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## Physics in Biology—Has D’Arcy Thompson Been Vindicated?

EVELYN FOX KELLER

One hundred years ago, D’Arcy W. Thompson began the first edition of *On Growth and Form* [1] with a claim that, to us at least, seems impossible to refute: “In general no organic forms exist save such as are in conformity with physical and mathematical laws.”

But he also claimed that, “of the construction and growth and working of the body, as of all that is of the earth earthy, physical science is, in my humble opinion, our only teacher and guide.”

And on that little word *only*, he was insistent, even while being abundantly aware that he was bucking a well-established tradition in biology. Indeed, even his contemporary, and enthusiastic reviewer, J. Arthur Thomson, demurred, suggesting that “it will be difficult to justify the word ‘only’” [2].

But the word was important to Thompson, for it was precisely the tradition of insisting that there was “something more” to biology—something that neither physics nor mathematics could explain—that was his target. Thompson was no vitalist. And if we want to understand why readers have been tempted to say (as his reviewer suggested they would), “magnificent, but not biology”—we need to ask, what exactly do we mean by the term “biology”?

Indeed, the problem arises with the very introduction of a new term, a term coined to designate the study of life as a distinctive endeavor. J.-B. Lamarck, writing at the beginning of the 19th century, was one of the first, and certainly most influential, to use the term. He defined biology as a subdivision of “terrestrial physics,” one that included “all which pertains to living bodies” [3]. Yet, despite explicitly placing the new subject under the rubric of terrestrial physics, and despite devoting the bulk of his *Philosophie Zoologique* (1809) to “an enquiry into the physical causes which give rise to the phenomena of life,” he was also committed to the need for a separation between the subdivisions. “Between crude or inorganic bodies and living bodies,” he wrote, “there exists an immense difference, a great hiatus, in short, a radical distinction such that no inorganic body whatever can even be approached by the simplest of living bodies.” Lamarck, it seems, was of two minds: on the one hand he vehemently rejected the evocation of extranatural causes: “Nature,” he wrote, “has no need for special laws, those which generally control all bodies are perfectly sufficient for the purpose.” Yet, he continued, “if we wish to arrive at a real knowledge of... what are the causes and laws which control so wonderful a natural phenomenon, and how life itself can originate those numerous and astonishing phenomena exhibited by living bodies, we must above all pay very close attention to the differences existing between inorganic and living bodies.”

Thompson, while sharing many of Lamarck’s concerns, sought understanding of biological

form by focusing not on the differences but on the similarities between inorganic and living bodies; and in doing so, he surely incurred the wrath of those invested in the inviolability of the gap between the two domains. One might read Lamarck as offering something of a comfort zone in which vitalists could hide (as many surely did). Thompson, however, did not allow his readers such a luxury. Faced with the choice between vitalism and mechanism, his answer was unambiguous. Mechanism could be his only guide.

But in any case, by the time Thompson embarked on his magnum opus, vitalism was already on the rout. Other debates (e.g., debates over the place of final vs. efficient causation; preformation vs. epigenesis)—closely related debates that were of even longer standing—surely continued to divide biological scientists, and on these divides Thompson also held strong views. But I suspect that none of them carried quite the same sense of mutual exclusion as did attitudes, often expressed in the 20th century, concerning the relation between biological and physical science. And this development, I want to argue, was a byproduct of the emergence in the 20th century of a new science of genetics, a science that was to reconfigure radically the entire landscape of biology.

William Bateson coined the term “genetics” in 1905 to refer to the study of inheritance and the science of variation, but the term does not appear in the 1917 edition of *On Growth and Form*. Thompson does refer to certain precursors of genetics, however, especially to Darwin’s theory of pangenesis, and in rather scathing terms. For example, he writes,

[I]n all such hypotheses as that of “pangenesism,” in all the theories which attribute specific properties to micellae, idioplasts, ids, or other constituent particles of protoplasm or the cell, we are apt to fall into the error of attributing to matter what is due to energy and is manifested in force. [1]

Indeed, he is utterly dismissive of all efforts to locate the roots of morphogenesis in the structures of the germ cell. He wrote,

In an earlier age, men sought for the visible embryo, even for the homunculus, within the reproductive cells; and to this day, we scrutinize these cells for visible structure, unable to free ourselves from that old doctrine of “pre-formation.

This dismissal seemed to include all those (and perhaps August Weismann especially) who “speak of a ‘hereditary substance,’ a substance which is split off from the parent-body, and which hands on to the new generation the characteristics of the old, we can only justify our mode of speech by the assumption that that particular portion of matter is the essential vehicle of a

particular charge or distribution of energy, in which is involved the capability of producing motion, or of doing ‘work.’”

But as Newton said, to tell us that a thing “is endowed with an occult specific quality, by which it acts and produces manifest effects, is to tell us nothing.”

Clearly, Thompson had little interest in such arguments. Indeed, in a debate with J. S. Haldane before the Aristotelian Society, he went so far as to acknowledge that “I for my part look forward, in faith and hope, to the ultimate reduction of the phenomena of heredity to much simpler categories, to explanations based on mechanical lines... that the special science which deals with it has at least found, in Mendel, its Kepler, and only waits for its Newton” [4].

Twenty-five years later, however, the successes of genetics could no longer be ignored. And in his second edition, Thompson acknowledges that “The efforts to explain ‘heredity’ by the help of ‘genes’ and chromosomes, which have grown up in the hands of Morgan and others since this book was first written, stand by themselves in a category which is all their own and constitute a science which is justified of itself” [5]. But he himself is still not much interested. “To weigh or criticize these explanations,” he continues, “would lie outside my purpose, even were I fitted to attempt the task... I leave this great subject on one side not because I doubt for a moment the facts nor dispute the hypotheses nor decry the importance of one or other; but because we are so much in the dark as to the mysterious field of force in which the chromosomes lie, far from the visible horizon of physical science, that the matter lies (for the present) beyond the range of problems which this book professes to discuss, and the trend of reasoning which it endeavors to maintain.”

So what has changed between the two editions? Clearly, Thompson’s focus on the physical forces involved in morphogenesis has not changed.

However great the successes of genetics, and however useful its focus on genes and chromosomes may have been in explaining heredity, Thompson has little confidence that it will prove useful for understanding the problems of morphology. Indeed, he warns the reader, “To look on the hereditary or evolutionary factor as the guiding principle in morphology is to give to that science a one-sided and fallacious simplicity.” The path he chooses is thus “to leave this great subject to one side,... to rule ‘heredity’ or any such concept out of our present account.” Perhaps the most conspicuous illustration of this decision is seen in his discussion of the differences between smooth and wrinkled peas. Here, he saw no need to invoke Mendelian factors; instead, he wrote, “The difference between a smooth and a wrinkled pea, familiar to Mendelians, merely depends, somehow, on amount and rate of shrinkage.”

But if Thompson was not impressed by the achievements of genetics, neither were geneticists impressed by his own contributions. As the cell biologist, J. W. Wilson, remarked in his review of the 1942 edition:

The ideas of *On Growth and Form* have played little part in the spectacular advances of biology since the book was first written. For this I think there is a very good reason: the point of view which the book represents is out of fashion, and is indeed the antithesis of the one now in vogue, to which these advances have been due [6].

As Wilson goes on to explain:

When the book was first published in 1917, experimentation in genetics was just beginning to produce its brilliant results... A rich harvest has been reaped in these fields with very slight if any influence of Thompson's book... [On] the other hand, almost every reviewer has complained that the new edition has not been influenced by this research, which is for the most part hardly mentioned... The failure to take the results of modern biological research into consideration... is related to the failure to make an important impact upon this research. They are both due to the antithesis of the fundamental ideas. On growth and form harks back to an older habit of thought...; it is not an essential part of contemporary biological advance.

If the rise of genetics did not compel a change either in Thompson's focus or in his argument, and if Thompson's arguments had no impact on the development of that field, what *is* its relevance to this history? What relation, *did* exist between the rise of genetics and the fate of Thompson's work? I want to suggest that, for the problems with which Thompson was concerned, the primary change induced by the rise of genetics was in its reconfiguration of the conceptual landscape of biology. Where earlier biological thought had surely been shaped by the divides between epigenesis and preformation, and later between vitalism and mechanism, the advent of genetics in the 20th century brought with it a new kind of antithesis, one that inherited much of the oppositionality of those earlier debates, but added to that oppositionality a new sense of mutual exclusion—the need to choose between genetic and physicalist explanations. Wilson claimed:

The nature of this organization [i.e., of the germ] may be considered from two points of view: biologically, from the point of view of heredity, as with the trend begun by Weismann and leading to modern genetics, or mathematically and physically as in Thompson's book.

Thompson's interest, he writes, "is not in the biological analysis of the organization of the germ,... He approaches the problem from the opposite direction."

My questions are these: what set Thompson's approach in opposition to genetics, and what

made it *antithetical* to contemporary developments? The separation of the biological from the physical had already been implied by the very coining of the term “biology” to name a distinct discipline. J. B. Lamarck was one of the first to use this term. But Lamarck had repeatedly insisted that separation need not (or at least not to him) imply opposition; one kind of analysis need not exclude the other. “Nature has no need for special laws,” he wrote, “those which generally control all bodies are perfectly sufficient for the purpose.”

In a similar vein, the longstanding separation of the animate from the inanimate should also be acknowledged: Thompson’s complaints about the traditional reluctance of zoologists to compare the living with the dead, the reluctance to abandon the expectation of “something more,” were well grounded and in evidence long before the advent of genetics. But I want to suggest that genetics, itself often represented as a reductionist science, in fact provided support for such reluctance; I would even argue that it offered a kind of fulfillment of the expectation of a “something more.”

To be sure, geneticists had no use for a vital force, but they had a seductive alternative, and that alternative was the gene. I submit that the concept of the gene provided the *something more*—the crucial element that set biological organisms apart, and that seemed inevitably (perhaps necessarily?) to be missing from physicalist accounts. The gene was immortal, and it seemed all but totally resistant to the effects of physical force. Most important, it seemed to have what Newton referred to as an “occult specific quality, by which it acts and produces manifest effects.” What was the basis of life? Not osmosis, shrinkage, torsion, or tension, but the gene. What was the source of biological characters? The answer generally proffered by classical genetics was “Gene Action.” These were the genes to which particular characters were associated—particles that one might even imagine seeing under the microscope—that were assumed, somehow, to produce their effects by their action. Indeed, these entities ushered in not only a new science, but a new kind of reductionist explanation. Whereas the standard form of reductionism, which had long prevailed in the physical sciences, assumed that the smallest (microscopic or submicroscopic) components of the system lay at the bottom of the causal chain, genetics introduced a new kind of causal chain, one that placed genes at the bottom of the causal chain. From genes, one obtains proteins and RNA, from which are formed cells, then tissues, organs, and finally organisms.

Two different causal chains, both linear and unidirectional, stand apart from one another. Indeed, by introducing its own causal chain, genetics introduced the appearance of an incommensurability between the explanatory goals of the two sciences. In both cases, the assumption of a linear causal chain promised explanatory reductionism, with the hope that an explanation of macro phenomena could ultimately be “reduced” to an understanding of the properties and behavior of the lowest-level entities—atoms (or lower) in the case of physics, and

genes in the case of biology. But until (or unless) the properties and behavior of genes could be characterized in physical terms, how could these two different models of explanation possibly be integrated?

As genetics continued to triumph, and in midcentury began to give way to molecular biology, confidence in the explanatory power of genes (or of DNA) grew ever stronger. The dramatic discovery of a code for translating DNA sequences to proteins lent particular strength to the belief in the causal power of DNA, and with that triumph, so too did the tendency to see biology and genetics as coterminus grow stronger. Indeed, the solidification of that equation was, I think, essential to the growing opposition between biology and physics.

How could this be, you might ask? After all, didn't physicists play a central role in the creation of molecular biology? Well, yes they did, but not necessarily qua physicists. Molecular genetics certainly welcomed the participation of physicists. (Especially, it welcomed their imprimatur, their prestige). But the contributions of most of these physicists (crystallographers aside) turned out to rely precious little on the application either of the tools or of the principles of physics to the problems of biology. One might even ask regarding Schroedinger's widely celebrated contribution to the emergence of molecular biology—namely, regarding his offer of the notion of a “hereditary code-script” embedded in an “aperiodic crystal” as an answer to the question “What is Life?”—where is the physics in this answer? Surely the discovery of a protein code was not in itself sufficient to substantiate the notion of code-script capable of determining “the entire pattern of the individual's future development and of its functioning in the mature state.” Schroedinger's attention to the subject has been credited by many for encouraging the movement of physicists into the field of molecular biology, but how much of his influence was due to the legitimation provided by his own prestige, and how much to his demonstration of the usefulness of the concepts of physics to biology? Throughout the next 50 years, during the first half-century of molecular biology, I can find little evidence of the application of physics to the study of biological development and morphogenesis (especially when construing physics, as Thompson seems to have done, as an inquiry into the role of physical forces).

Indeed, this was a period in which people interested in such subjects had an especially hard time finding support of any kind. I recall an anecdote from the late 1960s or early 1970s (a time when I was working in mathematical biology) that was told me by my colleague Mimi Koehl. Mimi, now a renowned leader in the field of biomechanics, had applied to the NSF for funding, but she'd been turned down. In recounting these events, she shared words from the letter of explanation she received: “This applicant,” wrote the reviewer, “seems to be under the impression that physics has something to do with biology.” I might note here the tacit equation—already explicit in Wilson's 1942 remarks but now only grown stronger—between biological and genetic.

In mid-20th century, I think we can all agree that *that* equation was new. If we couple that equation with the representation of biology as alternative to (even opposed to) physics, what room is left for a project such as Thompson's—a project that chooses to leave genetics aside and focus instead, and exclusively, on the physical and mathematical laws with which organisms must conform? To be sure, *On Growth and Form* is a work that has received a great deal of homage, but for most of its readers, it remained, as Stephen Jay Gould put it, “an unusable masterpiece.”

Even toward the end of the 20th century, when work in both mathematical biology and biomechanics first began to rebound (see, e.g., Odell et al. [7]; Koehl, M. A. R. [8]), such efforts continued to be met with puzzlement: where was the genetics? They might have asked (though I do not actually recall anyone doing so in the very early days) whether there was a way to integrate this work with what they had learned about genetics. Only in the 1990s did we begin to see the beginnings of a sustained effort to bridge this gap. (I'm thinking, e.g., of the work of people such as Maria Leptin, Donald Ingber, and Viola Vogel, and also of the emergence of a few papers on the role of mechanical forces in the regulation of gene expression (see, e.g., the work of Emmanuel Farge). But these efforts proved to be just the tip of the iceberg.

For the role of mechanics in gene expression, what really opened up the flood gates in my view was the turn, within molecular biology, from the search for “genes for” particular effects (in other words, the search for genetic causation) to a focus on the regulation of gene expression, and more specifically, to the roles of chromatin, epigenetic markers, and ncRNA in this regulation.

Today we are in a new century, one in which the landscape of biological thought is once again being reconfigured. With the maturation of molecular biology, the genome has been transformed from the executive director of biological development, or, as Schroedinger put it, from “architect's plan and builder's craft” to the immensely complex physical-chemical structure that seems to need no new laws of physics, only a Herculean effort of sifting through the jungle of physical and chemical interactions responsible for what it can and cannot do. This transformation is itself largely the result of the turn of research attention from questions about nucleotide sequences coding for amino acids to the much harder questions about how particular proteins are produced in the quantities, at the times, and in the places in which they are needed for the normal functioning of the cell. We may claim to account for the difference between wrinkled and smooth peas by Mendelian factors, but where is the account of how these factors actually give rise to their effects? If genes “act,” how do they act? If sequences of DNA inform, how and what do they inform?

With this shift—a shift that focuses attention on the complex relation between genotype and phenotype, we can finally return to Thompson. DNA, it has become clear, is not a mystical entity, no more so than is any other part of the organism. It is a very particular kind of

physical/chemical structure, and to the extent that it can be said to “act,” it can do so solely through its internal interactions (i.e., interaction among its parts) and the interaction of those parts with other physical/chemical components. What Thompson once said about the structure and conformation of organic forms can also be said about the structure and conformation of all the molecular components of organisms, including the organic forms of both DNA and what we have been calling genes: “no organic forms,” he wrote, “exist save such as are in conformity with physical and mathematical laws.”

How DNA is “read” for protein synthesis depends on its conformation as a physical structure. Its morphology differs from that of the forms on which Thompson focused in at least two ways: first, it is highly dynamic, and second, the processes involved operate on a molecular rather than a macro scale. Notwithstanding, it has recently become a tremendously fertile field for physicists looking to extend their horizons.

One of the most fruitful domains of investigation has been in the physical dynamics of the processes by which epigenetic markers regulate gene expression. This they do by way of regulating genomic conformation: exposed sequences of DNA can be transcribed and sequences that are hidden by the topology of the chromosome cannot.

Of the many epigenetic markers we know, perhaps the most extensively studied is that of methylation. Methylation means the attachment of a methyl group to a nucleotide (cytosine may be the frequently discussed example).

This alteration in the chemical composition of a nucleotide can change the mechanical properties of the DNA (it can change, e.g., its rigidity or flexibility), and hence it can change the conformation of the genome. In turn, and accordingly, such changes regulate the availability or nonavailability of particular sequences for transcription (gene silencing). Methylation also has many other effects: for example, it alters resistance to strand separation (necessary for both replication and transcription); it also helps regulate the positioning of nucleosomes, the basic unit of DNA packaging. Now all these changes are problems in physics, albeit on the molecular scale, where the physics involved seems to be that of polymer folding. But through their role in regulating genomic structure, they have profound—and trackable—effects on large-scale biological properties of the entire system.

There are other kinds of epigenetic markers as well—for example, DNA supercoiling is sometimes regarded as an example of a purely physical epigenetic marker, as is the condensation of chromatin into highly compacted forms known as heterochromatin. (This process too is implicated in gene silencing). In a review of “The Physics of Epigenetics” [9], the authors conclude:

By putting the rich and diverse biological literature under the new light of a physical approach, the emerging picture is that a limited set of general physical rules play a key role in the epigenetic regulation of gene expression.... Mainly, epigenetics display an intrication of physical mechanisms and specific biological entities, devised in the course of evolution to achieve an exquisitely coordinated and adaptable regulation of transcriptional activity. Our review demonstrates the need to take into account both aspects, within a dialogue between physics and biology, theory and living-cell experiments.

Even more recently, yet another branch of physics has emerged as a source of tools that can be put to use to understand other aspects of genomic and cellular organization—aspects that are crucial to the dynamics of the regulation of gene expression. I think of this work as belonging to condensed-matter physics. To find the literature that has begun to attract so much attention, just try googling “phase separation in biology.”

In essence, the problem is this: Cells contain tens of thousands of different molecular components, the activities of which need to be coordinated in time and space to sustain cell function. This coordination is achieved by compartmentalization of molecular components into diverse membrane-bound and non-membrane-bound cell organelles that perform distinct functions. One question that has particularly confounded cell biologists is how such organelles are assembled and maintained. And it is here that studies of liquid-liquid phase separation have proven useful.

One of the first such efforts to attract attention comes from the MPI, where researches have demonstrated the role of phase transitions in droplet formation in the specification of germ cell lineages. More recently yet (indeed, in the last couple of months), several papers have appeared that discuss the role of condensation and phase separation in the architecture of heterochromatin (where genes are mostly silent) and its separation from euchromatin (where sequences can be transcribed). As Mark Buchanan puts it [10], “we’re learning something about how biology uses geometry [and, of course, physics] for control.”

Because liquid-liquid phase separation is so sensitive to changes in environmental parameters, this work may be of particular interest for illuminating a mechanism for gene regulation by environmental cues. In doing so, it provides one of the few handles we have available for understanding the role of environmental variation in heredity, in development, and in evolution.

But will the tools that physicists have developed in other contexts prove equal to the task of providing a physical analysis of systems as complex as we find in biological morphogenesis?

Almost surely not. Biology introduces us to states of matter, to material processes, that are not often seen in nonbiological systems, and there is no reason to expect that available methods will prove adequate to the challenges posed by this unfamiliar terrain: new tools will almost certainly need to be developed.

Now, finally, we are brought back to the original question: Do such efforts, preliminary as they may so far have been, help to heal the divide in which Thompson was caught? Do they point to a way out of the need to choose between, for example, a Mendelian and a biophysical account of the difference between smooth and wrinkled peas?

I think they do. Indeed, I think they do so by offering a fundamental challenge to the simplistic models of explanatory reductionism, be they genetic or atomic—models that have traditionally prevailed in both disciplines. Earlier I suggested that these models, both of them linear causal chains, might be incommensurable. But now it has begun to appear that, in general, and even without such incommensurability, complex multicausal systems cannot be adequately described by linear causal chains of any kind, in whatever discipline they are found. The multicausal systems we encounter in biology seem to be especially resistant to unidirectional causal accounts because of the kinds of feedback, built in by evolution, that introduce crucial links between the different levels.

Annick Lesne is a mathematical physicist who has authored numerous efforts to model biological processes in physical terms; she is the director of a research group in theoretical biology at the CNRS. In a recent review [11], she writes,

Biological systems are a special instance... of complex systems; [they are] assemblies of interacting elements where emergent features directly or indirectly modify the elements. Such a... scheme is often termed circular causality, [a term that refers to] the coupling of bottom-up and top-down relationships, leading to self-organized and possibly adaptive behaviors. Typically, elements collectively modify their surroundings, in a way sufficient to influence back the elementary interactions, which in turn may change the collective behavior of the assembly. Only a few purely physical systems display such features...

By contrast, biological systems do display such features, and they do so typically. Indeed, it is just these features that render them to be what Lesne describes as “intrinsically and irreducibly multiscale processes,”—in other words, they lead us to conclude that no explanatory effort focusing on single scale can suffice. “Regulation of biological function,” she writes,

has to bridge the state of the cells and... surrounding features... in an adaptive way. [The] cell itself has to perform a multiscale integration. For instance, transcription in eukaryotes relies at the same time on information about DNA sequence and bound proteins, histone chemical status,... chromatin conformation..., nuclear localization (e.g., near a nuclear pore), cell state and its surroundings [mechanical constraints, and so on]...; it involves influences from each of these various levels, either directly [or indirectly].

“Our analysis and modeling,” she concludes, “should follow the same line.”

Similar conclusions are reached by philosophers of science Sara Green and Robert Batterman in their review of the rapprochement of physics and biology [12]. Their review focuses on the multilevel causal dynamics of early morphogenesis, and they, too, conclude, “There is no single approach that can account for all relevant aspects of multiscale systems.”

But what does all this imply about the prospects of integrating the different approaches to morphogenesis? Here is what Green and Batterman wrote:

Connecting the models formulated at different levels does not involve a process of reduction of one model to a more fundamental one. [Rather] The different models... are explanatorily independent but epistemologically interdependent.... The combination of models forms a pluralistic mosaic of different strategies rather than a reductive explanation.

The different strategies are

explanatorily independent in the sense that they describe different processes at characteristic scales while drawing on different (and often conflicting) theoretical frameworks. At the same time, the models are interdependent in the sense that the success of one model depends on sources of information that are not explicitly represented but covered via other models or sources of information.

In these formulations, reduction from one causal level to another goes out the window, effectively prohibited by the feedback between levels. But so too does the hope (or, for some, the fear) of the reduction of genetic explanations to the kinds of causality conventional in physics—that hope (or fear) is also radically undermined. Though I remain convinced that our accounts of biological effects in terms of “genes for” needs updating, and so, even I am not ready to dispense with genetic explanations. These may not belong in the linear hierarchy of explanatory

reductionism traditional in physics, but they almost certainly do belong in the “pluralistic mosaic of different strategies.” And this sort of mosaic might, after all, be the best we can aim for. It may not dispense with the need for genetic explanations, but it might, finally, dispense with that ancient dichotomy lurking behind between physics and genetics, namely, the dichotomy between the animate and inanimate.

### Note

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Massachusetts Institute of Technology  
77 Massachusetts Avenue  
Cambridge, MA 02139  
USA  
e-mail: [efkeller@mit.edu](mailto:efkeller@mit.edu)

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