UNDERSTANDING THE
Physics of Life

From Molecules to Systems:

Towards an Integrated Heuristic for Understanding the Physics of Life

A Roadmap for Understanding the Physics of Life

There is currently a schism in biology between, on the one hand, reductionist approaches that begin at the single molecule level and attempt to integrate molecules into larger systems of interacting molecules; and on the other, systems biology approaches that typically neglect molecular-scale phenomena and attempt to model the behaviour of whole biological systems. To understand Life we must resolve this fundamental problem. From the reductionist perspective, which typifies much of biochemistry, the challenge is that many biological phenomena seem too complex for there to be a realistic chance of achieving complete understanding that yields predictive power; for systems biologists there is a different challenge: many phenomena that affect entire systems (whether organisms, or ecosystems) have their origin in molecular-scale phenomena, and a complete description of biology must account for this.

Physicists have much experience of tackling cross-length-scale problems, including the grand challenge to build a unified theory of physics, integrating quantum mechanics with general relativity, or in statistical mechanics, description of the behaviour of ensembles of molecules using molecular-scale properties. The experience that physicists have of addressing difficult cross-length-scale challenges has provided them with unique insights that may be pivotal in solving the fundamental challenge of modern biology: how do we integrate molecular-scale and systems-level descriptions of biological phenomena?

This hypothesis was the starting point for our Network. Our activities during the past three years have enabled us to compile a picture of some of the important challenges that physicists and biologists, working in partnership, must solve in order to understand the physics of life.

1. Collaboration: Underpinning Everything

For progress to be made in addressing the grand challenge of understanding the physics of life, it is vital that physicists and biologists work together in partnership. Progress will not be made by physicists simply serving as tool-makers for biologists, or by physicists taking biological themes as a justification for work on their pet problem. Real progress in understanding the physics of life will result from a problem-focused partnership between biologists and physicists. Equally critical to the success of this shared venture are (i) respect by physicists for the complexity of biological problems; (ii) the recognition by biologists that physicists can bring uniquely valuable insights, and (iii) the recognition by physical scientists that great physics may start with a biological hypothesis.

(i) The Unique Insights of Physics

As noted above, statistical mechanics and the search for a grand unified theory of physics have provided physicists with an abundance of experience of the challenges associated with understanding cross-length-scale problems. These challenges are theoretical; the importance of theory, and the quality of much work already being done on the theory of biological problems, has been a key theme to emerge from our network. Theory is relevant to fundamental questions (for example, on the nature of evolution, or the flow of information in biological systems) and to problems closely related to the end-user challenges that we address in section 4 (for example, studies of swarming and collective behaviour that are relevant to the understanding of bacterial biofilms).

Above all else, physics – whether theoretical or experimental – is a quantitative discipline. Quantification drives us to ask harder questions and to formulate bolder hypotheses. While the contribution of physicists to understanding the physics of life must never be restricted to the provision of tools, it is nevertheless the case that huge leaps in understanding (for example the elucidation of the structure of DNA) have come through the development of physical methods. Some of the most important contributions that physicists can make to the understanding of Life will come through the development of innovative approaches to the quantitative characterisation of biological systems in space and time, yielding precise information on structure, properties and dynamics with which to test theories.

(ii) Great Physics may Begin with a Biological Hypothesis

Time and again our Network has enjoyed presentations of world-class physics that began with a biological question. “Why do birds flock, and fish mill (undertake circular swarming behaviour)?” is an illustrative challenge. Apparently fundamental, driven by a question about the behaviour of groups of animals, in the hands of a theoretical physicist this question led to new hypotheses about collective behaviour and new hypotheses about collective behaviour that may have much wider significance. We understand the challenge for peer-review panels in assessing proposals that start with a biological hypothesis. However, our firm conclusion is that to understand the physics of life, it is necessary for physicists to begin by asking important biological questions. The new and world-class physics will come from the development of innovative ways to address these questions; critically, these will be physics solutions because physicists bring to biology the twin distinctive characteristics that *they ask quantitative questions and they seek for answers that are underpinned by theory*. These characteristics ensure that biological questions will receive physical answers.

2. Coarse Graining

Ultimately we seek a complete integration of understanding across the length scales from a single molecule to an entire ecosystem. However, a full integration across all length-scales will not come in a single step. There are a variety of levels of description (“coarse-graining”) at which cross-length scale integration is elusive and would, indeed, be a considerable prize. The goal of achieving understanding across the length-scales, from molecules to systems, is key in all, but a full understanding across the whole range of biological length-scales will probably not be achieved until we have become better at understanding biology across smaller ranges of scale.

(i) The Living Cell

The cell is a fundamental structural unit in biology, but cells consist of very large numbers of molecules. The explosion of interest in single-molecule techniques has enabled biophysicists to make measurements on single-molecule behaviour in single cells, but understanding and predicting systems-level phenomena (for example, cellular reproduction) using such molecular-scale information remains challenging. For example, we may be able to locate and track the position of a membrane protein, but understanding how the different states of that protein regulate a biochemical pathway in the cell represents a significantly more substantial experimental challenge requiring the ability to monitor and characterise the interactions between a larger number of intracellular molecules.

(ii) Multicellular Systems

Human beings and biofilms both consist of large numbers of cells. Both exhibit collective behaviour not observed in isolated cells. A fundamental challenge in biology is to understand why and how assemblies of cells develop emergent behaviours. Even the simplest such systems are important: as antimicrobial resistance becomes more prevalent, understanding the collective behaviour of biofilms is a vital societal challenge. More widely, the importance of the microbiome for health, and of our symbiotic relationship with bacteria, is being recognised increasingly.

(iii) Synthetic Biology

Synthetic biology may assume increasing importance in understanding the physics of life. The development of synthetic constructs to facilitate the testing of biological hypotheses enables the formulation of quantitative approaches that combine physical theory and experiment. They enable us to address questions that are not readily explored in biological systems. Synthetic biology impacts on our understanding of both the Living Cell and Multicellular Systems. For example, there has been an explosion of work on synthetic cells driven by the desire to build artificial systems that replicate biological phenomena. Even if synthetic life does not emerge from such studies, they are already yielding insights into fundamental aspects of cellular behaviour (for example, despite extensive efforts, synthetic cells that sustain proton gradients as effectively as lipid vesicles are elusive).

3. Challenges for Understanding the Physics of Life

The following themes emerged as important during the life of our Network. Topics (i) – (viii) below were explored through focused workshops. However, this list is not exhaustive; with finite resource we could only explore a limited number of areas. Under (xi) below we list a number of other topics that are felt to have significance but which we did not have time to explore in our Focused Workshops. A characteristic of all of these challenges is that they are somewhat under-theorised: there is great scope in all of them to bring to bear the characteristics of quantitative experimentation allied with mathematical theory that are the distinguishing heuristic principles of physics.

(i) Forces in Biology

Forces are important in many ways in biology, including mechanisms of mechanotransduction (the biochemical response of cells to mechanical stress) and phenomena such as muscle contraction (understood at the level of tissue or the molecular level, through interactions between myosin and actin). A number of fundamental challenges are subjects of active enquiry. These include understanding the origin of forces (energy landscapes) and the measurement of forces in biological systems. For example, how is mechanical stress sensed and transduced? In evolutionary terms, how has mechanical function arisen? There is a need to develop tools for the measurement of forces inside cells, and also predictive modelling methods. It is known that cells exhibit important forms of mechanical behaviour, but obtaining quantitative data remains challenging. Understanding across the length scales – from single molecules to tissue – is required.

(ii) The Physics of Bacterial Infection

With the growth of antibiotic resistance, bacterial infection is likely to be a problem of growing importance. Bacterial infection is clearly connected with the problem of biofilm formation, but the two are not always connected. There are many ways in which physics can contribute to the study of infection. Techniques are required that enable mechanisms of infection to be studied in cells and organisms. The development of such techniques requires, for example: new bleach-resistant dyes, methods for measuring osmotic changes, non-perturbative imaging techniques, multi-channel measurement techniques and high resolution imaging methods. Basic biophysics needs to be understood better including understanding the packing of DNA, and how it is accessed, membrane biophysics, the interactions between eukaryotes and prokaryotes, and mechanisms of bacterial growth and division. We need to understand how hosts kill pathogens, what bacterial death looks like, the influence of heterogeneity, bacterial permeation barriers, the underpinning importance of the proton-motive force and bacterial evolution.

(iii) Life in Extreme Environments

The study of extremophiles offers many potential pathways to technological exploitation, as well as intellectual curiosity. The field is broad, with connections to astrobiology and studies of the origin of life. There is a need to study extremophiles in microenvironments, and to develop new ways to study systems of extremophiles. Better tools are required to achieve this aim. The interactions between proteins, and the behaviour of membranes and membrane proteins, in extremophiles are important. There is a need to understand the nature of ionic reactions in hydrogen bonding, the structures of functional molecules, and the effect of changes in protein flexibility.

Our understanding of dynamics, and of pathways through cells, needs to be improved. This could come from studies of naturally occurring organisms, or through the design of new organisms by the use of synthetic biology approaches. Three important themes that were identified included: the importance of the environment, sustainability and the origins of life. Understanding was needed of the development of metabolic and other pathways in extremophiles, their relationship to, extreme conditions and natural evolution.

(iv) Information Flow in Biology

This is a very broad topic that impacts on a wide range of biological problems. Living systems store, propagate and exploit information in a world governed by thermodynamics in order to delay their inevitable decay into an equilibrium inactive state. The link between information theory and non-equilibrium thermodynamics is thus of fundamental importance in understanding life.

Information flow is important on many length scales, and the integrated flow of information across length-scales (Molecules – Cell – Tissues - Organism) is important; this includes the idea of 'circular information flow', characteristic of biological systems (in the philosophical literature this is known as 'top down causation'). The subject has become particularly important following the recognition of the influence of the environment on heredity through the epigenetic modification of genomes. Two important examples include adaptation (the role of information flow from environment to organism and response) and emergent behaviour (focusing on models and experiment in non-equilibrium physics, for example, ‘useful noise’).

Evolution underpins our understanding of biology, and presents challenges for physics including: the role of genotype and phenotype maps; the need theories for selection, mutation drift, recombination and strong interactions between different parts of genome; the combination of these phenomena to yield a quantitative theory of evolution; and links to non-equilibrium physics as the driving force for life.

(v) The Physics of Cancer

Cancer presents many cross-length-scale challenges, with cell-cell, cell-tissue, tissue-tissue, and tissue-tumour physical interactions. Opportunities arise in studying the physics of metastasis, rare events in cancer neogenesis, physical heterogeneity in cancer, cancer detection, drug delivery, and the physics of emergence in cancer. Biology is beginning to use "new maths" to describe biology including edge of chaos, nonlinear, dissipative, noise, emergence and far-from-equilibrium approaches. Can we use this new maths to generate "new physics”, and apply these new physics to the biology of cancer? In tackling cancer, the broadest possible approach is required, and the involvement of clinicians and those from other scientific disciplines (eg chemistry) is desirable.

(vi) Compartmentalisation and Confinement

Fundamental questions concern the nature of compartmentalization, its physiological significance, relationship to membrane biophysics and interaction with signaling mechanisms. How does encapsulation influence protein evolution? What are the biological implications of compartmentalization, and how does compartmentalization differ in 2- and 3-D? How do compartmentalized structures grow? There is an important role for the development of protocells, and for the minimal cell concept, as a means to explore these fundamental problems. Modelling across the length scales is important, from vesicles to tissue, to address the integration of compartmentalized structures on various length scales into tissue. Systems biology approaches based on ordinary differential equations to models, based on the assumption that cells are uniform and well-mixed, which is typically false. Experimental methods are required to enable better imaging (super-resolution, Raman microscopy, electron microscopy and other techniques), to facilitate measurements inside compartments and to study dynamics.

(vii) Morphogenesis

Major challenges for the next decade include the development of multi-level modeling, understanding the mechanics of cell interactions, and the integration of genetics and biochemistry into these models. How do we expand our models to account for properties beyond elasticity, and how do we measure them? A fundamental challenge is to understand the interplay between evolution and mechanics in development – are living systems using a subset or a superset of autonomous pattern formation mechanisms? How are physical stimuli transduced? To understand these problems we need better 3-d models (arguably 4-d, if we describe time-evolution of morphology) and experimental tools to study cellular mechanics.

Two topics that are particularly timely include: the development of tools for dealing with the mechanics of developing systems; and theoretical/modelling tools for dealing with growing dynamic mechanical systems

(viii) Biofilms

Biofilms are pervasive. In some cases (eg. infections) they are pure, while in others they are mixed. We can think about them from a systems biology perspective. Quorum sensing is important, an important type of emergent behavior in prokaryotes. What happens in biofilms? (for example, motile structures, emergent structure). Biofilms are experimentally and theoretically (computationally) tractable; they are good targets for theoretical physics. What are the adhesion processes in biofilms (what are the molecular interactions)? This requires the development of new experimental and theoretical tools.

Can we disrupt the physics of biofilm cohesion and use it to tackle infection? And can biofilms be engineered to be protective?

(ix) Other Challenges

Quantum Biology

Quantum mechanics is the branch of physics that seeks to explain molecular structure and properties. There has been interest in examining the importance of quantum phenomena in biology, but it has been a matter of debate for many years whether quantum theory can offer decisive insights into biological problems. An important problem that has attracted much recent attention and appears to demand a quantum mechanical explanation is photosynthesis. Recent work by ultra-fast spectroscopy has suggested that delocalised excitonic states are formed in light-harvesting complexes isolated from plants and bacteria. Quantum mechanical investigations of energy harvesting and sharing in these systems may illuminate not only the basic physical processes that underpin much of life, but may also provide inspiration for the design of novel photovoltaic devices.

Protocells

Bacterial cells represent minimal living organisms. A significant challenge is to build a synthetic prokaryotic cell: if we could build a "living" entity then perhaps we might be able to claim to have understood life at some level. The synthetic challenges associated with constructing protocells cannot be separated from those associated with understanding their function – there is a need to understand the physical aspects of collective behaviour, self-organization, and compartmentalization. An extensive literature has grown around the concept of the "minimal cell" – what is the minimal structure required to replicate some of the functional characteristics of a prokaryotic cell? For example, what will its source of energy be? How could it digest nutrients? How could information be encoded to control replication? These are unsolved challenges. Although the construction of a functioning synthetic cell has proved elusive, much important science has been done along the way, and the fundamental nature of the challenge means that it may continue to drive novel science in the future. More broadly, there are important challenges associated with bottom-up approaches to synthetic biology and, indeed, to the study of the origin of life itself (how do molecular interactions lead to primitive functions?).

Biophysics of aging

Aging effects in cells and tissues is an area in which physical scientists may have an important impact. Each cell in a tissue can be considered a thermodynamically open system such that aging effects can be characterized by increases in structural disorder as biological functional loss is diminished, culminating ultimately in maximized entropy as thermal equilibrium is approached, which equates to cell death. This presents opportunities for theoretical analyses using the tools of statistical physics, in addition to finite element approaches to characterize age related effects of the mechanical properties of tissues. Physical science experimental approaches to measure complex viscoelastic features of aging biological matter across multiple length scales are also valuable, and a combination of theoretical and experimental physical science tools can be used to facilitate novel engineering approaches for developing biomimetic tissues for use in regenerative medicine.

4. Societal Challenges

Although the goal of understanding the physics of life raises fundamental challenges, it also bears upon matters that are of enormous importance in society. The following are illustrations; the list is by no means exhaustive.

(i) Bacterial Infection

The growth of bacterial resistance to antibiotics is widely reported in the media: in the near future, there are fears that routine surgery may lead regularly to death through bacterial infection. The development of new therapeutic measures will require an improved understanding of bacterial biophysics (for example, membrane structure, function and physical properties), and may draw inspiration from the sophisticated measures deployed by the immune system to target infection. Experimentalists and theoreticians have much to contribute to these formidable challenges.

(ii) Biofilms

Biofilm formation is relevant to the problem of bacterial infection, and to the challenge of antibiotic resistance, but is a wider problem, ranging from the colonisation of prostheses (for example, treatment of infection in catheters costs the NHS millions of pounds annually) to the coating of ship hulls to prevent fouling by marine organisms (leading to increased fuel consumption and maintenance costs). Biofilms are complex, and present multidisciplinary challenges. Experimental and theoretical physics have much to offer in addressing these.

(iii) Cancer

Cancer is a disease that is very much in the public eye. Death rates from most cancers have not changed markedly during the past 50 years, so it plainly presents a formidable challenge. Pioneering work in the US (through the National Cancer Institute Physical Sciences in Oncology initiative) has sought to draw upon physics to develop new approaches to studying cancer and has lead to controversial new theories of the origin and nature of the disease that suggest new approaches to the development of therapies. Again, experimental and theoretical physics have much to offer.

(iv) Pharmaceutics

More widely than cancer, the development of new pharmaceutical treatments (drug delivery systems, new drugs and therapies) offers physicists exciting opportunities. Many of the targets for pharmaceutical compounds are found in cell membranes, and a better (quantitative, predictive) understanding of membrane biophysics is required to increase rates of discovery. The UK has world-leading life-science industries, and the pharmaceutical industry is particularly important. Harnessing the physical sciences to support this vital sector of the economy more effectively should be an important goal.

(v) Energy

Nature has been very successful at developing systems for harvesting solar energy: it has been estimated that the quantum efficiencies of photosystems in green plants may be as high as 80-90%. Studies of biological energy harvesting may yield insights into the design of better synthetic photovoltaic devices. Progress in these areas will not be made without a thorough understanding of the underpinning physical mechanisms.

(vi) Food

As the Earth’s population grows, and its climate changes, food production systems will come under ever greater pressure. There will be challenges across a range of length scales to which physicists can contribute, through the development of new species designed to offer improved characteristics (drought resistance, yield, etc) – necessitating, perhaps, a better theoretical understanding of directed evolution, or the complex relationship between plant structure and properties – and through the development of models to predict the response of delicate ecosystems to environmental, land-use and other changes.

5. Delivering Change

The UK has a developing community working in biological physics. While there are some pockets of excellence, and a small number of groups have achieved the critical mass to have a world-leading presence, there is in general a need to build cohesion in the community. Significantly, at a recent winter school, only a third of the attendees had been exposed to biological physics at undergraduate level. The establishment of an EPSRC Grand Challenge in this area is a significant step forward for the field, but continued work is required to consolidate and strengthen it in the future. This will come through several forms.

Community building – the Summer School and Winter School organised by our Network addressed in a small way the shortfall in cross-disciplinary training in the life sciences for physics PhD students. More work needs to be done to support and encourage early career researchers, through training, and through the building of networks of collaborative relationships to support them through their careers. Through the Network’s Focused Workshops, we have explored a significant number of areas in which physicists may partner with biologists to drive forward understanding of the physics of life. However, we have not exhausted the potential subject matter. The Network may have a continuing role in this regard, and partnership with learned societies (eg. the Institute of Physics) may be valuable to augment EPSRC initiatives.

Supporting World-Class Research – our Network activities have provided very strong evidence that there are rich and urgent interdisciplinary research challenges that can be tackled through a ‘Physics of Life’ methodology. They have has also shown that the UK community is well-placed to take an international lead in many of these, but that the UK community is currently widely distributed. It is important to establish networks of research collaborations to bring together world-leading groups, giving focus and critical mass. In the next 3 years it would be possible to launch a few large-scale programmes to address an optimal subset of these topics. An efficient way to manage a transition from the current broad scoping function of the Network to such transformational research programmes might be a second phase of the Network, given the central task to develop a selection of the scoped workshop topics from Network 1 into full proposals.

The Broader UK Funding Context – the Nurse Review has argued strongly for better cross-council integration in order to address cross-disciplinary challenges more effectively. Understanding the physics of life is a grand challenge that reaches out in many directions – to BBSRC in basic science challenges, and to the MRC and charities, such as CRUK and the Wellcome Trust, in healthcare. Partnership is fundamental to all work in this area and for physicists to understand life, they must continue to reach out across boundaries. Engagement with research funders other than EPSRC will be an important goal in the future.

6. Summary

Understanding the Physics of Life is a fundamental challenge of the highest importance. Theoretical and experimental physicists offer unique insights and capabilities to biologists in the quest to heal the schism in modern biology between reductionist biochemical approaches and systems biology. Fundamental to the success of this venture is the forging of effective partnerships between physicists and biologists to undertake hypothesis-driven research. Work in which physicists serve merely as tool-makers, or in which biology is simply as a source of interesting justifications for physics, will not yield progress. World-class physics will result when physicists ask biological questions but bring to bear their distinctive approaches – quantitative experimental methodology grounded on mathematically rigorous theory. In partnership with biologists, such approaches can help us to understand the physics of life, and make transformative impact on major societal challenges of our day including antibiotic resistance, biofilms, cancer, pharmaceutics, energy and food.