Making sense of oxygen; quantum leaps with "physics-iology"

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In the first "Guest editorial" published in the July issue of Experimental Physiology, Dr Tulleken spoke to the powers of physiology, stating that, "…it is only physiology that has created an understanding of the body that can usefully guide an individual's approach to their own life" (van Tulleken, 2018). True words indeed, and since the landmark publication of Harvey's Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus in 1628 (Harvey, 1976), physiology's journey to prominence has been a colourful one. Originally rooted to anatomy and medicine through an organ-system approach, it has since matured into a distinct discipline that has made huge strides by taking an integrated molecular approach to provide ever more refined explanations of macroscopic phenomena and thereby illuminate the cellular and organismal "workings" of the human body. Indeed, we have much to thank Ivan Pavlov, the first physiologist to win the Nobel Prize, for this *hypothetica motus*, for it is he in 1897 who originally proposed that its future lay in understanding the "physiology of life molecules" (Pavlov, 1955). Yet despite over a century of research, a complete understanding of the complexities underlying physiological processes and systems are, oftentimes, incomplete and lack explanatory power, suggesting that we need to move beyond the "classical" to explore deeper meanings and further unravel how we as humans really work.

Quantum "physics-iology" (the "ics" being all important!) may well signal the break of a new dawn. Physiologists have taken up the quantum baton, becoming increasingly interested in the fusion of "quantum physics" with the "physiology" of life molecules to provide answers where traditional classical approaches have consistently failed (Wolynes, 2009; Natochin Iu, 2010). On the face of it, this makes intuitive sense since, after all every object in this universe, including you and I, is made up

of atoms, in fact a whopping 7×10^{27} (7 billion billion billion) of them in a 70 kg human (Freitas, 1999), arranged in a fortuitously obliging manner, complemented by an array of subatomic particles that are ultimately governed by the laws of quantum physics. Could life's molecular mechanisms exploit some of these notoriously counterintuitive behaviours for physiological gain and all of its complexity be reduced to some unifying differential equation? Why not, after all, physics is considered the most fundamental of all sciences?

But first, a brief word to those counterintuitive behaviours; mind-numbing paradoxes, puzzles and mathematical complexity that breathe fear into anyone with more than just a fleeting interest in what the quantum world has to offer the jobbing physiologist. Since Max Planck first suggested that electromagnetic waves were emitted in discrete packets of energy or quanta (Planck, 1901), quantum mechanics (QM) has evolved into the fundamentally non-deterministic revolution that has overthrown classical (common-sense) physics, it has since matured into the best theory there is to describe the world around us at the nuts-and-bolts level of atoms and subatomic particles; whose behaviour cannot be understood within a classical context. In theory, and to some extent in practice, its tenets demand that particles can penetrate through solid barriers (tunnelling), be in two places at once - both as particle and wave (superposition), and instantly exchange information despite being spatially separated - violating our intuition about locality (entanglement) that even Albert Einstein referred to as "spooky action at a distance", and led Niels Bohr, the father of the orthodox "Copenhagen Interpretation" of quantum physics, to remark "If quantum mechanics hasn't profoundly shocked you, you haven't understood it yet" (Griffiths, 2017).

Yet it was Erwin Schrödinger, famous for his wave equation for non-relativistic QM, popularised by his alive and dead cat conundrum, who was the first to venture across disciplines and ask if humans

can harness non-trivial quantum effects to perform a task more efficiently than even the best classical equivalent for selective advantage. In his landmark book, “What is Life?” he argued that life somehow opposes the entropic tendency towards dissolution feeding on negative entropy (second law of thermodynamics), and further anticipated a quantum molecular basis for human heredity with genetic information transmitted by an arrangement of atoms in an “aperiodic crystal”, which nine years later was confirmed to be the DNA molecule (Schrödinger, 1944); quite remarkable! However, the notion that the macroscopic order of life is somehow based on order at its quantum level was met with justifiable scepticism; since quantum phenomena are typically observed on the smallest of subatomic scales under vacuum at ultra-low cryogenic temperatures (avoiding the detrimental effects of decoherence and dephasing), and should simply fade away in the warm, wet, mess of the macroscopic (Ball, 2011).

Yet emerging evidence now suggests that quantum coherence can survive *in vivo* as life hovers in a posed realm between the pure quantum and incoherent classical world to improve our physiological lot. Much of these revelations have stemmed from our understanding of how electrons behave, the first subatomic particles to be discovered by Joseph Thompson (originally given the physiological term, corpuscle meaning “small body”) (Thomson, 1897), weighing in at an infinitesimal 9.10939×10^{-31} kg (to be precise!), whose position and momentum cannot be determined simultaneously with perfect accuracy thanks to the Heisenberg Uncertainty Principle (Heisenberg, 1927). Their quantum weirdness has helped explain: the mysteries of avian navigation, exploiting properties of electronic spin in birds’ retinas (Ritz *et al*., 2000); olfaction - whereby an electron within a smell receptor in our nose can "jump" or tunnel across it and dump a quantum of energy into one of the molecule's bonds, causing the molecular "spring" to vibrate resulting in smell (Turin, 1996); genes that may be “written in quantum letters” with quantum effects underlying the hydrogen bonds that keep the DNA double helix glued together (McFadden & Al-Khalili, 1999); general anaesthesia that is

accompanied by changes in electron spin, implicating a role for neuronal electron current in its effects (Turin et al., 2014) and, arguably the best described of all, light harvesting in photosynthesis, whereby excitons, generated by ancient green, sulphur-breathing bacteria, travel as a coordinated quantum wave in superposition rather than (classically) as a simple straight line, "feeling out" the most efficient pathway to transport energy to the plant's reaction centre within a staggeringly short, 10^{-9} s, achieving close to 100 % efficiency (Thyrhaug et al., 2018), considered until now, thermodynamically inconceivable.

These new ideas have since led to the concept of directed "quantum evolution", whereby quantum effects may have been selected for at the very beginning of life due to the ability to improve the efficiency of energy transduction, providing a tantalising alternative to how the first "self-replicator" molecules arose giving life the edge it needed to survive (McFadden, 2000). Even oxygen (O_2), the ancient gas that our mitochondrion has evolved to be so irreversibly reliant upon since it first appeared in the atmosphere during the Proterozoic aeon of the Precambrian period ~2500–540 million years ago, is defined by a quantum weirdness that simply beggars belief (Bailey, 2019). Its quantum structure reveals that in its most stable ground-state, O_2 exists in air as a potentially toxic, mutagenic free radical gas since it has two unpaired electrons with parallel spins in opposing orbitals (Figure A). Thankfully for us, this configuration means that O_2 is "spin-restricted" forcing it to accept electrons one at a time with the sequential formation of free radicals and reactive oxygen species (ROS) during its reduction to water in the mitochondria. This means that, despite its powerful oxidising nature (it is highly explosive rocket fuel after all!), O_2 reacts sluggishly with our body's organic biomolecules; indeed, if it wasn't for this thermodynamic quirk of fate, we would combust spontaneously in room air (Figure A). The fact that the Michaelis constant of the terminal reductant, cytochrome c oxidase, for O_2 is so extraordinarily low (0.03–0.3 mmHg) (Vanderkooi et al., 1991)

stands as further testament to how important it is to harness this molecule within "safe" physiological limits.

Thus, with O_2's Janus face, you'd be excused for assuming that the human brain would be especially prone to the ravages of free radical attack given that its evolutionary "drive for size" means that it now consumes a disproportionate 10 times more O_2 than that expected from its mass alone, coupled with limited regenerative capacity and histological susceptibility to oxidative damage (Herculano-Houzel, 2012; Bailey *et al*., 2018). Not surprising when you consider the brain has been estimated to hold up to a staggering 580 terabytes of information, equivalent to 5 years-worth of high-definition film! (Nunn et al., 2016). Yet rather than simply misbehaving as random, destructive "accidents" of *in-vivo* chemistry constrained to cellular oxidative damage and pathophysiology, free radicals, defined by their unpaired electron(s) and all of their quantum weirdness, are rapidly emerging as purposeful intra/extracellular signal transductants capable of titrating just the right amount of explosive rocket fuel to the brain (Bailey, 2018a). Given that its O_2 supply is indeed so delicate, walking the tightrope between too much or too little, the ability to "sense" changes in PO_2 and mount a defence against metabolic compromise and/or structural damage was likely one of the first roles of the central nervous system, and probably represented a major driving force in the evolution of the human brain, providing a selective advantage (Costa et al., 2014). Even the last universal common ancestor (LUCA), a genetically and metabolically diverse community containing the molecular origins of all present life forms, estimated to have appeared ~3.8 billion years ago, took advantage of O_2's univalent reductant, the superoxide anion ($O_2^{\bullet-}$) (Briehl, 2015), not terribly super in terms of its thermodynamic reactivity (one electron reduction potential of +940 mV, Figure A), yet nonetheless heralded as arguably the first signal transductant.

This ancient species has certainly stood the test of time and it has become increasingly clear that the brain, as indeed all other organ systems, relies on controlled mitochondrial $O_2^{\bullet-}$ and hydrogen peroxide (yet another rocket fuel!) formation in times of O_2 lack (hypoxia) as a "quantum trigger" providing superfast upstream control of blood flow and, importantly, stabilisation of the "mother gene", hypoxia-inducible factor 1α, resulting in transcription of genes that collectively preserve cerebral O_2 homeostasis (Figure B) (Chandel et al., 1998). Importantly, it appears that this mechanism may well exploit QM to optimise energy transduction since the speed at which many of these reactions proceed cannot be adequately explained by traditional (classical) "strait-jacketed" methods of thinking.

Mitochondrial formation of "spin-correlated radical pairs", generated through molecular O_2 activation by reduced flavins (Usselman *et al*., 2016), superposition, tunnelling, entanglement and altered coherence triggered by changing mitochondrial membrane potential, have since emerged as quantum contributors implicated in the coordinated regulation of cellular bioenergetics, coupling electron flow and protonation through a process known as redox tuning at a quantum coherence "sweet spot" (de Vries et al., 2015; Nunn et al., 2017). The nuclear spin properties of phosphorous allow for quantum processing in the brain via transfer of information (qubits) via quantum entangled pairs protected by so-called Posner clusters, affecting neurotransmitter release and neuronal firing rates, notwithstanding enhanced chemical reactivity of ROS (Fisher & Radzihovsky, 2018). Furthermore, proton (not just electron!) tunnelling has been shown to play a key role in enzymatic reactions with calcium, sodium and potassium, whose particle-wave duality accounts for ion channel selectivity - helping explain differences between those classically predicted by the Hodgkin–Huxley equation and experimental observations in neural circuits (Moradi et al., 2015). These emergent findings force a reappraisal of currently (i.e. classically) accepted concepts revealing more complex redox-regulated signalling mechanisms than previously thought (Bailey, 2019).

Whether energy/information transfer in the human brain takes advantage of nature's other more recently identified quantum tricks, such as quantum beating (thermal vibrations used to pump coherence and facilitate QM effects) (Weber *et al*., 1995), vibronic coupling (stimulation of vibrational modes in proteins to create a sweet spot for coherence and electron tunnelling, recently speculated to occur between mitochondria behaving like fused 'power cables' and microtubules, the latter contributing to resonant energy transfer and consciousness) (Srobar, 2012), or quantum criticality (proteins acting as charge carriers exhibiting properties between an insulator and conductor) (Craddock *et al*., 2014), remains to be explored, although designing studies to test these hypotheses remains a major experimental challenge. Yet it's a challenge worth taking given our current ignorance; take one of the world's most powerful supercomputers (Japan's Fujitsu-built "K"), the first to break the 10 petaflop barrier, or 10 quadrillion operations per second, that boasts computing power equivalent to 250,000 personal computers programmed to simulate 1.73 virtual billion neurons and 10.4 trillion virtual synapses, each holding 24 bytes of memory. While requiring more than 9 megawatts of power (equivalent to a small power station), approximately 450-750 × 10^3 more than that required to run the human brain (12-20 watts), it still took 40 minutes to crunch the data and replicate a meagre one second's worth of 1 % of human brain activity! (Sparkes, 2014). Current computer power, even at the exascale level (one quintillion "floating point" operations per second) fails to simulate the brain's level of "interconnectedness" (Bradler, 2018).

Perhaps the collaborative union of physics-iology, by transcending traditional disciplinary boundaries and bridging the gap between the atomic and the cellular, could be a winning formula that can reveal buried treasures and provide unique insight into the pathophysiology and treatment of neurodegenerative diseases that remain impervious to classical treatments. It is fitting to look into

the past to predict the future reminding ourselves of one of Richard Feynman's, (many) prescient quotations having won the 1965 Nobel prize in Physics for fundamental work in quantum electrodynamics, "…there is nothing that living things do that cannot be understood from the point of view that they are made of atoms acting according to the laws of physics" (Feynman, 1963).

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Legend

Quantum aspects underlying redox-regulation of cerebral oxygen sensing

A. Molecular orbital energy diagram of the most stable form (electronic ground state) of the diatomic oxygen (O_2) molecule ($^3\sum g^- O_2$) with each line denoting a molecular orbital with arrows representing electrons, the direction of which indicates their spin quantum number. Note that O_2 qualifies as a (di-)radical since it contains two unpaired electrons each occupying different π^*_{2p} anti-bonding orbitals (red arrows) with the same spin quantum number (parallel spin) in accordance with Hund's rule explaining why O_2 is paramagnetic. During the process of oxidation when O_2 looks to accept a (spin opposed) pair of electrons (↑↓), only one of the pair (↓, grey arrows) can "fit" into each of the vacant orbitals to create a spin opposed pair (dotted circles). Fortuitously from a thermodynamic perspective, O_2 prefers to accept only one electron at a time to conform with the Pauli Exclusion Principle forming other free radical/reactive oxygen species (ROS) during chemical reduction in the mitochondrial electron transport chain. This "spin restriction" means that O_2 reacts "sluggishly" with the brain's organic compounds with the organic donor having to undergo a "slow spin inversion'" preventing us from spontaneous combustion in room air! **B.** During normoxia, hypoxia-inducible factor-1 alpha (HIF-1α) is hydroxylated on prolines by the prolyl hydroxylases (PHD), tagging it for recognition by the von Hippel Lindau tumor suppressor protein (VHL) resulting in the continual ubiquitination and degradation of HIF-1α. During hypoxia, the mitochondrial formation of the superoxide anion (not so super given the low reactivity as indicated by its pedestrian one electron reduction potential ($E^{\circ\prime}$) of +940 mV) from the Qo site of the bc1 complex of Complex III are released into the intermembrane space and enter the cytosol to decrease PHD activity preventing hydroxylation resulting in HIF-1α stabilisation and transcription of genes that collectively preserve cerebral O_2

homeostasis. Quantum phenomena are outlined helping explain the speed and selectivity of redox-regulated O_2 sensing. HRE, hypoxia response element.