on ideas about genetic causation, Lewontin has a broader interest in debunking what he sees as a "Cartesian" strategy of explanation by dissection.[1] After opposing the "ideology" that we can study all the nature by breaking the world up into independent parts, and after condemning "obscurantist holism", Lewontin continues: "The problem is to construct a third view, one that sees the entire world neither as an indissoluble whole nor with the equally incorrect, but currently dominant, view that at

every level the world is made up of bits and pieces that can be isolated and that have properties that can be studied in isolation."[2] In effect, Lewontin wants to resist the hegemony of molecular biology without lapsing into mysticism. So do I. In what follows I shall try to articulate an anti-reductionist view that sees molecular studies as an important part of, but not the whole of, contemporary biology. I suspect that this view will assign molecular biology a more important role than that which Lewontin would favor.

II

Although the idea of the hegemony of molecular biology is often presented by philosophers in terms of the notion of intertheoretic reduction, a more common formulation in biology discussions would emphasize two themes.

(H1) All organisms are composed of molecules.

(H2) Real (rigorous, complete) explanations of the properties of living things trace those properties to interactions among molecules ("Life is to be explained at the molecular level").

(H1) is a truism. The real debate centers on (H2).

Proponents of (H2) envisage a reformulated biology in which the properties of organisms are described in a language that allows for application of biochemical principles to derive biological consequences. The first objection is that the envisaged derivations are unobtainable because we can't produce the appropriate language. The second is that, even if we had such derivations, they would not always be explanatory. One very obvious way to pose the first is to ask how we could ever hope to provide a biochemical explication of such notions as *species, predator,* and *ecosystem*. But the issue can be more sharply posed if we focus on what seems to be a much more promising case for the hegemonist, to wit genetics.

Consider two statements from classical genetics.

(G1) Human beings who are homozygous for the sickling allele experience crises at low levels of oxygen.

(G2) Genes on different chromosomes, or sufficiently far apart on the same chromosome, assort independently.

Hegemonists can point to (G1) as a partial success, but, as I'll argue, (G2) represents total failure.

Since the late 1940s, biologists have known how the hemoglobin transcribed and translated from the sickling allele differs from that translated

from the normal allele. Ignoring complexities of development, they can treat erythrocytes as sacs containing hemoglobin, and, using principles of chemistry, they can then show that, under conditions of low oxygen, the mutant hemoglobin would tend to clump in ways that produce the characteristic rigid crescents that give sickle-cell anemia its name. Once it's recognized that these crescents would tend to block narrow capillaries, we have an explanation for (G1). Although that explanation isn't fully molecular – recall that we've ignored the developmental process entirely and have taken a very macro-level view of the pertinent physiology – it's a start.

The envisaged explanation would start with the derivation of the normal and mutant sequences of amino acids from the specifications of DNA sequences and the genetic code. Of course, to achieve that, we only need the sequence specification of particular alleles. By contrast, when we turn to (G2), the reformulation in biochemical terms would require a specification of the general property *being a gene*. That is, what is needed is completion of the open sentence.

x is a gene if and only if *x* is ....

Now surely we know *something* about how to complete this. An important necessary condition on genes is that they be segments of DNA or RNA; but of course there are lots of segments of DNA and RNA (most of them, in fact) that are not genes. The task is thus to identify the property that distinguishes the right segments of nucleic acid from the wrong ones.

There is an important constraint on doing this, a constraint that's sometimes unrecognized. If the principles of chemistry are to be employed in deriving the reformulated biological conclusion, then we'll need a characterization of the pertinent entities – in this instance genes – that will mesh with standard ways of drawing chemical consequences. That meant that the characterization will have to be *structural*, identifying genes in terms of their constituent molecules. Hence a proposal to specify genes as functional entities, for example those nucleic acid segments that are transcribed and translated to produce polypeptides, won't serve the hegemonist's turn.[3] (I should note that this proposal is also inadequate because it wrongly excludes segments that happen to lose their regulatory regions.)

No structural specification of the general notion of a gene is currently available. That's not because the project of finding one wouldn't be important to contemporary molecular biology. On the contrary, as masses of sequence data pour in, investigators hunting for genes would welcome a systematic method of searching the long string of A's, C's, G's and T's. The best they can do is to pick out Open Reading Frames – relatively long stretches bounded by start and stop codons – treating these as candidates and then checking to see if they can discover corresponding mRNAs.

Further, as the intricacies of genomes become more evident, the possibilities of split genes, overlapping genes, truncated sequences that are still associated with regulatory regions, sequences that have lost their regulatory regions, embedded genes, and so forth make any structural and functional criteria, with ORFs coupled with functional mRNAs as the central instances and with peripheral examples settled by conventions that sometimes vary from study to study.

The first trouble with (G2) is thus that the required cross-science identifications aren't available. I'll now argue that, even if they were, a derivation of (G2) from principles of chemistry wouldn't be explanatory.

III

I'll begin indirectly with a motivational story. In 1710, John Arbuthnot, a physician, pointed out that the previous 82 year in London were all "male" – that is, in each of these years, there was a preponderance of male births in London. Publishing his finding in the *Philosophical Transactions of the Royal Society*, Arbuthnot calculated the probability that this occurred by chance, and, finding that probability to be minute, he chalked up the phenomenon to Divine Providence. Let's imagine two secular characters who try to give a better explanation.

First is the Mad Mechanist. His guiding principle is that "life is to be explained at the molecular level", and he puts this to work in offering an explanation. More exactly, he provides a recipe for an explanation, admitting that, because of his ignorance of trillions of details, he can't go further. The recipe runs as follows:

> Start with the first birth of 1628. Go back to the copulatory act that began the pregnancy resulting in this birth. Give a molecular characterization of the circumstances that preceded fertilization. From this characterization derive a conclusion about the sperm that was incorporated into the zygote. Continue with the molecular account of the course of the pregnancy and birth. You have now explained the sex of the first infant of 1628.
>
> Continue in the same fashion with the second birth, the third birth and so on. When you are done, add up the totals for both sexes. You now have a complete explanation of why 1628 was a male year.
>
> Repeat the same procedure for subsequent years until you reach 1709. Stop. You now have a complete explanation for why all 82 years are male.

Actually you don't.

To see why, consider our next character, the Sensible Sex-Ratio Theorist. She proceeds from R.A. Fisher's insight about the evolution of sex ratio.

> In species without special conditions of mating (including *Homo sapiens*) if the sex ratio at sexual maturity departs from 1:1, there will be a selective advantage to a tendency to produce members of the underrepresented sex (this will show up in terms of increased numbers of expected grand offspring). In human populations that are sufficiently large, we should thus expect the sex ratio at sexual maturity to approximate 1:1 (the more closely the larger the population; even in the seventeenth century London had a large population).
>
> If one sex is more vulnerable than the other to mortality between birth and sexual maturity, then that sex will have to be produced in grater numbers if the sex ratio at sexual maturity is to be 1:1. In human beings, males are more vulnerable to pre-pubertal death. Thus the birth sex ratio is skewed towards males.

I claim that the SST would give a better explanation than the MM, even if the latter could actually deliver the details. Part of the reason is that the SST's account shows that Arbuthnot's data are no fluke. The significant point for our purposes is that we don't need the masses of accidental molecular minutiae: we want to see how a regularity in nature is part of a broad general pattern.

A Not-So-Mad Mechanist would see the point and modify his position. Recognizing the fact that the best explanation of the phenomenon doesn't grub through the molecular details, he might ask whether there are different facets of this situation that molecular research might illuminate. Indeed there are. SST tells us why years are male (or, more exactly, likely to be male for large populations). But that leaves it open how various populations of *Homo sapiens* find their ways to (rough) equilibrium. NSMM will propose a division of explanatory labor. After SST has shown the shape of the explanation, physiologists can delve into the mechanisms of Y-biased fertilization (are Y-bearing sperm faster? are vaginal conditions more suited to the voyages of Y-bearing sperm? are there polymorphisms in human populations?), leading eventually to a molecular understanding of the most important processes. I'll return to the significance of this point below.

Now back to (G2). We can envisage a counterpart to MM, bravely trying to show how gory chemical details yield the independent assortment of genes (provided that the genes are on different chromosomes or are sufficiently far apart on the same chromosome). But there's no reason to think that these efforts would be any more illuminating than MM's. For there's also a counterpart to SST, whose explanation goes as follows.

> Consider the following kind of process, a *PS*-process (for *pairing* and *separation*). There are some basic entities which come in pairs. For each

> pair, there's a correspondence relation between the parts of one member of the pair and the parts of the other member. At the first stage of the process, the entities are placed in an *arena*. While they are in the arena, they can exchange segments, so that the parts of one member of a pair are replaced by the corresponding parts of the other member, and conversely. After exactly one round of exchanges, one and only one member of each pair is drawn from the arena and placed in the *winner's box*.
>
> In any PS-process, the chances that small segments that belong to members of different pairs or that are sufficiently far apart on members of the same pair will be found in the winner's box are independent of one another. (G2) holds because the distribution of chromosomes to gametes at meiosis is a PS-process.

This, I submit, is a full explanation of (G2), an explanation that prescinds entirely from the stuff that genes are made of. Understanding the probabilistic regularities that govern the transmission of genes is a matter of seeing that transmission is a PS-process, and it's irrelevant whether the genes are made of nucleic acid or of swiss cheese.

The conclusion we ought to draw is that some important biological regularities cannot be captured in the language of molecular biology – or, more strictly, in a molecular biological language that restricts itself to structural notions[4] – and that these regularities are fully explained without grinding out molecular detail. An enlightened hegemonist ought to appreciate the point, recognizing the need to absorb functional concepts, and claims involving those concepts, from traditional areas of biology. EH will insist, however, that there are important molecular issues about the functionally characterized regularities – question concerning the mechanisms of Y-biased fertilization or the molecular underpinnings of the pairing of homologous chromosomes at meiosis. That point, I'll argue later, is correct. If EH is ambitious, however, there may be a further proposal: Although it is right for molecular biology to absorb functional insights from the classical areas of biology, further investigations in these areas are unnecessary; from now on, molecular biology is all the new biology we need. I now want to suggest that we ought to resist such hegemonist yearnings.

IV

In 1917, D'Arcy Wentworth Thompson published a remarkable book. Like Tom Stoppard's Lady Thomasina, Thompson yearned for the mathematics of the animate world.[5] In recent years, mathematical biologists have begun to realize Thompson's program, and the result, I'll suggest, is a view of devel-

opmental biology that both assigns an important place to molecular studies and deepens the challenge to the hegemony of molecular biology.

For present purposes we'll only need to consider the most elementary parts of a few major approaches, and I want to emphasize that the simple models I'll describe are elaborated in much more subtle versions. I begin with the use of *Lindenmeyer systems* – L-systems – to characterize the growth of plants. A *string OL-system* is a triple <*V, I, P*> where *V* is a vocabulary, *I* is an initial string, and *P* is a set of production rules. A *developmental sequence* in an OL-system is a sequence of strings whose first member is the initial string and such that the *n*+1st member is obtained from the *n*th member by applying all the production rules that can be applied to the *n*th string. So, for example, consider the L-system

I: a_r
P_1: $a_r \rightarrow a_l b_r$
P_2: $a_l \rightarrow b_l a_r$
P_3: $b_r \rightarrow a_r$
P_4: $b_l \rightarrow a_l$

Within this system, we can obtain the following developmental sequence:

a_r
$a_l b_r$
$b_l a_r a_r$
$a_l a_l b_r a_l b_r$
$b_l a_r b_l a_r a_r b_l a_r a_r$
. . .

This formalism can be used to model the development of a multicellular filament found in the blue-green bacteria *Anabaena catenula* (the *a*s and *b*s represent different types of cell and the suffixes show the polarity; see Figure 1).[6]

In general, L-systems model the development of plants by supposing that there are elementary biological processes that are applied recursively to certain kinds of structures: intuitively, in a growing plant, a particular kind of structure gives way to a different kind of structure, and the process of replacement is represented by a production rule. Note that this treats the development of plants in an extremely abstract way, prescinding from the details of the types of processes involved. Thus the growth of two quite different plants could be represented by the same L-system, if in the one

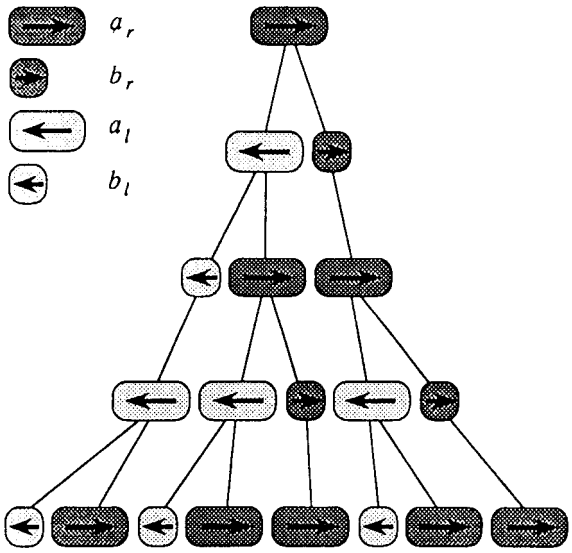

Figure 1. Development of a filament (*Anabaena catenula*) simulated using a DOL-system (From A. Lindenmayer and P. Prusinkiewicz *The Algorithmic Beauty of Plants*).

instance a production rule called for the replacement of a particular kind of nodal cell with a branch and in the other it specified that a very different type of cell should be surrounded by a specific geometrical cluster of certain kinds of cells.

For a less abstract treatment of issues in development, we can turn to the mathematics of diffusion equations. Inspired by work of Alan Turing,[7] a number of biologists have explored the possibility that various kinds of patterns could be generated through "activator-inhibitor" systems. Basic to this approach is the thought that a cell might start to produce greater concentrations of a particular molecule, that this molecule could then diffuse into adjacent cells, with the activation and diffusion prompting the production of an inhibitor. In the boring case, an entire tissue of cells reaches a uniform steady state. Much more interesting is the possibility that a local departure from uniformity gives rise to a stable pattern.

Once again, I'll focus on the very simplest system. We imagine an interaction among two molecules, the activator (whose concentration is a) and the inhibitor (whose concentration is b). The inhibitor is assumed to diffuse much more rapidly than the activator and also to reach equilibrium almost instantaneously. The concentrations are governed by the differential equations:

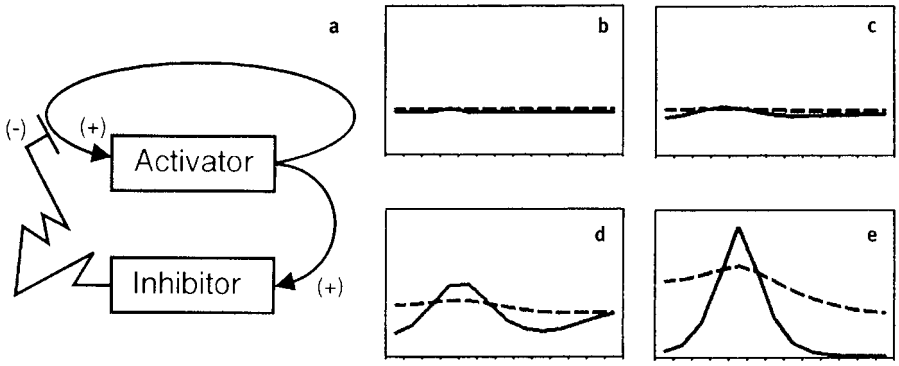

Figure 2. Pattern formation by autocatalysis and long-range inhibition. (a) Reaction scheme. An activator catalyses its own production and that of its highly diffusing antagonist, the inhibitor. (b–e) Stages in pattern formation after a local perturbation. Computer simulation in a linear array of cells. A homogeneous distribution of both substances is unstable. A minute local increase of the activator (——) grows further until a steady state is reached in which self-activation and the surrounding cloud of inhibitor (- - - -) are balanced [S22] (From H. Meinhardt *The Algorithmic Beauty of Sea Shells*).

$$\partial a/\partial t = a^2 - a$$
$$\partial b/\partial t = a^2 - b.$$

It's not hard to see that there's a steady state at $a = b = 1$. It's possible to generate a pattern, however, if one cell in an array has a slightly increased activator concentration. Because of the assumption that the inhibitor diffuses rapidly, it responds to the average concentration of the activator, and thus remains virtually constant. Hence the activator will continue to increase (since, by the first equation, the time-derivative of its concentration will be positive). Once the increase becomes sufficiently large, there will be an effect on the average sufficient to produce inhibitor to stop the process. We thus obtain a steady state with a locally high concentration of activator and relatively elevated levels of inhibitor elsewhere (see Figure 2).[8]

Suppose, then, that the growth of sea shells is a process in which concentrations of activator molecules and of inhibitor molecules are governed by a coupled set of partial differential equations that allow for non-trivial steady states. If the difference between these concentrations is associated with pigmentation (or possibly with differentially directed cell growth and division), then it is possible to understand how patterns of various kinds emerge. Hans Meinhardt has explored a wide range of growth processes, showing how the patterns found in a diverse class of sea-shells can be generated from particular sets of equations. His analysis, while less abstract than the Lindenmayer-Prusinkiewicz treatment of plants, continues to prescind from

the molecular details. Two shells might result from the same growth process – accretion of new material at the margin – and might conform to the same set of differential equations, even though the molecules that play the roles of activator and inhibitor are different in the two cases. It might even turn out that, in the one instance, the relationship between the molecules produces a pigmented pattern while, in the other, that relationship yields a pattern of relief (ridges and valleys on the shell surface).

My last example inches further in the direction of diminished abstraction. Meinhardt's attempt to find a general set of models for shell pattern ranges more widely than an endeavor of James D. Murray to explain the diversity of mammalian coat patterns.[9] Following Turing, Murray considers a reaction diffusion system governed by the following equations:

$$\partial u/\partial t = \gamma f(u, v) + \nabla^2 u, \qquad \partial v/\partial t = \gamma g(u, v) + d\nabla^2 v$$
$$f(u, v) = a - u - h(u, v), \qquad g(u, v) = \alpha(b - v) - h(u, v)$$
$$h(u, v) = \rho uv/(1 + u + Ku^2)$$

Here u and v are molecular concentrations, a, b, d and γ are dimensionless parameters, d being the ratio of diffusion coefficients and γ a scaling parameter (γ varies as the area of the surface on which the pattern is being laid down).[10] Murray shows that, when $d > 1$, processes conforming to these equations can give rise to spatially inhomogeneous patterns. Whether such a pattern occurs, and what form it takes, depends on the value of γ. As this value increase, the character of the pigmentation pattern changes from uniform to bicolored to blotched to striped to spotted (see Figure 3).

It's now possible to arrive at a clever "theorem". Assume that mammalian coat markings are generated from reactions among chemicals that satisfy the given system of equations. For a given value of $d > 1$, provided that it allows for both striped and spotted patterns, there'll be a threshold γ^*, such that, for $\gamma \geq \gamma^*$, the resultant pattern will be spotted, and for $\gamma < \gamma^*$, the pattern will be striped. The value of γ for an animal body will always be greater than the value for that animal's tails (bodies are always bigger in area than tails). Hence it can't happen that the value for the tail lies above the threshold and the value for the body below the threshold. In other words we have the "theorem":

> Although there can be spotted animals with striped tails, there can't be striped animals with spotted tails.

Murray's model of mammalian coat patterns thus explains a regularity we find in nature.

Consider now three different proposals for research in developmental biology. The first, the original hegemonist position, suggests that studies of

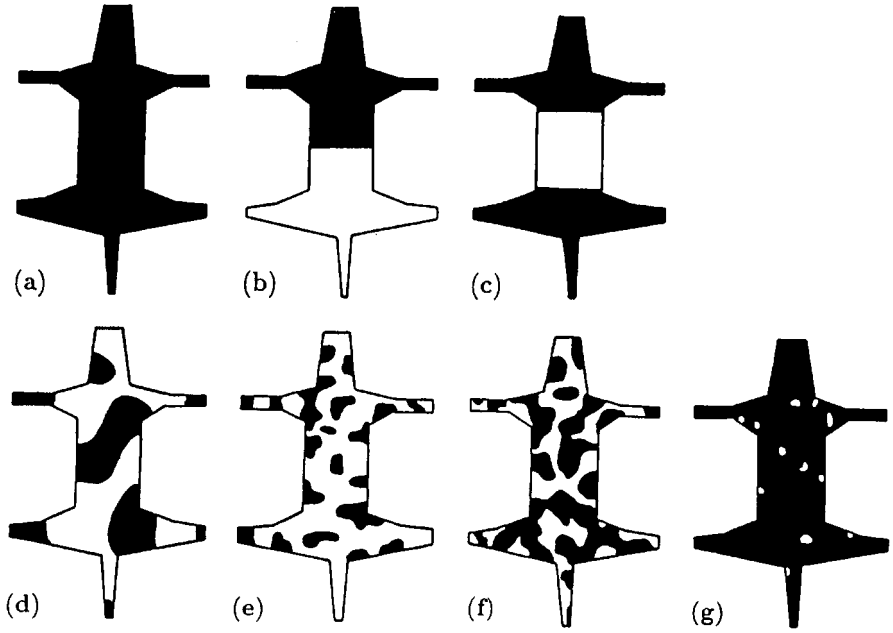

Figure 3. Effect of body surface scale on the spatial patterns formed by the reaction diffusion mechanism (Mammalian Coat Patterns – 'How the Leopard Got its Spots') with parameter values $\alpha = 1.5$, $K = 0.125$, $\rho = 13$, $a = 103$, $b = 77$ (steady state $u_s = 23$, $v_s = 24$), $d = 7$. Domain dimension is related directly to γ. (a) $\gamma < 0.1$; (b) $\gamma = 0.5$; (c) $\gamma = 25$; (d) $\gamma = 250$; (e) $\gamma = 1250$; (f) $\gamma = 3000$; (g) $\gamma = 5000$ (From Murray 1980, 1981a) (From J. D. Murray *Mathematical Biology*).

organismic development are best pursued by starting with a complete understanding of the genetics, continuing with an investigation of the ways in which different genes are activated and suppressed, and, on this basis, exploring the molecular bases of cellular differentiation. In light of the considerations raised in earlier sections, hegemonists may concede the need for supplementing the "bottom up" analyses with functional concepts drawn from classical physiology (and other traditional disciplines), but see no reason for further functional analyses that do not attend to the molecular details. The examples I've chosen from the mathematical study of development are intended to show that this concession is too limited. A third, and more enlightened, approach would view the mathematical and molecular programs as working in tandem.

At the most concrete level of mathematical analysis, theorists may try to formulate differential equations that govern the interactions of molecules whose identities they don't know, seeking in this way to understand a general pattern of development in some group of organisms – as in Murray's treat-

ment of mammalian coat patterns, with its pretty result about spots and stripes. Their research then poses the problem of trying to find the hypothetical molecules, and, quite possibly, of rebuilding the model to accommodate the complexities that emerge.

Above this is a level of analysis represented by Meinhardt's work on sea shells, where the emphasis is on a family of related models. Here theorists attempt to discover more general regularities, consisting in conformity to a family of sets of differential equations. For this enterprise to succeed it will be important to show how particular phenomena in particular organisms are governed by particular members of the family, and, in consequence, to supplement the mathematical details with the identification of the pertinent molecules.

Even more abstract is a style of anlaysis that focuses on formal features of growth without reference to a specific interpretation of the biological processes represented by formal transformation, and without specification of equations that are to be satisfied. The study of plant growth in terms of Lindenmayer systems allows for various physiological "readings" of the production rules, interpretations that might be given in terms of macroscopic plant physiology, in terms of some mathematically characterized process, or in terms of molecular interactions. It's easy to see how there could be a nested sequence of abstract accounts, subsumed at the most formal level in claims about L-systems, with intermediate levels of mathematical biology that eventually are instantiated in detailed studies of heterogeneous molecules in very different organisms.

If the hegemonist's likely mistake consists in the loss of understanding through immersion in detail, with concomitant failure to represent general regularities that are important to "growth and form", the mathematical analyst can easily lose touch with the biological realities. Hegemonic grumbling about the ease with which one can make up pleasing mathematical models is unfair – it isn't so easy – but it has a point. The multi-levelled picture of theorizing about development that I have recommended needs its molecular base. To admit that is to recognize that the questions about individual mechanisms that excite molecular biologists (partly, of course, because they have powerful tools for addressing them)[11] are important, both for their confirmation of the more abstract models and for their uncovering of constraints on model-building. The mistake is to think that these are the *only* important questions, that once we have PCR there is no further need of classical "whole organism" biology. D'Arcy Thompson's vision should be integrated with the achievements and programs of contemporary molecular biology to generate a multi-levelled study of development.

V

I return, in conclusion, to Lewontin's concerns about the hegemony of molecular biology, expressed in his critique of the "Dream of the Human Genome".[12] Because of much of the propaganda that has surrounded it, the Human Genome Project has become a symbol of the hegemony of molecular biology. In part, Lewontin's critique focuses on different questions from those that have concerned me here. He sees, quite correctly, that the basis on which the HGP was advertised consists of a dubious set of claims about the causal roles of genes and about the existence of a royal road to a future molecular medicine of enormous power. There's no reason to believe that, when we've mapped and sequenced the human genome, we will "understand who we are".[13] Similarly, merely knowing the sequences of lots of human genes isn't going to tell us very much directly, given the difficulties of the protein-folding problem, the uncertainties of methods of tracing protein function, our ignorance of developmental pathways, and so forth. The immediate biomedical upshot of the HGP well be an enormously enhanced ability to give genetic tests, and both Lewontin and I have doubts about whether this is likely to be socially beneficial. Even if it is in principle possible to apply the new means of testing to promote the welfare of citizens (as I have argued at some length), it is becoming depressingly clear that the needed safeguards are not likely to be in place by the time the technologies flood the marketplace.[14]

But I want to distinguish the status of the HGP as part of a sociomedical agenda from its role in contemporary biological research. Lewontin's critique, and the kindred remarks of historians and philosophers of biology,[15] convey the message that the HGP is biologically misguided, either because the mass of sequence data it will generate is useless or because it is inextricably entwined with a reductionistic research program. These reactions reflect a disposition to accept the propaganda for the HGP at face value. It is quite right to point out that there is nothing biologically special about the genome of our own species and to question the hegemonist suggestion that we can proceed from knowledge of sequence data to knowledge of genes and thence to all manner of biological understandings. Yet the research actually conducted under the auspices of the HGP fully absorbs these points.

From a biological point of view, the most important work being conducted with HGP funding (or the parallel research carried out with private support, most notably that of Craig Venter and his colleagues) consists in fine-grained mapping and sequencing of non-human organisms, from bacteria to yeast, to nematode worms and, still in progress, flies. The fruits of this research are likely to make any number of research projects in physiology and developmental biology enormously easier in coming decades (as well as paving the

way for evolutionary insights obtained from comparisons of the genomes of closely related species). Specifically, molecular biologists working on *Caenorhabditis elegans*, *Drosophila melanogaster* and *Dictyostelium discoideum* already envisage the possibility of identifying major developmental pathways, possibly pathways that have been highly conserved in the evolutionary process. There's no automatic route to picking out such pathways but the ability to discover which genes are activated in which cells (which will flow from complete genome sequencing) is likely to offer important clues.

There should be no illusions that this molecular work can proceed by ignoring macro-level studies of development and physiology. On the contrary, the full exploitation of the sequence data generated by the genome project will require just the kinds of functional studies – including mathematical modelling – that I have emphasized throughout this essay.[16] Critics of the HGP may be correct in thinking that the current balance of research in biology has tipped too far towards this particular molecular endeavor, that it is not the *only* project of biological value. It is wrong, however, to overstate the claim by taking the project to be devoid of biological significance and to accuse it of commitment to the hegemonist manifesto. Provided we have a rich enough repertoire of visions, the dream of (say) the fruitfly genome is a dream worth having.

Notes

[1] This opposition is evident in many of the contributions to *The Dialectical Biologist* (Harvard, 1986), a volume of essays, some of which are by Lewontin alone, some by his colleague Richard Levins, and some that are jointly written. The attack on genetic determinism also permeates this volume, as well as surfacing in *Not In Our Genes* (written with Leon Kamin and Steven Rose; New York: Pantheon, 1984) and the more recent *Biology as Ideology* (New York: Harper, 1992). I discuss the varieties of Lewontin's critique of genetic determinism in "Battling the Undead: How (and How Not) to Resist Genetic Determinism", forthcoming in a *Festschrift* for Dick Lewontin; that essay should be seen as a companion piece to my efforts here.

[2] *Biology as Ideology*, p. 15.

[3] This problem affects the suggestion made in a provocative essay by C. Kenneth Waters "Genes Made Molecular", *Philosophy of Science*, 61, 1994, 163–185.

[4] In fact, contemporary molecular biology is permeated by language that can't be replaced with an austere physico-chemical idiom. Consider the standard account of transcription. One talks of RNA polymerases "associating" with DNA. The suggestion, of course, is that the RNA polymerases come close – but how close is close enough? Well, that's going to depend on the conformation of the DNA, and there's no general structural criterion. In effect, molecular biologists, here and elsewhere, quietly take over functional concepts. This moved Sylvia Culp and me to suggest that molecular biology turns out not to be reducible to molecular biology (see our "Theory Structure and Theory Change in Contemporary Molecular Biology, *British Journal for the Philosophy of Science*, 40, 1989, 459–483).

[5] D'Arcy Thompson On *Growth and Form*, Cambridge University Press, 1917; an abridged version, edited by the distinguished developmental biologist John Tyler Bonner was published by Cambridge University Press in 1961. Thompson's wish for a mathematical account of development and morphology is echoed in several speeches by the heroine of Stoppard's *Arcadia*.

[6] This example is used as the first (simplest) illustration by Przemyslaw Prusinkiewicz and Aristid Lindenmayer in their book *The Algorithmic Beauty of Plants* (New York: Springer, 1990). The example comes from p. 5 (I have slightly modified the notation). As Prusinkiewicz and Lindenmayer note, L-systems are related to Chomskyan grammars. Subsequent examples reveal the possibilities of far more complex relations between symbols and biological entities (particularly through processes that draw out shapes dependent on the symbols), context-dependence, three-dimensionality, probabilistic systems and so forth. The resultant systems can simulate the growth of flowers and trees, generate the Fibonacci spirals found in sunflowers, and model compound leaves, among other achievements.

[7] Specifically a paper, "The Chemical Basis of Morphogenesis" (*Philosophical Transactions of the Royal Society*, B, 237, 1952, 37–72). This essay was written shortly before Turing's tragic suicide. It is interesting to ponder whether, if he had lived, the pace of work in mathematical developmental biology would have accelerated, producing a very different distribution of work in the current field.

[8] This extremely elementary example is from Hans Meinhardt *The Algorithmic Beauty of Sea Shells* (New York: Springer, 1998). As Meinhardt shows, much more complex sets of partial differential equations give rise to a wide variety of patterns, including the elaborate branching and meshwork found in some shells. The case in the text is the foundation of a system that will yield regular stripes.

[9] In fact, Murray has a very broad program of trying to understand pattern-formation, but I'll only consider one aspect of it here. The discussion is drawn from Chapter 15 of J.D. Murray *Mathematical Biology* (New York: Springer, 1989), although the essentials were already given in Murray's "On Pattern Formation Mechanisms for Lepidopteran Wing Patterns and Mammalian Coat Markings", *Philosophical Transactions of the Royal Society*, B, 295, 1961, 473–496. Murray provided an accessible overview in "How the Leopard Gets its Spots", *Scientific American*, 258, 1988, 80–87.

[10] Murray provides a lucid discussion of these equations in Chapter 14 of *Mathematical Biology*. He notes there that the equations describe the chemical kinetics of a substrate-inhibition system, which has been studied experimentally. Real instantiations of the system are thus known.

[11] As in other parts of science, techniques in molecular biology have a life of their own, sometimes inspiring people to pursue questions because they can be addressed. For an illuminating study of the ways in which instruments and experimental skills possess an inertia that shapes the course of research, see Peter Galison's *Image and Logic* (University of Chicago Press, 1998) which pursues this theme in the context of particle physics.

[12] Originally published in the *New York Review of Books*, and reprinted in *Biology* as *Ideology*.

[13] Lewontin's attacks on this specific form of genetic determinism are quite devastating. I've tried to argue similar points in *The Lives to Come* (New York: Simon & Schuster, 1996) especially Chapter 11. In general, however, my critique of genetic determinism differs from that which has featured most prominently in Lewontin's recent writings. See my essay "Battling the Undead" (cited in note 2 above).

[14] I argued for the in principle possibility in *The Lives to Come*. Since I finished writing that book, there has been virtually no progress in addressing the problems of the proliferation of

genetic tests, not only in the United States, but also in other affluent nations. Of course, the United States is especially backward because of its notable lack of commitment to universal health care coverage. My current position is thus much closer to Lewontin's pessimistic view of the likely social effects of the HGP.

[15] See, for example, Alexander Rosenberg "Subversive Reflections on the Human Genome Project", *PSA 1994* (East Lansing: Philosophy of Science Association, 1995), Volume II, 329–335 and A. Tauber and S. Sarkar "The Human Genome Project: Has Blind Reductionism Gone Too Far?", *Perspectives in Biology and Medicine*, 35, 1992, 22–235.

[16] In a forthcoming essay, Kenneth Schaffner argues for similar themes. Schaffner's lucid analysis of investigations of behavioral genetics in the nematode *C. elegans* reveals exactly the need for multi-levelled studies that I've been emphasizing. It seems to me also to show the fruitful possibilities of combining molecular work with mathematical studies of the properties of networks. Interestingly, the same cross-fertilization of intellectual disciplines is already envisaged in work on the development of the soil ameba *Dictyostelium discoideum* (in the work of William Loomis and his colleagues).