CHAPTER 10

What Is the Problem of Form?

It is well known that amphibians such as frogs and salamanders have a remarkable ability to regenerate severed limbs. What may not be so commonly realized is that, if you graft the tail bud of a salamander onto the flank of a frog tadpole at the place where a limb would normally form — and also near the time when metamorphosis of the tadpole into a frog will occur — the grafted organ first grows into a salamander-like tail, and then, in some cases, more or less completely transforms into a limb, albeit a dysfunctional one. Among other changes, the tip of the tail turns into a set of fingers (Farinella-Ferruzza 1956).

The experiment can remind us how biologists commonly try to learn about life by severely disrupting it. But the current point is that, in this particular experiment, the transformation of the tail into an approximate limb cannot be the result of local causes, since the local environment of the fingers-to-be is a tail, not a limb. The power of transformation is, in a puzzling manner, holistic. The part is caught up within the whole and moves toward its new identity based, not merely on local determinants, but also on the form and character of a whole that is *not yet physically all there*.

This may remind us of the rather different experiment we heard Harvard biologist Richard Lewontin describing in Chapter 6 (“Context: Dare We Call It Holism?”): if a researcher excises the developing limb bud from an amphibian embryo, shakes the cells apart, allows them to reaggregate into a random lump, and then replaces the lump in the embryo, a normal leg develops. This shows that the currently unrealized form of the limb as a whole is the ruling factor, redefining the parts according to the larger, developing pattern (Lewontin 1983).

But how can this be? How can spatial position within a not yet fully realized form physically determine the future and proper sculpting of that form, and do so even when parts are surgically jumbled?

In one way or another, the problem is universal. A key feature of holistic, end-directed, living processes is that the end plays a role in shaping the means. (See many of the preceding chapters, and especially Chapter 2, “The Organism’s Story”, Chapter 6, “Context: Dare We Call It Holism?”, and Chapter 8, “The Mystery of an Unexpected Coherence”.) Tadpoles with faces engineered to be highly abnormal “nevertheless largely become normal [adult] frogs: the craniofacial organs move in abnormal paths until a proper frog face morphology is achieved” (Levin 2020). In other words, the means are modified, even becoming entirely unprecedented if necessary, in order to achieve a characteristic result.

We find the same principle when we look at cascades of gene expression, such as the sequential expression of the various genes that have been said to “determine” left-right asymmetry of the vertebrate body. The normal expectation would be that if one blocks or changes the expression of earlier genes in the sequence, the disorder should accumulate and be magnified, perhaps explosively, in downstream gene expression, since proper cues for the later steps are missing. But

> Surprisingly, this is not actually what occurs: each subsequent step has fewer errors than

> the previous step, suggesting that the classic linear pathway picture is importantly incomplete. Embryos recognize transcriptional deviations from the correct pattern and repair them over time … The existence of corrective pathways in embryogenesis and regeneration raises profound questions about the nearly ubiquitous stories our textbooks and “models” tell about the molecular explanations for specific events (Levin 2020).

All this may remind us of E. S. Russell’s remark that in biology “the end-state is more constant than the method of reaching it” (Chapter 2, “The Organism’s Story”). We also see here the principle that cell biologist Paul Weiss enunciated so clearly at mid-twentieth century, when he pointed out that the whole “*is infinitely less variant from moment to moment than are the momentary activities of its parts*”. At the lowest level of biological activity, molecules in the watery medium of a cell have degrees of freedom (possibilities of movement and interaction) that would spell utter chaos at higher levels if it were not for the fact that the lower-level activity is “disciplined” from above.

Weiss’ point is that, whatever the level we analyze, from macromolecular complexes, to organelles, to cells, to tissues, to individual organs, to the organism as a whole, we find the same principle: we cannot reconstruct the pattern at any level of activity by *starting from parts and their interactions*. There are always organizing principles that must be seen working from the whole into the parts. (See the discussion of Weiss in Chapter 6.)

One further example. During development, the lens of an amphibian eye derives from the outer layer of cells in the developing head, at the point where an outgrowth of the brain comes into contact with the epidermal cells. But if an already developed lens is removed from one of these animals, something truly remarkable happens: a new lens forms from the upper edge of the iris, a structure that has nothing to do with lens formation in normal development. The procedure runs like this (Gilbert 1994, p. 40):

1. Cells from the upper part of the iris — cells that have already reached an endpoint of differentiation — begin multiplying;
2. these multiplying cells then proceed to dedifferentiate — that is, to lose their specialized character, including the pigmentation that gives the iris its color;
3. the newly multiplied, iris-derived cells migrate so as to form a globe of dedifferentiated tissue in the proper location for a lens; and finally,
4. they start producing the differentiated products of lens cells, including crystallin proteins, and are thereby transformed into transparent lens cells — all in the nuanced spatial pattern required for the formation of a proper lens.

And so, lacking the usual resources and the usual context for formation of a lens, the animal follows an altogether novel path toward the restoration of normal form and function.

One sometimes gets the feeling that a single, well-documented example of developmental plasticity of this sort, if taken seriously enough and contemplated deeply enough, could transform all of biology and deliver biologists from the worn-out fantasy of the mechanistic organism. But it doesn’t happen. As many have observed, paradigms of explanation, once established, can be very difficult to overturn merely by citing evidence contradicting them.

In any case, it is impossible to believe that these complex and intricately coordinated responses to the loss of the lens were somehow already *physically* determined or programmed or otherwise specified in the animal's one-celled zygote. Nor is it easy to imagine how there could ever have been a sustained and large population of lens-injured amphibians with otherwise functional eyes — a population large enough, that is, to enable a supposedly mindless process of natural selection to evolve over great lengths of time a specific, novel solution to the problem of lens regeneration.

The problem of form exists even at the molecular level

The problem of form has long been central to biology, where each creature so notably reproduces after its own kind and according to its own form. "It is hardly too much to say", wrote geneticist C. H. Waddington, "that the whole science of biology has its origin in the study of form". In both their descriptive and theoretical activity, biologists "have been immersed in a lore of form and spatial configuration" (Waddington 1951, p. 43).

"Immersed in a lore of form" is, however, an oddly mild way of putting it. "Hopelessly adrift upon a fathomless sea of mystery" might be more fitting. An observer surveying the biological disciplines today (some seventy years after Waddington's comment) can hardly help noticing that every organism's stunning achievement of form has become an enigma so profound, and so threatening to the prevailing style of biological explanation, that few biologists dare to focus for long on the substance of the problem.

We will find it necessary in our further discussion to keep in mind that the mystery is at least as apparent on the microscopic (and even the molecular) level as it is at more easily recognizable levels. We have already seen this in earlier chapters. For example, in Chapter 2 ("The Organism's Story"), we heard the English neurophysiologist, Sir Charles Scott Sherrington, describing how a severed motor nerve in some animals manages to grow back, through many obstacles, toward the far-distant muscle it was originally attached to.

Somehow the minuscule nerve "knows" where it is within the vast three-dimensionality of the animal's body — knows its own place in contradistinction to that of all the other nerves in different parts of the body. It likewise "senses" where it needs to get to in the local context, and how to find its way there. It's as if it had a detailed map of the terrain.

When we consider the more general case of wound healing described in Box 10.1, we find ourselves watching how the nerves, blood vessels, muscles, and all the diverse, mangled tissues in a wound sort themselves out. It is all somehow governed by what the description's author calls "an over-arching sense of the structure of the whole area in which [the] repair takes place". The original form is restored as far as possible. But what is being sensed? how is it sensed? and "who" is doing the sensing? — these most basic questions remain unanswered.

We saw in Chapter 8 ("The Mystery of an Unexpected Coherence") that a similar problem faces us when we look at the several scores or hundreds of molecules engaged in the intricate molecular "surgery" known as *RNA splicing*. We know that all the complex, carefully sequenced, splicing interactions respect every bit of physical and chemical understanding we have amassed, and so we can go about explaining them in that sense. But a *biological* understanding — an understanding of the effective, flexible, context-dependent coordination of physical events toward a desirable result — remains indescribable in the currently acceptable terminology of biology.

Box 10.1

The Miracle of Wound Healing

Here is a description offered by English biologist Brian Ford (2009):

"Surgery is war. It is impossible to envisage the sheer complexity of what happens within a surgical wound. It is a microscopical scene of devastation. Muscle cells have been crudely crushed, nerves ripped asunder; the scalpel blade has slashed and separated close communities of tissues, rupturing long-established networks of blood vessels. After the operation, broken and cut tissues are crushed together by the surgeon's crude clamps. There is no circulation of blood or lymph across the suture.

"Yet within seconds of the assault, the single cells are stirred into action. They use unimaginable senses to detect what has happened and start to respond. Stem cells specialize to become the spiky-looking cells of the stratum spinosum [one of the lower layers of the epidermis]; the shattered capillaries are meticulously repaired, new cells form layers of smooth muscle in the blood-vessel walls and neat endothelium; nerve fibres extend towards the site of the suture to restore the tactile senses …

"These phenomena require individual cells to work out what they need to do. And the ingenious restoration of the blood-vessel network reveals that there is an over-arching sense of the structure of the whole area in which this remarkable repair takes place. So too does the restoration of the skin. Cells that carry out the repair are subtly coordinated so that the skin surface, the contour of which they cannot surely detect, is restored in a form that is close to perfect."

And so the problem of form, even when we try to approach it at the molecular level, seems intractable from the standpoint of conventional biology. In the case of RNA splicing, we can ask how each molecule among the large crowd cooperating in the activity of splicing is synthesized in the right amount; how each one is brought to the right place for splicing, and at the right time; how it manages to interact with properly selected molecules among all the available partners in the operation, doing so in a carefully choreographed sequence; how the overall cooperation among all the molecules is achieved; and how this cooperation is properly aligned with the *needs* of the cell at a particular time — a time when one form of the spliced RNA rather than another happens to be called for, requiring the "surgery" to be performed with unique variations.

Need is not a term of physical science. Further, all this occurs in a fluid or highly plastic medium, with no crucial and precisely machined channels of communication such as those carved in silicon chips at our high-tech factories. The externally imposed mechanistic constraints, such as those required for the operation of our machines, simply are not there in the organism.

Of course, researchers have traced all sorts of molecular syntheses, movements, and interactions. We can be sure that everything in the entire picture proceeds lawfully, and in this very constricted sense every local event looks necessary. And yet we can find no combination of physical laws capable of “enforcing” the proper form of all the different parts of the body of this or that animal. In the case of a wound, there is no purely physical necessity to achieve the “proper” form in the face of wildly variable conditions.

In other words, the mere fact of physical lawfulness does not explain the *coordination of events* along an extended timeline in the narrative of healing, from infliction of the wound to the final restoration of normalcy. Nor does it explain the narrative of RNA splicing, from the occurrence of an RNA molecule in need of reconfiguration, to the final product of those scores or hundreds of participating molecular “surgeons”. We can watch the molecules performing in a way that gives expression to the overall sense, or meaning, of the activity, but we do not have even the barest beginnings of a purely physical explanation for their commitment to that meaning.

Michael Levin: Revolutionary

I wrote above that every organism’s stunning achievement of form has become an enigma so profound, and so threatening to the prevailing style of biological explanation, that few biologists dare to focus for long on the substance of the problem. Michael Levin is one of those few. An enthusiastic, prolific, hyper-achieving researcher, he appears to represent at least part of the future of biology. As the Vannevar Bush Professor at Tufts University near Boston, Levin is principal investigator of the Levin Lab there, director of the Tufts Center for Regenerative and Developmental Biology, and team leader of the Allen Discovery Center at Tufts. He also holds positions at Harvard and MIT. The wide-ranging work under his supervision includes pioneering explorations of the role of electrical fields in the production of biological form. (See Box 10.2.)

But what is perhaps most impressive about Levin is his willingness at least to make a start at acknowledging certain extraordinarily difficult questions biologists must raise if they want to face organisms squarely, as we actually observe them. Chief among these is the problem of organic form.

Levin is particularly explicit about this problem in a paper entitled “The Biophysics of Regenerative Repair Suggests New Perspectives on Biological Causation”, published in *Bioessays* (Levin 2020). We will now give particular attention to this paper, which will be the source of all quotations unless otherwise indicated.

The way in which tissue voltage patterns prefigure the developing form of embryos has been central to Levin’s thinking (Box 10.2). This prefiguring, he emphasizes, is not in the first instance a genetic event, but “a [much higher-level] physiological event … causally responsible for a given patterning outcome” — and therefore also a cause of the gene expression required for that outcome.

In other words — and this is where Levin particularly sees himself offering something new — there is a kind of causation, somehow active in the larger pattern, that we cannot understand by adding together the causal action of molecular-level entities upon each other. The tissue-wide electric potentials can fairly be said to play a decisive role in stimulating cascades of gene expression on the way toward formation of entire organs. But, in the reverse direction, genes cannot be said to cause, or explain, the patterns of electric potential.[2]

Similarly with the examples in the opening section of this chapter. They all raise the problem of causation from whole to part — and (although this is not a point Levin raises) they all vex our efforts at strictly physical understanding. The question we need to ask ourselves is this: “How can the physical body of a relatively undeveloped organism — a body already exhibiting coordinated physical processes perfectly adapted to its present state — redirect and transform those well-adapted physical processes so as to conform to a different and more ‘mature’ pattern that is not yet there?”

Box 10.2

Electricity in the Developing Tadpole

In the summer of 2011 a team of researchers at Tufts University produced a startling, time-lapse video of a developing tadpole embryo[1] (Vandenberg et al. 2011). Due to the use of special dyes reporting the electric potentials across cell membranes, areas of the embryonic surface successively lit up brightly and then went dark. For a few seconds of the time-lapse film (representing the events of several hours), the featureless part of the embryo that would eventually become the animal’s head flashed the image of a tadpole face.

But no actual face had yet developed. Nevertheless, the electrical pattern did “signal” where key elements of the tadpole’s face, such as its eyes, would eventually appear. Regional changes in electric potential, these scientists concluded, “regulate expression of genes involved in craniofacial development”.

According to Michael Levin, head of the laboratory where the tadpole research was performed, “Ion flows and the resulting [membrane voltage] changes are components of long-range conversations that orchestrate cellular activities during embryonic development, regeneration, and … tumor suppression”. He adds that “bioelectric cues are increasingly being found to be an important regulator of cell behavior”, controlling the proliferation and death of cells, their migration and orientation, and their differentiation into different cell types.

“We are”, he wrote further, “just beginning to scratch the surface of the bioelectric code — the mapping between voltage properties and patterning outcomes, akin to the genetic, epigenetic, and perhaps other codes remaining to be discovered” (Levin 2012).

Levin’s team quickly went on to manipulate the distribution of membrane voltages in developing embryos so as to provoke the generation of eyes in decidedly unexpected places — for example, on the back and tail, and even in the gut, of a frog embryo. The results were fragmentary and rather chaotic — the ectopic (“out of place”) eyes were partial or deformed — but the result was nevertheless as startling as it was monstrous (Pai et al. 2012).

Whole-part, future-oriented causation

Why does holistic causation refuse strictly physical understanding? A key difficulty, as I have been emphasizing, lies in the observation that every embryo seems, in its holistic manner, to be *reliably guided* toward a future state. It is as if that future state were somehow present and influential along the entire path of its own material realization — as if the developing embryo were expressing from the very beginning its own *telos*, or the essential idea of its ultimate maturity and wholeness, as a very real and present power.

In a moment we will have to ask to what degree Levin clearly recognizes how thoroughly the problem of causation running from whole to part and directed toward the future disrupts conventional thinking. He is, in any case, fascinated by what he often refers to as “top-down causation” — “an important distinct type of causation” in which ”a future state … guides the behavior of the system”. He recognizes the “incredibly tangled details underlying system-level outcomes in biological systems”, and instead of immediately pivoting away from the challenge of future-directed, higher-level causation in order to resume the analysis of microstates, he questions the wisdom of such a strategy:

> Embryonic patterning, remodeling, and regeneration achieve invariant anatomical outcomes despite external interventions. Linear “developmental pathways” are often inadequate explanations for dynamic large-scale pattern regulation, even when they accurately capture relationships between molecular components.

That is, even in the face of the researcher’s deranging intrusions, the embryo does its best to re-organize itself in the light of a characteristic outcome yet to be fully realized — all in a way that does not seem to be explained by the activity of lower-level entities.

The common expectation, which dominated twentieth-century molecular biology, had been that we would learn to track every microstate in every cell and organism, and in doing this we would gain all the understanding of biological processes we could ask for. Levin wonders whether this expectation isn’t having the unfortunate effect of “delaying the development of higher-level laws” that could advance our interests more effectively.

So, then: what might he mean by “higher-level laws”?

Michael Levin: Counter-revolutionary

Levin has seen deeply into decisive and overlooked problems of biology. It is, therefore, all the more revealing of the state of modern biology to see how conventional dogma sets bounds to the solutions he can conceive. Despite his desire to frame a new paradigm of causation in living beings, his work testifies to the deeply entrenched power of conventional biological thinking. In fact, at times he seems drawn to the most abstract and least biological aspects of this thinking.

Counter to what you might have thought based on the preceding descriptions, Levin's interests center emphatically on *machine-like* models, *control*, and *prediction*. (I count forty-eight occurrences of the word "control" in the main body of his article.) He repeatedly expresses his confidence in explanatory models based on "top-down" techniques already "exploited very successfully by control theory, cybernetics, computer science, and engineering of autonomous robotics" — and is also impressed by "new developments in information theory that help to rigorously identify and quantify tractable macrostates with maximal causal power". These top-down tools of control could now "enable transformative advances in biomedicine".

By "top-down" Levin typically means: driven by something like an engineer-designed computer program embodied in things like circuits and switches. The *new* in his "new paradigm" consists largely of the fact that the program is thought to be (somehow) distributed throughout tissues and organs, rather than encoded in the tight "logic" of the DNA sequence.

Even the bioelectric features of tissues (Box 10.2) become, for Levin, the manifestations of digital devices. When he looks at these features, he sees circuits, biolectric networks that serve as "a rich computational medium", and feedback loops "equivalent to transistors — fundamental building blocks of logic circuits and decision-making machinery".

And so, he is convinced, appropriate machine models present a wonderful opportunity: we may gain "predictive control in regenerative medicine and synthetic biology". All that is required is a high-level focus on "control mechanisms that harness cell behavior toward specific organ-level outcomes". His complaint about microstates as presumptive causes is that they do not enable us "to make quantitatively accurate predictions with respect to the complex final outcome … which is the key property we require from a purported explanation of a biological process".

One might have thought that at least one key thing we want from biological explanations is an understanding of the unique, qualitative ways of being distinguishing the life of one organism from another — for example, the zebra from the lion (Holdrege 2020). The narrow interest in "quantitatively accurate predictions", on the other hand, stems from the long-running commitment of science to the discovery of clear and unambiguous causes of a certain sort — reliable causal factors that, within carefully controlled systems, *consistently make specific things happen*, and therefore can be used technologically.

Certainly we do want a maximally *effective* medicine, just as we want a maximally effective political or educational system. But this does not mean we can healthily understand political or educational processes by grounding ourselves in machine models of causation. And the same goes for medicine.

The main problem we have in following Levin is that we arrive at neither a revolution nor a new paradigm for causation merely by changing our level of observation from microstates to macrostates — from molecules to tissues and organs. As long as we remain committed to the same physical and mechanistic notion of causation that has dominated biology for the past few centuries, we can hardly claim to have arrived at a profoundly new understanding of biological causation.

I believe Levin has glimpsed the fact that something *can* radically change when one begins to talk about top-down causation — especially if one realizes that, in organisms, we are looking not only at causes running from the whole toward the parts, but also at a kind of future-oriented causation. But he has compromised this insight by forcibly marrying it to tired, machine-based habits of explanation that represent nothing but the old paradigm.

Of course, he might well object to this. His references to cybernetics, control theory, and computational neuroscience show that he sees himself focusing on a *distinct type* of machine — namely, those operating under some form of programmed control and feedback. Don't we see in these machines a kind of top-down and purposive causation that seems to match that of organisms? The inadequacy of current thinking about biological causation, he is suggesting, lies in biologists' failure to exploit the analogies between living beings, on one hand, and machines *of this particular sort*, on the other.

He is right — and importantly so — about biologists' failure to take seriously the fact of purposive biological processes. But does he himself fully acknowledge the purposive dimension of organic activity? Or does he instead think in terms of activity that only *looks*, rather illusorily, "as if" it were purposive? And do programmed machines point us toward a useful understanding of biological causation?

In what sense are machines end-directed?

In his paper, Levin addresses the idea of "setpoints as causes". Setpoints, he says, are not-yet-existing "future states" that somehow "guide the behavior of the system" toward a realization of those future states. As it stands — and in relation to living beings — the assertion is as vague as it is radical. But Levin makes clear the kind of thing he has in mind: it is illustrated above all by the kind of feedback and control systems we routinely rely upon in devices we use daily.

In such systems, the setpoint is embodied in a mechanism or controller that can be set to some value. In a very simple case, this could be a thermostat set to a particular temperature. That temperature is the setpoint, and the thermostat uses it to control a heating system, such as the one in many homes.

A more complex case would be a computer taking input from buttons you may have on your automobile's steering wheel, where the input represents a desired cruise control speed. Or think of a cruise missile flexibly seeking out a specified target with the help of "sensing" instruments and a complex, computerized guidance system. The target (set point) must, in one way or another, be entered into the computer.

It is obvious that we can say, abstractly and analogically, that organisms pursuing their own purposes have "setpoints". The lion (in some sense) races "like" a cruise missile toward the antelope, adjusting its course as the antelope turns this way and that. And, likewise, the lion embryo flexibly pursues a reliable "trajectory" toward its mature form. But — although Levin often seems to forget the fact — such remote analogies fail to show that the lion can in any meaningful sense be explained as the functioning of a programmed machine. This would have to be demonstrated.

Surely (to change the image) it is difficult to find much commonality between the transformation of a single zygotic cell into a mature eagle, on one hand, and the "development" of a missile, on the other. If, before venturing upon its flight, the missile were to "mature" from a single transistor (or circuit board) into the totality of a functioning, deadly efficient vehicle; and if, during its flight, all its physical constituents were metabolizing and metamorphosing as an essential part of the overall operation; and if, instead of a single "setpoint", there were a massively interwoven and nearly infinite collection of "setpoints" governing each of the missile's "organs", each "cell", the entire missile as a whole, and all its environmental relations — well, as you can see, taking the comparison with living beings seriously could get silly fast.

In any case, the decisive issue is not difficult to grasp. Cruise missiles — and, for that matter, kitchen blenders, electric hand drills, and textile looms — consist of materials we articulate together for use as tools in accomplishing our own tasks. The "top-down" ideas guiding assembly are ours; they do not come to expression through holistically active developmental processes in which all the growing parts participate. *Our* ideas are not native to the collection of parts. Our ideas are not active at the very root of material manifestation in the way that physical laws and biological principles are inseparable from the substance in which they work. We merely rearrange, in an external manner, materials already given to us. We cannot penetrate to the inherent lawfulness of physical materials with the force of our wills, except in moving our own bodies. (And even there, the doing is currently inaccessible to our understanding.)

When we want to explain the operation of a kitchen blender (or a missile), we require no reference to its intentions, or to any striving toward a future state. When we do make such reference, we are really talking about our own purposes in structuring the device for employment in service of our interests. There is no more an *immanent* end-directness in a cruise missile than in a blender. Both devices are simply put together in accordance with *our* purposes.

By contrast, a developing organism's living "trajectory" results from its *growing* directionally into its mature functioning. We never see a designing power or force that assembles an organism from pre-existing parts in anything like the way we build tools and machines. *Organisms are not designed and tinkered with from without, but rather are enlivened from within*. The wisdom we find at play in them is intrinsic; it is their own in a sense wholly untrue of the external intelligence with which our mechanical inventions are structured.[3]

Does this not make a great difference for our thinking about causation in organisms and machines? The act of structuring and programming a physical device such as a cruise missile is our own. The missile itself has no intentions, and is not "aiming at" anything, no matter how great our role as inventors and builders. In this regard it is simply a more complex kitchen blender. We may have gotten more sophisticated in shaping tools to our own ends, but that is our development, not the machine's.

A deep issue, unaddressed

I have several times mentioned in these pages that all biologists do recognize the agency — the *telos*-realizing, purposive, task-oriented, and storytelling (narrative) activity — of organisms. Biological research is structured by our interest in the things organisms do and accomplish so differently from what rocks "do" and "accomplish", from gene expression, to DNA replication and cell division, to growth and development, to animal behavior.

But, as I have also mentioned, this awareness of agency remains, for most biologists, blindsighted, and therefore does not make its way into biological theory and explanation, or even into the biologist's own clear consciousness. Levin therefore provides a valuable service by encouraging a more general awareness of what he occasionally refers to as the "teleological" dimension of biology.

I do regret, however, that despite his extraordinarily wide-ranging familiarity with the technical literature, he shows no evidence of having mined the rich wisdom in the works of the organicist biologists of the twentieth century — figures such as E. S. Russell and John Scott Haldane (not to be confused with his son, J. B. S. Haldane) in Britain, and Paul Weiss in America.[4] These prominent and well-respected researchers had already grasped the centrality for biology of the coordinating ("top-down") agency at work in organisms seen as wholes.

A familiarity with this earlier work might have prodded Levin to take a more critical approach to the machine models he so insistently applies to organisms. As it is, he makes no very apparent effort to justify a substantive comparison of living activity to humanly designed machine operation. He does, however, assure us that, with respect to developing organisms, "work is ongoing to understand the molecular nature of the processes that measure the [current] state, maintain the setpoint, and implement the means-ends process to achieve the target morphology".

But, in the work he cites, I see nothing to suggest answers to the most obvious questions. Where might a machine-like setpoint be physically embodied — where might it even *conceivably* be embodied — so as to represent the entire, infinitely detailed and intricately interwoven morphology of a given animal? Once found, how might this setpoint actually direct and coordinate all the animal's living activity over a lifetime — or over a single healing episode such as described in Box 10.1? And where do we find evidence that an organism's fundamental activity of *growth*, *striving*, and *self-transformation* can be understood on the model of our technological devices?

Much of the work Levin draws upon to illustrate machine-based theorizing about the top-down performance of organisms comes from neuroscience, and especially computational neuroscience. The naïveté expressed in this work can be startling. This is illustrated by how quickly, in the dawning computer age, neuroscientists decided that neurons (the only cells in the brain taken with any seriousness at the time) were essentially binary, on-or-off devices more or less like transistors. Even today that basic mind-set seems entrenched, despite the inevitable complicating factors emerging year after year.

It all reminds me of the prominently honored theoretical neuroscientist, Larry Abbott, who, in a genuine attempt to support the prevailing mindset, wrote a book chapter about the brain entitled "Where Are the Switches on This Thing?" (Abbott 2006). There turns out to be no obvious answer.[5]

An unquestioned model

The machine model seems so deeply embedded in Levin's thinking that one can only surmise he has never thought of questioning it. He seems to think it inevitable that any analogy anyone puts forward between an organism and a machine, however remote and abstract, means the organism must work the way the machine works. He is properly struck by the remarkable achievements of development and regeneration we mentioned earlier in this chapter. But when he looks at these achievements, he immediately, and without further question, sees in them "extensive proof-of-principle of control circuits that enable efficient self-repair and dynamic control of multicellular, large-scale shape" (Pezzulo and Levin 2015).

In other words, the fact that we see the organism developmentally transforming itself and healing wounds — and doing so as a coherent whole — is already proof for him that we are dealing with large-scale "control circuits". Certainly there *is* a physical activity through which the organism's transformation and healing are realized. But nowhere in the physical lawfulness of this activity do we find the requisite principles of coordination and control. The fact that we can build machines with certain kinds of controls does not show that organisms function causally in the manner of these machines.

As for the *predictability* in which Levin sees evidence of top-down controls, his prime illustrations are the achievement of his laboratory in stimulating the development of eyes on the tails (or in the guts) of tadpoles, and in producing two-headed flatworms — all by means of bioelectric manipulations. It is true enough that when we forcibly intervene in an animal's life, giving it biological signals that would not normally occur, it can only take the signals as reality and respond holistically as best it can. Presumably, if we intervene to keep experimental conditions constant, we might (more or less predictably) expect similar insults to produce similar responses.

But it isn't clear how "throwing a wrench into the works" by deranging an animal's normal developmental processes, thereby causing the formation of dysfunctional eyes and supernumerary heads, constitutes the kind of predictability we would want from an understanding of the *true nature* of an organism. And, in any case, none of this testifies to the machine-like nature of the processes by which an organism carries out even deranged living activities.

It is precisely *because* every organism is, in a holistic sense, an agent, that it can respond to violent interventions in a meaningful and creative manner. This holistic response is what seems to entrance Levin. He wants other biologists to recognize the organism's top-down performance. But not only does he fail to reckon with the work of earlier biologists who both described such holistic agency *and* denied the machine interpretation; he sees no need to make his own case for that interpretation. He just takes it for granted.

Given his promise as a biologist, I could dearly wish that Levin would consider something like the process of RNA splicing described in Chapter 8, or DNA replication and damage repair, or cell division, or just about any other sustained biochemical or physiological activity in living beings. And then I would love to see him view this activity in light of the observation by Paul Weiss we heard above: The behavior of the whole "is infinitely less variant from moment to moment than are the momentary activities of its parts". Where are the machine models that can meaningfully elucidate the overall *coherence* of these largely fluid phenomena?

I am sure Levin would be pleased to see how Weiss' work thoroughly supports his own interest in top-down causation. And I suspect that he would recognize the wisdom in Weiss' refusal of machine-based explanation.

WHERE ARE WE NOW?

Organic Form and Machine Models

We have been introduced to the problem of form — the problem Michael Levin so eloquently brings to the biologist's attention. How does an organism move in a persistent, adaptive, and sometimes strikingly novel way toward the realization of a living shape and functioning that are in some sense "given in advance"? Levin has clearly seen that this sort of activity, like purposive or future-oriented activity in general, requires us to recognize a kind of causation that somehow works not only from the present into the future (or, perhaps better, from the future into the present), but also from the whole into its parts.

But we also see in Levin's response to this problem the remarkable and seemingly unshakable power of machine-based thinking in contemporary biology, especially as exemplified in computers. Having effectively posed questions that could radically re-shape today's biology, he is content to return to the worst tendencies of the life sciences. As I have tried to show in this and the preceding chapters, the machine model fails the organism at virtually every point of comparison. Nor is the matter particularly subtle. It does not require much insight to see that the notions of wired cells, master controllers, computer-like instructions conveyed from here to there, or inert, unliving, machine-like parts coming together to form a living cell or organism simply don't carry any convincing weight.

In sum, machine-based ideas are neither revolutionary nor particularly helpful for our approach to questions concerning the character of biological activity.

In the next chapter we will look at another take on the problem of biological form — the one offered by evolutionary developmental biologist Sean Carroll in his book, *Endless Forms Most Beautiful*. He, too, is enamored of machine- and computer-based thinking. But his way of approaching the problem of form will enable us to get at a rather unexpected conclusion: form is not something we should be feeling a need to explain, least of all to explain with our familiar mechanistic notions. Once we rise above those notions, we may be able to gain our first glimpse of a game-changing question: Might it be that the proper apprehension of form is itself the understanding we were really seeking all along?

Notes

1. Vandenberg et al. 2011. As of December 7, 2024, the video was available here.

2. The point is that bioelectric fields across tissues are the result of physiological processes at a considerable remove from gene expression. While genes are certainly required for the production of the ion-transporting proteins that help produce electric fields, these genes can hardly be said to control the subsequent activity of these proteins. This activity includes the elaborate and sensitively shifting play of bioelectric signaling of the sort involved in craniofacial patterning of the tadpole.

3. The poet and philosopher, Samuel Taylor Coleridge, captured the distinction between machine and organism very well when he wrote:

> The form is mechanic when on any given material we impress a predetermined form, not necessarily arising out of the properties of the material — as when to a mass of wet clay we give whatever shape we wish it to retain when hardened. The organic form, on the other hand, is innate; it shapes as it develops itself from within, and the fullness of its development is one and the same with the perfection of its outward form. Such is the life, such is the form (quoted in Guite 2017, p. 365).

The original source is given as *Lectures 1808-1819 on Literature*, by Samuel Taylor Coleridge, edited by R. A. Foakes, vol. 1, p. 495.

4. See, for example, Weiss 1962, Weiss 1968, Weiss 1973, Russell 1930, Russell 1945, Russell 1938, Haldane 1917, and Haldane 1923.

5. The thing that stands out most egregiously in Levin’s various discussions of theoretical work in neuroscience is his casual conflation of chemistry and cognition. In describing naïve, switch- and circuit-based theorizing about neurons, he seems to assume that he is also talking directly about cognitive activity such as decision-making, learning, and memory formation. “High-level mental processes”, he claims, illustrate how “encoded information” possesses “causal power” (Pezzulo and Levin 2015).

Is he actually talking about high-level *mental* processes, or instead referring to collections of neurons? The two seem indistinguishable in his thinking. And yet cognitive scientists today (generally by their own admission) do not yet have any clue as to how the meanings of the chemist and physiologist relate to the qualities and meanings at work in our mental and cognitive activity. No one doubts that, in thinking, we employ our brains (and, presumably, much else). But we can no more say that brain activity *is* our thinking than we can say, “muscle activity *is* our willing” or “neuronal activity connected to the retina *is* our perceiving”.

Surely Levin is right in arguing for the causal effectiveness of our mental activity. What is disturbing is the way this immediately translates for him into an assumption about the applicability of the models used by mechanistic- and computational-minded neuroscientists.

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