The Guy Foundation

FROM BIG QUESTIONS TO SMALL DETAILS: THE MACRO-MICROSCOPIC DIVIDE

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Driving innovation in medicine through quantum biology

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FROM BIG QUESTIONS TO SMALL DETAILS: THE MACRO-MICROSCOPIC DIVIDE

– BETONY ADAMS AND ALISTAIR NUNN

The Guy Foundation's 2021 Spring Series began with big questions. What is life? What might quantum immortality mean? This ambition was tempered, however, by practical suggestions as to how these questions might be approached. To understand life, the best place to begin is, arguably, the beginning. There is some suggestion that proton gradients in hydrothermal vents might have been instrumental in providing the protometabolic drive to kickstart life. While this would seem to suggest that metabolism trumps information in the question of which came first, the reality is perhaps less exact. Electrochemical gradients across membranes are integral to metabolic processes in cells, harnessed by ATPase to produce ATP in all forms of life, from prokaryotes, to plants, to humans. Research suggests, however, that electrochemical gradients are also a fundamental source of information for living organisms, changing the shape of life on a macroscopic scale. Whereas information in biology is conventionally attributed to the genetic code, the role of the bioelectric code is of growing importance, with electric fields having measurable effects from the organelle to the organism scale.

Electromagnetic radiation – or light, as we know it – is also potentially both a source of energy and a means of signalling used by living organisms. Light drives photosynthesis, harvested by chromophores associated with electron transport chains (ETC) that resemble those found in mitochondrial metabolism. Interestingly, light can still manipulate the animal ETC, and there is even evidence that adding derivatives of chlorophyll to animal mitochondria can enhance energy production. It has also been suggested that these ETCs give rise to endogenous photons, or autoluminescence, created out of the reactions of biomolecules with reactive oxygen species – especially during oxidative stress. First observed in the 1920s, this was later called "biophotonic emission" – although it is of a very low intensity. This led to a whole new theory about the role of electromagnetic fields in life, which, perhaps unfortunately, was usurped by the discovery of genes. Whether this autoluminescence is merely a metabolic artefact or plays a more defining role remains to be seen. However, there is evidence that these photons can pass information from one cell to another. Here, too, the role of light in life might be less clear. Perhaps it is both metabolic product and a way to transmit information. While the point is tentative the evidence is more compelling. Light, at least the exogenous kind, seems to play a role in that most complex of all information processors: the brain. And, more practically, can undo damage that profoundly alters our ability to process information. Specifically, flickering light at a frequency of 40 Hz, can undo neurodegeneration typical to Alzheimer's disease, promoting gamma entrainment and neuroprotection.

The interaction of light with matter is inextricably linked to the emergence of quantum mechanics. The ultraviolet catastrophe and the photoelectric effect were both seminal to the development of the new theory. Quantum biology, by extension, might be seen as the interaction of light with living matter. In the beginning, then, when life could still be defined by the microscopic actions of protons and electrons and photons, quantum effects might very well have played a role. On the microscopic level, in metabolic processes that still bear a

resemblance to proto-processes, it appears that quantum mechanics may indeed still play a role. Proton tunnelling in enzymes, for instance, appears to employ quantum effects to achieve remarkable enzymatic rate accelerations, while life seems to have selected for optimal electron tunnelling distances in the ETC. But life as we know it today is also concerned with macroscopic outcomes and the integration of information across the scale of an entire organism. While less research has been done in this area, it appears as though the single-celled amoeboid organism, *Physarum polycephalum*, can compute information and find efficient solutions to computationally expensive questions. As such it may provide an interesting biological substrate in which to advance quantum computing research as well as a way to imagine the interplay between – as one Spring Series presenter put it – the microscopic quantum elements of living systems and their macroscopic classical outcomes.

INTRODUCTION TO THE GUY FOUNDATION – GEOFFREY GUY

The Guy Foundation has been set up to support and promote 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 not only been essential for life to get going, but also enabled it to grow in complexity by amplifying these effects both in space and time. For example, all life is based on iron-sulphur compounds that can display interesting tunnelling properties, which could be enhanced by the addition of proteins and chromophoric molecules. These molecules were all created by well understood geochemical/interstellar chemical processes long before life got going, which coupled with established thermodynamic mathematical principles involving self-organisation of dissipative structures in energy gradients, do provide the basis of a starting point for life. In short, if significant quantum effects are part of life, the failure to maintain this state probably plays a role in disease and thus, the ageing process.

Of course this raises a question, why hasn't anybody thought of using quantum mechanics to explain biology? Well, actually, as indicated in the preface, they had, right from the beginning from the days of the pioneers of quantum physics, and over the years, several leading scientists have discussed the possibilities that biology could be using significant quantum effects. Some, such as Roger Penrose, have even gone as far as suggesting it could explain consciousness itself, which, even today in the 21st century, is still far from being understood. In fact, with time, despite the 20th century optimism that by the 21st century mankind would have found cures for cancer and many other diseases, and possibly even for ageing itself, a deeper understanding of life seems to be still out of reach. It could be even further away as emerging global obesity appears to be *shortening* both a healthy and absolute life expectancy, which is resulting in spiralling health care costs across the planet. Despite mankind's emerging technical mastery of nature, we still have a very long way to go in terms of truly understanding it.

This therefore brings us neatly back to quantum mechanics and biology and the aims of the Foundation. Quantum mechanics is intuitively difficult to understand, and, as has been said, if you think you understand it, then you don't. Only now, after nearly 100 years, is technology reaching the point where one of the most difficult of concepts, quantum entanglement, can be tested. Einstein called it "spooky action at a distance", as he simply didn't believe it because it didn't fit with his general theory of relativity, and despite being one of the founders, he openly said that quantum mechanics had to be incomplete. He often argued with Niels Bohr over this. For many years the concept of "quantum realism" has stood quietly like a large elephant in the room, as many thought that only when a conscious observer observed something did its wave function collapse to give us the Newtonian universe we all understand. The latest experiments to test whether or not quantum entanglement exists continue to suggest that it clearly does, which indicate that two entangled particles, which share the same wave function, can still somehow communicate, instantaneously, even if they are on opposite sides of the galaxy. In fact, it is now finding uses, like other quantum effects, such as tunnelling, in everyday practical devices, such as eaves-dropper safe communication. Thus, it is likely that conventional

biology, and quantum mechanics, despite the odd attempt to communicate, have largely passed as ships in the night for nearly a century. The Foundation therefore aims to provide a platform and a forum for upstream pull through and downstream push through of the understanding of the role of quantum effects in biology in health and disease. We recognise these notions to be extremely avant-garde, oftentimes incomprehensible. However, we take a long view and see ourselves as pioneers in a new wave of medicinal science.

With an emphasis on building a research community to further investigate these interests, The Guy Foundation operates in a spirit of collaboration rather than straightforward grant funding, to advance the course of useful knowledge towards the mainstream and bring it to the attention of more conventional funders. We aim to do this in various ways. By curating a programme of scientific meetings and publications that incorporates the diverse aspects of the field and facilitates engagement from scientists across relevant disciplines. By identifying what we see as research priorities and building a network of interested scientists through the funding of Guy Foundation collaborative projects to accelerate relevant high-quality scientific research.

Professor Geoffrey Guy MB BS, LRCP MRCS, LMSSA, DipPharmMed, BSc, DSc

Founder and Chairman of the Board of Trustees, The Guy Foundation

FULL PROCEEDINGS

ABOUT THESE ABSTRACTS – ALISTAIR NUNN

Director of Science, The Guy Foundation

These are abstracts of a series of talks, hosted by the Foundation, that were given on line to an invited audience during the spring of 2021. They were held virtually due to the COVID-19 pandemic caused by the SARS-COV-2 virus, which resulted in travel being highly restricted.

They have been written by the presenters and have not been formally peer-reviewed. We hope you enjoy them; video recordings of the full lectures can be viewed on the Foundation's website www.theguyfoundation.org.

THE SHAPE OF LIFE FROM THE BEGINNING: THE ROLE OF ELECTROMAGNETIC FIELDS IN THE PREBIOTIC WORLD

– PROFESSOR ALISTAIR NUNN

Director of Science, The Guy Foundation, and also Visiting Professor in quantum biology & bioenergetics, Research Centre for Optimal Health, University of Westminster.

There are many unanswered questions about life: how did it begin; why do we age; what is consciousness; are we alone; is it using quantum effects? All pivot around how it started. There are many theories, ranging from metabolism to information first and did it use solar or geochemical energy? Did it start in warm little ponds, the sea's surface, deep sea thermal vents, hot springs, or meteorite impact sites? Certainly, the smorgasbord of chemicals can be created abiotically, but what cooked them up to become life? Physics indicates that thermodynamics and dissipation can result in order out of chaos and negentropic and self-replicating structures far from equilibrium. One further clue is routed in an old idea developed in the 1920s and now being supported by new data; the shape of life is determined not by genes as such, but by morphogenetic electromagnetic (EM) fields. EM fields are generated by the movement of charged ions, and given how ancient ATPase is, this does hint at the alkaline thermal vent as being a strong contender. We suggest that the flow of ions gave rise to an EM field that acted as the ethereal skeleton for abiotic chemicals to condense around – an "attractor" generating an area of negative entropy, that, by incorporating information, enabled natural selection to act, with ion channels being an early resultant structure. Given that the movement of electrons in this system could potentially give rise to photons, and that many abiotic molecules were chromophoric, this might also suggest that photons continue to play a role in homeostasis. Not only would this suggest the sequence of events at the beginning, but also that life is using quantum effects. Today, the reliance of all life on uncoupling is perhaps also strong evidence for a process that generates this field.

WHAT IS LIFE TODAY? LIGHT AS SCAFFOLD FOR ORGANIZING WHOLE BIOLOGICAL SYSTEMS AND THE FUTURE OF QUANTUM IMMORTALITY

– DR PHILIP KURIAN

Founding Director of the Quantum Biology Laboratory (QBL) at Howard University.

Now one century after Schrödinger finished his first article on atomic theory in 1921, we find ourselves at a new precipice of discovery in quantum biology, where we can re-examine the implications of several question(s) posed in his now-famous 1944 tract. Philosophers, biochemists, and physicists have each in their own way attempted to define exactly *what is life*, with definitions ranging from the all-inclusive (e.g., Spencer's "the continuous adjustment of internal relations to external relations") to the more narrowly defined (Bernal's "open system of linked organic reactions" for carbon-based biology). The denial by Bohr and others of the validity of EPR's 1935 criterion of physical reality has paved the way for an alternative definition characterized by Heisenberg uncertainty and nonlocality. Quantum mechanics thus asserts the role of the first-person subjective—a Gödelian self-referential system—in third-person "objective" measurement, highlighting the fallacy of a strict empiricism that denies the existence of what cannot yet be measured. The unitary (deterministic) evolution of Schrödinger's equation is contrasted with (nondeterministic and nonlinear) state reduction processes, which have only recently been demonstrated as reversible when coupled weakly to other deterministic systems. Multiscale biological systems across many orders of magnitude (e.g., the brain) may be able to drive, harness, and even synchronize such quantum deterministic events with the necessities of mesoscopic and macroscopic functionality. Nonequilibrium pumping in dissipative environments—the hallmark of order and self-organization in living systems—raises fundamental questions regarding Poincaré-Zermelo and Fermi-Pasta-Ulam-Tsingou recurrences in the cell, which can be driven far from equipartition and ergodicity by active metabolic states. Dyson's 1979 conclusion that "it is impossible to calculate the long-range future of the universe without including the effects of life and intelligence" is found consistent with the weak and strong anthropic principles. A many-worlds interpretation of quantum mechanics, with analyses of the Wigner friend and Everett friends paradoxes, leads to the possibility that an "Ultimate Observer" located at the Omega Point—a final singularity in a closed universe, or a future timelike infinity in an open universe—collapses the wavefunction. I define *quantum immortality* as the "eternally living" branch of a linear superposition of Schrödinger cat states for a macroscopic biosystem when the number of binary life-death trigger events approaches infinity. I conclude with a discussion of the etherealization of consciousness beyond the organismal body into light, concurring with Penrose that the information processing bounds set by the soft, wet "hardware" of the (atomic-scale) brain are beyond all exascale computing speeds and pose steep challenges for even a rudimentary AI replica of human consciousness.

NONINVASIVE SENSORY STIMULATION TO INDUCE GAMMA ENTRAINMENT AND NEUROPROTECTION

– PROFESSOR LI-HUEI TSAI

Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences, Director of the Picower Institute for Learning and Memory, MIT.

Rhythmic neural activity in the gamma range (30-80 Hz) is modulated during various aspects of cognitive function and has been shown to be disrupted in several neurological conditions, including Alzheimer's disease (AD). It is well established that local network oscillations at specific frequencies can be induced in cortical areas using sensory stimuli. We have applied this approach, which we term Gamma Entrainment Using Sensory stimuli (GENUS), using patterned light and sound stimulation at 40 Hz in AD model mice. Remarkably, GENUS augmented gamma oscillation power in multiple brain regions. Moreover, chronic application led to marked reduction of amyloid and tau pathology, attenuated neurodegeneration, and improved cognitive function in multiple AD mouse models. These beneficial effects elicited by GENUS are likely to be mediated by microglia activation, and increased capillary mediated clearance. In humans, combined light and sound stimulation increases gamma oscillation power in extended brain regions including deep brain areas such as the amygdala, hippocampus and posterior insula. We found that GENUS is safe even after prolonged exposure. Preliminary data suggests that GENUS in AD subjects reduces sleep fragmentation and repairs structural and functional connectivity in the brain. We are continuing the treatment and evaluation of GENUS treated human subjects.

AMOEBA-BASED COMBINATORIAL OPTIMIZATION PROBLEM SOLVER AS A POTENTIAL PLATFORM FOR QUANTUM-BIO COMPUTING

– PROFESSOR MASASHI AONO

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Choosing a better move correctly and quickly is a fundamental skill of living organisms for their survival, which corresponds to solving a computationally demanding problem and may be related to a primitive form of intelligent behavior. We demonstrated a bio-computing system to evaluate the problem-solving ability of a single-celled amoeboid organism, a plasmodium of true slime mold (Physarum polycephalum), that changes its shape into an optimal one by maximizing its body area for foraging and by minimizing the risk of being exposed to aversive light stimuli [1]. The system that we call the "amoeba-based problem solver (APS)" is used to search for a legal solution to the travelling salesman problem (TSP), an NP (Nondeterministic Polynomial time)-hard combinatorial optimization problem. APS has shown to find an approximate solution to TSP in the time that grows linearly as a function of the problem size (the number of cities), while the number of solution candidates grows factorially. The linear-time search performance was reproduced well by our mathematical model "AmoebaTSP [2]" and its electrically-implemented circuit "analog electronic amoeba [3]." Some authors have shown that the organism's problem-solving/decision-making capability seems to be supported by forming microtubules networks [4], where the microtubules have shown to function as channels for transmitting information on light for over macroscopic scale [5]. These observations might suggest that APS may be used as an interesting experimental platform to advance quantum-bio computing studies, bridging between "micro (quantum, molecule, microtubule, light)" and "macro (classical, cell, individual, intelligence)."

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HOW DO CELLS RESPOND TO AND GENERATE ELECTROMAGNETIC FIELDS – DR MICHAL CIFRA

Head of research team/Senior scientist at Institute of Photonics and Electronics, Czech Academy of Science

The focus is on selected topics at the molecular level of how electromagnetic field is generated within organisms and how organisms can be affected by electromagnetic field. In the first part, we briefly presented our recent contributions to research of dielectric properties of biomolecule solutions[1]–[3] and short intense pulsed electric field effects on biomolecules and cells [4]–[6]. We showed in both all-atom molecular modelling [7]–[9]and experiments that the tubulin microtubule systems can be affected by intense electric field at the nanosecond time scale. The second part of the talk focused on endogenous biological electromagnetic field. We briefly outlined general biophysical mechanisms which could generate electromagnetic field in various parts of the spectrum ranging from few kHz to the visible band [10]. We covered our hypotheses on microtubule based microwave fluctuations [11]–[17]. We also showed that organisms are source of ubiquitous biological autoluminescence (a.k.a. ultra-weak photon emission, or biophotons). This luminescence is due to chemiexcitations occurring as a result of reactions of biomolecules with reactive oxygen species [18]. Biological autoluminescence was showed to correlate with growth and metabolism [19], [20], oxidative metabolites [21], [22], is suppressed by antioxidants [20], [23] and enhanced by oxidants [19], [20], [24]. Biological autoluminescence was also speculated to be involved in light-based communication between cells and organisms [25]–[27] . We hold that regardless of its biological role, if any, biological luminescence and its analysis can be applied as non-invasive, almost real-time, low operation costs and label-free diagnostic technique for monitoring oxidative processes.

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AT THE INTERFACE OF QUANTUM AND CLASSICAL BEHAVIOR IN NATURE: LOOKING INTO THE EYE OF QUANTUM TUNNELING IN ENZYMES AND THE ROLE OF A NOISY ENVIRONMENT

– PROFESSOR JUDITH KLINMAN

Professor of the Graduate School, Klinman Lab, at the Departments of Chemistry and Molecular and Cell Biology and the California Institute for Quantitative Biosciences at the University of California, Berkeley

The theory of enzyme catalysis continues to be presented in textbooks within the context of transition state theory, that posits enhanced binding of the “transition state” as the origins of biological catalysis. In contrast, several decades of evidence for through the barrier, tunneling processes in enzyme catalyzed reactions has altered this perspective (1,2). An interplay between the protein scaffold and the active site chemistry is now seen to be an essential part of effective barrier crossings, with experimental probes uncovering site specific thermal conduits that lead from protein/solvent interfaces to active sites (e.g., 3-5). Multi-dimensional non-adiabatic theories have been developed for proton coupled electron transfers that allow separation of the mass dependent wave function overlap for the tunneling particle from the temperature dependent activation of the protein environment (6,7). The latter increases the probability of the coherent states that are a prerequisite for tunneling. One of the fascinating properties to emerge is a similar or identical activation energy for tunneling of both protium and deuterium (8), behavior previously thought to be restricted to very low temperatures (near absolute zero)(9). This property emphasizes the possible interplay of quantum tunneling in biological reactions and the ability to achieve highly compacted active site structures as the source of huge enzymatic rate accelerations.

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