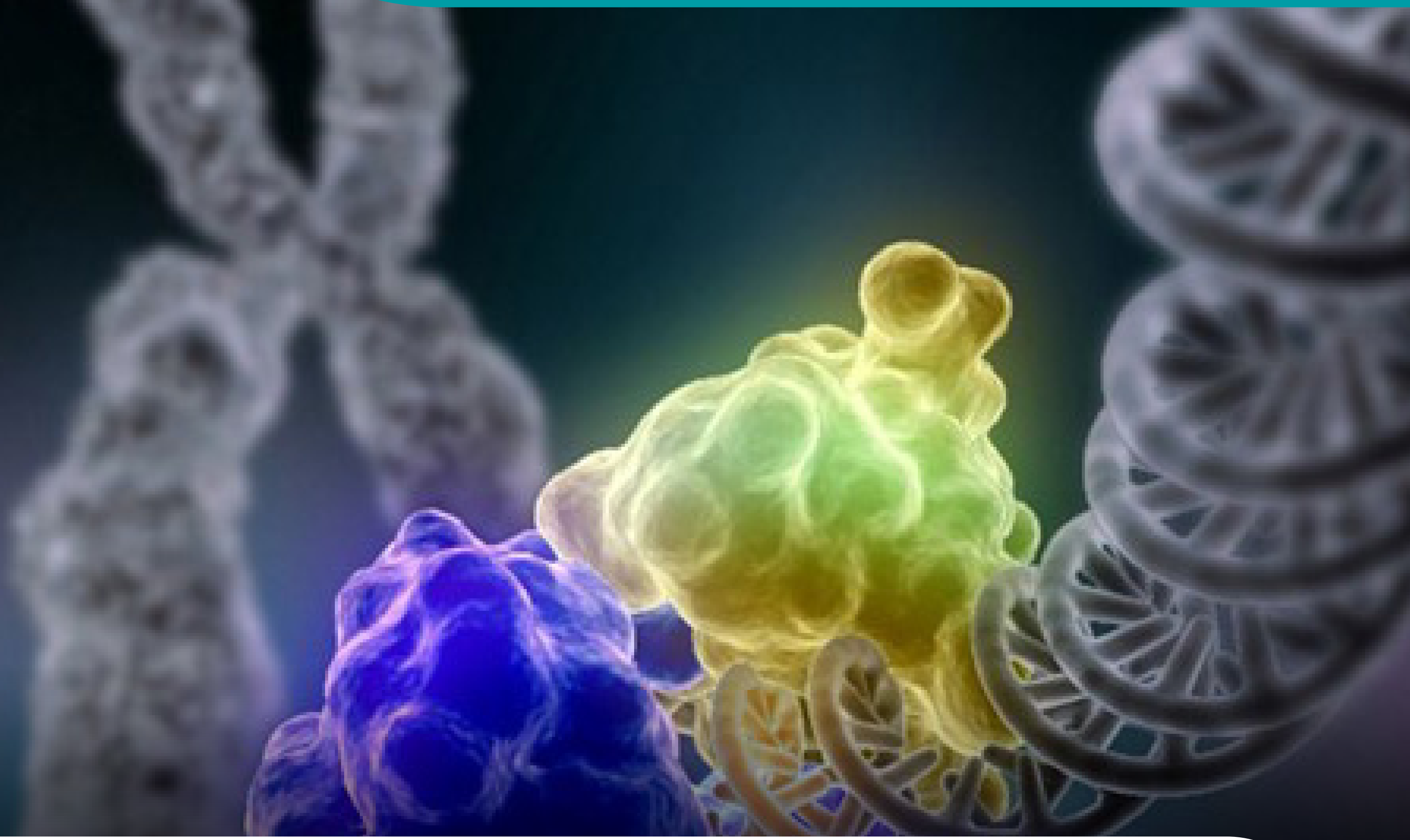
UNDERSTANDING THE
Physics of Life

Physics of Life Roadmap 2025



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Executive summary

Physics of Life has the potential to transform discovery and translational research in the biosciences, advancing the prosperity of the UK and the health of its people through developing new insights to how disease emerges or by tackling antimicrobial resistance. By building on the momentum achieved to date we have the potential to make transformative impact in all key national strategic priority areas for research and innovation. But to achieve this, it needs sustained community coordination across partners and truly multidisciplinary partnerships to drive forward quantitative knowledge and understanding from physics into the life sciences that underpins national growth.

The key topic areas involve:

- Distilling the complexities of living systems through effective mathematical models
- Creation of innovative physics technology to answer biological questions
- Development of designer biology through engineering simplified experimental systems
- Understanding disease and ageing through innovative physics approaches
- Tackling infections through leveraging new biology insights through advances in physics
- Combating climate change and ensuring food security through physics applied to biology

This Roadmap aims to summarise the UK Physics of Life research community's view of research challenges and opportunities at the physics-life science-biomedicine interface with a 15-year horizon. It synthesizes outcomes of an extensive process of community and stakeholder engagement carried out over a two-year period and provides a series of recommendations aimed at funders, universities and the community itself that will enable the transformative potential of the field.

The Roadmap lays out the breadth of "Physics of Life" research and outlines future opportunities. Physicists build conceptual, mathematical and experimental tools to uncover the basic principles that govern the natural world. In this Roadmap, we divide these into three Underpinning themes used to tackle the pressing questions and societal challenges presented by four overarching application themes. Underpinning themes include technology, method developments and analytical innovations that have transformed both biology and healthcare, such as next generation sequencing, magnetic resonance imaging (MRI), and experimental and AI- driven protein structure determination central to drug discovery – these underpinning themes can grow over a timescale of 15 years into a vibrant national capability in the physics of life that allows connected multidisciplinary teams to develop new tools and insights that underpin improved understanding of living systems. The application themes link these directly to challenges of our times: chronic disease and ageing, infectious disease, climate change and food security, and the opportunities that controlling living systems present for commerce. Physics of Life is an area where basic science discoveries can turn into societal impact with remarkable pace.

To realise the UK's potential for leadership in this critical field, building on our strength in life sciences, the unique research opportunity provided by the NHS[1], and the UK's extensive history of successfully translating fundamental physical science research into life changing biomedicine and healthcare technology, we propose to build on the initiatives developed through the Physics of Life Network (PoLNET) including mentoring, cross-university training, linking with translation through organisations such as the National Institute for Health and Care Research, industry (biotech and pharma), research charities and regional programmes. Stronger partnerships with major existing national research facilities will also be developed.

UK Physics of Life is establishing "good practice" in enabling impactful interdisciplinary research; for example, supporting a culture of early "co-creation" of research ideas, and developing strategies for balancing and integrating skills and priorities across a range of different scientific, engineering and mathematical disciplines. Importantly, these developments have been made not through isolated efforts of individual research teams, but as a national community.

Over the next 25 years, strategic and sustained support for Physics of Life research will transform outcomes across multiple sectors including healthcare and the life sciences in the development of new technologies, approaches and translational applications. Interpolating from the UK's current transformative research, newly disruptive activities could emerge from:

- **Integrating transformative AI approaches to develop new theoretical predictive frameworks spanning all biomolecular structures and cellular processes**
- **Creating innovative correlative physics technologies, including emerging quantum technology approaches, to enable cross-scale questions to be tackled from molecular to tissue levels currently impossible with existing tools**
- **Establishing new paradigms in 3D cellular engineering through artificial organoids-on-a-chip and new biomaterials in tissue replacement-therapy to transform understanding and treatment of tissues and to help develop new pharmaceutical therapeutics**
- **Inventing new physics bioimaging tools integrated with real time machine learning to transform our understanding, diagnosis and treatment of neurodegenerative diseases**
- **Combing in silico biomolecular engineering, state-of-the-art structural biophysics, new single-cell measurement technologies and new AI methodologies to develop new targets and approaches for tackling infections and antimicrobial resistance**
- **Developing new physics solutions to fix atmospheric carbon dioxide inspired by biology**
- **Utilising new physics to establish predictive paradigms for complex tissue development with transformative impact into regenerative medicine and new biomaterial discovery**

By supporting early career researchers, fostering national and global collaboration, and addressing societal challenges, the UK can maintain its leadership in Physics of Life and drive innovations that benefit science and society. Investments in education, public engagement, and infrastructure will ensure the field's long-term growth and impact for a resilient and sustainable UK.

1. See https://wellcome.org/reports/from-research-to-reality

Roadmap aims

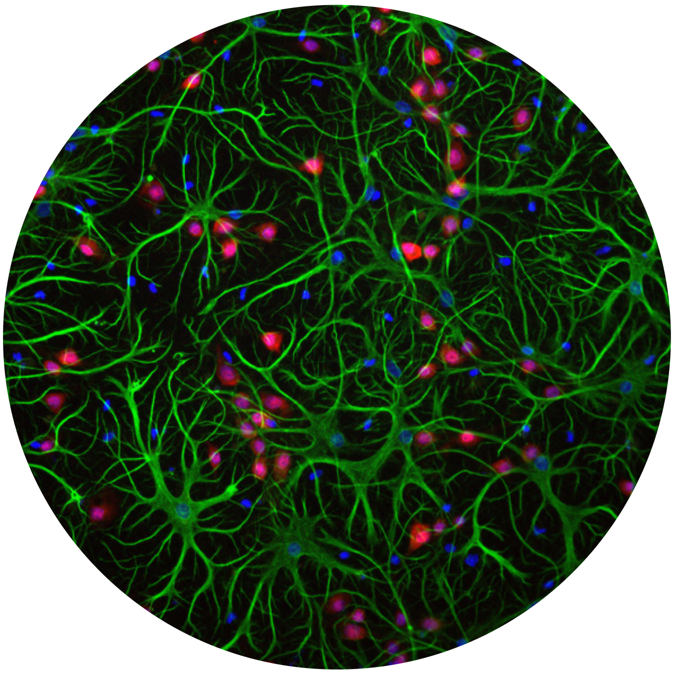
UK Research and Innovation (UKRI) invited the community to launch a horizon scanning exercise to survey the science driven by Physics of Life and its future direction of travel. This Roadmap consultation aimed to:

- Survey, and engage with, the UK Physics of Life research community, and relevant stakeholders, to review UK research strengths and opportunities in this area of research.

- Synthesise and publish a summary of the Physics of Life research community's view of research challenges and opportunities, along with an assessment of the significance and potential benefits of these challenges and opportunities.

- Articulate UK strengths in Physics of Life research in an international context and identify key opportunities for development in this space for the next 5, 15 and 25 years.

- Review the impact of PoLNET on the research community and recommend how funding, training and research environment should develop over the coming years.



'The UK Physics of Life Roadmap aimed to engage the research community, assess challenges and opportunities, and guide the development of research strategies to enhance the global impact and potential of this field over the next 25 years.'

Intended audience and use

The primary roles of this Roadmap report are to:

- Inform the Physics of Life research community and wider stakeholders of the opportunities and potential of Physics of Life in its entirety, not just focused on specific funding programmes.

- Act as a resource for funders to inform research strategy by contributing towards the understanding of the importance and potential impact of Physics of Life research and the key opportunities that it presents in the short, medium and long term.

- Provide recommendations for how the potential of Physics of Life research can best be realized in the medium to long term.

Essential features of this Roadmap

Broad community engagement is key to the value of this Roadmap. To ensure this, we have worked hard at obtaining substantial buy-in and co-development from across this research community and relevant stakeholders.

- Some research areas within the Physics of Life landscape are more established than others. Care has been taken to be as inclusive as possible in reviewing this landscape and to consider where generalisations could and could not be made.

- Engagement has gone beyond academia and drawn on wider stakeholders including representatives of learned societies, charities and potential users of technology including industry, public sector bodies like the NHS and government departments, and the voluntary sector.

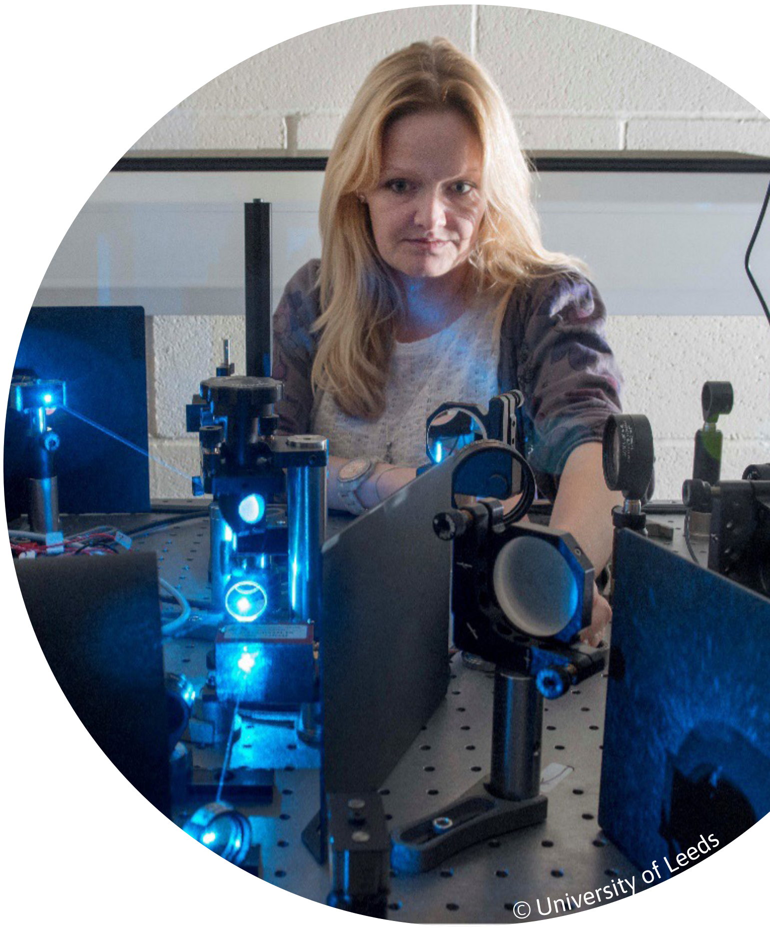
This report also sought international perspectives, so that UK research strengths and opportunities could be described in an international context.

To include different perspectives, input was gathered through various approaches, including surveys, webinars, workshops, and roundtables.

This report also features case studies showcasing how Physics of Life research has enhanced our understanding of life science challenges and is beginning to shed light on potential solutions. Full details of the Roadmap process and participation are provided in Appendix 3.

‘This Roadmap emphasises broad community engagement, including diverse stakeholders to ensure a comprehensive and inclusive review of the UK Physics of Life research landscape and its potential impact.’

Introduction



This report synthesises the outcomes of multiple community surveys, in-person and virtual open consultations, and directed roundtable discussions. The community membership of researchers focused on Physics of Life in the UK has grown exponentially since the inception of the UK Physics of Life network PoLNET in 2012. There is now a combined membership of several thousand researchers spanning all career levels from graduate students to full professors. PoLNET has become a pivotal force in advancing interdisciplinary research in the UK, originally established as part of a Grand Challenge research theme funded by EPSRC and BBSRC. Over the years, it has successfully fostered UK collaboration between the physical and life sciences, driving innovative research aimed at addressing critical biological and medical challenges. The network has progressed through three phases: PoLNET1 (2012-16), PoLNET2 (2017-20), and PoLNET3 (2020-25), solidifying its role as a central player in the UK scientific landscape (Appendix 1).

Why "Physics of Life"?

The separation of science into different compartments has allowed it to be taught and studied, with remarkable success. However, it is hugely detrimental to the rapid development of our understanding of the living world, in which the separation of biology from chemistry and physics has slowed progress, and hindered researchers from all three backgrounds. Similarly, the physics that helps us to understand biological systems does not neatly fit into the compartments that biologists have developed when seeking to describe and understand life. To support Physics of Life research requires consideration of funding and research environment that is distinct from that which is desirable for monodisciplinary physics, biology or medicine.

Lynn Gladden

Professor Dame Lynn Gladden is the Shell Professor of Chemical Engineering at the University of Cambridge and Past Executive Chair of the Engineering and Physical Sciences Research Council (EPSRC).

"Physics of Life builds on a decade-long focus with the research community to bring together physics and the life sciences to improve our understanding of living systems. Through a wide range of innovative approaches, these projects will generate important new knowledge that will help us to answer some of science's biggest problems."

Physics of Life today: Economic impact and intellectual relevance.

Physics of Life research has a rich and global history involving many of the top international scientists of the day from multiple different areas of expertise homed in both the physical and life sciences (see Appendix 4). In the UK Physics of Life today has a track record of delivering impactful and world-leading cross-cutting research. It has made leading contributions comparable to the best efforts of other EU nations, US and China, in pioneering curiosity-driven discoveries, including next-generation DNA sequencing, genomics and biosensing technologies. These avenues have led to economic growth globally and were a crucial factor in the agile UK response to COVID-19, including world-leading surveillance testing and vaccination programmes.

Jackie Hunter

*Jackie Hunter CBE is ex-O BBSRC and Former SVP GSK, member of BP plc Innovation Council, and currently Board director BenevolentAI, Board Chair Brainomix Ltd, Biocortex LLC and Stevenage Bioscience Catalyst, Member A*Star Board Singapore.*

"We need to bring together scientists from both physical disciplines and biological disciplines to create a multidisciplinary ecosystem."

Michael Dunn

Dr Michael Dunn is Director of Discovery Research at Wellcome. Citations 2. and 3. were originally reported 17 February 2022 in **www.ukri.org/news/using-physics-to-transform-our-understanding-of-life/** *for the funding call outcome of the Strategic Priorities Fund (SPF) in 'Building collaboration at the physics of life interface'.*

"It is important to recognise that progress in the life sciences has at times been greatly accelerated by collaborating with other scientific fields. With interdisciplinary teams of physicists, engineers and biologists, the Physics of Life projects will draw on cross-cutting expertise, helping to deliver exciting new insights with the potential to improve life, health and wellbeing."

Outlook

This Physics of Life Roadmap comes at a propitious time. The pace of discoveries at the intersection between physics and the life sciences continues apace, furthering the long history of this dynamic partnership. We expect that the approaches developed under Physics of Life will lead to deep mechanistic insight, providing a "ground truth" that complements the huge international investment and effort in data-driven machine learning approaches to biology and medicine. Synergies between the two approaches could lead to an unprecedented surge in discovery, amplifying the impacts from each. Physics of Life therefore provides a unique opportunity to maintain the UK's lead in bioscience, with targeted investment now likely leading to substantial intellectual, societal, and economic returns over the years to come.

UK Physics of Life: Groundbreaking, Cross-cutting, and Impactful

Based on direct evidence from community surveys, together with analysis of recently funded research, high-impact articles, and transformative data, there are core *underpinning* themes which address pressing challenges, distilled as overarching *application* themes. The activities of the Physics of Life network have been instrumental in helping to both establish and nurture vital researcher collaborations in the UK to support the inception and development of these themes and is well-placed to reach out beyond national boundaries to cognate international partners.

Underpinning themes

1. Development of mathematical models that distil the complexities of living systems.

Living systems are highly complex and their understanding requires the integration of concepts that in other fields are usually considered separately. By constructing conceptual, mathematical and computational frameworks that combine the key physical components, the aim is to develop fundamental insight into the physical rules of biological processes through a transformative mathematical understanding that is both quantitative and predictive. In many cases living systems are too complex to develop truly predictive understanding without such models. These frameworks use insights from statistical physics, active matter, information theory and computational methods as well as the quantitative output of modern experimental approaches.

This theme has underpinned paradigm shifting advances in biology and medicine such as protein structure determination through DeepMind's AlphaFold, and the use of computation and simulation in drug discovery [Box 1]. Spanning length scales, examples of current transformative capabilities include polymer models of chromatin within the nucleus that have completely changed our understanding of how DNA is packaged and how genes are turned on and off, mesoscale models which explain how cells process information through organelles and condensates, and models of stochastic branching that explain the seemingly deterministic formation of the shapes of organs such as the lungs.

Looking forward, we expect:
In 5 years: a library of multiscale systems approaches that can be easily adapted and applied for different systems.

In 10 years: a transformation of molecular biophysics understanding from single DNA molecules upwards to predict cellular behaviour in health, disease, infection and the environment.

In 15 years: the use of this predictive ability empowered by innovative AI approaches to allow biomolecular structure, cell processes and systems to be controlled with applications in precision, personalized medicine, biotechnology and beyond.

Box 1

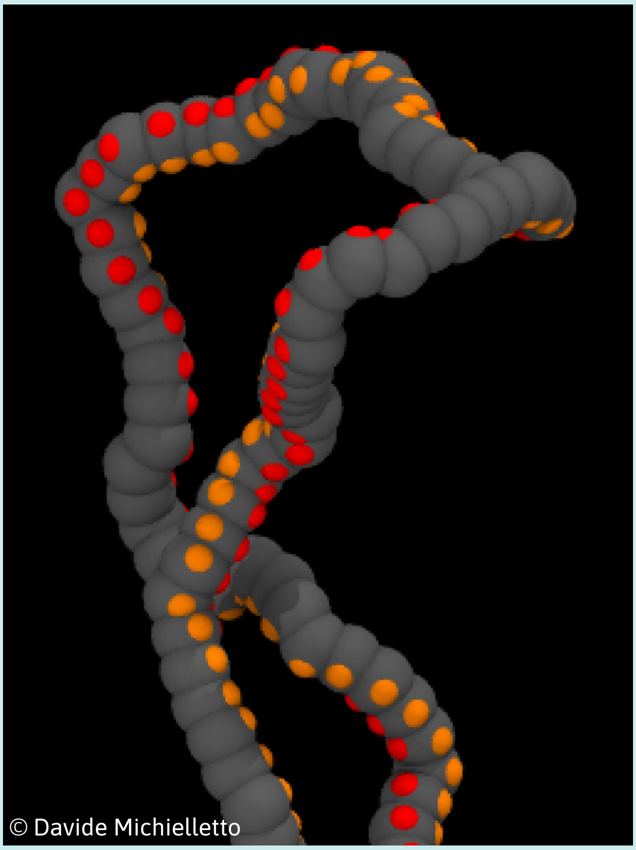
Sarah Harris, University of Sheffield

Prof Sarah Harris is a biological molecular dynamics expert and the Chair of the UK's Collaborative Computational Project for Biomolecular Simulation (CCPBioSim).

Molecular recognition is one of the most fundamental concepts in structural biology and biochemistry, being key to information transfer between biological molecules and to rational drug design by the pharmaceutical industry. Molecular recognition uses the principles of classical thermodynamics to describe selective binding by relating the binding affinity to the free energy change when a molecule binds to its receptor.

'Understanding the balance of contributions to the free energy is key to rational drug design by the pharmaceutical industry.'

Understanding the balance of contributions to the free energy is key to rational drug design by the pharmaceutical industry, and in understanding enzyme catalysis. This has given rise to a wealth of computational tools that use physics-based modelling to describe the thermal fluctuations of biomolecules and the solvent that surrounds them. The invention of classical MD and quantum mechanics/molecular mechanics (QM/MM) methods was awarded the Nobel Prize in Chemistry in 2013. Techniques such as molecular docking, which makes an estimate of binding free energy based on shape matching of molecules into their binding sites, and free energy perturbation, which calculates free energy differences in binding of similar compounds, are now endemic in the pharmaceutical industry. However, the underlying thermodynamics of molecular recognition, especially when large conformational changes in the protein are involved, remain poorly understood theoretically and requires further research in helping to transform impact into the arena of biosensing and personalised medicine in the future.



2. Development of instrumentation to answer biological questions.

The ability to develop new, and adapt existing, instrumentation allows focus to be maintained on pressing challenges, opening new fields of research and overcoming entrenched dogma. Recently this has been complimented by the development and integration of new analysis algorithms including AI and machine learning. There is a long tradition of techniques being developed in physics and applied to biology and medicine that span from the development of new service technologies to being an integral part of discovery-based living systems research.

In medicine, magnetic resonance imaging (MRI) sprang from the fundamental understanding of matter and complex electromagnetic instrumentation development and now provides routine non-invasive clinical imaging of diseases in all body areas. Initially focused on fundamental research, the cryo-EM resolution revolution has given us previously inaccessible structures of many protein machines, providing the training data that enabled AlphaFold to include large proteins, and underpinning the rapid development of new drugs, as exemplified through the determination of the COVID-19 spike protein structure and subsequent vaccine development [Box 2].

Box 2

Jim Naismith, University of Oxford

Prof Jim Naismith is the Head of the Mathematical, Physical, and Life Science Division at the University of Oxford. He was the inaugural Director of the Rosalind Franklin Institute and Director of the Research Complex at Harwell.

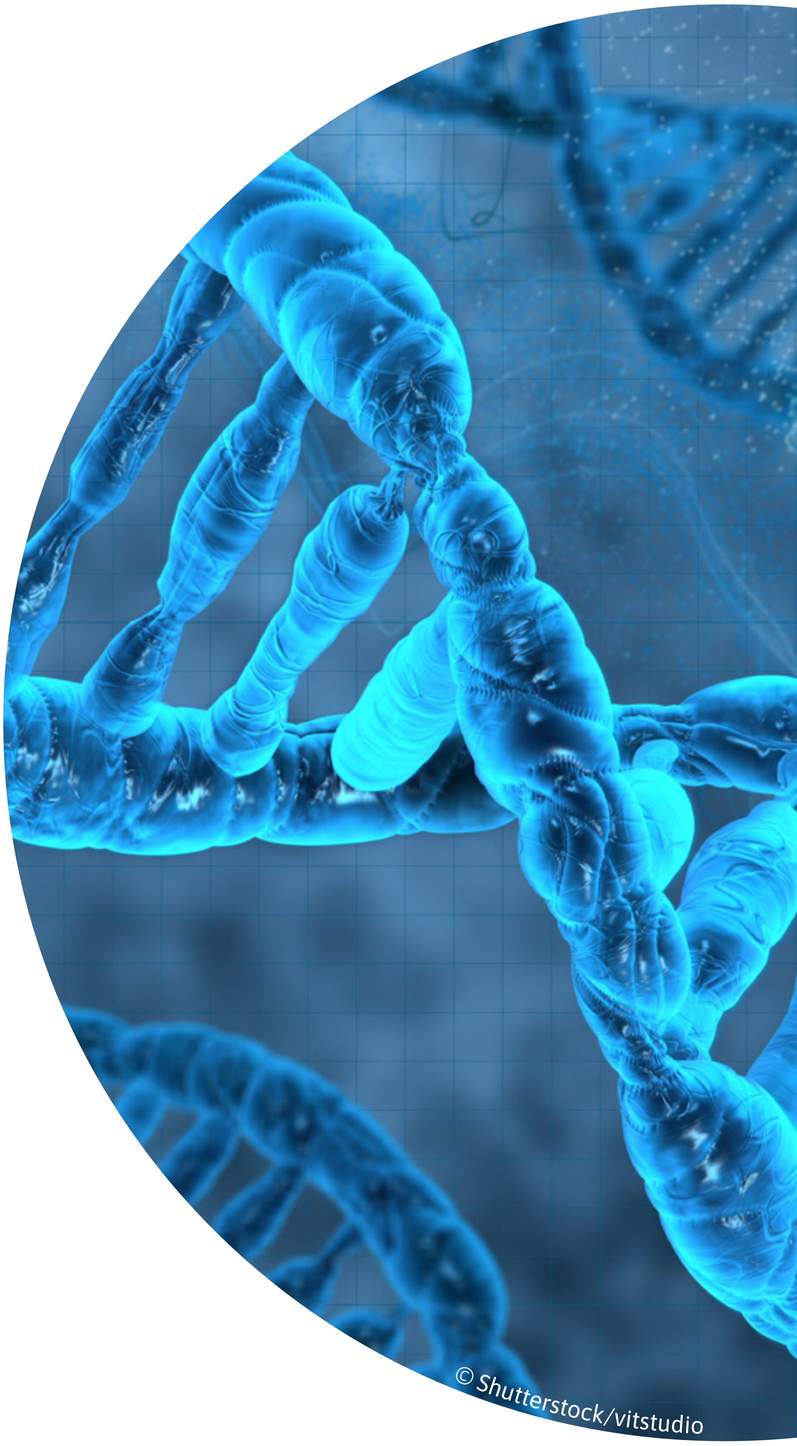
From the day the pandemic arrived, it was known that the so-called Spike protein was the major player in SARS-CoV-2 infection. Blocking its interaction with human cells, either by stimulating the immune system (vaccine) or by injecting blocking molecules (antibodies, nanobodies, and other binders), was an obvious way to treat the disease. The intact trimeric spike, with over 3600 amino acids, multiple glycans, and weighing over 500 kDa, was (and remains) not susceptible to crystallization. Cryo-electron microscopy (in the USA) was able to produce a structure of the Spike only weeks after the sequence of the protein was determined. Three UK labs made critical early contributions using cryo-EM. Oxford University described neutralizing antibodies, important in understanding how vaccines might work; The Crick revealed the dynamics of the protein, illuminating how it targets human cells; and the newly created Rosalind Franklin reported the first structure of neutralizing nanobodies. By combining the cryo-EM with crystal structures of portions of the spike with the nanobody, and biophysical measurements, the precise molecular and energetics of recognition were characterized. The critical role of residue E484 in the Spike protein as a target for immune response was noted; this residue famously mutated in more virulent strains. The nanobodies discovered by the Franklin were shown to be highly effective by nasal administration in an animal model, both as a prophylactic and as a therapeutic.

Super-resolution optical microscopy has provided a direct link between the individual molecules of life and the cellular and organ scale of disease. Optical and magnetic tweezers and atomic force microscopy (AFM), alongside novel ways of analysing and postprocessing the output of these techniques, have allowed direct measurement of the forces that drive molecular biology and that are provided by molecular machines. Optical biophysics-based approaches to DNA sequencing have enabled the genomic revolution, as well as providing the "new COVID-19 variant" warnings that saved thousands of lives in the pandemic. New technologies that are now routinely used in healthcare often came from fundamental question-driven research and biophysics method development. The role of national facilities, such as the Rosalind Franklin Institute, ISIS Facility, Henry Royce Institute and National Physical Laboratory, complement research activities within academic institutions in technology development.

Looking forward, we expect:
In 5 years: Integration of machine learning and mathematical models into imaging will transform the rate of discovery and provide numerous opportunities for spin out into medical diagnostics and biotechnology.

In 10 years: Methods for routine multimodal correlative approaches that allow cross-scale analysis from molecules to cells to systems will be transforming our spatial and temporal understanding of living systems.

In 15 years: Integrating a new range of correlative physics technologies to enable new biological questions to be addressed, utilising, for example, emerging quantum technologies such as entanglement-based sensing, and allowing new insights and diagnostic approaches from molecules to whole living organisms.



3. Development of simplified experimental systems - from designing biology to engineering life

Building simple systems that encapsulate the key physical aspects of a system but are experimentally and theoretically tractable is an important tool for understanding complex phenomena. Examples exist across scales, including reconstituted cytoskeletal proteins for gaining insights into cellular motility, biomimetic condensates for new therapeutics, synthetic microfluidic environments for modelling bacterial biofilms, and multicellular organoids for studying developmental biology. This encompasses the broad idea of 'designing biology' and has translational outputs that can be distinct from the original biological question being addressed, i.e., biotechnology and engineering biology.

There is a strong intersection with the synthetic soft matter physics community, with biological molecules and materials being taken out of their 'living' context and studied as inert systems. While initially focused on biological questions, increasingly the drive is towards commercial output and engineering biology. For example, the development and optimisation of lipid vesicles started as a tool for understanding cell membranes and compartmentalisation but has found direct application as carriers for pharmaceuticals such as RNA vaccines. Similarly, development of innovative approaches to engineer de novo peptides and proteins using both biophysical computational design and rational design, taking inspiration for synthetic structures from those already established in nature, is starting to impact the creation of new bio-sensing tools and therapeutics.

Looking forward we expect:
In 5 years: integration of microfluidic single cell approaches into healthcare technology for diagnostics and drug discovery.

In 10 years: Development of next-generation synthetic engineered biomaterials for use in tissue-replacement therapy in wound healing and disease management.

In 15 years: Routine use of "organnoid-on-a-chip" approaches for developments in pharmaceutical and biotechnology applications.

Combining themes 1-3 provides transformative potential
Together, these three underpinning themes provide the toolkit that the Physics of Life community brings to the table when tackling biological and biomedical challenges. Although we have separated them here, in many cases they are used in combination, or all three are combined in cooperative ways whose impacts far exceed the simple sum of their parts. With the growth in approaches for dealing with large data sets, there are increasing opportunities for automated integration across the toolkit, with mathematical models incorporated into image processing pipelines, and synthetic-biological hybrid systems that can be manipulated to give predictable and potentially valuable outputs. While "tools" can be developed separately from application, in many cases the driver to develop a new tool comes from the need to answer a pressing biological question.

Application themes

4. Addressing chronic and degenerative disease and ageing

This theme is focused on an area that includes a substantial fraction of UK healthcare costs. It is underpinned by a diverse range of funders, including UKRI but also disease specific charities (such as Cancer Research UK, Alzheimer's Society), as well as wider health related charities such as Wellcome. As such, it attracts substantial research activity across the spectrum from clinically facing healthcare technologies to underpinning biophysical science for health. The UK has led the world in translating physics into the clinic, with physics-based imaging technologies including MRI [Box 3], PET, ultrasound and CT now central to clinical care. At the same time, medicine is increasingly characterised by the development of mathematical models of the disease or therapy, an advance driven by the rapid increase in the amount of clinically-informative data. For example, renal dialysis is underpinned by mathematical models of dialysis dose which enables dialysis adequacy to be robustly assessed. The Physics of Life community is increasingly active in understanding disease and working in teams developing approaches to tackle disease. Here we focus on activity in cancer, neurodegenerative disease and ageing, while recognising that there is extensive activity across the broader theme.

Phillip Kukura

Prof Phillip Kukura is a Professor of Biophysical Chemistry at the University of Oxford and CEO of the mass photometry instrumentation company Refeyn.

"Underpinning advances in this area can come only from breakthroughs in physics, co-developed with life scientists. For mass photometry, it was the back-and-forth between what the technology could do, and what genuinely novel information could be provided, and used, by the user, that drove the development. Supporting research at this interface, while asking the key question "why?" is a critical approach to ensure future breakthroughs and competitiveness for the UK in this enormously important future growth area."

Susan Short

Prof Susan Short is a clinical oncologist based at the University of Leeds and Leeds Teaching Hospitals with a specialist research interest in treating adults with primary brain tumours. She is Co-director of the Leeds Cancer Research Centre, President of the European Association of Neuro Oncology (EANO), and President of the British Neuro Oncology Society (BNOS).

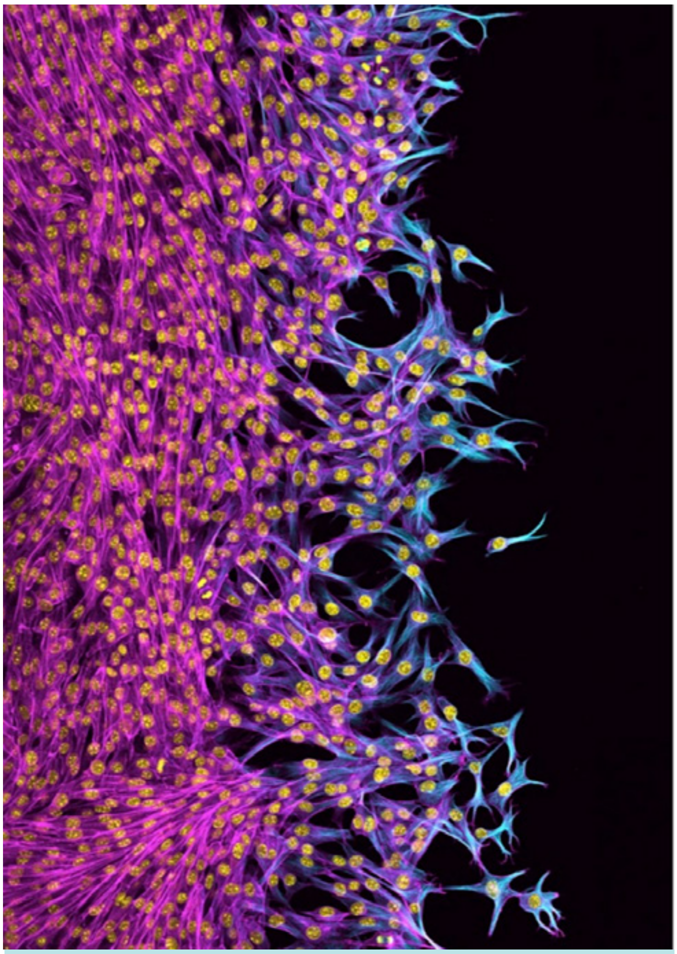
"Despite an excellent understanding of biology we are still confronted by stubborn difficulties to treat cancers where conventional approaches have not yielded the expected benefit. Using a better understanding of the interface between physical science and biology holds promise to unlock new targets and new therapies for these diseases. This is an exciting opportunity that the Physics of Life community is uniquely positioned to exploit."

In cancer, mathematical models of the interaction between chemotherapy resistant and susceptible cells are leading to new treatment approaches that are starting to move into clinical use, opening promising avenues of treatment for cancers with clear biomarkers, such as prostate cancer. Advances in the physics of active matter including understanding of activity-driven flows and active turbulence have provided insights into the budding process characterising metastasis. Modelling and interrogation of the circadian rhythm is leading to methods for specific targeting of stem cell-like phenotype of some cancer cells. The application of AI to optimising identification of biomarkers in digital analysis of tissue pathology, and the use of microfluidics in the study of liquid biomarkers is having transformative impacts in democratising efficient clinical diagnosis. In neurodegenerative disease the use of statistical physics is informing our understanding of the collective behaviour of neurons and neural processing, the study of malfunctions in cellular phase transitions and the physics of biomolecular condensates that apply to diseases such as Alzheimer's. The development of novel non-invasive imaging techniques is enabling quantitative cellular-scale measurement in living humans of, for example, disruptions of the motor system controlling eye movements in Parkinson's and motor neuron disease. New insights into the ageing process are being obtained by combining statistical physics approaches and mechanical property measurements, leading to an understanding of how epigenetics and cellular changes in mechanics affect stem cell fate choices across the lifespan.

Looking forward, we expect:
In 5 years: Widespread integration of mathematical model-based approaches into treatment of cancers with clear biomarkers.

In 10 years: development of new physics based bioimaging technologies for early detection and treatment of cancer and chronic disease.

In 15 years: Integrative, predictive and quantitative understanding of emergent behaviours leading to chronic and degenerative disease resulting in new approaches for prevention especially for neurodegenerative disorders.



Migrating, invading cancer cells imaged using transformative new 'MEGA-FLIM' biophysical technology developed in UK labs. Image courtesy of Prof Laura Machesky, University of Cambridge.

'This theme highlights the significant impact of Physics of Life research in addressing chronic and degenerative diseases, including cancer, neurodegenerative disorders, and ageing, through innovations in imaging, mathematical modeling, and AI-driven diagnostics.'

Box 3

Jim Wild, University of Sheffield

Prof Jim Wild is an expert in medical physics, focused on technology for hyperpolarsied gas MRI, and is Executive Director of the Insigneo Institute.

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"Magnetic resonance imaging (MRI) is used across the world as the first-choice for clinical imaging of soft tissues and organs throughout the human body. The technique's development was firmly rooted in University of Nottingham and University of Aberdeen physics and medical physics labs in the early 1980's, driven by basic curiosity-led studies of nuclear magnetic resonance (NMR), radio frequency engineering, electromagnetics, relaxation of matter and signal processing. Collaborating with clinical researchers resulted in the development of commercial MRI systems with rapid diagnostic adoption by the NHS in a matter of years. Subsequent physics developments added to MRI's technical capabilities such as high-field superconducting magnets for improved detection sensitivity and precision. Cutting-edge progress of optical and low temperature cross-polarisation physics is being applied in collaborative UK projects at the physical-life sciences interface to 'hyperpolarise' nuclei of other atoms of medical interest for targeting metabolic and respiratory biomedical questions."

5. Tackling infectious disease

Infectious agents, whether viral, bacterial, fungal, parasitic, or prion-based, continue to pose a significant healthcare problem for UK and global society. This includes the underlying disease burden of seasonal influenza, pneumonia caused by bacteria such as *Streptococcus pneumoniae*, and sexually transmitted infections (STIs), as well as the threat of future pandemics. The COVID-19 pandemic highlighted the established importance of innovative biophysical approaches, from using cryo-EM technologies to identify viral protein structures which catapulted the development of a vaccine into a viable possibility, to the now universal use of biophysics-inspired rapid next-generation sequencing for new variant identification [Box 4].

The growing impact of antimicrobial resistance (AMR) on both the treatment of infections and on routine surgical procedures is well documented, with important insights being made through close synergies between physics and biology. These issues are all exacerbated by climate change that is predicted to help the spread of existing pathogens into new geographical areas, as well as new zoonotic ("from animal") transmission threatening agriculture, animal farming and human health.

The use of microfluidics and automated analysis at single cell and subcellular scales is transforming understanding of biofilms, microbial competition and the interaction between immune cells and pathogens. New microscopy approaches are overturning established dogma in our understanding of bacterial structure and providing critical insights into how pathogens become resistant to antimicrobials. Mathematical models are leading to better understanding of virus assembly and underpinning increasing use of virus-like particles in drug delivery and vaccination. The growing threat of AMR highlights the need to develop new technologies and methods for rapid sensing, clinical diagnostics, sequencing and tracking of infections and the host response, which the Physics of Life community is responding to.

Looking forward, we expect:
In 5 years: Widespread application of single cell approaches for pathogen diagnosis and treatment development.

In 10 years: Development of discovery pipeline for tackling antimicrobial resistance with mechanistic understanding and quantitative approaches that enable identification of new drug targets and new drugs.

In 15 years: Predictive understanding of protein interactions coming from theoretical, simulation, machine learning and experimental approaches so bespoke drugs can be quickly produced to target emerging infection challenges (e.g. the "next pandemic").

Box 4

Next generation sequencing for COVID next variant identification

Next-generation sequencing (NGS) technologies have enabled rapid DNA and RNA sequencing at scale. Two leading international NGS companies, Illumina (originally the British company Solexa, which was acquired by Illumina for $600M in 2006 creating a company with an annual revenue over $4B and a market capitalization over $80B[2]) and Oxford Nanopore, (which has a current market capitalization of £1.07B[3]) grew originally from the discovery-lead biophysics research in UK-based academic labs. The use of NGS during the COVID-19 pandemic was absolutely pivotal for identifying new variant strains of the Coronavirus, which had a crucial impact in enabling an agile and effective scientific response in the UK affecting millions of people.

2. https://www.clarehall.cam.ac.uk/directory/john-west/#:~:text=In%20 2004%2C%20he%20became%20CEO,market%20capitalization%20 over%20$80%20billion.
3. https://markets.ft.com/data/equities/tearsheet/summary?s=ONT:LSE.

6. Combating climate change and ensuring food security

The climate crisis is the existential threat of our time, and science needs to be applied wherever it can contribute. While climate change reaches into all areas of human health and into many areas of the global economy, Physics of Life approaches can make a substantial impact in carbon capture and food security [Box 5]. There is a pressing need to ensure that staple crops are resistant to inevitable climatic change and that new approaches are developed to mitigate the effects of fungal and other infections on productivity that will be exacerbated by climate-induced stress. At the same time, we must develop robust approaches for capturing and storing as much carbon from the atmosphere as possible, as well as minimising carbon production by finding new manufacturing routes, learning from the efficiency of biological systems.

Insights into how fungal pathogens such as wheat rust spread are leading to mathematical models that are now guiding policies and decision making by farmers. New understanding of the biophysics of plant pathogen infection will inform strategies for increasing crop resistance and contribute to food security. Modelling of how plants sense temperature fluctuations and how this information is integrated through epigenetic memory has led to new insights into the control of flowering time which have now been translated into a predictive model of flowering in oilseed rape, the UK's third most important crop. Biophysical understanding of plant stomata mechanics is feeding into the development of more drought resistant crops. Understanding the fundamental physical rules of carbon fixation through photosynthesis can lead to new approaches for optimising crops and carbon capture. Approaches for low energy computation inspired by or building on natural systems, such as the data storage efficiency of DNA will also contribute to mitigation of climate change.

Looking forward, we expect:
In 5 years: leveraging new single cell technologies developed for human infections for studying plant pathogens (such as fungi) to build food security.

In 10 years: Optimised photosynthesis in model microbial systems for improved carbon capture, utilizing emerging quantum physics insights.

In 15 years: Synthesizing new biomimetic molecular machinery from microbial systems into food crops to transform atmospheric carbon dioxide fixation and developing resilient global food sustainability solutions.

Box 5

Steven Chu,
Stanford University, USA

Prof Steven Chu FREng ForMemRS HonFInstP won the Nobel Prize for Physics in 1997 in developing a laser trapping technology for single atoms which was later applied to many biological applications. He was the 12th secretary of energy in the US and is the William R. Kenan Jr. Professor of Physics and Professor of Molecular and Cellular Physiology at Stanford University, USA. Citation is taken from a presentation given 16 February 2025 in the President's Symposium: Biophysics for a Sustainable Future of the 69th Annual Meeting of the US Biophysical Society in Los Angeles, USA.

"Those who don't study history are doomed to repeat it... we need a 4th agricultural revolution... Carbon capture is needed for fossil fuel power generation, production of cement, steel, chemical plastics and the atmosphere... The world is still currently on a collision path to > 3°C... that is where biophysicists can help."

7. Controlling biological outcomes from a single cell to complex organisms

The mechanisms behind basic developmental processes promise novel insights into the programmes that control tissue regeneration and repair, cutting across into improvements in healthy ageing and tackling disease. To build a net zero future requires radical technological change. Controlling tissue development and shape is important for improving crops and will be vital in production of new alternatives to meat. The use of biological systems for commercial production through engineering biology and biotechnology requires understanding of the physical role played by all component parts and ultimately control over their activity.

Starting with D'Arcy Thompson more than a century ago, it is widely accepted that concepts from physics are needed to understand the emergence of biological form. Turing provided a mathematical framework which has underpinned developmental biology for fifty years. Now, developments in microfluidics, micropatterning and material design have led to the development of stem cell-derived embryo models and 3D organ culture systems, allowing detailed study of living human tissue. These facilitate the study of regenerative and pathological processes while revolutionising our understanding of the basic science of tissue development as well as improving our predictions of disease outcomes, drug testing and the design of therapeutic strategies. Advances in single-cell gene expression profiling, genetic engineering, and super-resolution and single-molecule fluorescence microscopy have driven a step-change in our ability to probe, manipulate and perturb living organisms. This curiosity-led research has fueled translational impact across multiple scales from the molecular through to cell culture and organoids on a chip for rapid drug screening, helping to replace, reduce and refine the use of animals in scientific research. The emergence of cell and gene therapies, techniques which modify an individual's cells and/or genes to treat or cure disease, have played a major role in transforming the biopharmaceutical industry. Innovative engineering biology approaches that involve close synergies between physics and biology are now demonstrating technical capabilities for precise biometrology required to characterise the efficacy of these therapies in delivering re-engineerered genes in the correct cells and tissues and at safe and therapeutic dosage levels.

Looking forward, we expect:
In 5 years: fabrication of micropatterned and functionalized scaffolds to design and manipulate 3D organ culture and co-culture systems, with applications in regenerative medicine, disease modelling and drug design.

In 10 years: understanding developmental biology from single cells to the genesis of tissues and organs utilizing concepts and methods from active matter, field theory and statistical physics integrated with "on chip" experimental systems.

In 15 years: predictive, quantitative understanding of development of complex living systems allows integration into regenerative medicine and biotech materials discovery and production.

Aline Miller

Prof Aline Miller is a Professor of Biomolecular Engineering in the School of Chemical Engineering and Analytical Science at the University of Manchester, and in 2014 co-founded her own spinout PeptiGelDesign (Now Manchester BIOGEL) Ltd.

"Novel materials can provide biocompatible, injectable, and translatable scaffolds for in vivo applications such as drug and/or cell delivery for tissue repair and regeneration; or fully synthetic and controlled micro-environments for in vitro applications such as growth of multi-cellular organoids for disease modelling and drug toxicity and efficacy testing."

Recommendations

Working towards a transformative new environment for UK Physics of Life

The biggest challenges in society are fundamentally interdisciplinary – put simply, Physics of Life approaches can solve big questions that affect millions of people in a way that mono-disciplinary research fields simply cannot. However, until resourcing for interdisciplinary science research becomes as accessible and attainable as that for mono-disciplinary areas, the UK will be hindered from embracing these overarching national strategic priorities. Genuine normalisation for resourcing science that crosses disciplines requires innovative thinking about the national system of support for research. Proper resourcing will deliver the most impactful outcomes, enable strategic support of groundbreaking research at all levels, enhance partnerships that catalyse engagement with societal and economic challenges, deliver sustainability in a highly skilled workforce, and maximise inclusivity of talent for future investment into interdisciplinary science research.

Hagan Bayley

Prof Hagan Bayley FRS, FLSW, recognised by the Science Council in 2014 as "one of the UK's 100 leading practising scientists", holds the position of Professor of Chemical Biology at the University of Oxford and applied biophysics. He uses protein and organic chemistry-based research to the develop protein pores as biosensors and "nanoreactors", which led to the formation of DNA sequencing company Oxford Nanopore, with current global cash assets of approximately £500M.

"In research, it has been essential to breach the boundaries that have been used to establish university departments or rationalise undergraduate teaching."

1. Establish strategic and sustained investment In UK Physics of Life over all scales from now until deep into the future.

Investing on the momentum achieved to date will catalyse the disruptive potential of Physics of Life research.

1.1. Normalise resourcing for multidisciplinary research that bridges physics and life sciences to help release the potential to address the biggest societal problems.

1.2. Investing in programme grants and fellowships will provide the flexibility and interactions required for tackling complex challenges.

1.3. Additional funding streams to facilitate leadership opportunities for early career researchers and new academics will allow flexible application of new tools and approaches to multiple problems without the need for large and high-risk teams.

1.4. Pump-priming to prove and/or test new collaborations is valuable to de-risk careers in this area of science, helping early career researchers navigate a route to independence.

1.5. A dedicated interdisciplinary funding panel will help ensure that the most transformative ideas go forward. .

1.6. Funding for international collaborations and projects worldwide will stimulate disruptive open science initiatives globally.

1.7. Building on the “co-PI” concept across the physical-life sciences interface will help nurture crucial co-design and reciprocal benefits of the most impactful research.

2. Develop a new research landscape that facilitates the best research outcomes for the UK.

We recommend a distributed system of support for Physics of Life research across the UK, beyond and across individual universities.

2.1. Introduce new external, cross-university networks to support interdisciplinary scientists to share best practice in overcoming the barriers imposed by discipline centric university structures.

2.2. Synergise groundbreaking outcomes through such sub-networks, coordinated by PoLNET, to enhance knowledge exchange across research centres.

2.3. Invest in shared infrastructure such as advanced imaging, high-performance computing, and Physics of Life technology labs in academia and national facilities.

2.4. Stimulate integration across all disciplinary interfaces in UK Physics of Life, between the physical and life sciences and between experimental research, theoretical and computational activities including development of artificial intelligence and machine learning approaches.

2.5. Structure new and delocalised national training in Physics of Life which maximises the exceptional and diverse talent of researchers across the UK.

David Klenerman

Prof Sir David Klenerman FRS FMedSci is a Professor of Biophysical Chemistry at the University of Cambridge. In 2007, the British owned company Solexa which he jointly created was acquired by the US company Illumina, which rolled out the DNA sequencing pioneered by Solexa on a global scale. Illumina now has current global assets of approximately 1 billion USD.

"The important element behind our success was the funding of multi-disciplinary basic science to explore the frontier between disciplines, especially cutting-edge physical science... and biology."

Carrie Ambler

Prof Carrie Ambler is a Professor of Biosciences at Durham University and Fellow of the Wolfson Research Institute for Health and Wellbeing. In 2016, she joined up with two partners (at the Universities of York and Oxford) to spin off LightOx, founded on core interdisciplinary principles and practices at the life and physical sciences interface, as a leading biotechnology company aimed at developing new therapies for oral cancers.

"We've been able to leverage this interdisciplinary work for a good amount of industrial funding, both in terms of LightOx supported funding, but importantly, we've, received nearly £2M of funding from Innovate UK"

3. Drive new productivity between discovery and translation at the physical-life sciences interface.

Establishing mechanisms to join the dots between discovery and translation in UK Physics of Life to tackle the biggest societal challenges and drive new economic growth.

3.1. Enhance geographical research diversity through increased regional engagement for UK Physics of Life.

3.2. Establish new links between combined authorities, the NHS (via the National Institute for Health and Care Research) and biomedical research foci, local industries and schools.

3.3. Target new investment to help catalyse the growth of Physics of Life startups and spin-off companies.

3.4. Grow academia interactions with national research facilities to help widen out and open access to the full extent of the UK Physics of Life research community, and create roles in junior researcher support and training.

3.5. Work with cognate international networks to expand the UK's global activity.

Sophie Hartley

Sophie Hartley is the Sector Development Relationship Manager (Trade and Investment) in Health and Life Science Innovation for the York and North Yorkshire Combined Authority.

"Networks like PoLNET are crucial for fostering economic growth in our region. They not only help build relationships with existing businesses but also attract potential businesses looking to expand within the UK or internationally. These networks' innovative interdisciplinary approaches will enhance opportunities for future collaboration between industry and research, while also supporting the next generation of research, which is vital for the region's Health and Life Sciences sector."

4. Train and support an exceptionally skilled new generation at the physical-life sciences interface.

Supporting interdisciplinary training to equip researchers and technicians with skills in both physics and biology is invaluable.

4.1. Establish national-scale mentoring and educational resources to inspire the next generation of Physics of Life researchers and technicians.

4.2. Create cross-university training and outreach, to develop skills required at the physical-life sciences interface and communicate the importance of Physics of Life to the public and policymakers.

4.3. Engage with schools to establish new teaching resources to stimulate greater and earlier connectivity between physics and biology.

4.4. Establish universal standards of training by creating a national Master's Programme in Physics of Life.

4.5. Create robust and clear career pathways for research officers and technicians in the Physics of Life.

Aisha Syeda

Dr Aisha Syeda, a postdoctoral researcher jointly working between the School of Physics, Engineering and Technology and the Department of Biology at the University of York, won a PoLNET Postdoctoral Research Associate Call award for her project entitled "A twist in the tale: Exploring DNA topology changes with multiple molecular machines using optical tweezers".

"As an early career researcher keen to establish my independence, the PoLNET grant gave me the perfect opportunity to test my ideas on a risky yet exciting project. The mentorship offered by PoLNET during the application stage was super useful and helped me develop confidence in my ideas. My next steps will be to build on this project and target funding schemes that will support me for longer durations and establish myself as an independent scientist."

'Supporting interdisciplinary training programs and early career researchers, along with fostering cross-university collaboration and public engagement, is crucial to advancing Physics of Life research and developing a skilled workforce for the future the future.'

5. Reach Physics of Life's full potential through equality, diversity and inclusion.

To build on the promising momentum of UK Physics of Life requires equitable funding to maximise inclusion and diversity. An example of how this might be achieved is:

5.1. Establish a new interdisciplinary funding panel to oversee an 18-month period of open call appraisal within the Physics of Life.

5.2. Configure panel review dates at 6-monthly intervals, to avoid challenges of single-call/single-deadline which disfavour researchers on maternity/medical leave and those who have domestic caring commitments but time-sensitive teaching duties.

5.3. Welcome grant proposals within this call towards the most groundbreaking areas of Physics of Life, but support proposals across a spectrum from pump-priming through to programme grants to ensure equitable support across all career levels.

'Achieving the full potential of Physics of Life requires equitable funding, diverse inclusion, and flexible grant opportunities to support researchers at all career stages and from all backgrounds.'

Afterword

This UK Physics of Life Roadmap collates evidence gathered over the past two years from a wide and diverse community of stakeholders, including established and early career academic researchers, funders and a plethora of non-academic partners.

Our recommendations emerge from a synthesis of data from all the stakeholders associated with UK Physics of Life. The Roadmap working group unreservedly support the recommendations in this report, which will enable the enormous disruptive potential of Physics of Life research to be realised, with positive impacts for UK science and the economy over the next 25+ years.

Prof Mark Leake,
Chair of the Physics of Life Roadmap Working Group

Mark Leake is the Anniversary Professor of Biological Physics, jointly hosted by the School of Physics, Engineering and Technology and the Department of Biology at the University of York. He is the Chair of the UK Physics of Life Network (PoLNET) and Chair of the Physics of Life Roadmap Working Group.

Appendices

Appendix 1 – History of the Physics of Life Network (PoLNET)

The Physics of Life Network – or PoLNET – was seeded in 2012, catalysed with initial funds from a grand challenge resourced by EPSRC and BBSRC. Since its inception, PoLNET has helped to seed and grow collaborations between the physical and life sciences in the UK, with a core aim to catalyse groundbreaking research which addresses critical biological and biomedical challenges. As a network it has progressed through three phases — PoLNET1 (2012-16), PoLNET2 (2017-20), and PoLNET3 (2020-25) — solidifying its role as a central player in the UK scientific landscape:

The beginning: PoLNET1 (2012-16)

The PoLNET1 phase, launched in 2012 under the leadership of the University of Sheffield, marked the beginning of the network's journey. The primary goal was to build an integrated framework for understanding biology by bridging molecular and systems biology perspectives. This inaugural phase focused on fostering an interdisciplinary physics and life sciences community through a variety of activities such as plenary events, residential workshops, and early-career researcher summer schools. By the end of PoLNET1, the network had established a vibrant and diverse community, laying the foundation for the network's subsequent expansion and growth.

Expansion and growth: PoLNET2 (2017-20)

PoLNET2, led by Durham and York Universities, ran from 2017 to 2020. This phase marked a shift toward active research programs and the development of new funding opportunities. The actions outlined in the "Roadmap for the Physics of Life" created during PoLNET1, were implemented, further enhancing the network's impact.

This phase helped to establish a broader range of events and funding actions including town meetings, workshops, sandpits, summer bursaries and graduate training schools. Each event offered invaluable opportunities for both established and emerging researchers to connect around shared interests, strengthening the network's commitment to interdisciplinary collaboration.

Towards the end of PoLNET2, growing momentum led the network to advocate for substantial UKRI funding, resulting in the launch of the UKRI 'Building Collaborations at the Physics of Life Interface' initiative, also supported by Wellcome. The network was delighted that this resulted in a total of £33m of community investment divided across two calls (2019 and 2022) which funded a total of 17 projects covering the full scope of Physics of Life (see testimonial section: Appendix 2). During this same phase the Network's steering group received the IoP Rosalind Franklin Medal and Prize for 'contributions made to catalysing the substantive growth of the Physics of Life community in the UK by stimulating new, adventurous partnerships between multiple researchers in UK biological physics.'

PoLNET3 (2020-25): building on success

The third phase of the network, PoLNET3, led once again by Durham and York Universities, ran from 2020 to 2024 and continued to broaden the network's scope. With continued support from UKRI (EPSRC, BBSRC) and new backing from MRC, PoLNET3 was launched. Additional funding from the Rosetrees Trust facilitated the development of a newly linked Physics of Medicine initiative, extending the network's impact to medical challenges through the application of physics. This phase delivered a range of traditional PoLNET activities alongside clinically focused workshops, including 19 workshops, 3 sandpits, 36 student bursaries, 2 graduate schools, and 1 ECR bootcamp. It also marked a major milestone achieved through collaboration with IoP, BBS, Physics of Living Matter and Physics meets Biology - the launch of the UK's first international Biological Physics conference, Physics of Life, Harrogate 2023.

Additional funding and strategic focus (2024-25)

The network successfully secured additional funding support from UKRI (EPSRC, BBSRC, MRC) and Wellcome to deliver this Physics of Life Roadmap and to establish a Physics of Life PDRA scheme, which supported 17 associated Postdoctoral Research Assistant (PDRA) projects to help springboard their careers towards independence. PoLNET also secured targeted BBSRC funding to enhance its commitment to equality, diversity and inclusion, particularly for students from low-income backgrounds, caregivers, and women in science. The network also has continued its role in supporting the second edition of the UK's second international Biological Physics conference, Physics of Life, Harrogate 2025.

The success of PoLNET can be attributed to its inclusive and collaborative approach, which has consistently promoted the integration of physical and life sciences. By welcoming both UK and international researchers to join freely, PoLNET has now grown into a community which engages regularly with over 3,000 individuals (via monthly mailing alerts and a JISC mail platform). This cross-disciplinary collaboration has sparked new research opportunities, driving forward progress in tackling urgent biological challenges. Researchers from across the UK have come together to address key problems, drawing on the resources and supportive community that PoLNET has nurtured.

Looking ahead, the network is actively pursuing funding for PoLNET4, which will support the continued growth and success of the community and help coordinate the implementation of the recommendations this Roadmap report, ensuring ongoing collaboration and the advancement of research at the intersection of the physical and life sciences

Physics of Life Network

Phase 1 (2012 – 2020)

3
plenary events

9
workshops

2
early career researcher summer schools

Final
summit leading to a Roadmap for Biological Physics

Phase 2 (2017 – 2020)

£254k

9
sandpits

2
early career researcher summer schools

3
town meetings

18
workshops

11
student project awards

Phase 3 (2020 – 2024)

£350k

Creation
of £33m for UKRI's Physics of Life SPF (now also with Wecome)

Launch
of PoLNET3 and Rosetrees Trust Physics of Medicine

19
workshops

36
student project awards

3
early career researcher schools/bootcamp training events

Conference
1st UK international Physics of Life conference 'Physics of Life 2023'

Phase 3 addition (until 2025)

£481k

Conference
2nd international Physics of Life conference 'Physics of Life 2025'

Physics of Life Roadmap

PDRA scheme
(17 awards)

For all info, see: https://www.physicsoflife.org.uk/

Medical Research Council

Engineering and Physical Sciences Research Council

Biotechnology and Biological Sciences Research Council

Appendix 2 – Testimonials from grant holders of the Strategic Priorities Fund in ‘Building collaborations at the physics of life interface’

In 2018, UKRI announced a Strategic Priorities Fund (SPF) in ‘Building collaboration at the physics of life interface, delivered by EPSRC, BBSRC and MRC, which ran in two calls, Call 1 (2018-19, £15M total budget) and Call 2 (2021-22, £18M total budget, which included an additional contribution from Wellcome of £3M). The funded applications are listed below, with lay descriptions of the research activities and outcomes written by the respective research teams:

Call 1:

Stochastic fluctuations during mammary development and breast cancer morphogenesis

Co-PIs: Guillaume Salbreux (The Francis Crick Institute), Axel Behrens (The Francis Crick Institute & Institute of Cancer Research), Chris Dunsby (Imperial College London).

Differences between organisms in biology can come from differences in genes, but also due to natural variability. This natural variability arises from random (stochastic) physical processes in cells, and the variability exhibited by biological tissues is currently not well understood. This project aimed to quantify and analyse the natural random variability in the three-dimensional shapes adopted by multicellular lab-grown structures called organoids. Part of the variability that we sought to explore arises from how cells exert forces and interact mechanically with each other, and part of it arises from the dynamics of stem cells. Cells use their cytoskeleton, an internal architecture capable of exerting forces, to move relative to each other. In addition, stem cells ensure that tissues function properly by dividing and giving rise to different cell types. For example, stem cells replace damaged cells during the repair of injured organs. Also, in cancer there are stem cells, so call cancer stem cells, and these cancer stem cells (CSC) are believed to be required for cancer to spread to other sites in the body (metastasis) and are also linked to the re-emergence of cancer (relapse) after therapy. The ultimate aim of this work is to use improvements in our understanding of natural variability to better understand organ development and diseases such as cancer.

During the project, we developed a novel light-sheet microscope called dual-view oblique plane microscopy (dOPM). This was able to provide unprecedented sub-cellular imaging of 50 live organoids in parallel – divided into different biological conditions in a multiwell plate – in three spectral channels at 15-minute intervals over more than 6 days. The technology developed was a major component of a successful subsequent CRUK Accelerator grant application where it has been further improved and replicated at 4 different research institutes. dOPM is being patented by Imperial and potential routes to its commercialisation are being pursued. During the project, we developed transgenic mouse mammary organoids with fluorescently labelled membrane and actin networks, and we used the dOPM system to image dynamics in these organoids. To analyse the resulting data, we developed a novel and sophisticated image analysis suite that combines advanced ‘classical’ 3D image segmentation approaches with deep-learning 3D segmentation in a synergistic way. We made this tool freely available, and the software has been complemented by online documentation, usage examples and tutorials. The project also developed a novel modelling and simulation framework for cell aggregates in three dimensions based on interacting active surfaces. Cell mechanics are captured by a physical description of the acto-myosin cortex that includes cortical flows, viscous forces, active tensions, and bending moments. Cells interact with each other via short-range forces capturing the effect of adhesion molecules. We applied this framework to small and medium-sized aggregates and considered the shape and dynamics of a cell doublet, a planar cell sheet, and a growing cell aggregate. The tools developed during this project open the door to the systematic exploration of the cell to tissue-scale mechanics of cell aggregates, which plays a key role in the morphogenesis of embryos and organoids.

The Physics of Antimicrobial Resistance

Co-PIs: Jamie Hobbs, Simon J. Foster (University of Sheffield); Co-Is: Rosalind Allen and DH Arvind (University of Edinburgh); Pietro Cicuta (University of Cambridge), Waldemar Vollmer (Newcastle University), Alexandra Porter and Ian Mudway (Imperial College London).

The development by bacteria of resistance to antibiotics (antimicrobial resistance, AMR) is a global challenge that threatens to undermine many of the advances of modern medicine and cause terrible human and financial loss. AMR is a multi-faceted problem in which processes occurring over many different length and timescales interact, leading to the emergence of viable resistant bacteria. To obtain a predictive understanding of this complexity we took an interdisciplinary approach, bringing together quantitative experimental and mathematical physics with cutting-edge microbiology and biochemistry. Our long-term aim is to reveal exploitable fitness costs associated with AMR, i.e. ways in which the bacteria become more vulnerable as the price they pay for becoming resistant to particular antibiotics. We focused on two AMR bacteria, the "hospital superbug" methicillin resistant *Staphylococcus aureus*, MRSA, and mecillinam resistant *E. coli*, a common source of urinary tract infection complications. We elucidated in molecular detail the architecture of the *S. aureus* cell wall and showed for the first time how front-line antibiotics (such as penicillin and vancomycin) actually kill bacteria. We showed that MRSA requires two independent mechanisms to become high level antibiotic resistant, revealing that it utilises a new mode of cell division that bypasses the need for otherwise essential architectural structures in the cell wall. We laid the groundwork for understanding the physical processes that enable MRSA to survive and revealed potential new targets for combating this important pathogen. Physics based modelling gave us important new conceptual insights into the factors controlling antibiotic susceptibility, and we found remarkable parallels in the molecular processes that occur in antibiotic induced death in *E. coli* as well as hints at commonalities between resistance mechanisms. More broadly, we worked with Syngenta to transfer our new approaches to study fungal wheat pathogens, discovering unexpected synergies across different kingdoms of life that may be important in future food security, while analytical methods spun out an unexpected new imaging approach that is being taken forward by the UK semiconductor quality control metrology company Infinitesima Ltd, showing the serendipitous nature of technology development.

Health assessment across biological length scales for personal pollution exposure and its mitigation (INHALE)

Co-PIs: Fan Chung (National Heart and Lung Institute, Imperial College London), Christopher Pain (Department of Earth Science and Engineering, Imperial College London); Co-Is: Ian Adcock (National Heart and Lung Institute, Imperial College London), Rossella Arcucci (Department of Earth Science and Engineering, Imperial College London), Fangxin Fang (Department of Earth Science and Engineering, Imperial College London), Yi-Ke Guo (Data Science Institute, Imperial College London), Alexandra Porter (Department of Materials, Imperial College London), DK Arvind (School of Informatics, University of Edinburgh), Prashant Kumar (Global Centre for Clean Air Research, University of Surrey).

INHALE assessed the impact of pollution on personal health in outdoor/indoor urban environments through the development of a physics-based multi-scale approach across biological length scales from the cell, lung, person (surrounded by green infrastructure) up to the neighbourhood scale. We examined the biophysical components of pollutants that determine their cellular fate, their potential for cell and tissue damage and how this relates to health outcomes. We used airway models to assess particle deposition and effects on people's health as well as trace the pollution particles through an individual person down to the cellular level.
Key outcomes from INHALE included the use of neural networks, a method in artificial intelligence (AI) that teaches computers to process data in a way that is inspired by the human brain, to represent multiple responses to air pollution including human, personal and cellular responses. We also characterised the chemical composition of particulate matter (PM) to discover what organic matter and trace metals were present in the air pollution at five separate microenvironments;

1. indoors, 2. around green infrastructure (dense hedge), 3. an open park, 4. London Underground station platform, and 5. a traffic intersection. Most notably, we observed that toxic polycyclic aromatic hydrocarbons (organic compounds) and redox active metals (which can damage human cells) in ultrafine PM were detected in both indoor and London Underground sites. We conducted an in-depth study of the types and concentrations of air pollution and its chemical composition on the London Underground platform. We produced unique chemical maps of the smallest size fractions (fine and ultrafine) of PM collected on the underground that show they are composed of iron and oxygen in the form of magnetite (20nm) and nanosized (<100nm) mixtures of potentially toxic metals, including chromium, aluminium, nickel and manganese. Furthermore, we compared PM and carbon dioxide concentrations whilst trains were running and not running to draw conclusions about the stratification, or settling out of, and mixing of particulates and gasses as well as the ventilation levels in the underground.

Biological metamaterials for enhanced noise control technology

Co-PIs: Marc Holderied (University of Bristol), Richard Craster (Imperial College London); Co-Is: Bruce Drinkwater (University of Bristol), Daniel Robert (University of Bristol).

We set out to understand a fundamental biological question: How has the evolutionary arms-race between bats and moths created sound absorbing surfaces with performance beyond anything man-made? Specifically, our discovery of a unique ultrathin sound absorbing stealth coating on the wings of moths holds the promise to improve noise control technology for human use. The aim of this project hence was to understand the underlying mechanism so it can be replicated and translated into new technology. Our multidisciplinary team worked together on both the fundamental science and the design of new materials to impact upon a timely issue, the ever-increasing noise pollution, that significantly affects human health.
This project resulted in several top tier publications in which we elucidate the moth wing as an ultrathin sound absorber material. We also took crucial steps towards turning this technology into functioning prototypes. Having reached this level of maturity in our technology we then managed to secure follow-up impact development support from Innovate UK (ICURe spinout training), EPSRC Impact Acceleration Awards, BBSRC Follow-on fund and University of Bristol spinout and patenting support. Total funding for this project since 2015 stands at £3m FEC. As a direct outcome of the work done in this project, we filed a patent application in 2023 and are in the process of spinning out our company, Attacus Acoustics, with the aim to bring to market thinner and lighter solutions for architectural retrofit (acoustic wallpaper), or specialist acoustic solutions. Our work reached a global audience when an explainer video reached 1.2 million viewers on the TikTok platform alone, for one year making it the most viewed HE content from the UK ever. Through this work we have come a great step closer to providing bio-inspired solutions that can help us live quieter and healthier lives.

Transcription and nuclear phase transitions

Co-PIs: Daniel Hebenstreit (School of Life Sciences, University of Warwick), Vasily Kantsler (Department of Physics, University of Warwick); Co-Is: Robin Ball, Matthew Turner (Department of Physics, University of Warwick), Louise Dyson (School of Life Sciences and Warwick Mathematics Institute, University of Warwick).

Liquid-liquid phase separation (LLPS) is a process where certain proteins, often together with RNA molecules, associate to form droplets or clusters inside cells, much like oil droplets forming in water. These clusters are not solid structures; they are dynamic, liquid-like and can merge, grow, or shrink. It has been proposed that LLPS of a number of proteins plays a role in transcription, the process of making RNA from DNA, but details remain unclear.

In this project, we explored the different ways LLPS can form clusters inside cells and how these clusters affect gene activity and the organization of the genome in systematic fashion. We identified several patterns of interaction between these clusters, the 3D arrangement of DNA and proteins bound to it and transcription. We found that large clusters can disrupt the normal organization of the genome and have a repressive effect on gene activity. On the other hand, smaller clusters can enhance transcription, including effects on temporary interruptions of the transcription process termed ‘pausing’, based on their assembly and disassembly dynamics.

These findings reveal how cellular clusters influence gene activity, which is key to health and disease. Understanding these mechanisms is not only interesting from the perspective of basic science but may also lead to new treatments for diseases where LLPS plays roles, such as cancer and neurological disorders, by targeting how cells organize and regulate gene expression.

MEGA-FLIM: quantum technologies for megapixel time-resolved imaging and control across biological scales

Co-PIs: Laura Machesky, Daniele Faccio (University of Glasgow).

Quantum technologies and specifically single photon cameras are a field of active research for various imaging applications, ranging from LIDAR to deep space imaging. Microscopes can also benefit from the ability for these cameras to capture extremely low light levels and at very high frame rates, with temporal resolutions of order of 0.1 nanoseconds or less. This makes single photon cameras particularly attractive for fluorescence lifetime imaging even if somewhat held back by the typically low (e.g. 1000) pixel counts of commercially available cameras. We developed a new approach to fluorescence lifetime imaging that uses low-resolution single photon cameras in combination with high resolution standard CMOS cameras. The former have very high temporal resolution but low spatial resolution. The latter have no temporal resolution but high spatial resolution. We developed computational algorithms that are able to fuse the data from just one single image of the sample and provide a final measurement that has the best of both worlds: picosecond time-resolved fluorescence lifetime imaging at megapixel resolution. This technique is called SiSIFUS (Single sample Single Image Fusion UpSampling) and has been filed as a patent with results from this and related approaches published in PNAS [Kapitany et al. PNAS **120**, e2214617120 (2023)] and Science Advances [Kapitany et al. Science Advances **10**, eadn0139 (2024)] and applied to the imaging of cancer cells. Recent work (in progress) has extended this approach to real-time imaging of fast dynamic transients at 200 frames per second e.g. of Ca2+ waves in cardiomyocyte assays. This new technology is providing new opportunities to explore transient biology with fluorescence lifetime imaging at time scales and frame rates not previously accessible. Ongoing work is not focusing for example of cardiomyocyte imaging as mentioned above and neuron activity.

Biological physics of protein clustering in epigenetic memory and transcriptional control

Co-PIs: Caroline Dean (John Innes Centre), Martin Howard (John Innes Centre), Mark Leake, (University of York).

In recent years it has become clear that many proteins act collectively inside single cells by teaming-up in large numbers into dense molecular clusters. However, how these clusters form and what biological function they perform often remains a mystery. The research team, jointly hosted by the John Innes Centre and the University of York and comprising substantive expertise across experimental and theoretical biophysics and plant biology, aimed to unlock these mysteries by investigating two types of clustering at a single target. This target was a gene called Flowering Locus C in a plant called *Arabidopsis* often used by researchers. The first type of clustering is caused by proteins gathering together in a more ordered way, such that close association of a critical number of proteins will then stimulate further feedback to recruit more proteins into the cluster. This phenomenon is called oligomerisation. The second type of protein clustering has a different physical origin: many proteins undergo what is called liquid-liquid phase separation, where they will spontaneously separate themselves from the surrounding medium and form a self-assembling compartment. This process is analogous to the spontaneous separation of oil in water into droplets. The team were able to use transformative Physics of Life approaches to mechanistically understand the formation and biological function of both types of clusters. They used a diversity of range of techniques and expertise from both biology and physics, with “physics thinking” being vital since the mechanisms by which the clusters are believed to form, oligomerisation and phase separation, are intrinsic physics phenomena. Furthermore, physics instrumentation developed in order to address the core biological questions led to a transformative new microscopy technology called "SlimVar". This tool can uniquely track single biomolecules deep into living tissues, relevant not only to plants but with likely future applications into animal tissues, including human. The team were also able to use molecular biology and genetics to perturb the components of the clusters and examine their effects on gene expression. Using advanced single-molecule imaging techniques to observe the clusters, they were able to measure cluster dynamics and count the number of molecules involved. Finally, they developed detailed theoretical physics models of the clusters, incorporating results from the experiments, revealing how new kinds of biological physics have been exploited by biology to provide the exquisite control needed for transcriptional regulation.

Molecular Mechanics of Enzymes

Co-PIs: Frank Vollmer, Jennifer Littlechild (University of Exeter).

This interdisciplinary project explored the molecular mechanisms of enzymes, nature's catalysts, using a highly sensitive optoplasmonic sensor, a Whispering Gallery System. The goal was to determine whether enzymatic activity can be monitored at the single-molecule level. The study focused on phosphoglycerate kinase; an enzyme known for its significant conformational changes during turnover. The enzyme was immobilised onto gold nanoparticles in a specific orientation on the sensor. When provided with chemical energy, in the form of ATP and the substrate 3-phosphoglycerate, a repeating signal assigned to a single enzyme turnover could be monitored. This project has developed new single-molecule measurement techniques to reveal the protein movements occurring during enzyme activity that were previously inaccessible by other biophysical methods. The results have enhanced our understanding of the nanoscale bioenergetics that underpin sensor signals from a single enzyme molecule and have provided insights into how these signals relate to the behaviour of multiple enzyme molecules in solution. These fundamental principles have academic implications for biophysics, enzyme protein engineering and de-novo enzyme design. They will also have impact for industry for sustainable applications in applied biocatalysis and biotechnology.

Call 2:

Early-stage embryo as an active self-tuning soft material

Co-PIs: Guillaume Charras (University College London), Julia Yeomans (University of Oxford); Co-Is: Cornelis J. Weijer and Rastko Sknepnek (University of Dundee).

Our project is to apply the physics of active matter to help understand gastrulation, a key step in embryonic development that lays the foundation for the body plan in virtually all animals. In the project, advanced imaging and computational modelling are combined to investigate the key biophysical mechanisms that control the spectacular way in which thousands of cells divide, migrate and differentiate in concert to form an embryo. We have developed models that show how flows driven by active forces within some of the cells can drive gastrulation, and we explore these theories experimentally by investigating how changes in mechanical stress perturb the embryonic patterning. This is a step towards understanding how genetics, chemical signalling and active bio-mechanical processes combine to shape life. Our research will not only improve our ability to prevent and treat the many congenital diseases that are caused by errors during gastrulation but is also relevant to explaining how complex life has evolved on Earth.

Reverse engineering morphogenesis

Co-PIs: Tim Saunders (University of Warwick), James Briscoe (The Francis Crick Institute); Co-I: Guillaume Charras (University College London).

We aim to understand how complex biological tissues form their shape and organisation during embryonic development. To do this, we study a simplified model of tissue grown from human embryonic stem cells, which reproducibly forms organised patterns of different cell types that are characteristic of the developing body. Using microscopy, measurements of forces, and computational modelling, we have investigated how mechanical forces between cells interact with genetic programmes to drive tissue organisation - similar to how physical forces shape soap bubbles, but in living, actively changing materials. Starting with a flat layer of stem cells, we observed how the cells organised themselves into a complex 3D structure over just three days. The cells naturally separated into two main types: neural cells (which form brain and spinal cord tissue), and mesodermal cells (which form muscle and skeletal tissue). This organisation mirrors what happens in human embryo development. By changing the shape of the surface the cells grow on, we could control how the tissue organises; and by adjusting the timing of specific chemical signals, we could alter the types of cells that formed and how they arranged themselves. These findings advance our basic understanding of early human development and are beginning to reveal how tissues are shaped by the combination of mechanical and molecular processes during their formation.

Understanding self-organised tissue patterning across scales

Co-PIs: Alexander Fletcher and David Strutt, (University of Sheffield).

Creating a functional animal body, with correctly formed tissues and organs, requires intricate organisation across different levels, from the microscopic to the whole organism. Individual cells must have the correct shape, size, and position within the body. Furthermore, within each cell, proteins must be precisely located to determine the cell's specific functions. Understanding how this complex pattern emerges across different scales is a formidable challenge. In this project, we aimed to gain a fundamental understanding by studying the developing wing of the fruit fly, Drosophila. This model system allows for detailed investigations due to its relatively simple structure and well-established genetic tools. We employed a multidisciplinary approach, combining cutting-edge quantitative microscopy, genetic and physical manipulations, and multiscale computational modelling. This enabled us to visualise and count individual protein molecules involved in shaping and patterning cells, analyse their dynamic interactions, and use computer simulations to understand how their collective behaviour contributes to pattern cells and the tissue. As well as giving new insights into the mechanisms of pattern formation, this research has led to the development of novel genetic and computational tools that can be used in future studies. Ultimately, a deeper understanding of body patterning has the potential to inform our understanding of developmental disorders and diseases such as cancer, where these fundamental processes go awry.

A fresh look at visual sampling: How are fixational eye-movements optimised? [PhysFEM]

Co-PIs: Hannah Smithson (Department of Experimental Psychology, University of Oxford), Daniel Read (School of Mathematics, University of Leeds (originally Tom McLeish, Department of Physics, University of York)); Co-I: Martin Booth (Engineering Science, University of Oxford); Collaborator: David Brainard, (Department of Psychology, University of Pennsylvania).

How should a sensory system optimally sample the world? Human vision is a fascinating example - for even when the gaze is 'fixed' onto a target object the eyes are in constant, apparently-random, motion. One might assume that such movements of the eye could only 'blur' vision, but there are reasons to believe that they might actually enhance it. One reason for suspecting this is that we know that many aspects of vision have evolved towards the best performance possible. A second more specific reason is that when an image is stabilised on the retina, our perception of it fades: eye motion may overcome this fading. This project addresses the challenge of these ever-present movements of our eyes by combining ideas, methods and people from theoretical physics of random motion, and from the life sciences of visual neuroscience and psychology. We are developing a theoretical framework for thinking about the effects of these eye-movements on transmission of information through the human visual system. We are testing these ideas through state-of-the-art experiments that project highly controlled images onto the retina and record the trajectories of eye movements with high precision, during execution of a visual task. Finally, we are building computational models that integrate this theoretical and experimental work with known biological details of retinal processing. Our measurements of eye motion show that the motion is not completely random. Rather, at spatial and temporal scales relevant to neural processes in the retina, the eye persists in its direction of motion. Our calculations show there is an advantage to such persistent motion. We also find that eye motion is particularly good at resolving edges in the image where there are abrupt changes from dark to light. For computational vision, this project provides insight to efficient processing; and for medical science it allows disruptions to visual processing – such as may be seen in neurodevelopmental and neurodegenerative disorders – to be quantified. This project shows that the tools of theoretical physics are well adapted to understand the ubiquitous process of information acquisition in biological systems, with broad application from cellular sensory processes to ecological systems.

Statistical Physics of Cognition

Co-PIs: Simon Schultz and Henrik Jeldtoft Jensen (Imperial College London).

This study shows that multiple avalanches of neural activity can overlap in the cortex, each operating near—but at varying distances to—a critical point between order and disorder. Crucially, these co-occurring avalanches carry different types of information (some related to pupil diameter and others to visual stimuli) and propagate along distinct pathways, with pupil-related avalanches appearing closer to criticality. The results suggest that operating near this critical phase transition enhances information processing, highlighting how the confluence of overlapping near-critical avalanches may underlie complex cognitive functions.

Optimising light-tissue interaction to enable multi scale imaging of neuronal dynamics deep within the neocortex

Co-PIs: Angus Silver, (University College London), Martin Booth (University of Oxford).

Neocortical circuits learn new tasks by adjusting the strengths of their synaptic connections and altering neuronal excitability. The adjustment in synaptic weights required to improve task performance is thought to occur via feeding back error signals to the network. But the nature of information available to neurons during learning, and thus the efficiency of their learning strategies, remains unknown. Non-invasive sampling of neural activity dynamics spanning large spatiotemporal scales is required to address this fundamental biological problem. Novel physics is required to address this problem because the depth of optical imaging is limited by scattering of light, restricting high spatiotemporal resolution measurements of synaptic activity to superficial cortical layers. By combining realistic simulations of light propagation with measurements of tissue refractive index, we are developing new approaches to overcome light scattering in brain tissue by using wavefront shaping technology to extend functional imaging to deeper brain regions. The transformative new methods that arise from advancing our understanding of light propagation through tissue are revealing physiological processes in deep structures that were previously inaccessible, enabling important biological questions to be addressed across neuroscience, cancer and organoid research. This project is only possible through a highly collaborative multidisciplinary approach with cross-institutional expertise involving teams of physicists, microscope developers and neuroscientists at UCL and Oxford.

The York Physics of Pyrenoids Project (YP3): Nanostructured Biological LLPS: Next-Level-Complexity Physics of CO2-fixing Organelles

Co-PIs: Mark Leake (originally Tom McLeish), Luke Mackinder; Co-Is: Michael Plevin, Charley Schaefer (University of York).

Photosynthesis underpins life on earth, using energy from the sun to convert atmospheric carbon dioxide into carbohydrates and releasing oxygen into the atmosphere. The dual threats of climate crisis and population expansion have motivated new research strategies towards photosynthesis for improving both crop yield and enhancing carbon fixation. However, a traditional roadblock has been the inefficiency of photosynthesis in most crops. To address this challenge, we turned to photosynthetic algae, which have evolved a mechanism to improve the photosynthesis efficiency. The enzyme Rubisco, the most abundant protein on the planet, is responsible for converting CO2 into organic carbon in photosynthesis, but it is slow and poor at selecting its substrate. Algae overcome these limitations by concentrating CO2 to effectively "suck" it out of the local environment, drastically improving Rubisco efficiency, by adapting liquid demixing into a specialised "biocondensate" called the pyrenoid and then pump in high concentrations of CO_2. Models predict that if the same mechanism could be imported into plants significant improvements in yields and CO_2 removal could be obtained. To achieve that goal, we aimed to determine which pyrenoid components are key and establish how to re-engineer synthetic pyrenoids into crops, by characterising their physics across different length and time scales.

The physical pathway of pyrenoid self-assembly is liquid-liquid phase separation (LLPS), a widespread phenomenon in the Universe and crucial to several core processes in biology where proteins with appropriate properties interact and demix from the bulk solvent. The liquid-like properties of the resulting condensate are dependent on the composition of interacting species and kinetics and thermodynamics of their association. We are successfully determining the core physical rules that underpin LLPS in pyrenoids. We have used statistical thermodynamics and soft matter physics theory to develop coarse-grained models that describe Rubisco association with intrinsically disordered linker proteins, and to predict critical concentrations and properties of these proteins and their interactions. Our models support results from our suite of advanced biophysics experiments[1]. We have also determined key structural and compositional determinants of linker proteins that interact with Rubisco, which comprise multiple binding motifs separated by unstructured sequences, and have evaluated their interactions from previously uncharacterised algal systems, including resolving 3D structures of protein complexes at atomic resolution. Our approach has been enormously integrative across theoretical, computational and experimental biophysical around the framework of challenging life science questions from algal and plant molecular biology: this hugely correlative dialogue between multiple disciplines has been crucial in stimulating new growth of our research beyond the original consortium by co-opting a diverse mix of key international collaborator labs, and allowed us to establish the core scientific principles that govern LLPS in pyrenoids[2-4]. This new understanding is now driving efforts to engineer algae and plants with improved photosynthetic properties, which may have a truly transformative impact on a global scale.

1. doi: 10.1103/PhysRevLett.132.218401
2. doi: 10.1038/s41477-024-01812-x
3. doi: 10.1093/plphys/kiae450
4. doi: 10.1101/2023.06.15.545204

Infections in complex physical environments: Life and death in the sinuses

Co-PIs: Teuta Pilizota (University of Edinburgh and University of Cambridge) and Eric Lauga (University of Cambridge); Co-Is: Pietro Cicuta (University of Cambridge), Bartlomiej Waclaw (University of Edinburgh), Clare Bryant (University of Cambridge), Iain Hathorn (NHS Scotland), Luke McNally (University of Edinburgh).

Long-term infections and inflammatory conditions are complex host-pathogen responses that are often poorly understood because of the multi-scale nature of the response and numerous physical and biological factors that are involved. Building experimental and conceptual frameworks is necessary to gain a predictive understanding of such complex systems and to link the local interactions and responses to overall emergent behaviour. The results will offer far reaching insights at the life sciences/physics interface. We proposed to study chronic rhinosinusitis (CRS) as a model of such an approach. CRS is defined as an inflammation of the nose and paranasal sinuses present for more than 12 weeks and affecting 5-12% of the general population. CRS not only significantly reduces the quality of life of patients but also incurs very high healthcare costs. Pathogenesis of CRS is attributed to a unique combination of dynamic physical, chemical and biological factors that are present in the host sinus microenvironment. We proposed to build a model system of such an environment characterised by the shape and geometry of the sinus cavity, the mucosal response of the innate immune cells, linked to the chemokine expression and inflammatory response against the infection, and the role of goblet and ciliated epithelial cells that constantly generate and displace a mucus lining, ordinarily an effective defence against microbial infections. Furthermore, bacterial growth is a significant factor in CRS, but its precise role has been difficult to elucidate. We propose to study the role of relevant bacterial communities in our model system, once established. With a clinician in the team, we expect our conceptual and experimental approaches to understanding this system will aid in treating CRS. We also expect that many results obtained will be applicable to a wide variety of other complex living systems, where flow, microbes and host response interact, e.g. gut, lungs or urinary tract.

By analysing the CT scans of sinuses and theoretically studying the action of cilia beating, mucus production and gravity, we have developed the first model of active mucociliary clearance in the sinuses. Informed in part by the model, we are completing the experimental minimal sinus model, which will represent a first reliable experimental system where ciliary beating is oriented in the flow direction. We have also made necessary steps needed to produce a unique data set of mucus characteristics, from healthy cells and those infected by bacteria, whereby we characterise the mucus rheology, protein content and cytokines production. We were also able to achieve a unique working environment, where a group of people of different interdisciplinary skills is effectively communicating with each other answering questions that would otherwise not be possible to answer.

Integration of functional and structural knowledge across scales to decipher information processing in the mammalian brain

Co-PIs: Andreas Schaefer (The Francis Crick Institute), Alexandra Pacureanu, (European Synchrotron Radiation Facility).

The SPF grant, titled "Integration of Functional and Structural Knowledge Across Scales to Decipher Information Processing in the Mammalian Brain," is led by Co-PIs Andreas Schaefer (Francis Crick Institute) and Alexandra Pacureanu (European Synchrotron Radiation Facility). The project seeks to uncover how mammalian brains process information by combining advanced in vivo functional imaging, synchrotron X-ray nano-holo-tomography, and electron microscopy. This integrative approach focuses on the mouse olfactory bulb, a model system for exploring neural circuitry. Key research outcomes include datasets that connect functional neuronal activity with structural analysis, revealing new insights into stereotypical neural circuits and information transformation across brain regions. Broader impacts of this work include advancing multiscale imaging technologies, improving our understanding of neural processing, and fostering a collaborative framework at the interface of physics and neuroscience. This research sets the stage for future innovations in both fundamental neuroscience and imaging technology, in particular, large-volume nanobioimaging with X-ray tomography.

Appendix 3 - Summary of the Physics of Life Roadmap Process and Participation

Contributors and experts consulted in preparing this report

Physics of Life Roadmap Working Group

Karis Baker *(University of York)**
Olwyn Byron *(University of Glasgow)*
Sonia Contera *(University of Oxford)*
Lorna Dougan *(University of Leeds)*
Nigel Goldenfeld *(University of California San Diego)*
Jamie Hobbs *(University of Sheffield)*
Martin Howard *(John Innes Centre)*
Mark Leake *(University of York)***
Davide Michieletto *(University of Edinburgh)*
Michelle Peckham *(University of Leeds)*
Alice Pyne *(University of Sheffield)*
Teuta Pilizota *(University of Edinburgh)*
Petra Schwille *(Max Planck Institute of Biochemistry)*
Ben Simons *(University of Cambridge)*
Stephen Smye *(University of Leeds)*
** PoLNET Project Manager;*
*** Roadmap Working Group Chair.*

Physics of Life Network (PoLNET) Steering Group

Martin Cann *(Durham University)*
Pietro Cicuta *(University of Cambridge)*
Susan Cox *(King's College London)*
Carina Dunlop *(University of Surrey)*
Simon Hanna *(University of Bristol)*
Graham Leggett *(University of Sheffield)*
Gareth Davies *(Procter & Gamble)*
Andrew Turberfield *(University of Oxford)*
Peter Weightman *(University of Liverpool)*
Rivka Isaacson *(King's College London)*

Institute of Physics Biological Physics Group (BPG) Committee

Peter Adams *(University of Leeds)*
Nirvana Caballero *(University of Geneva)*
Matteo Degiacomi *(Durham University)*
Diana Fusco *(University of Cambridge)*
Isabella Guido *(University of Surrey)*
Chiu-Fan Lee *(Imperial College London)*
Marco Mazza *(Loughborough University)*
Timothy Saunders *(University of Warwick)*
Margarita Staykova *(Durham University)*
Massimo Vassalli *(University of Glasgow)*
Bartek Waclaw *(University of Edinburgh/University of Warsaw)*

British Biophysical Society (BBS) Committee

Svetlana Antonyuk *(University of Liverpool)*
Tharin Blumenschein *(University of East Anglia)*
Alex Chizh *(The Francis Crick Institute)*
Peter Crowley *(NUI Galway)*
Ann Dixon *(University of Warwick)*
Guy Grant *(University of Bedfordshire)*
Rebecca Farthing *(King's College London)*
Mathew Horrocks *(University of Edinburgh)*
Ioanna Mela *(University of Cambridge)*
Ehmke Pohl *(Durham University)*
John Sanderson *(Durham University),*
John Seddon *(Imperial College Londn)*
Anthony Watts *(University of Oxford)*

Experts external to PoLNET, BPG and BBS

Somenath Bakshi *(University of Cambridge)*
James Briscoe *(The Francis Crick Institute)*
Rosana Collepardo *(University of Cambridge)*
Buddhapriya Chakrabarti *(University of Sheffield)*
Guillaume Charras *(University College London)*
Nynke Dekker *(University of Oxford)*
Lorenzo di Michele *(University of Cambridge)*
William Durham *(University of Sheffield)*
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Alexander Fletcher *(University of Sheffield)*
Kevin Foster *(University of Oxford)*
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Andrew Goryachev *(University of Edinburgh)*
Philip Greulich *(University of Southampton)*
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Alexander Mietke *(University of Oxford)*
Ewa Paluch *(University of Cambridge)*
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Ralf Richter *(University of Leeds)*
Susan Rosser *(University of Edinburgh)*
Charlie Schaefer *(University of York)*
Linus Schumacher *(University of Edinburgh)*
Vahid Shahrezaei *(Imperial College London)*
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Austin Smith *(University of Exeter)*
Hannah Smithson *(University of Oxford)*
Steven Spoel *(University of Edinburgh)*
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Matthew Turner *(University of Warwick)*
Reidun Twarock *(University of York)*
Alison Walters *(Cancer Research UK)*
Stephen Wallace *(University of Edinburgh)*
Kees Weijer *(University of Dundee)*
Dek Woolfson *(University of Bristol)*
Jenny Zhang *(University of Cambridge)*

Acknowledgements

We thank **Kristian Bond** *(Qube Design Associates Limited)* for their assistance in the graphic design of the roadmap report. The Roadmap consultation was an independent process facilitated by funding from the Engineering and Physical Sciences Council EPSRC to a grant award the Physics of Life network (reference EP/T022000/1).

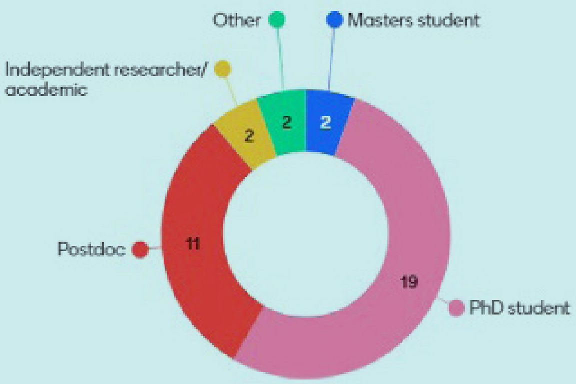
Initial Roadmap consultation sessions

The Roadmap process was initially introduced and discussed at a series of sessions held at several UK workshops and events, including:

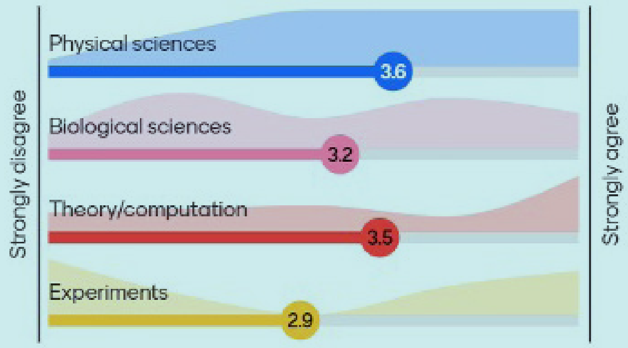
- **Physics of Life Winter School 2023: Challenges and Opportunities in Physics of Life**, 12-14 December 2023, Durham University (50 participants)
- **Biological Filaments: Structure, Dynamics, and Functio**n, 31 January - 1 February 2024, Living Systems Institute, University of Exeter (30 participants)
- **The Astbury Conversation: Illuminating Life,** 8-9 April 2024, University of Leeds (150 participants)

In these preliminary consultation sessions, we captured Mentimeter data concerning the career level, perception of scientific expertise, questions relating to dissemination, training and securing funds, and a word cloud relating to challenges/ opportunities within the Physics of Life and/or expectations of that particular workshop event, as exemplified in this typical raw Mentimeter output taken from the Physics of Life Winter School 2023:

Me

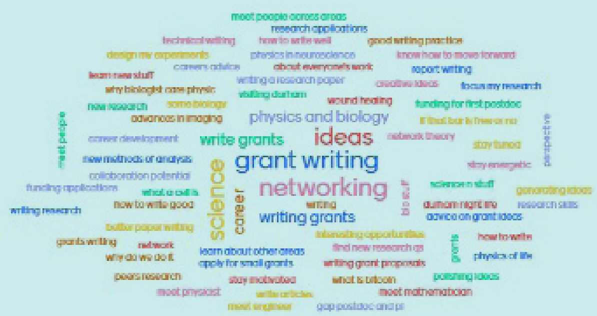


Expertise



Reflection

3 things I'd like to learn at Winter School



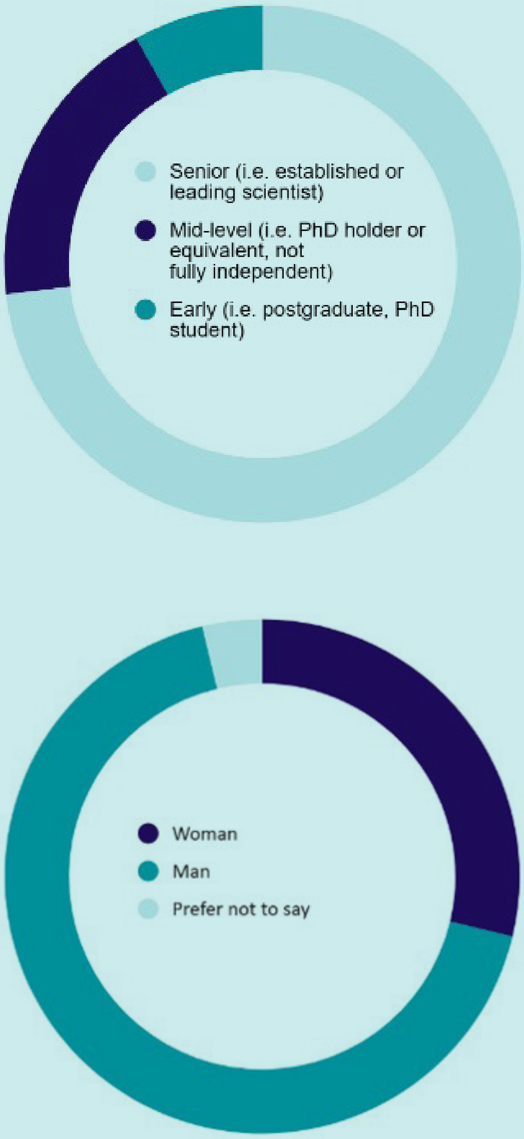
Working Group surveys
To prepare for a broad community survey, an initial survey was distributed to all working group members. This served as a trial run for the subsequent community survey while consolidating the perspectives of the working group. (Survey and questions: https://forms.office.com/e/EvW5Hdtg7z).

Community webinar
In May 2024, Prof Mark Leake ran a Physics of Life community webinar to provide an open platform for community members and stakeholders to learn about the Roadmap initiative and ways to actively engage with the Roadmap process. This webinar also introduced the launch of an extensive, community-wide survey and invited participation (see below).

Community surveys
A community-wide survey was developed to engage researchers across diverse disciplines within the Physics of Life. The survey, which ran from March to July 2024, aimed to gather insights on key questions and emerging topics in the field. (Survey and questions: https://forms.office.com/e/s8CXn3HfKr)

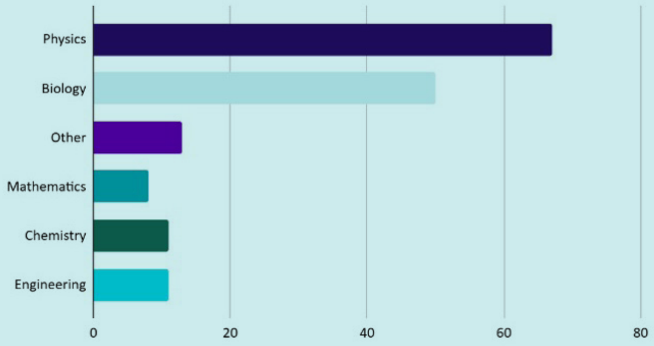
With 161 responses, spanning 36 UK and 14 international universities and institutions, the survey provided invaluable feedback that directly influenced the Roadmap's development. As exemplified from the following typical raw outputs, we captured evidence for:

(i) Career level and gender

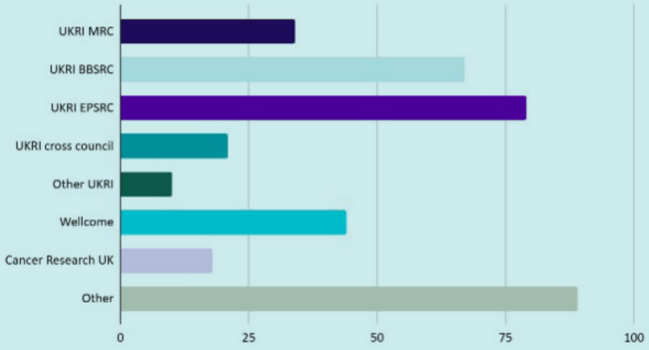


(ii) Primary scientific discipline, source of funding, and perception of Physics of Life as their representative community

What is your primary scientific discipline?



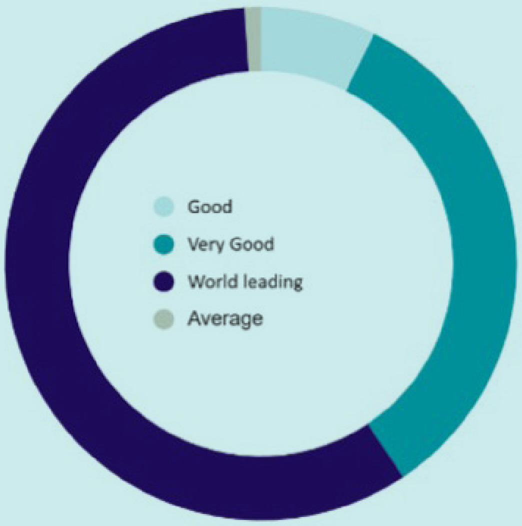
Who has funded your research?



Count of Do you see yourself/your work as represented by the Physics of Life umbrella?

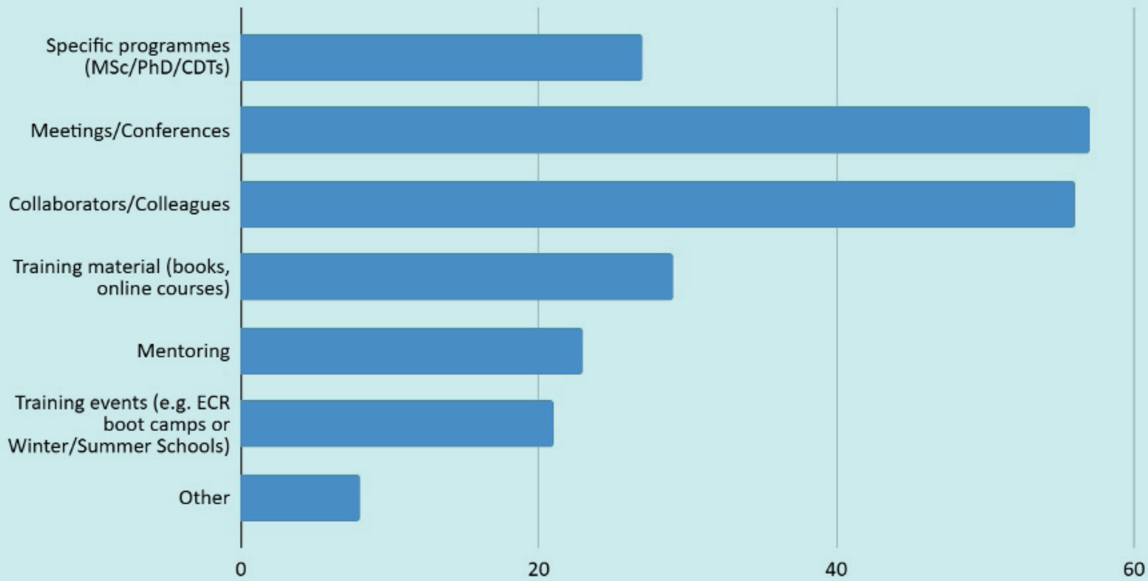
(iii) Perception of the competitiveness of UK Physics of Life internationally, specific training received in the Physics of Life, and areas where training is currently lacking

Count of How would you rank PoL areas internationally?



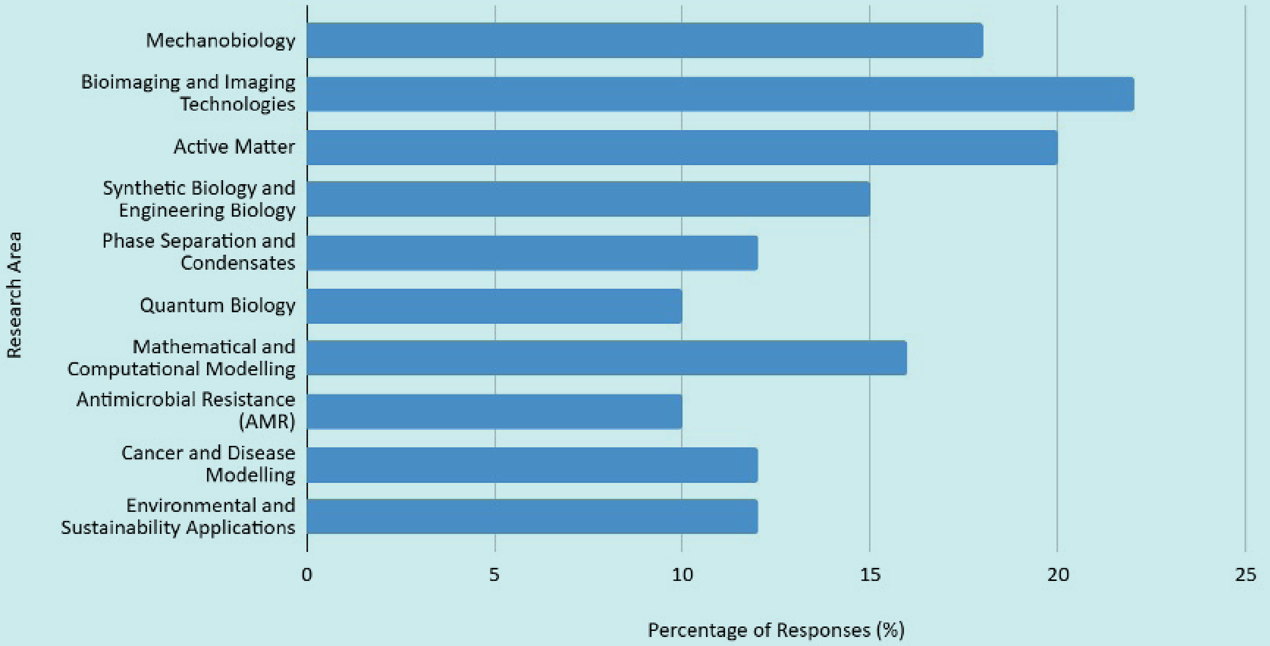
Count of Are there key skills that are currently hard to obtain for Physics of Life research?

Describe the training you have received to help you engage with Physics of Life research?

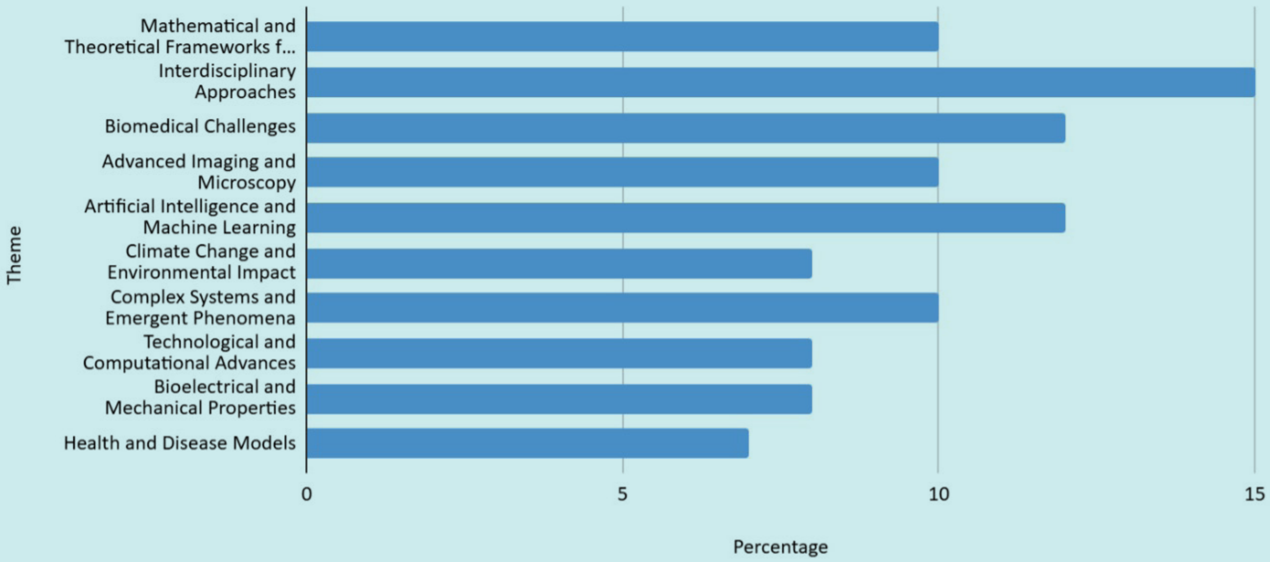


(iv) Research areas that are the most important and exciting in UK Physics of Life currently, and potentially over the next 5-10 years

Distribution of research areas based on representation in responses. What are the most important and exciting Physics of Life research sreas within the UK currently?



What new research challenges could Physics of Life address in the next 5-10 years? Percentages based on representation in responses.



Guided by these results, along with accessible data for funded proposals involving research at the physical-life sciences interface, in addition to available data from research outcomes, the working group began outlining seven disruptive and emerging areas/themes within UK Physics of Life. Collaborative online working group meetings were held to refine these focus areas. Subsequently, the working group divided into smaller teams, each assigned to one of the identified areas/themes. These teams consulted relevant experts outside the working group to finalise concise written summaries, which formed the foundation of the Roadmap. Further details and written summaries are available at: The UK Physics of Life Roadmap. These expert teams are listed below, with the preliminary associated theme titles indicated:

- **Expert Team 1** - Simple models and systems to unlock complex molecular processes inside cells: Lorna Dougan (University of Leeds), Nigel Goldenfeld (University of University of California San Diego)*, Sarah Harris (University of Sheffield), Martin Howard (John Innes Centre)*, Alice Pyne (University of Sheffield)*.

- **Expert Team 2** - Improving health, ageing and wellbeing: Olwyn Byron (University of Glasgow)*, Tuomas Knowles (University of Cambridge), Susan Short (University of Leeds), Anne Skeldon (University of Surrey), Hannah Smithson (University of Oxford), Alison Walters (Cancer Research UK), Stephen Smye (University of Leeds)*, Julia Yeomans (University of Oxford), Peter Weightman (University of Liverpool).

- **Expert Team 3** - Tackling infection - from the physics of microbial systems to host immunity: Somenath Bakshi (University of Cambridge), William Durham (University of Sheffield) *, Pietro Cicuta (University of Cambridge) *, Kevin Foster (University of Oxford), Seamus Holden (University of Warwick), Bart Hoogenboom (University College London), Jamie Hobbs (University of Sheffield)*, Cait MacPhee (University of Edinburgh), Syma Khalid (University of Oxford), Ralf Richter (University of Leeds), Reidun Twarock (University of York).

- **Expert Team 4** - Physical principles of embryo and organ development to understand regenerative, ageing and disease processes: James Briscoe (Crick Institute), Ray Goldstein (University of Cambridge), Zena Hadjivasiliou (Crick Institute), Martin Howard (John Innes Centre, Norwich), Ewa Paluch (University of Cambridge), Timothy Saunders (University of Warwick)*, Ben Simons (University of Cambridge)*.

- **Expert Team 5** - Translating engineering biology across scales: Rosana Collepardo (University of Cambridge), Lorenzo di Michele (University of Cambridge), Lorna Dougan (University of Leeds)*, Yuval Elani (Imperial College London), Chris Holland (University of Sheffield), Sarah Harris (University of Sheffield), Tuomas Knowles (University of Cambridge), Tanniemola Liverpool (University of Bristol), Davide Michieletto (University of Edinburgh)*, Sally Peyman (Herriot-Watt University), Susan Rosser (University of Edinburgh), Charlie Schaefer (University of York), Andrew Turberfield (University of Oxford), Jamie Hobbs (University of Sheffield), Stephen Wallace (University of Edinburgh), Dek Woolfson (University of Bristol).

- **Expert Team 6** - Physics of Life approaches that impact climate change and food security: Sonia Contera (University of Oxford)*, Antoine Jerusalem (University of Oxford), Mark Leake (University of York)*, Luke Mackinder (University of York), Andrew Millar (University of Edinburgh), Teuta Pilizota (University of Edinburgh)*, Steven Spoel (University of Edinburgh), Jenny Zhang (University of Cambridge).

- **Underpinning Approaches Expert Group**: Nigel Goldenfeld (University of University of California San Diego), Mark Leake (University of York), Michelle Peckham (University of Leeds)*, Alice Pyne (University of Sheffield)*.
  * Co-chairs.

The draft theme/areas were subsequently opened for further input through a second consultation 'theme' survey advertised via the UK Physics of Life mailing lists and a series of Roadmap roundtable discussions led by various experts and members of the working group. The second consultation 'theme' survey was opened for 1 month (August to September 2024) and received 36 responses (Survey and questions: https://forms.office.com/r/WvPSumJARp). The primary objective of the survey was to ask community members whether they felt their research was adequately represented. If not, respondents were encouraged to identify any gaps or missing elements in the theme descriptions created by the working group and expert teams. After this, a series of Roundtable Meetings was held following a similar format, with discussions centred around refining the themes and gathering further input.

Physics of Life Roadmap roundtable meetings

- British Biophysical Society Biennial Meeting: 11-14 September 2024, University of Swansea; roundtables led by Karis Baker, Olwyn Byron, Lorna Dougan, Sergi Garcia-Manyes, Mark Leake, Luke Mackinder, Davide Michieletto, Michelle Peckham, Alice Pyne (200 participants).

- AI for Biological Physics: 9-10 September 2024, Institute of Physics, London; roundtables led by Karis Baker, Matteo Degiacomi, Chiu Fan Lee, Mark Leake, Marco Mazza (40 participants).

- BioimagingUK: 30 September 2024, The Francis Crick Institute, London; roundtables led by Maddy Parsons, Michelle Peckham (100 participants).

- Royal Microscopical Society's Frontiers in Bioimaging: 11-12 November 2024, Leonardo Royal Hotel, Oxford; roundtables led by Kurt Anderson, Mark Leake (120 participants).

Evidence gathered in real-time using Mentimeter was then discussed with the whole audience to clarify and collate details, and then open discussion captured further specific evidence for the perceived challenges and opportunities within UK Physics of Life. Sessions were led by Prof Mark Leake and workshop co-organisers and designed to gather initial insight, perspectives and data from the Physics of Life community which would be relevant to the Roadmap. Sessions provided immersive, collaborative environments where diverse participants, from early-career researchers to senior academics, could contribute to initial ideas regarding themes and identifying key research challenges, enablers, and barriers. During focused breakout discussions, groups were assembled through participant choice into the different preliminary themes/areas of UK Physics of Life, and evidence was captured and collated which addressed the following questions posed to each breakout group:

(i) Within this theme what areas is the UK currently leading on?

(ii) What are the future areas the UK could potentially lead on and why?

(iii) Thinking about future research areas within this theme, what do you consider to be the main UK challenges and opportunities to address them?

(iv) Is your own research represented within the draft Physics of Life Roadmap webpage provided on https://www.physicsoflife.org.uk/physics-of-life-roadmap.html?

(v) Is there anything missing from the theme summaries within the draft Physics of Life Roadmap webpage?

Feedback from each breakout group was then reported to the whole workshop audience, discussed and collated, to help shape the next steps. The outcomes of these discussions were used to further refine the Roadmap through discussion within the working group. This inclusive feedback process ensured that diverse perspectives, spanning different career stages and disciplines, were incorporated into the Roadmap's development. Insights gathered from these discussions led to the refinement of the seven initial areas, ultimately culminating in the identification of high-level priorities and cross-cutting themes presented within this final Roadmap.

Appendix 4 – History of the Physics of Life

What is the Physics of Life?

Since the early days of physics, with the microscopic discovery of cells by Robert Hooke in the 17th century, physicists have consistently employed their instruments and theories to investigate biological phenomena, following their mission to deepen their understanding of the universe and the rules that underpin our complex experience of it. Modern "biophysics" was seeded in the 1950s with developments from physics technologies and theory applied to basic biology questions of biomolecular structure and physiology. With the development of these new approaches it became possible to identify the molecular building blocks of life, leading ultimately to advances in the 21st century where sub-cellular molecular processes can be observed in real time in living cells. The development of what is generally known as molecular biophysics naturally led to a mechanistic narrative of the life cycle of the cell, one founded in physics and biochemistry and paralleling the major advances in reductionist explanation of physical phenomena that characterised the development of high energy physics and solid-state physics.

During the 1970's solid-state physics underwent a transition to a more expansive field focusing not only on atoms and single electrons but also collective phenomena including fluids and other forms of matter, now known as condensed matter physics. Similarly, in the late 20th and early 21st century, with the maturing of mechanistic descriptions of biological phenomena came the desire to expand the scope of molecular biophysics to the myriad collective phenomena arising both within the cell and at higher levels of organisation, including tissues, organs, organisms, and even social, ecological and evolutionary scales. The emerging discipline of the Physics of Life represents an increasingly mature approach to living matter, encompassing the full range of biological phenomena at all scales of space, time, complexity and organisation, and has allowed physicists to participate in such diverse fields as neuroscience, cancer and ecological transitions, using their full arsenal of conceptual and experimental techniques.

Physics and biology are joined at the hip.

Conversely, biologists often turned to physics to seek explanations for their empirical observations, especially at the molecular and cellular levels. In fact, the interaction between physics and biology is bidirectional, although the examples of this are rarer and not so frequently emphasised. It was the work of botanist Robert Brown, whose observations of the spontaneous motion of pollen particles in solution inspired the theoretical work of Albert Einstein on diffusion and the experiments of Jean Baptiste Perrin and Theodor Svedberg, which led to the acceptance of the existence of atoms and molecules. Both were awarded Nobel Prizes in 1926, Perrin in Physics for his "work on the discontinuous structure of matter" and Svedberg in Chemistry "for his work on disperse systems".

Continuing milestones in the Physics of Life.

A century after these groundbreaking achievements, the Physics of Life has become an established area of science, with milestones celebrated by a variety of other Nobel Prizes in Physics, Chemistry, and Physiology and Medicine. A pivotal development came with the work of Andrew Huxley and Alan Hodgkin (1963 Novel Prize in Physiology or Medicine) for their insights contributing to our understanding of the action potential in electrically-mediated signaling in the nervous system, involving both innovative physics technologies in measuring relatively small and transient electrical signals in giant nerve fibres found in squid, but also in the applying quantitatively rigorous mathematical models founded on basic laws of physics to explain their experimental observations. Another key milestone is the work of theoretical physicist Max Delbrück and microbiologist Salvador Luria that used statistical arguments to demonstrate that "bacteria, like more complex organisms, develop [evolve] via mutations" (1969 Nobel Prize in Physiology and Medicine). Another is the development of

super-resolution microscopy by Eric Betzig, Stefan Hell and William Moerner (2014 Nobel Prize in Chemistry), enabling imaging of biological processes in living cells with sub-diffraction resolution, revolutionising our understanding of cell biology in real time at the molecular level.
Early on, it was recognised that biological structure is a major determinant of function, and a huge and sustained effort was made by the physical and life science communities to develop the X-ray crystallographic determination of protein structure From the late 1920s, biophysicist William Astbury carried out groundbreaking work using X-rays to study the molecular structure of wool fibres for the textile industry, driving the first studies of the structure of DNA. The successful work of Max Perutz on hemoglobin (1962 Nobel Prize in Chemistry), and Dorothy Hodgkin on insulin (1969), and the discovery of the double helix structure of DNA by James Watson and Francis Crick, built on X-ray crystallographic observations by Rosalind Franklin and Maurice Wilkins (1962 Nobel Prize in Physiology and Medicine to Watson, Crick and Wilkins). The development of X-ray diffraction prompted interdisciplinary collaborations between chemists, physicists, biologists, and even computer scientists. This has culminated in the development of a methodology for experimentally determining the atomic structures of proteins, and through the advent of machine learning techniques, the ability to predict and design protein structure, as recognised by the award of the 2024 Nobel Prize in Chemistry to David Baker, Demis Hassabis and John Jumper. And to close the circle, the 2024 Nobel Prize in Physics to John Hopfield and Geoffrey Hinton recognises the pivotal role that principles of statistical physics have played in the development of machine learning.

Translational impact of the Physics of Life on medicine.

The partnership between physics and biology has also had major ramifications for medicine, beginning with the determination of the structures of molecules such as penicillin and insulin, which were elucidated by Dorothy Hodgkin during WWII (1964 Nobel Prize in Chemistry). The nuclear physicist Rosalyn Yalow developed radioimmunoassays for peptide hormones, and with Solomon Berson, used this to demonstrate that type II diabetes is a result of the inefficient use of insulin (1977 Nobel Prize in Physiology and Medicine).

The major concepts and innovations in physics have consistently engaged with biological research through history, demonstrating that fracturing barriers between disciplines opens spaces for new fields to emerge, new technologies to appear, and novel insights to be obtained which would otherwise have been missed.

Physics of Life today: economic impact and intellectual relevance.

Physics of Life as a field is beginning to mature into something that goes beyond simply “biological physics”, “biophysics” or “physical biology”. Rather, it brings together multiple researcher stakeholders at the interfaces of the physical and life sciences. Physics of Life in the UK has a track record of delivering impactful and world-leading crosscutting research. It has made leading contributions comparable to the best efforts of EU nations, US and China, in pioneering curiosity-driven discoveries, including next-generation DNA sequencing, genomics and biosensing technologies. These avenues have led to multi-billion £ scientific research portfolios within the UK that enabled crucial agility in the COVID-19 vaccination programme?

Outlook.

This Physics of Life Roadmap comes at a propitious time. The pace of discoveries at the intersection between the physical and life sciences has not slackened, continuing the long history of this dynamic partnership, hinted at above. In the near future, Physics of Life approaches will provide deep mechanistic insight that will “groundtruth” and complement the huge international investment and effort in data-driven machine learning approaches to biology and medicine. Synergies between the two approaches could lead to an unprecedented surge in discovery, amplifying the investment in each. Physics of Life therefore provides a unique opportunity to maintain the UK lead in bioscience, with targeted investment now likely leading to substantial intellectual, societal, and economic returns over the years to come.

UNDERSTANDING THE **Physics of Life**

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