



Review

Beyond D'Arcy Thompson: Future challenges for quantitative biology



Thomas Gregor

Joseph Henry Laboratories of Physics and Lewis–Sigler Institute for Integrative Genomics, Princeton University, Princeton, NJ 08544, United States

ARTICLE INFO

Article history:

Received 22 February 2017

Accepted 15 March 2017

Available online 15 March 2017

ABSTRACT

The centennial of “On Growth and Form” is a good opportunity to reflect on the progress of the quantitative study of living systems and where we would like to see it heading. The era of the physical sciences being a mere vehicle for tool building for biological investigations is over. The approaches taken nowadays are analogous to those that physical scientists have taken within their respective fields for centuries, only that now they ask them about biological phenomena and function. Here I give a brief reflection on where we are and where we should direct our focus next, both from the perspective of the research endeavor as a whole, but also with respect to teaching the next generation of scientists joining the field.

© 2017 Elsevier B.V. All rights reserved.

Contents

References	12
----------------------	----

D'Arcy Thompson's, “On Growth and Form” (Thompson, 1942), admirably encapsulates the use of physical and geometric principles in biology, in a manner that was well ahead of its time. It has been widely admired by biologists, physical scientists, and anthropologists for more than half a century. His elegant descriptions of the scale and shape of living structures inspired numerous influential thinkers, including biologist Conrad Waddington, mathematician Alan Turing, and anthropologist Claude Lévi-Strauss. Its impact reached well beyond the scientific community, as a fine work of literature; including an active influence on modern architecture (Beesley & Bonnemaïson, 2008).

“On Growth and Form” has played a pioneering role in the emergence of a subfield of developmental biology: the intersection of morphogenesis with the physical sciences and mathematics. Nowadays, this interdisciplinary path has become well established, and its core goal is a mathematical formulation of the physical mechanisms underlying morphogenesis. Strikingly, many current themes in the field are foreshadowed in Thompson's work: the pursuit of general theories of biology based on physical constraints (Nelson, 2008; Bialek, 2012; Phillips et al., 2013) and the importance of emergent structures in the organization of biological systems (Anderson, 1972; Langer, 1980; Goldenfeld & Kadanoff, 1999). The centennial of “On Growth and Form” provides an occasion to reflect on how the study of

morphogenesis has progressed and where we would like to see it head. In doing so, it is helpful to not only recognize the founding contributions of Thompson's quantitative take on morphogenesis to the field, but also its shortcomings. Among those are the lack of motivating experiments and testable predictions, of which Thompson was well aware, as well as his rejection of natural selection, bordering on the ideas of vitalism (Ball, 2013; Medawar, 1982). The latter, of course, is difficult to reconcile with the central role that evolution plays in modern morphogenesis. As such the development of the field has differed from Thompson's early vision and these differences will play a prominent role in the future.

Since the publication of Thompson's book, the field has developed dramatically. We have fully integrated the notion that qualitative phenomena, similar to those highlighted by Thompson, have correspondingly deep explanations that go beyond description. As such, from a modern perspective, taking role models from those who have led the transition from qualitative to quantitative in the life sciences may be more productive. The pioneering works of Galvani and Volta on animal electricity that led to the invention of the first battery (Geddes & Hoff, 1971), or the tight collaboration between experiment and mathematical modeling at the core of the triumph of Hodgkin and Huxley's understanding of action potentials in the squid giant axon (Abbott & Kepler, 1990), are perhaps a better guide and inspiration to aspiring young scientists. More broadly, most people motivated by problems at the interface between physics and biology have revealed in Schrödinger's little

E-mail address: tg2@princeton.edu.

book “What is Life?” (Schrödinger, 1944); and some of the excitement in the early part of the twentieth century about the subject is brilliantly captured by the essays of Bohr (Bohr, 1933) and Delbrück (Delbrück, 1949; Delbrück, 1970). Furthermore, some of the classical physicists such as Ohm (Ohm, 1843), Helmholtz (von Helmholtz, 1924–5; von Helmholtz, 1954), and Rayleigh (Rayleigh, 1945) have put their mark at the advent of this field.

Today, the use of physical principles and mathematics in studies of morphogenesis – and generally in the life sciences – is widespread and generally accepted as a powerful and important tool. The 21st century marks an era in which a plethora of quantitative data is available. The availability of increasingly precise data opens the door to dissect intricate problems, which qualitative description has not been able to unravel. Quantitative analyses can now be used to test theoretical predictions and confront falsifiable mathematical models. This scenario represents a stark contrast to the past when experimental data collected by biologists was not easily converted into numbers and theories weren't necessarily falsifiable. With the advent of sequencing and quantitative microscopy, however, data is inherently represented as numbers, and there is a sense that biological complexity can be tackled if the right mathematical framework can be found (National Research Council Committee on CMMP, 2010).

The landscape of the field is constantly changing: not only that the availability of quantitative data is increased, but there is also an increased ability of what scientists can do with these numbers. Biochemistry has been, to a certain degree, quantitative for a long time; but even if the outcome of an experiment was represented by a number, there has not been a sense that this number should serve as a test for a mathematical model or a larger physical principle. This fundamental change is also altering the kinds of questions that can be asked, by offering a theory or a model that can drive these questions. The era of the physical sciences being a mere vehicle for tool building for biological investigations is over. The questions we ask nowadays are questions physical scientists have asked within their respective fields for centuries, only that now they ask them about biological phenomena and function (Anderson, 1972).

Some examples of systems where a physical science approach has born fruit: cellular identities arise through the interaction of many genes within regulatory networks (Shmulevich et al., 2005; Torres-Sosa et al., 2012; Krotov et al., 2014), computation in the nervous system originates from interactions among many neurons (Hopfield, 1982; Hopfield & Tank, 1986), schools of fish or flocks of birds or swarms of insects grow out of social interactions among hundreds or thousands of individuals (Cavagna et al., 2010; Attanasi et al., 2014; Katz et al., 2011), and even the structures of individual protein molecules emerge from interactions among hundreds of amino acids (Socolich et al., 2005; Bialek & Ranganathan, 2007). Furthermore there is a belief that it should be possible to characterize all these collective phenomena in a common language, e.g. that of statistical physics (Bialek, 2012). Single cells adapt by adjusting the expression levels of genes, and networks of genes determine cellular fates; individual neurons adapt to their inputs, and networks of neurons learn; organisms evolve to match their environments, and the immune system provides an example of evolution in a microcosm; in each case the dynamics implements an algorithm that drives toward improved performance, and in many cases that performance is determined by the physics of the problem that the system has been selected to solve (Dyson, 1985; Goldenfeld & Woese, 2011; Neher & Shraiman, 2011; Bialek, 1987).

With this context in mind, what are the future challenges for the field? After a long period during which the contribution of the physical sciences was crucial in providing the tools for discovering the building blocks of biology, while at the same time mathematics entered as a language to describe interactions of these components through phenomenological modeling, the 21st century might be the time when the physical sciences should reach for an even bolder approach. Both at the level of theory and experimentation, the physical scientist should

aspire to a level of precision and rigor in the life sciences that have been so successfully used for understanding inert matter: aiming for unifying principles that explain many biological phenomena at once and providing measurements that allow distinctions between competing quantitative theories.

For example, Berg and Purcell have worked out a limit analogous to shot noise in counting photons, at which bacteria cease to sense concentration gradients due to the random nature of molecular motion (Berg & Purcell, 1977). Under most conditions, both photons and molecules arrive at random at their respective sensor and thus there must be shot noise in counting such arrival events. It has been shown that bacteria are indeed able to operate reliably at this fundamental limit, but only if the cell compares independent concentration measurements over time (Segall et al., 1986). Later it was shown that this same limit is also encountered at the level of gene regulation in the arrival of transcription factors molecules arriving at regulatory DNA binding sites to activate transcription (Bialek & Setayeshgar, 2005; Gregor et al., 2007). In this case it was even possible to separate the components of spatial vs. temporal averaging necessary to overcome the observed noise levels (Little et al., 2013) – a case of careful measurement allowing distinction between competing quantitative theories.

The history of physics makes apparent that progress is facilitated by a lively interplay between theory and experiment. On the one hand, theories predict new places to look for insight and thereby generate new experimental challenges, and on the other hand, theories in turn are challenged by new experiments that point to places that are not encompassed by the initial theory. Prominent recent examples of this interplay are the discovery of the Higgs particle in fundamental high-energy physics (ATLAS and CMS Collaborations, 2012), or the discovery of gravitational waves and their relationship to Einstein's general relativity theory (Abbott et al., 2016). In both cases theories predicted the existence of some new fundamental state of matter, and in both cases the experimental validation that came many years after the prediction brought with it new puzzles that require our thinking to look past the current theories. Central to both of these examples was that the theories had produced testable quantitative predictions for which experiments could be designed that could challenge the prediction. In fact, for these kinds of interplays between theory and experiment, both the predictions and the measurements produce numbers that can be rigorously compared to each other in a way that error bars and the origin of these error bars matter. Such interplays, which hold the highest promise for uncovering fundamental laws in the physical sciences, is still largely missing in our investigation of the mysteries of living matter. But therein lies the hope for the future of quantitative biology, in going beyond mathematical descriptions of complex biological phenomena toward a principle driven understanding that employs the formulation of actual theories that can be tested with physics-style measurements (Bialek, 2012).

Traditionally, our thinking about biological problems has been centered on a particular model organism these problems could be addressed in, which naturally created boundaries for both tool development and the kinds of questions that could be asked. Some of these boundaries have been overcome by the recent dramatic developments in biology itself, facilitating the use of a common set of molecular tools across a broad swath of organisms. For example, we commonly use the same techniques to analyze genetic circuits in bacteria that we use to understand the differentiation of various types of neurons in the human brain (Chalfie, 2009; Primer on Optogenetics, 2010).

In addition the conceptual questions that we now ask increasingly cut across the natural organization of biological hierarchies. For example the problem of functional reliability in the presence of molecular noise is faced by almost every biological process and can therefore be addressed in a multitude of different contexts. Individual cells must sense their physical environment and determine their own internal state from signals that are encoded, e.g. in graded concentrations of messenger molecules: how do cells tune the signal-to-noise ratio and achieve efficient

coding of information in all these cases? The above-mentioned Berg and Purcell limit has been used to understand sensing in bacterial chemotaxis but it has also been successfully applied to gene regulation and cell fate decisions.

It remains to be seen whether these questions, which manifestly have more of a physical science flavor to them, will in fact lead to a more principled and unifying understanding of living matter. But starting to ask these new questions is making an impact on both biology and on the physical sciences, which nurtures the hope that a new branch of science comprising the interplay between theory and experiment might emerge that centers around the beautiful and intricate phenomena of modern biology.

Just as D'Arcy Thompson's avant-garde attempts to develop physical descriptions of biological systems lead to excitement at the interface of the physical sciences and biology last century, there is now a renewed sense of excitement at this same interface at the beginning of the 21st century. Many biologists believe that we are at the brink of another revolution that turns biology into a quantitative science, much like the physical sciences themselves. In parallel, the physical science community has embraced the complexity of the striking phenomena of life as a chance to broaden the boundaries of their respective fields rather than just an opportunity for application of well-established tools and approaches to biology. At the end of this process the distinction between life and physical sciences will vanish, and hopefully an understanding of the living world will emerge that matches the profound understanding that the physical sciences have established for the inanimate world.

In order to achieve these goals we need to rethink our approach to teaching aspiring young scientists about the phenomena of life. Biology can no longer be taught alone as a non-quantitative science. The early curriculum of a beginning biologist needs to have a heavy mathematical and physical science component, and that component needs to accompany the students along every step of their life science education. At the same time, aspiring physical scientists need to be brought very early to the beautiful phenomena of the functional behavior of living systems. But these systems provide obvious entry points into our teaching of physics, chemistry, engineering, and even computer science, since living systems can be analyzed at these various levels of description. There is therefore a real opportunity to make a profound impact on the field at the earliest levels of education such that in due time the boundary between the physical sciences and biology will indeed erode.

References

- ATLAS and CMS Collaborations, 2012. *Discovery of the Higgs Boson*, arXiv:1207.7214 [hep-ex] and arXiv:1207.7235 [hep-ex].
- Abbott, L.F., Kepler, T., 1990. *Model neurons: from Hodgkin–Huxley to Hopfield*. In: Garrido, L. (Ed.), *Statistical Mechanics of Neural Networks*. Springer–Verlag, Berlin, pp. 5–18.
- Abbott, B.P., et al., LIGO Scientific Collaboration and Virgo Collaboration, 2016. *Observation of gravitational waves from a binary black hole merger*. *Phys. Rev. Lett.* 116 (061102).
- Anderson, P.W., 1972. *More is different*. *Science* 177, 393–396.
- Attanasi, A., Cavagna, A., Del Castello, L., Giardina, I., Grigera, T.S., Jelić, A., Melillo, S., Parisi, L., Pohl, O., Shen, E., Viale, M., 2014. *Information transfer and behavioral inertia in starling flocks*. *Nat. Phys.* 10, 691–696.
- Ball, Philip, 2013. *In retrospect: on growth and Form*. *Nature* 494, 32–33.
- Beesley, P., Bonnemaïson, Sarah, 2008. *On Growth and Form: Organic Architecture and Beyond*. Tuns Press and Riverside Architectural Press.
- Berg, H.C., Purcell, E.M., 1977. *Physics of chemoreception*. *Biophys. J.* 20, 193–219.
- Bialek, W., 1987. *Physical limits to sensation and perception*. *Annu. Rev. Biophys. Biophys. Chem.* 16, 455–478.
- Bialek, W., 2012. *Biophysics: Searching for Principles*. Princeton University Press, Princeton NJ.
- Bialek, W., Ranganathan, R., 2007. *Rediscovering the Power of Pairwise Interactions* (arXiv.org:0712.4397 [q-bio.QM]).
- Bialek, W., Setayeshgar, S., 2005. *Physical limits to biochemical signaling*. *Proc. Natl. Acad. Sci. U. S. A.* 102, 10040–10045.
- Bohr, N., 1933. *Light and life*. *Nature* 131, 421–423.
- Cavagna, A., Cimarelli, A., Giardina, I., Parisi, G., Santagati, R., Stefanini, F., Viale, M., 2010. *Scale-free correlations in starling flocks*. *Proc. Natl. Acad. Sci. U. S. A.* 107, 11865–11870.
- Chalfie, M., 2009. *GFP: lighting up life*. *Proc. Natl. Acad. Sci. U. S. A.* 106 (25), 10073–10080.
- Delbrück, M., 1949. *A physicist looks at biology*. *Trans. Connecticut Acad. Arts Sci.* 38, 173–190.
- Delbrück, M., 1970. *A physicist's renewed look at biology: twenty years later*. *Science* 168, 1312–1315.
- Dyson, F., 1985. *Origins of Life*. Cambridge University Press, Cambridge.
- Geddes, L., Hoff, H., 1971. *The discovery of bioelectricity and current electricity The Galvani-Volta controversy*. *IEEE Spectr.* 8 (12), 38–46.
- Goldenfeld, N., Kadanoff, P., 1999. *Simple lessons from complexity*. *Science* 284, 87–89.
- Goldenfeld, N., Woese, J., 2011. *Life is physics: evolution as a collective phenomenon far from equilibrium*. *Annu. Rev. Cond. Matt. Phys.* 2, 375–399.
- Gregor, T., Tank, D.W., Wieschaus, E.F., Bialek, W., 2007. *Probing the limits to positional information*. *Cell* 130, 153–164.
- von Helmholtz, H.L.F., 1924. *Helmholtz' Treatise on Physiological Optics*. Translated from the third German edition of 1910, by JPC Southall. Optical Society of America, Rochester NY (1924).
- von Helmholtz, H.L.F., 1954. *On the Sensations of Tone as a Physiological Basis for the Theory of Music* Second English edition, translated from the fourth and last German edition of 1877, by AJ Ellis. (HLF von Helmholtz (Dover, New York, 1854)).
- Hopfield, J.J., 1982. *Neural networks and physical systems with emergent collective computational abilities*. *Proc. Natl. Acad. Sci. U. S. A.* 79, 2554–2558.
- Hopfield, J.J., Tank, D.W., 1986. *Computing with neural circuits: a model*. *Science* 233, 625–633.
- Katz, Y., Tunstrom, K., Ioannou, C.C., Huepe, C., Couzin, I.D., 2011. *Inferring the structure and dynamics of interactions in schooling fish*. *Proc. Natl. Acad. Sci. U. S. A.* 108, 18720–18725.
- Krotov, D., Dubuis, J.O., Gregor, T., Bialek, W., 2014. *Morphogenesis at criticality?* *Proc. Natl. Acad. Sci. U. S. A.* 111, 3683–3688.
- Langer, J.S., 1980. *Instabilities and pattern formation in crystal growth*. *Rev. Mod. Phys.* 52, 1–28.
- Little, S.C., Tikhonov, M., Gregor, T., 2013. *Precise developmental gene expression arises from globally stochastic transcriptional activity*. *Cell* 154 (4), 789–800.
- Medawar, P., 1982. *Pluto's Republic*. Oxford University Press, pp. 228–241.
- National Research Council Committee on CMMP, 2010. *Condensed-Matter and Materials Physics: The Science of the World Around Us*. 2007. The National Academies Press (Solid State Sciences Committee).
- Neher, R.A., Shraiman, B.I., 2011. *Statistical genetics and evolution of quantitative traits*. *Rev. Mod. Phys.* 83, 1283–1300.
- Nelson, P., 2008. *Biological Physics Energy, Information, Life*. Freeman and Company, New York.
- Ohm, G.S., 1843. *Ueber die Definition des Tons, nebst daran geknöpfter Theorie der Sirene und hnllicher tonbildender Vorrichtungen*. *Ann der Physik* 59, 513–566.
- Phillips, R., Kondev, J., Theriot, J., Garcia, H., 2013. *Physical Biology of the Cell*. Garland Science, New York.
- Primer on Optogenetics: E Pastrana (2010). "Optogenetics: Controlling cell function with light". *Nature Methods*. 8 (1): 24–25. Editorial: "Method of the Year 2010". *Nature Methods*. 8 (1): 1. 2010. (Commentary: K Deisseroth (2010). "Optogenetics". *Nature Methods*. 8 (1): 26–9).
- Rayleigh, Baron, 1945. *The Theory of Sound* Second revised edition, with a historical introduction by RB Lindsay. (JW Strutt, Baron Rayleigh (Dover, New York, 1945)).
- Schrödinger, E., 1944. *What is life?* Cambridge University Press, Cambridge
- Segall, J.E., Block, S.M., Berg, H.C., 1986. *Temporal comparisons in bacterial chemotaxis*. *Proc. Natl. Acad. Sci. U. S. A.* 83, 8987–8991.
- Shmulevich, I., Kauffman, S., Aldana, M., 2005. *Eukaryotic cells are dynamically ordered or critical but not chaotic*. *Proc. Natl. Acad. Sci. U. S. A.* 102, 13439–13444.
- Socolich, M., Lockless, S.W., Russ, W.P., Lee, H., Gardner, K.H., Ranganathan, R., 2005. *Evolutionary information for specifying a protein fold*. *Nature* 437, 512–518.
- Thompson, D'Arcy Wentworth, 1942. *On Growth and Form*. Courier Corporation.
- Torres-Sosa, C., Huang, S., Aldana, M., 2012. *Criticality is an emergent property of genetic networks that exhibit evolvability*. *PLoS Comput. Biol.* 8, e1002669.