THE GUY FOUNDATION

Ageing

Abstract proceedings of the 2024 Spring Series

Driving innovation in medicine through quantum biology

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Published June 2024

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Ageing

Introduction to the 2024 Spring Series

The Guy Foundation team

The 2024 Spring Series focused on ageing: the current state of our knowledge and the new insights which might advance this knowledge. Ageing remains one of the primary questions in biology. Why do living organisms all tend, to a greater or lesser degree, towards degeneration and death? It is a question that has recurred throughout The Guy Foundation symposia over the past five years, most recently in the 2023 Autumn Series in the context of space health. Astronauts display a number of physiological changes that mimic those associated with ageing, ranging from increased cancer and diabetes risk, to cardiovascular pathologies. Given The Guy Foundation's long interest in bioenergetics, it is interesting to note that mitochondrial changes underlie many of the pathologies seen in different organ systems. Mitochondria have also been implicated in ageing, and the diseases associated with it.

As such, the aim of the 2024 Spring Series was to take a closer look at ageing, what exactly is meant by the term and what are the leading theories. The Series opened with a presentation by Professor Joao Pedro Magalhaes from the University of Birmingham. His research aims at understanding the genetic cellular, and molecular mechanisms of ageing but his presentation focused more specifically on the genes that are implicated in ageing, and what this may mean in the quest for longer lifespans. In particular he discussed how the use of network and machine learning approaches can be used for predicting longevity genes and compounds. He also outlined how research into ageing can benefit from investigating the comparative genetics between short and long-lived creatures, such as the naked mole rat or bowhead whale.

In the second session, Dr Ken Raj, from Altos Labs, Cambridge Institute of Science, built on this genetic foundation by examining the epigenetics of ageing. Gene expression is a flexible process, highly

responsive to environmental and internal factors, such as mitochondrial function. Understanding how this responsiveness changes over a lifespan seems crucial to understanding mechanisms of ageing. To this end, the development of the epigenetic clock, which classifies the specific epigenetic markers associated with ageing, offers a powerful tool with which to investigate longevity. Ken also made a distinction between programmed ageing and ageing as 'wear-and-tear', and how the former seems implicated in the embryonic development of organisms.

The third session moved from mechanism to intervention and, as Professor Alistair Nunn explained, examined ways in which the pathologies associated with ageing might be to some extent mitigated – in particular, via physical activity. It is widely accepted that exercise is one of the most effective ways in which to reduce age-related degeneration, which seems to be largely related to the induction of a healthy mitochondrial population. Alistair outlined how this may have emerged from the management of energy flux at the origins of life, through the dissipative self-organisation of biomolecules. To explore this theme further, Professor Wayne Frasch from Arizona State University gave a presentation on a key component of mitochondria, the F_1F_O ATPase.

Our fourth session continued on the theme of mitochondria, with Professor Nick Lane from University College London presenting his thoughts on ageing mitochondria. Nick discussed how a closer investigation of the reverse Krebs cycle might offer insights into mechanisms of ageing. He also presented intriguing new experimental results on the relationship between mitochondrial DNA and ageing. And finally, Professor Alistair Nunn, from The Guy Foundation and University of Westminster, speculated on what new insights about ageing might be gleaned from advances in quantum biology research and a closer look at thermodynamic principles.

Introduction to The Guy Foundation

Professor Geoffrey Guy

Founder and Chairman, The Guy Foundation

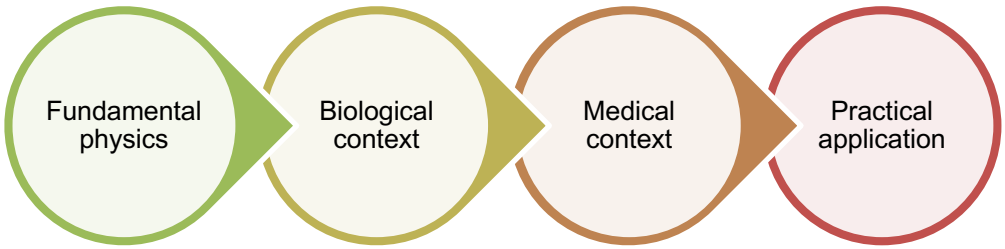
The Guy Foundation supports and promotes the investigation of quantum effects in biology, with the aim of improving our understanding of disease and thus medicine. Our belief is that significant quantum effects may well have been essential for the origins of life as well as the evolution of complex living organisms and thus a better understanding would help unlock new ways of tackling the health and disease issues that we see today.

With the development of technology, the study of quantum effects in biology has been gaining rapid pace in recent years. Classical pharmacology-based explanations for the effects of medicines remain insufficient; we aim to develop research into the effects of electromagnetic fields (both endogenous and exogenous) on biological systems. This will expand the conventional 'ball and stick' or 'lock and key' mechanisms which dominate our understanding of physiological processes, including the action of many pharmaceutical interventions. To this end we focus on the role of intracellular bioenergetics and the role of mitochondria from the point of view of dissipative thermodynamic and quantum theories. In short, if significant quantum effects are part of life, the failure to maintain this state probably plays a role in disease and ageing, and will thus be of importance to medicine.

We have also identified space travel as a key area that will benefit from a greater knowledge of the role that fields play in biology. If life is dependent on significant quantum mechanisms to function, then optimal function will be coupled to the planetary environment in which it evolved: a "Goldilocks zone" of environmental conditions. The Foundation believes that a focus on the ways in which the electromagnetic, gravitational and other effects of the space environment can be potentially mitigated, will optimise the health of astronauts and future passengers. This research would also accelerate progress in quantum biology and the advancement of medicine in general.

It is clear to us that the next generation of significant steps in medicine will need to engage with quantum biology. Our role at the Foundation is to help facilitate this mindset shift to bring quantum biology into the mainstream of medicine for the benefit of healthcare issues including ageing, neurodegeneration, metabolic syndrome, neuropsychiatric disease in the young, cancer and others. The Guy Foundation thus leads, supports and contributes to quantum biological and related research with the ultimate aim of advancing the development of new medical diagnostics and therapeutics.

The Foundation believes this advancement can be achieved in a number of ways, which is reflected by the research we fund as well as the topics we address in our scientific symposia. Our approach is summarised as encompassing research from bench to bedside:



Our priorities encompass the spectrum of theoretical, experimental, and practical advances. Understanding the fundamental physics (e.g., quantum mechanics, electrodynamics, thermodynamics) is important. More specifically we aim to understand this physics within the biological and physiological contexts, with the emphasis on furthering the study of medicine. Overall, we would like to see this knowledge translated and applied in clinical practice.

The Foundation therefore aims to provide a platform and a forum for upstream push through and downstream pull through of the understanding of the role of quantum effects and bioenergetics in biology in health and disease. We have curated and fund a collaborative research group to further investigate these interests, to advance the course of useful knowledge towards the mainstream and bring it to the attention of more conventional funders. We convene a programme of scientific meetings and publications that incorporates the diverse aspects of the field and facilitate engagement from scientists across relevant disciplines.

Abstract Proceedings

These are abstracts of a series of talks, hosted by The Guy Foundation, that were given online to an invited audience during the spring of 2024.

They have been written by the presenters and have not been formally peer-reviewed. We hope you enjoy them; video recordings of the lectures are available on the Foundation's website **www.theguyfoundation.org**. To receive notifications about new videos, subscribe to our **YouTube channel**.

Genes regulating ageing and the quest for immortality

Professor Joao Pedro Magalhaes

University of Birmingham

View the video recording **here**.

People have always sought eternal life and everlasting youth. Although the causes of ageing remain largely mysterious, hundreds of genes are now known to regulate ageing in model organisms. Genes can increase longevity by up to 10 fold and retard the process of ageing as a whole in animal models. Applying this knowledge to improve human health would have huge benefits. In this talk, I will present systems approaches aimed at deciphering the genome and increasing our knowledge about how genes and processes impact on ageing. I will present network and machine learning approaches for predicting longevity genes and compounds, which we validated experimentally. Besides, lifespan varies dramatically between similar species: mice die of old age at 3-4 years of age, dogs cannot live more than 30 years, yet humans can live over 100 years and some animals can live even longer. Studies of species with exceptional longevity or disease resistance, like naked mole rats that are resistant to cancer or bowhead whales that live over 200 years, may help treat and prevent human diseases.

Understanding the mechanisms underlying epigenetic changes with age

Dr Ken Raj

Altos Labs Cambridge Institute of Science

View the video recording **here**.

The cause of ageing is perhaps one of the oldest unanswered questions that continues to garner interest and hypotheses, of which the "wear-and-tear model" is the simplest, and most widely accepted. This intuitive notion, however, is called into question by recent development of epigenetic clocks, which are mathematical descriptions that can accurately predict the age of a person based on the degree of modifications (methylation) on specific positions on their DNA. The specificity of these age-related methylation changes in genome location and in time, in every healthy human being, cannot be readily explained by random wear-and-tear. Instead, it strongly advocates a non-random process. Epigenetic clocks have since been developed for many specific mammalian species, suggesting that the process that drives human ageing is similar to those that do so across all mammals. This proposition of the universality of the ageing process is very strongly supported by the Universal Mammalian clock, which is a single mathematical description that can accurately predict the age of all mammals regardless of species. Clues to the underlying process of ageing emerge from the features of the specific genomic locations that undergo methylation changes with age. These sites are located primarily in promoters that regulate expression of genes that participate in the process of embryonic development. They are called bivalent promoters as they are marked by two opposing modifications on histones, which are proteins around which DNA is wound. One modification stimulates expression and the other represses it. Importantly, methylation of these promoters causes the loss of bivalency. This leads to the loss of the cell's ability to regulate the expression of developmental genes. Consequently, some genes are inappropriately expressed, others cannot be expressed when required. Collectively, in time, cells, tissues, and organs reduce their efficiency and function, resulting in the gradual ageing of the organism.

From exercise to mitochondrial health to ATPase

Professor Alistair Nunn

The Guy Foundation and University of Westminster

View the video recording **here**.

One theory on the origins of life suggests it arose via a self-organising dissipative thermodynamic process in an alkaline thermal where the upwelling of protons mixed with sea water containing carbon dioxide. To begin with, this process didn't need to be that efficient, but still led to dissipation of this energy gradient by the generation of more complex structures, such as fatty-, amino- and nucleic acids, with the latter helping to carry information, further enhancing temporal stability. Hence, it was largely a biosynthetic process and is reflected in modern life in the autocatalytic roundabout we call the Kreb's cycle, which is tightly coupled to chemiosmosis and ion channels. However, at some point, the system evolved to go into reverse, enabling life to extract energy from other sources and create its own proton gradient. This then enabled it to develop a very stable system to convert this energy into something very useful, ATP; it seems that the optimal mechanism for doing this was a turbine, which also had the benefit that it could also run in reverse to maintain the gradient. The precise sequence of how this system evolved is not clear, but it certainly happened very early in prokaryotic evolution – billions of years ago. Importantly, this system results in "flux stability" and adaptability, a property predicted by thermodynamics and dissipative self-organisation, which is reflected in the observation that all life apparently wastes 20-40% of its energy in futile cycling but is pivotal in controlling redox. This might be why mitochondria seem to run "hot". The implications are fascinating, as they suggest that movement is not only one way of dissipating, but also of maintaining structure, as it ensures dissipative self-organisation: for some species, including humans, energy flux through movement may have become canalised to ensure optimal health and robustness. In terms of ageing, we know that the inability to maintain protein structures, in particular, involving proteostasis, is pivotal. In more complex organisms, this is linked to autophagy, genomic stability and inflammation, which can be linked via mitochondrial function, as they are key in controlling epigenetics and redox. Physical activity stimulates a healthier population of mitochondria and ATPase throughout the body and slows ageing – which is reflected in the associated pathways, in effect, it broadens our "metabolic flight envelope", so improving our metabolic engine. This physical activity induced adaptation is encapsulated by the concept of hormesis, implying that movement is essential to maintain age-defying protein structure at the most basic level, including the turbines of life.

Age-dependent impacts on the F_1F_O ATP synthase

Professor Wayne Frasch

Arizona State University

View the video recording **here**.

The primary source of cellular energy in all life forms is ATP, which is synthesized from ADP and inorganic phosphate by the F_1F_O ATP synthase. Photosynthetic or respiratory electron transfer complexes (ETCs) initially convert the variety of energy sources consumed by organisms into a proton-motive force (pmf) by pumping protons across a membrane away from equilibrium, which also creates a membrane potential. In mitochondria, these processes occur on the inner membrane that is tightly folded due to long strands of F_1F_O dimers. By transporting the protons to their equilibrium position via subunit-a, the F_O complex generates torque on its ring of c-subunits, and this rotation drives the synthesis of ATP in the attached F_1 complex. If the membrane becomes leaky to protons, the pmf collapses and ATP synthesis decreases as it becomes 'uncoupled' from the ETCs. In eukaryotes, this process occurs in mitochondria, which originated from an α-proteobacterium that was engulfed by an ASGARD archaebacterium. Mitochondria retain several copies of DNA (mtDNA), which now encode only 13 proteins including F_O proteins subunit-a Atp8. Because the mitochondria in an adult derive from those present in the oocyte, the mitochondria undergo fission with each cell division. Age-related damage of mitochondrial proteins and mtDNA occurs from UV light or highly reactive oxygen species (ROS) generated by ETCs. Many devastating neurological and neuromuscular diseases derive from age-related mtDNA mutations alter single amino acids in subunit-a that impede proton translocation. Cellular aging can be delayed by mitochondrial fusion to restore mild functional losses. The balance of mitochondrial fission and fusion maintains a healthy organism.

Cells stop dividing as they age, which decreases mitochondria biogenesis and compromises ATP synthesis capacity. Life span is increased when damaged cells are cleared by autophagy, which is closely linked to mitophagy that eliminates damaged mitochondria. Mitophagy is initiated by PINK and Parkin proteins, which ubiquinate the outer mitochondrial membrane and depolarizes membrane potential to facilitate removal, concurrent with increased ROS-consuming enzyme activity. The mitochondria permeability transition pore (mPTP) forms in the inner membrane, which swells, then bursts to release cytochrome c and induce cell death. The progression of age-related mitochondrial degeneration is visible by cryo-tomography as an initial decrease in the density of packing of

mitochondrial cristae in the inner membrane, which leads to a dissociation of cristae junctions that alters proton can calcium fluxes. Cristae membrane curvature is lost due to dissociation of F_1F_O dimers, which become uncoupled to decrease ATP synthesis. Accumulating evidence supports the hypothesis that formation of the mPTP results from a conformational change in F_1F_O that has not been defined to date. Liver and kidney mitochondria showed greater extents of age-dependent degradation than those in cardiac muscle indicating that tissues age at different rates.

Thoughts on ageing mitochondria

Professor Nick Lane

University College London (UCL)

View the video recording **here**.

Cells function through three interconnected systems: energy flow, metabolism and genetic information. Recent work suggests that these systems arose in that order from the origin of life itself: a geochemical protonmotive force across cell-like inorganic pores in alkaline hydrothermal systems drove CO2 fixation into spontaneous protometabolism with a similar topology to the deeply conserved core of metabolism, which gave rise to genes through direct physical interactions. The core of metabolism is the Krebs cycle, which in bacteria may be driven in reverse by membrane potential to fix CO2, generating the precursors for cell growth. Even in modern eukaryotic cells the Krebs cycle rarely functions simply as an oxidative cycle. In cancer and viral infections such as Covid, Krebs cycle flux can be driven partly in reverse by membrane potential to form useful biosynthetic precursors, which in turn upregulate the mTOR axis and downregulate sirtuins and autophagy. This rewiring may also happen with age, shaping epigenetic state and mimicking a pseudo-programme for ageing. Work in isogenic fly lines with mismatched mitochondrial DNA shows that complex I function impacts not only on oxidative phosphorylation but also Krebs cycle flux, intermediary metabolism, gene expression and phenotypic outcomes including fitness and longevity. Suppression of complex I expression can maintain ROS flux within homeostatic limits, even at the cost of viability. Such drastic changes could be offset by mitochondrial dynamics, notably changes in cristae structure. More open cristae will lower membrane potential and ROS flux, making it easier for complex I to pump and restoring redox state, but at what cost beyond lower ATP synthesis? Work on the mechanism of volatile general anaesthetics in flies suggests that complex I can act as a supramolecular engine, in which synchronized electron flow and proton flux through parallel cristae can generate oscillating magnetic fields with sufficient strength to signal to the plasma membrane. Disruptions in cristae structure with ageing are likely to affect the dynamics of such mitochondrial integration within cell and tissue networks.

Quantum and thermodynamic perspectives on ageing

Professor Alistair Nunn

The Guy Foundation and University of Westminster

View the video recording **here**.

Life can be viewed as an emergent property of the planet that is driven by entropy to equilibrate energy potentials via dissipation. It may have started in an alkaline thermal vent where upwelling hydrogen met carbon dioxide containing seawater. The transfer of electrons and protons was likely encouraged by FeS like compounds, leading to self-organising far from equilibrium autocatalytic networks and evolution of complex chemistry; these processes may well have relied on quantum mechanics. The movement of these ions could have also generated electric fields, which helped in stabilising these emerging systems. In time, these became recognisable as life, and further evolved to use other chemical energy sources to create their own proton gradients using electron transport chains, as well as photons, which gave rise to photosynthesis. At some point, bacteria and Archaea underwent symbiosis to form the modern eukaryote, with the former becoming the mitochondrion.

Today, nearly all life dissipates energy by uncoupling and futile cycling, so maintaining adaptive bioelectric fields. It is thus informative that manipulation of uncoupling can modulate redox and inflammation, which supports the role of mitochondria in inflammation and hormesis. If we view these phenomena from the perspective of adaptive thermodynamics to maintain dissipation, they could be applied to all scales of life – from the molecular all the way up to species. Critically, each dissipating "negentropic" component is disposable if it fails – as it could damage other functioning dissipating units, which suggests a role for natural selection, and of course, use of information and memory. Not only would this result in the evolution of complexity, and more robust systems, but also of programmed cell death and the "deconstruct to reconstruct" principle following damage. In effect, dissipative failure recapitulates phylogeny.

This may explain "inflammaging", and why proteostasis and management of redox are likely the oldest markers of ageing: maintaining functional proteins has been key from the beginning. Life evolves to become more adaptable, usually by cooperation and complexity, but if the stress is too great, it has to recapitulate phylogeny, relying more on genetics and simplicity. This is replicated in individual organisms, which can, to some degree, regenerate components via a process intimately linked to inflammation – an ability that is lost as the organism ages, probably through natural stochastic

degradation of molecular fidelity. This also highlights the possibility that this process results in a reducing ability to maintain quantum effects, which themselves are key in detecting changes in the environment. It would therefore seem that those factors that tend to ensure dissipation and structure, such as movement, are essential for functional longevity. It might also explain why calorie restriction can increase longevity, as too much energy would force replication due to loss of internal order – cells, due to thermodynamics, can only get so big. Indeed, biosynthesis is likely the earliest form of dissipation, while energy restriction and the need to move drove new modes of dissipation. The origins of hormesis are thus ancient.

In summary, if life is viewed at the global scale, every component is expendable if dissipation starts to fail, if this happens, the damaged “nodes” are removed. This global homeostatic system is reliant on the flow of electrons and protons, which channel through highly evolved proteins that lose fidelity, so renewal has to occur – hinting that ageing is an evitable component of maintaining dissipation and entropy. As suggested by Hayflick, although all organisms age due to the loss of molecular fidelity, individual longevity seems to have evolved from enhanced repair mechanisms, which does hint at methods to slow ageing. However, survival of life on earth is ultimately achieved by natural selection of the fittest dissipating units; the fastest evolving will be the simpler ones - hence why inflammation/hormesis are essentially scale free. Finally, if, as it seems, entropy has driven the emergence of life, which with technology is accelerating dissipation, anything that might stop this, for instance, nuclear war, raises the question about the emergence of artificial intelligence as another mechanism to prevent this by removing the damaging “node”. Is this “entropy’s dark laughter” and something humans, in particular, should heed?

Closing Note

Professor Geoffrey Guy

Founder and Chairman, The Guy Foundation

View the video recording presenting a recap of the series talks and the questions for roundtable discussion **here**.

The 2024 Spring Series roundtable discussion raised more questions than it resolved. This wasn't surprising, given the range and depth of the different presentations, which began with gene-centred theories of ageing and ended with field-based electromagnetic signaling processes, thermodynamics, and quantum biology, and how these might offer new directions in ageing research. Between these two extremes a number of possible ageing measures and mechanisms were discussed. Longevity is to some extent heritable, associated with identifiable genes: a gerontome. However, genes only confer potential on living organisms, most simply: a set of building materials. The complex ways in which these materials are assembled within specific environments – their epigenetic realisation – allow for the variety and adaptability that is life's hallmark. Epigenetic clocks systemise this flexibility, by examining the consistency of epigenetic markers, in particular those accumulated during ageing. What is fascinating is how universal and predictable the epigenetic clock is in the context of ageing, both within and across mammalian species.

What this predictability suggests is that ageing is a programmatic process rather than purely due to material degradation. This distinction came up a number of times in the different presentations. Joao Pedro Magalhaes hypothesised that ageing is less about accumulated damage than it is an information problem. Ken Raj concluded that ageing is a dysfunction in cellular programming by demonstrating how epigenetic clocks are associated with fundamental processes such as nutrient sensing and mitochondrial function. He then drew a distinction between this epigenetic ageing and ageing as wear-and-tear, the latter of which involves markers of ageing such as genomic instability and telomere reduction. This distinction seems a useful way to make explicit the slightly different aims of longevity research: immortality versus mortality compression. The former, as an attempt to extend lifespan beyond currently accepted limits, seems contingent on understanding how ageing relates to organismal development, why the epigenetic clock seems bound up in processes of embryonic specialisation, and how the epigenetic modifications associated with ageing – such as histone bivalency – might be mitigated. Mortality compression, on the other hand, seems a more readily

achievable longevity measure, focusing on lifespan quality rather than overall extension. In this context the maintenance of structural integrity is one possible site of intervention. To this end, there was an excellent discussion by Alistair Nunn and Wayne Frasch, which focused on how biological structure – from whole bodies down to the biomolecules such as proteins that constitute these bodies – is related to energy and entropy management. Indeed, as noted by Alistair, ageing may be seen as the natural consequence of inevitable molecular degeneration in a self-organising system driven by entropy, where natural selection is constantly happening to select for functional units. As reinforced by Nick Lane's presentation, the Krebs cycle, with its involvement in both energy production and biosynthesis, thus seems a promising focus for insights into healthy ageing. This brings mitochondria once more into sharp focus.

In closing, while the discussion raised many questions without easy answers, some broad conclusions might be drawn. The Spring Series highlighted the exciting breakthroughs, such as the epigenetic clock, that have been made in the field of ageing research. These gene-centred advances, however, might be augmented by new research directions. One way in which to do this is to look at the physiological effects of travel to new environments, such as space. Mitochondria, implicated in the accelerated ageing phenotype observed in astronauts post space-travel, are equally important in terrestrial ageing. Space thus offers a laboratory for research into the markers and mechanisms of ageing. Novel environments might also include those conditions out of which life emerged. Various presentations in this series returned to the idea that a closer look at the origins of life is a valuable lens through which to examine ageing. Understanding the generation of life, its simplest underlying mechanisms, may help to understand life's degeneration. Mitochondria are again the focus here, implicated in teasing out how living organisms originated out of dissipative processes, self-assembling as a strategy to manage energy gradients.

And finally, in addition to novel environments, we might look to novel approaches, such as quantum biology and bioelectricity, whose focus is electromagnetic rather than genetic. On that note, the 2024 Autumn Series 'Genes and metabolism: bioelectricity and the quantum spark of life' will focus directly on what bioelectric approaches can add to more established biological approaches. We look forward to seeing you there.

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www.theguyfoundation.org

June 2024

The Guy Foundation Family Trust Registered Charity No. 1178782