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EDITORIAL

Life and death in biophysics

Editor-in-Chief

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I would like to thank the Editorial Board and Publishers of *Physical Biology* for inviting me to be the new Editor-in-Chief. It is an honour to be trusted with guiding this journal for the next few years. I would also like to thank Terry Hwa, for his role as founding Editor-in-Chief. His good judgement and deep understanding of biophysics have carried *Physical Biology* a long way since its creation in 2004.

Looking now to the future, what I hope we can emphasize in *Physical Biology* is the understanding that the physical sciences can bring insights to all areas of biology. Historically the greatest successes for biophysics have been at the molecular scales. I believe that these successes can be matched in the years to come at higher scales of biological complexity, such as cell and developmental biology, population biology and evolution. It is also true that, historically, medical physics has provided some of the most important tools for the diagnosis and treatment of human disease. I believe the physical sciences can also have an impact on medicine at the level of causation and prevention of disease, by applying physical principles and methodologies to human biology at the cellular scale. Naturally, this is a huge swath covering the whole of life science, and most of these areas are well represented within their home disciplines by specialized journals. However, there is an acute need for a journal to cater for interdisciplinary research which combines keen physical insight and methodology with pressing biological questions and data across all scales. *Physical Biology* can fulfil this role, and particularly welcomes contributions from multidisciplinary teams comprising both physical and life scientists.

In collaboration with Publisher Andrew Malloy, we have emphasized these ideas in the revised scope of the journal, and expanded the expertise represented on the Editorial Board. I would like to welcome the new Editorial Board members, thank the continuing members for their previous and future work on the journal, and extend my sincere gratitude to retiring members for their hard work and commitment to the journal.

Allow me now to present a personal take on a topic of interest to all: the life and death of biophysics.

A tale of two disciplines

It is the best of times, it is the worst of times, ...

I will refrain from torturing readers with a botched rewrite of Dickens' masterpiece, but his famous antithetical description of England and France in the late 18th century provides an insight into the state of biology and physics in 2011.

I believe that a close alliance between physics and biology would result in an unprecedented advance in our understanding of living systems, and yet I also think that our ability to forge this alliance at a community scale is uncertain. To succeed we must learn to appreciate the differences between the physical and life sciences, and how these differences are a natural result of the phenomena under study. Only then will we be able to lay down a foundation of common trust, respect and collaboration; a foundation from which to grow new science at the biophysics interface.

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It is unfortunate that physicists and biologists generally have difficulty understanding each other, not just in the words that they use, but in a deeper philosophical sense. Such is the gulf between these two communities, that the easiest option for an individual in either camp is to listen passively to the other camp, be reassured that what one heard was incomprehensible, and resume activities as normal. There are cultural stereotypes associated with each camp that are quite amusing, and reassuring when one feels threatened. “Physicists want to reduce everything to a single equation or parameter”, “they think they can reinvent biology, but they don’t know anything”, etc, and “biologists are just butterfly collectors”, “they focus on tiny exceptions, and hide behind endless terminology”, etc. In the cold light of day, we should be able to convince ourselves that judging individuals by the group to which they belong is foolish and old-fashioned. Each person in science brings a unique talent, yet that talent is moulded by their education and experience. Happily, so long as one is willing to listen and learn, the constraints of education can be loosened, and one’s perspectives thereby broadened.

This has been my experience over the past 11 years. As the new millennium dawned I was a theoretical physicist specializing in non-equilibrium statistical mechanics, nearing the end of my *n*th postdoctoral position, and working on diffusion processes in 46 dimensions (which sounds baroque, but is actually quite interesting). By chance, I began talking to Janis Antonovics and Cornelis Weijer, deep thinkers in population biology and developmental biology, respectively, and I quickly became passionate about living systems. I avidly read biology books, attended biology seminars and, most importantly, talked to biologists of all stripes: ecologists, developmental biologists, neuroscientists, cell biologists, molecular biologists, etc. The more I was exposed to biology, the more the big picture began to emerge, and the more I felt that the whole of biology presented opportunities for physical scientists. Over the intervening years I have experienced alternating phases of enthusiasm, bafflement and despondency, as my research in biology developed, along with my understanding of the physics–biology interface. The most important lesson I have learned is to keep the phenomena of living systems constantly in view. These phenomena, the understanding of which is our ultimate goal, are insensitive to the artificiality of disciplinary boundaries and the short-sightedness of human territoriality.

Life and death

So, what is the ‘life and death of biophysics’? For the purposes of this editorial, it is merely a play on words, as illustrated below; a handy mnemonic to represent a list of nine concepts which help explain the fundamental differences between physical and biological systems. At a deeper level, ‘life and death’ aptly indicates the urgency with which physics must respond to the shifting scientific challenges and culture of the 21st century, and the health of biophysics is irrevocably tied to the health of one of its parents! But that is a topic beyond the scope of this editorial. Let us return to the mnemonic:

Length scales
Independence of scales
Feedback between scales
Equilibrium

Demographics
Emergence of complexity
Active dynamics
That which is optimized
Heterogeneity

Length scales

Physicists love to think in terms of length (or time, or energy) scales, and so this is a good place to start. The arena of length scales in physics is truly vast. Physics concerns itself with quarks and gluons at sub-femtometer scales, all the way to the large-scale structure of the observable universe at a scale of 10^{26} metres.

The length scales relevant to biology cover a modest range compared to those in physics—a mere 16 orders of magnitude from the nanoscale of nucleotides to the size of planet Earth.

Independence of scales

Despite the enormous range of length scales relevant to physical phenomena, there are chasms separating scales of fundamental phenomena (putting to one side the continuous spectrum of electromagnetic radiation). Nuclear particles at the femtometer scale are separated by five orders of magnitude from atoms at the Ångström scale with, as far we know, nothing of fundamental significance inbetween. Fundamental collective physical phenomena, such as turbulence, superconductivity and magnetism occur in materials comprised of very large numbers of molecules, with system sizes in the range of microns and larger. Important physical structures, such as eddies in a fluid, or magnetic grains in a ferromagnet, are many orders of magnitude greater in size than their constituent atoms. At higher scales still, there are no fundamental length scales until gravity comes into play. Astrophysical structures have representative length scales determined by a balance between gravitational forces and, for example, nuclear processes.

By contrast, the more modest range of length scales in biology is crammed with fundamental objects at nearly all orders of magnitude, and which are relevant to nearly all living organisms. As we zoom out from the nanoscale, nucleotides form genes and amino acids form proteins. Nucleic acids and proteins give way to chromosomes and organelles. Thereafter the cell, which arguably defines the most fundamental scale in all biology, appears at one to ten microns. Eukaryotic animal cells comprise epithelial and stromal tissues, which surround organs within organisms. These form groups and populations which comprise ecosystems spanning the continents.

Feedback between scales

As Steven Weinberg wryly remarked [1], “if you’ve seen one electron, you’ve seen them all”. The essence of the fundamental microscopic entities of physics are insensitive to higher scales and their own historical milieux. An electron or hydrogen atom has the same fundamental essence whether it was previously encased in a rock, a human or a star. Once Schrödinger’s equation for the hydrogen atom was solved, there was no need to solve it ever again.

The fundamental microscopic units of biology are the genes. Their composition differs from organism to organism and from species to species, ever changing, due to the constant process of evolution. Biological dynamics at the largest length and time scales, namely competition between and within populations of different organisms, directly feeds into the structure and frequency of genes. All other biological scales, sandwiched between populations and genes, are directly influenced by, and are the direct historical result of, this evolutionary feedback mechanism. It is a commonplace to emphasize the importance of evolution at every scale in biology. Perhaps what is less appreciated is the profound difficulty this mechanism imposes on scientific investigation. The ancient fitness landscapes on which populations competed in the past are long gone, and it is impossible to reconstruct them. Essentially, we are presented with complex biological systems, such as cells and organisms, as a *fait accompli*. The agenda of life science is to distill meaning and understanding by probing present-day biological systems, wherein lies four billion years of evolutionary dynamics. If such a feedback from large to small occurred in physical systems, there would be no mathematical theory of the atom, and the lexicon of physics would be as necessarily cumbersome as that of biology.

Equilibrium

The physics of complex systems has been extraordinarily successful, with quantitative understanding of diverse phenomena such as phase transitions, the quantum Hall effect and semiconductivity. This success, while impressive, is mainly confined to complex systems in thermal equilibrium. Ludwig Boltzmann's genius at the turn of the last century yielded statistical mechanics, which can be applied in the form of a recipe to any system in thermal equilibrium. In the century that followed, physicists and chemists tried to apply and extend Boltzmann's theory to systems far from thermal equilibrium. Despite some progress, most notably by Nobel prize-winning chemists Lars Onsager and Ilya Prigogine, a general theory is still lacking. Research into non-equilibrium statistical mechanics remains a frontier area of physics.

Most biological systems exist far from equilibrium. As Schrödinger emphasized in his famous little book, organisms are negative entropy machines [2]. It is a fundamental law of physics that the entropy of any isolated system will steadily increase until it is maximized. Hence, living systems must maintain strong energy and matter fluxes with their environments if they are to keep entropy from scrambling the ordered architectures essential to life.

Demographics

Another convenience of complex systems in physics is the magnificent number of their constituents, essentially Avogadro's number. The enormity of this number quells fluctuations in nearly all cases, and allows complex systems to be described by a few gross characteristics, such as temperature, pressure and conductivity. As the number of constituents becomes smaller, statistical self-averaging breaks down, and fluctuations rule. Gross characteristics are necessarily replaced by spatio-temporal variation and statistical distributions. This is the stuff of mesoscopic physics, and is another research frontier.

Most biological systems exist at the 'mesoscale'—not necessarily in terms of size, but in terms of the number of their discrete constituents. Ecosystems are typically composed of thousands of species. Populations are often composed of thousands of organisms. An early embryo or cancer tumour is composed of thousands to millions of cells. A cell will have copy numbers of particular types of proteins which may be in the hundreds or even smaller. Clearly, fluctuations are an essential feature of biological systems, and require sophisticated statistical approaches for their characterization.

Emergence of complexity

Nearly all complex systems in physics exhibit emergence; they are examples of what one might call 'simple complexity'. Physicists have created effective theories of phenomena such as fluid turbulence, superconductivity, and phase transitions. These theories are quantitative and predictive, yet rely on new abstract concepts such as 'renormalization' and 'order parameters'. Despite the technical intricacy of the theories, it is important to stress that the complex phenomena emerge directly at the macro-scale from a few simple interactions at the scale of atoms and molecules.

Complex systems in biology appear for the most part to be of a different ilk, 'complex complexity', so to speak. The coordinated dynamics of a cell is not emergent in the same sense as the coordinated dynamics of a fluid vortex. The cell's complexity cannot be traced back to a few pairwise interactions between atoms; it is, rather, the result of a vast network of interactions that has arisen from millennia of construction, deconstruction, innovation and fortuity fuelled by evolution.

Active dynamics

Energy is a fundamental descriptor of nearly all physical systems. Conservation of energy allows powerful theoretical machinery to be focused on the problem at hand. The first question many physicists ask of a new problem is 'What's the Hamiltonian?' In other words, 'What's the energy function?'

Energy is of course conserved in biological systems too, but its importance as a descriptor is severely hampered by the complex flux of energy between the constituents of the biological system, and between the system and its environment. A new aspect here is metabolism. Biological systems from cells to organisms have a metabolism, meaning a network of energy pathways, connecting chemical and mechanical processes, that allow functionality and active dynamics. Pushing on a cell can be well described by Newton's equations for the first second or so. After that, cell biology takes over. Decisions are made, metabolic processes are activated, and minutes later the cell may die, move away, or change its phenotype. Such active processes lie well beyond the descriptive realm of classical mechanics.

That which is optimized

Some of the most powerful theories of physics are most neatly described using the language of optimization. All classical physics can be described in terms of minimizing the 'action'. Systems in thermal equilibrium can be described in terms of minimizing their 'free energy'. Isolated systems in equilibrium maximize their 'entropy'.

Biology currently lacks quantities in inverted commas which can be minimized or maximized to provide a fundamental and predictive description of the system in question. The discovery of such quantities would revolutionize our understanding of living systems. It is almost an article of faith for many physicists that such quantities exist. If they do not, the power of physics to reveal a new fundamental understanding of biology may well be significantly reduced.

Heterogeneity

High quality physics experiments typically rely on purification of the sample under examination. Working on homogeneous systems clearly aids interpretation of data. Most physical theories assume homogeneity in order to maintain mathematical elegance and the possibility of analytic understanding. Heterogeneous physical systems, such as glasses, remain a research frontier.

Biological systems are, by their very nature, heterogeneous. In many cases it is not possible to reduce the heterogeneity of a living system without killing it. Cells have tens of thousands of different kinds of constituent proteins. Embryos have dozens of different types of cells and hundreds of different signalling molecules. Even a single-species population comprises a diverse array of genotypes. Heterogeneity is at the heart of biology, it is a fact of life. Clearly, it is also a non-trivial inconvenience which hampers the interpretation of data and the construction of mathematical theories.

And whence from here?

This list of fundamental differences between physical and living systems is indeed daunting. Many physicists, in pursuing similar lines of reasoning, have likely turned their backs on biology as too messy or too hard. I think, though, that this perspective provides a solid foundation for biophysical enquiry and collaboration. I think it alerts physicists to the need to embrace biological complexity and guard against over-simplification and reductionism. I think it alerts biologists to the fact that a quantitative understanding of biology requires techniques that lie at numerous frontiers of physics research. This, surely, should be enough common ground to warrant bringing these two communities closer together.

References

[1] Weinberg S 1998 The revolution that didn't happen *New York Review of Books* **45** 48–52
[2] Schrödinger E 1944 *What is Life?* (Cambridge: Cambridge University Press)