PERSPECTIVE

A Perspective: Robert B Laughlin

To cite this article: Robert B Laughlin 2014 Phys. Biol. 11 053003

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Abstract
Despite their cultural differences, physics and biology are destined to interact with each other more in the future. The reason is that modern physics is fundamentally about codification of emergent law, and life is the greatest of all emergent phenomena.

Keywords: physics, computers, emergence

Like most physicists, I have been keenly interested in biology for a long time—three decades or more. This interest is perfectly understandable. While modern physics is often explained as the Theory of Everything, it is more fundamentally about classifying and quantifying emergent phenomena. Life is the grandaddy of emergent phenomena. Good physicists are therefore attracted to this subject like moths to a flame.

However, interests like mine have been notoriously difficult to satisfy. Theorists, such as myself, are in the business of making sense of things. We do this by wading into experimental literature, internalizing key laboratory techniques and results, and then identifying aspects of them that don’t add up properly or are confused. We never build theories on other theories. Working through a body of experiments is always a formidable undertaking, but it is doubly so in the life sciences because the literature is so large and fragmented. The traditional opportunity cost barrier is also worse. Good experimentalists in any field tend to have a better grasp of what they are doing than just about anyone else, and they don’t need a lot of help in deciding what to do and think. This is especially so when experimental techniques are freshly invented, and there are lots of obvious applications for them that have not yet been tried.

Nonetheless, the precedents of emergent phenomena in inanimate matter persistently tell us that physics has a lot to say about modern biology, especially about the pitfalls of primitive measurement technologies and large datasets generated by them. A proper conversation about this matter will probably not occur until proceeding empirically becomes sufficiently exasperating, for that’s the pattern that has played out before in other disciplines. One cannot help recalling George Santayana’s observation that those who fail to learn from history are doomed to repeat it. A terse distillation of the conversation that hasn’t happened yet is that organizational physical principles, not human creativity, determine what one can and cannot learn from a coarse experiment. They do this by dictating when errors matter and when they don’t. The idea that one can dismiss errors of detail as not mattering according to criteria one makes up is quite wrong. There is already ample evidence that understanding life well enough to engineer it is a matter of rocket science, not computer science.

The physical issues in play are best illustrated with a simple example. Consider snowflakes. They fall from the sky when the weather is cold in universal ways that are the same around the world. They exhibit well known geometrical patterns that are both stable and sophisticated. They are also varied, per the saying that no two snowflakes are exactly alike. Most of us can remember learning that snowflakes have six-fold symmetry because ice crystals have six sides. However, crystal symmetry alone will not account for very large structures. An example
would be the elaborately branched dendritic flakes 0.5 cm across featured in snowflake photo albums. It is also necessary to postulate that the six-fold symmetry forms when the crystal is small and then gets maintained by growth conditions that are violently time-dependent, yet exactly the same on the six sides. The seed crystal is another logical loose end. No one knows why small crystals have the morphologies they do. Small crystals often have rounded corners or lumpy imperfections; sometimes they have three sides rather than six. A thermodynamic argument called the Wulff construction can, in principle, account for both the six-fold symmetry and aspect ratio of ice crystals, but only if the number of water molecules in the crystal, not the chemical potential, is held fixed. The aspect ratios of the smaller crystals in snow clouds are observed experimentally to have powerful functional dependence on at least two control variables of the air: the temperature and the partial pressure of water. These variables also control the crystal’s habit, its tendency to elongate into needles, flatten into plates, or grow preferentially at the tips to make dendrites. Sometimes snow falls as symmetric flakes. Sometimes it falls as corn grains. Sometimes it falls as needles. Sometimes it falls as hexagonal columns with holes drilled down the center. Sometimes it falls as hexagonal columns capped with plates.

The parallels between snowflake growth and organism growth are fairly evident, but let us sharpen the key ideas: The macroscopic shapes in snow are sparse and adiabatically distinct. In other words, there no intermediate forms. One can imagine slowly deforming a needle into a flake keeping the volume constant. Somewhere along the deformation path the length and width have to become comparable, whereupon you get a chunky polyhedron. But real snow consists of all flakes or all needles, never a mixture of transitional forms like chunky polyhedra. This sharp transition between needle and flake as control parameters vary is sometimes explained as basal and hexagonal faces growing at different rates, with the ratio depending on the controls. However, the specific microscopic details are not important. They also cannot be falsified by extant experimental techniques. The important thing is that emergent phenomena generally and always evolve a broad continuum of initial conditions and growth conditions into a small handful of macroscopic forms. One knows for certain that this is happening in living things because their genomes are not large enough to encrypt the endlessly complex details of their form and function.

There is nothing vague or imprecise about these concepts. They are codified in a body of mathematics known as the renormalization group. It is highly quantitative and well tested in systems that one can control precisely and measure accurately. The renormalization group came to us originally from elementary particle theory, where it was inferred from the scale invariance of quantum fields. But its greatest applicability has been in table-top studies of thermodynamic phase transitions. It accounts, among other things, for their universalities, the fact that certain behaviors are exactly the same in systems with different microscopics.

Emergence is, unfortunately, a double-edged sword. On the one hand, it gives us predictive power; on the other, it makes first-principles prediction impossible. For example, if snowflake growth under particular conditions results in needles, we can model the growth with any equations that give needles. The equations do not have to be exactly right because any small perturbation to the system will still produce needles. The specific physics term for the insensitivity to detail is irrelevance. Thus, small physical perturbations are irrelevant, meaning that their effects become less and less visible as the sample size grows. The phenomenon of irrelevance is what justifies the practice of describing things using equations that one just makes up. Obviously it is not generally possible to get physically accurate results starting from wrong equations. When the perturbation becomes large, the system can suddenly transition from producing needles to producing flakes. Once it does, the idea of irrelevance again applies, but with the emergent form stable to
perturbations being the flake rather than the needle. But exactly at the transition, small perturbations have enormous effects that become bigger and bigger as the sample size grows. Modeling thus tends to fail whenever there is relevance. In fact, computation often fails even if one starts with the correct equations because small errors in executing a calculation amplify catastropically.

This schizophrenic nature of emergence—its ability to bestow predictive power or take it away, depending on circumstances—reveals both the relevance of physics to biology and also the limitations. For example, suppose one has encountered a suspected genetic regulatory circuit and wishes to determine whether it’s really true. An extremely good test is to attempt writing down equations for it. If the circuit is both correct and stable, irrelevance must be in force, so any one of a huge family of equations should do. Failure to find even one that worked would thus indicate that one’s hypothesis was wrong. By contrast, suppose one encountered a genetic regulatory system making a dense web of decisions, such as might occur in late embryogenesis. One could not proceed the same way in this case, at least without extraordinarily detailed measurements, because each decision is a point of instability full of relevance, where details matter. One is unlikely to have a Theory of Everything for sophisticated eucaryotic organisms such as ourselves. Even if one had the correct equations, one could never solve them with sufficient accuracy to correctly anticipate experiment. The goal of computing life from quantum mechanics is completely impractical, even though the Schrödinger equation is the correct microscopic description of atoms and molecules.

Of the contributions that physics is poised to make to life science, a centrally important one is to push back against the false belief that one can understand life merely by engaging ever more powerful computers. For clarity: an equation is a proposed quantitative relationship among measured quantities. A correct equation is a proposed quantitative relationship among measured quantities that is true. A computer program is a numerical evaluation of an equation. Thus a computer program is functionally the same thing as an equation. It can be either true or untrue, just as an equation can. Data means a collection of measurements recorded digitally for later use by a computer program. There is no dispute that the growing mass of biological data has not produced the greater understanding of ourselves that many people had hoped for. The human genome, now sequenced to completion in a large number of distinct cases, is an especially glaring instance of this problem. The usual explanation is that the computation going from the genome to structure, function and behavior of organisms is very difficult and will take a long time to do properly. But it would be more accurate to say that the computation is impossible. The blockage comes from the instabilities that must be present in any emergent system that makes a dense series of decisions. The errors involved in guessing the evolution equations, and also in the measurements recorded in dataset itself, become amplified by the physics of development through extreme relevance and eventually produce nonsense. Making the computer bigger does not alleviate this problem because it does not make the calculation more true. It simply enables the computer to more thoroughly misidentify fictitious stable emergent states encrypted in wrong equations and slightly erroneous measurements.

The barriers to understanding erected by emergent instability are easy to spot once one knows to look for them. For example, the first step in the gene-to-function pathway, protein folding, is highly problematic. One would like to proceed logically from a sequenced open reading frame to a three-dimensional protein structure measured by x-rays or magnetic resonance. The simplest variant of this task is when the folded structure is uniquely determined by thermodynamics and the buffered water environment solely. One makes a de novo computer model with substantial simplifying assumptions (i.e. errors), reckoning that these will not significantly affect the final outcome because the latter is robust. But attempts to
actually do this have proved notoriously difficult, even given the flexibility of fine-tuning (fictitious) equations of motion to known properties of similar proteins. The length to which people will go to overcome these difficulties include crowdsourcing, gaming, and international competitions with cash prizes. But physics dictates that the only proteins one has any hope of going after by this method are the small, stable ones, such as the collagen molecule or amyloid beta. Any protein that is big or has mechanical states or makes decisions, such as myosin or RNA polymerase, is completely out of the question. A molecule that has mechanical states and makes decisions is obviously unstable because this is how it works. Any modeling of it is thus sensitive to errors. Attempts to approach the folding problem by drawing analogies with shapes measured in the past, the track record of which is much better, amount to assuming that folding is emergent and searching through a large but limited set of emergent stable states.

Despite the dominance of pure chemistry in biology at the moment, the great problem of how life comes into being organizationally is destined to become the purview of physics. The reason is that it happens through the agency of emergent law. There is already much circumstantial evidence for this, and the idea is quite mainstream among practicing biologists, although most of them would not articulate it quite this way. The important task ahead is not a modeling endeavor. It is to walk away from unsubstantiated reductionist beliefs, separate stable situations from the unstable ones, identify the stable laws as they come into focus, render them into equations, and then work out how these laws interact with one another to beget child laws, and so on hierarchically, until the complexity falls away, and the engineering principles begin to make sense.