Обзоры

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Physiology returns to the centre of biology

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Abstract. The Neo-Darwinist Modern Synthesis of evolutionary biology mistakenly relied on Crick`s Central Dogma of molecular biology as excluding any control of genome sequences by organisms. The mistake can be unraveled by considering how DNA is replicated. The most important part of that process is open to control by organisms. The reason is that only a small part of the process can be attributed to a mechanism of replication "like a crystal", as proposed by the Selfish Gene theory. The larger part is attributable to extensive proof-correction by cut and paste enzymes that are coordinated by the living cell. That process reduces the error rate of replication from 1 to 10^4 nucleotides to 1 in 10^{10}, which is a million-fold increase in accuracy. There is therefore no replicator separate from its vehicle, the living cell. That error rate is under control by organisms. The mechanisms by which Electro-Transcription (ET) coupling is achieved have now been identified. Similar mechanisms must exist for Electro-Gene-engineering (EG) coupling. Such mechanisms change the fundamentals of biology.

Keywords: physiology of evolution, Electro-Transcription coupling, jumping genes, DNA replication and repair, Central Dogma, Weismann Barrier, trans-generational inheritance

Без знания того, кто я и зачем я здесь,
жизнь невозможна.
Without knowing who I am and why I am here,
life is impossible.
Lev Tolstoy "Anna Karenina"

Introduction

This article sets out the reasons why physiology was systematically excluded from developments of the theory of evolution, why that exclusion was a profound mistake, and how physiology now needs to rise to the challenge of repairing the damage to the fundamentals of biology. This is nothing less than "The Fight for the Future of Biology" (Noble 2022c).

Where the Modern Synthesis theory of Evolution went wrong

I begin with a question: Why was physiology excluded from the central problem in biology: how organisms evolved? The answer to that question comes from studying the way in which the theory of evolution developed into the Modern Synthesis in 1942, and how the subsequent development of that theory became hardened and dogmatic in the mid 1960s.

The Modern Synthesis was first defined by Julian Huxley in his book *Evolution: The Modern Synthesis* (Huxley 1942). That book was subtitled "The Modern Synthesis" because it explained how evolutionary biology had developed during the first half of the 20th century from a synthesis of neo-Darwinism and Mendelian genetics. Neo-Darwinism contributed the ideas of the Weismann

Barrier (strict isolation of the germline cells from influences from the body and environment) and the elimination of organism choice (Darwin's sexual selection idea, and Lamarck's "pouvoir de la vie"). Mendelian genetics provided the basis for a gene-centric view of evolution, using the Weismann Barrier as justification for isolation of the genome from the body and environment. The Weismann Barrier idea eliminated the inheritance of acquired characteristics, as Weismann himself intended (Weismann 1892; 1893). This became the motivating factor for the Modern Synthesis.

Yet, there was no experimental evidence for the Weismann Barrier (Noble 2016). Moreover, the first edition of Huxley's book was a relatively broad interpretation of evolutionary biology within its chosen framework. It did not, for example, commit itself to what exactly constituted the Mendelian idea of a gene. As Johannsen said, it was seen as anything (*ein Etwas*) that could transmit the phenotype characteristic from generation to generation (Johannsen 1909). Although it was a gene-centric view of evolution, the question what exactly is a gene was open. In fact, Huxley's book included many physiological processes by which evolution occurs (see historical analysis in Noble, Noble 2023b), even including control of the genetic material in response to stress. Full-blown gene-centrism, and the consequent marginalization of physiology, had to wait until the nature of the genetic material became clearer.

That happened when DNA was found to contain the templates on the basis of which organisms could determine the amino acid sequences for building proteins. When the double helical nature of DNA was discovered by Watson and Crick, using the X-ray data of Rosalind Franklin, the idea grew that gene centrism could become what Crick called the Central Dogma of Molecular Biology (Crick 1958; 1970). This idea (which should never have been called a 'dogma') is that DNA templates are used first to create RNA templates, which are then used to specify amino acid sequences in proteins, with no possibility of 'back-translation' from proteins to DNA.

On the basis of Crick's 'dogma', Julian Huxley and other adherents to the Modern Synthesis concluded that molecular biology had "dethroned proteins in favour of DNA" and that "the Weismann Barrier was now embodied in the Central Dogma" (Huxley 1963). The full history of this development can be found in Noble and Noble works (Noble, Noble 2023a; 2023b). Gould called this the hardening of the Modern Synthesis, in which the study of development and functions within organisms became rigidly excluded from playing any role whatsoever in the evolutionary process (Gould 2002). Physiology became completely excluded from evolutionary biology and, in many countries, evolutionary biology was no longer taught within physiology and medical courses in universities. Nor has physiology been taught in Evolutionary Biology courses. Several generations of scientists have now been brought up to think that the two subjects have nothing to contribute to each other since the Weismann Barrier was interpreted to be absolute.

Discoveries of new maternal and paternal physiological effects

Yet, physiologists have of course continued to discover many embryonic and early life effects that must have epigenetic, not genetic, origins. These have been fully reviewed elsewhere (Allis et al. 2015; Hanson, Gluckman 2014; Hanson, Skinner 2016). These are only some of the many experimental discoveries that require re-examination of the hardened version of the Modern Synthesis (see Noble 2021; Shapiro, Noble 2021 for many further examples), but they alone are sufficient to demand an answer to the question: How can such processes somehow bypass the prohibition of the Central Dogma? Would they require back-translation of amino acid sequences to nucleotide sequences?

Surprising as it may seem to many scientists brought up on acceptance of the Central Dogma, there is no reason why such back-translation should ever be required! It is not required because, as I shall show, this is not how organisms can control their genomes. The key to resolving this issue lies in the way in which DNA replicates.

DNA replication processes

Accurate copying during cell division cannot be explained in the way "how crystals are formed" (Dawkins 1976, 17). On the contrary, it becomes replicated via two quite distinct processes (Noble 2018), only one of which bears any resemblance to crystal formation:

The first process allows us to draw an analogy with the way crystals self-replicate. Crystals do this when molecules in solution fit themselves into the crystal lattice somewhat as a key fits into a lock. DNA in a living cell is not at all like a crystal. Instead, it takes the form of a flexible double helical thread, where each of the two threads mirrors the other, so that an A bonds with a T and a C with a G, and when the threads are unwound, an A will attract a T, and a C will attract a G. This bears comparison with the process of crystal replication, and in organisms such as prokaryotes, that is all there

is to the process of DNA replication—two new double helical threads can be formed almost automatically from one. *Almost* — but in eukaryotes 'almost' is far from sufficient.

This purely biochemical process cannot be accurate enough in nucleotide strands of more than around 10,000 base pairs (Noble 2018; Rennie 1991). The natural error rate of the process is one error in around 10,000 base pairs. Such short genomes, for which this error rate is not critical, are found only in small viruses. In a human genome of 3 billion base pairs that error rate would generate nearly a million errors (Preston et al. 2010). Organisms would not be able to survive such a high error rate. The genome would become seriously degraded and useless after only a few cell duplications. So, there must be, and there is, another and more important process.

The second process is the organisation by the living cell, *and only by the living cell*, of a set of cut and paste enzymes that proof-read and correct almost all of those errors. This is a physiologically controlled process, and living organisms use that control precisely to side-step the Central Dogma! Here is the central mistake in the Modern Synthesis of evolutionary theory: in contradiction to Dawkins' (1976) selfish gene theory, the replicator (DNA) is not separate from its vehicle, the living cell. Furthermore, such physiological control is universal in biology. Physiological control must continually sense what is needed to drive the correction, in the case of genome replication, these are the mismatch errors.

As an example, consider the way in which the immune system constructs new immunoglobulins with the correctly shaped variable part designed to fit and neutralize a new invading virus or bacterium. In a highly targeted part of the genome, that forms the template for the variable part of the immunoglobulin protein, the cell generates new immunoglobulin sequences using a non-random cut and splice process (Fig. 1). This region of the genome then hypermutates to augment specificity. The result is that large numbers of new DNA sequences are generated through the creation of targeted stochasticity. When some of those succeed in producing the correct shape of immunoglobulin to neutralize the new invader, the successful cells are induced to reproduce. Others are induced to apoptose. I call this kind of process the harnessing of stochasticity (Noble 2017), since it uses chance to generate a highly targeted functional outcome. The harnessing of stochasticity breaks the fundamental rule of the Modern Synthesis, according to which all DNA variations must be purely random and cannot be physiologically functional. Once a variation gets selected and harnessed, we can no longer call it random. Neo-Darwinists should have no difficulty in understanding this form of selection because it is precisely what they attribute to the process of Natural Selection. All they need to add is that selection of random change can also occur within organisms, as part of their normal physiological functioning.

Is the immune system just a rare example? Not at all. Barbara McClintock (1953), in plants, and James Shapiro (2011; 2013; 2022), in bacteria, found much the same control of chance variations to achieve new functional DNA sequences. McClintock's work on Indian corn (maize) showed that the process can cause large sections of chro-

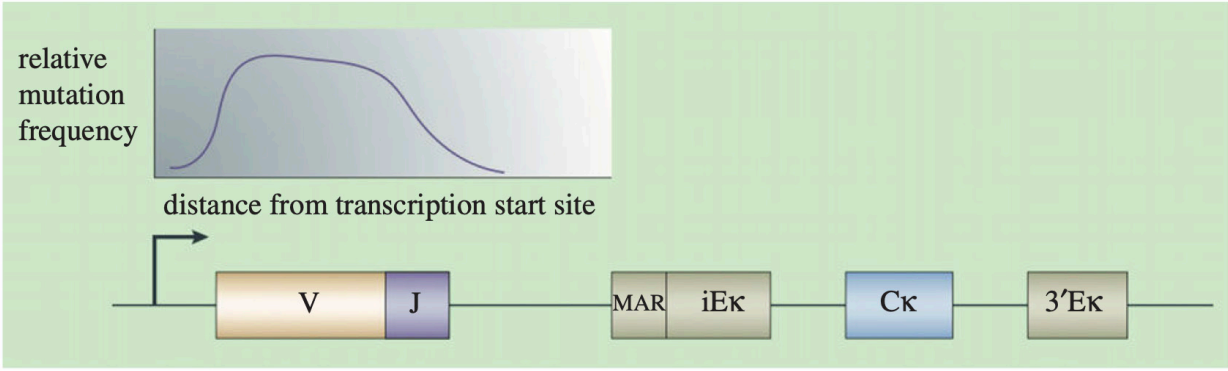

Fig. 1. Schematic diagram of gene-specific targeted hypermutation in immunoglobulin gene loci. The mutation rate is greatly increased only in the variable part of the genome, which is an approximately 1.5 kb region in each of the three immunoglobulin loci. In this figure, the graph above the rearranged variable (V) and joining (J) gene segments that form the variable region of Igk depicts the mutation domain in the k-light chain (Igk) locus. 30Ek, Igk 30 enhancer; Ck, Igk constant; iEk, Igk intronic enhancer; MAR, matrix attachment region (from Odegard, Schatz 2006)

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mosomes to jump around in the cell nucleus, so discovering the phenomenon of 'jumping genes', for which she won the Nobel Prize in 1983 (McClintock 1984). A similar process can occur in bacteria as they rapidly evolve resistance to antibiotics. Cancer tumours also use hypermutation to evade aggressive forms of chemo- and radiotherapy (Shapiro, Noble 2021b). The process of physiologically controlled hypermutation seems to be universal in organisms.

Have these processes been involved in macroevolution leading to speciation over millions of years? Clear evidence for that being true emerged when the first results of the human genome project were announced in 2001 (International Human Genome… 2001). Figure 2 shows domain accretion in chromatin proteins. From this we can see that these proteins must have evolved when species like yeast, worms, flies, vertebrates, humans diverged from their common ancestors. The chances of such domain accretion occurring entirely by chance are effectively zero. Organisms must therefore have the ability to select functional parts of the genome when shifting them around, just as the immune system is able to select just the variable domain of immunoglobulins.

This highly significant outcome offers a marvellous opportunity for further investigations in physiology. Just as it is impossible for the immune system to function without careful targeting of specific regions of the immunoglobulin genome, so it must be true that organisms have the ability to distinguish functional from non-functional regions in other protein-coding genome domains. The opportunity arises because, in both cases, we do not yet know precisely how physiological control processes achieve these outcomes. We just know that they do, and that those processes must exist. I predict major accolades for those researchers who can discover the precise pathways involved.

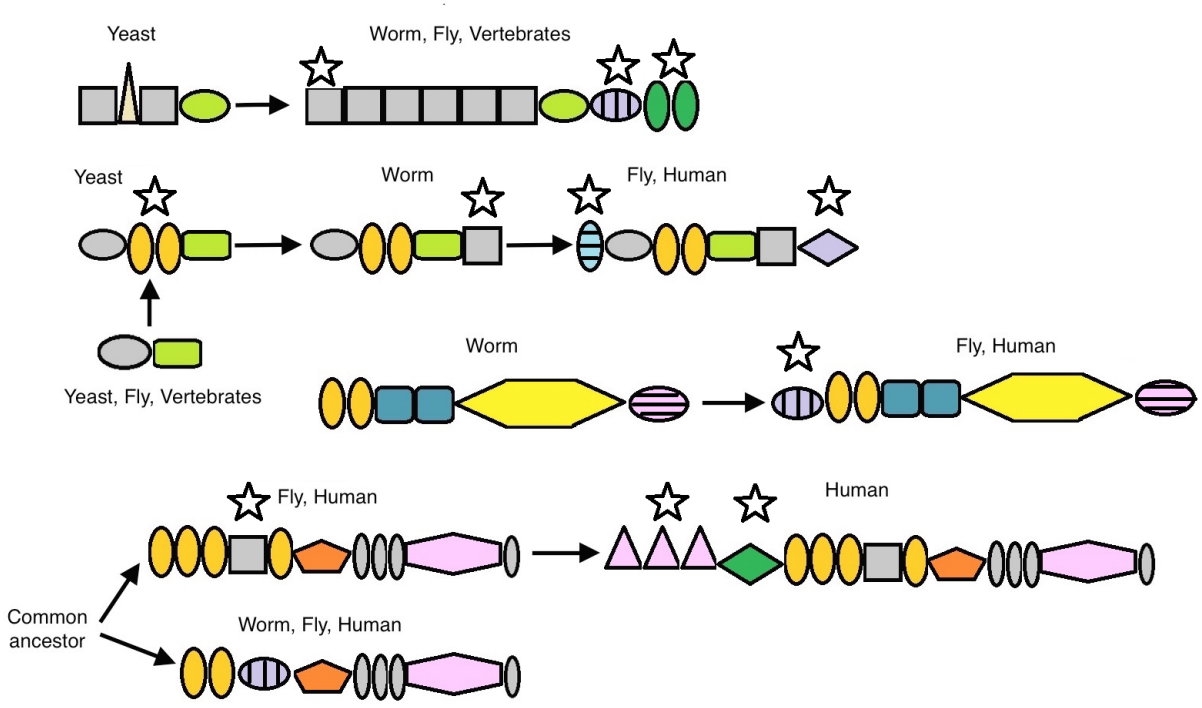

Fig. 2. Evidence for how gene domains must have moved around during evolution to form different functional proteins by domain accretion. This figure shows diagrammatic representations of three groups of individual proteins that contribute to the formation of chromatin, the backbone of chromosomes. Each coloured shape shows a single protein domain. Each protein is made up of several domains. In each case, as we move from yeast (unicellular) to worm, fly, various vertebrates and the human, the number of domains increases. The significant fact is that the development from one to the other did not occur by gradual accumulation of small mutations. Instead whole domains hundreds of amino acids in length have come together to form the new protein. The white stars show the domains that must have moved in this way. It is extremely unlikely that this result could have been achieved by gradual accumulation of small random mutations (Redrawn from Fig. 42 of International Human Genome... 2001, as Fig. 7-4 in Noble 2016). For full details of the domains and proteins involved see the original Nature paper (Noble 2016)

Summary of ways of bypassing the Central Dogma

Figure 3 shows what those control processes must be capable of achieving. The diagram is based on the experimental facts I have already presented in this article. But many of the physiological details remain to be worked out.

The processes involved in Crick's formulation of the Central Dogma are shown at the bottom of the diagram. Crick's original 1958 version was severely restricted to the horizontal black arrows: DNA —> RNA —> protein. The important 1970 modifications are represented by the gray arrows: back transcription from RNA to DNA, and replication of RNAs. Both of these modifications are important

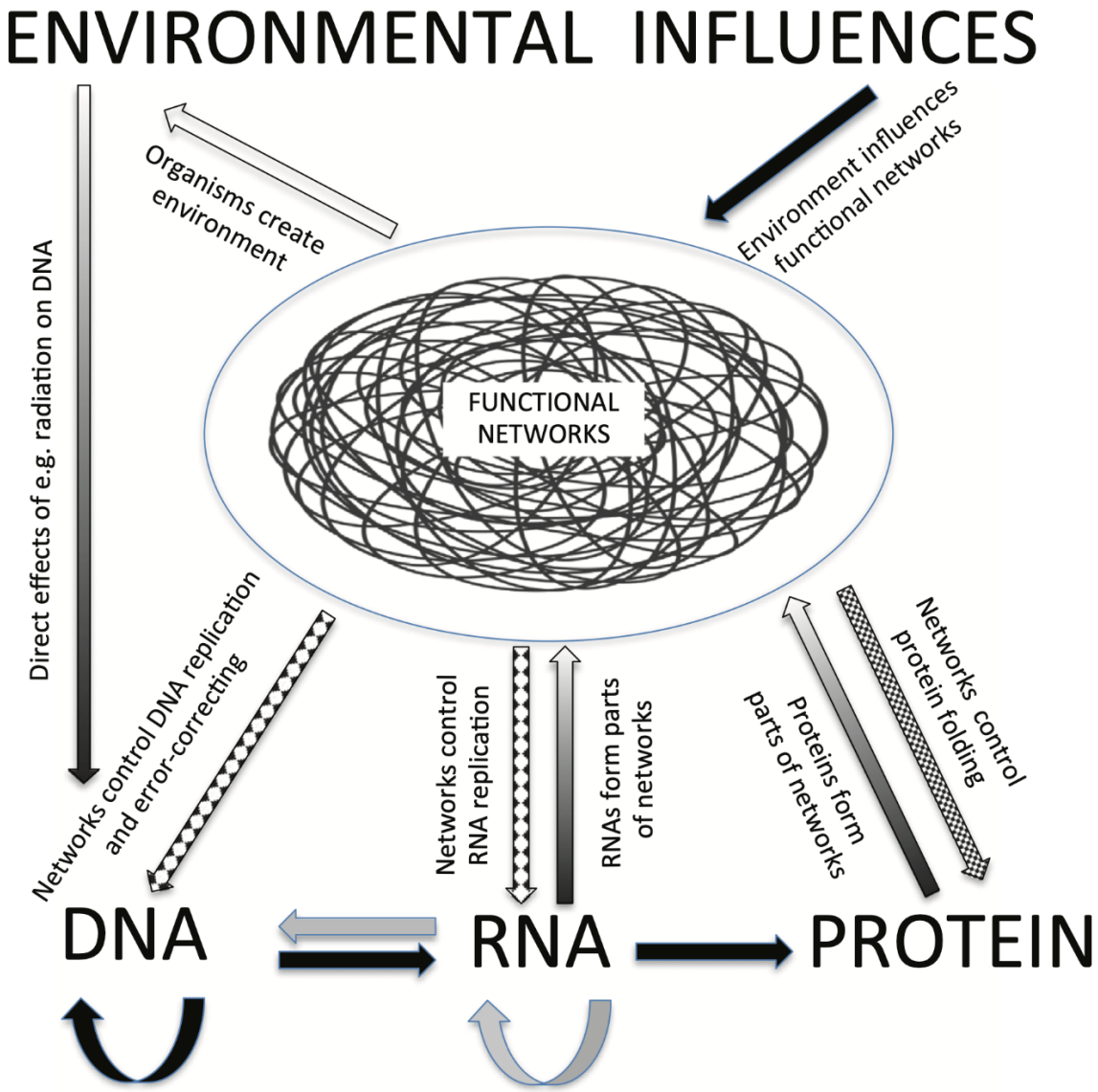

Fig. 3. How the processes that the Central Dogma seeks to describe (that is, the relations between DNA, RNA and proteins shown on the bottom row) fit into the context of physiological control by the functional physiological networks. Those networks are subject to environmental influences (black arrow) as well as contributing to the environment (white arrow). The networks control DNA replication, proofreading, mutagenesis and rearrangement. DNA expression and reorganisation is therefore under control by the functional networks (hatched arrow). RNAs and proteins form important components of the functional networks (upward shaded arrows), while the functional networks determine how protein amino acid chains are folded (downward arrow from networks to proteins). The physical environment also has direct effects on DNA, for example, through radiation breakage (Noble 2022a)

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since they mean that new DNAs can be incorporated into the genome from new RNAs and that RNAs can also be replicated. Most representations of the Central Dogma show only those arrows that represent the processes Crick envisaged. Clearly, something must be missing since I have already shown that the Central Dogma has been bypassed.

So my diagram adds in all the interactions involving cellular physiological networks, (represented by the functional networks in the centre). Control of DNA replication and the error correcting processes is represented by the left hand downward arrow from networks to DNA. A similar downward arrow (middle) represents possible control of RNA replication. The networks may also control protein folding (right hand downward arrow) which is critical to their physiological function. There are also biochemical modifications, such as methylation, acetylation, ubiquitinylation and proteolytic cleavage. The physiological networks also interact in both directions with the environment. Finally, the environment can also directly cause DNA changes via radiation and chemicals, represented by the vertical downward arrow at the far left.

Note that I speak of "Functional Networks" rather than using terminology like "Gene Regulatory Networks." There are two reasons for this. One is that, in the context of reductive gene-centric explanations of living systems, the more usual terminology slides too easily into thinking that genes are themselves causally regulating the networks, whereas the reverse is true. One of the purposes of the cellular networks is precisely to regulate gene expression, control the accuracy of replication, and to exploit stochasticity by generating new sequences. The second is that the functional networks are not just located at the cellular level in multicellular organisms. All levels of interaction are important.

The big challenge for physiology now is to discover ways of filling out this kind of diagram. We can already say that the diagram is broadly correct, but we are still woefully ignorant of many of the precise mechanisms.

Physiologists have already signposted the way forward

Nevertheless, physiologists have already discovered important clues to how physiological control of the genome happens. In concluding this article I will therefore describe two examples, since I believe they point the way forward to physiology's role in the future development of the mechanisms that have been used in the processes of the evolution of life here on earth.

The problem is to discover how living cells can directly control the DNA in their nuclei when stimulated by processes in their environment. Thus, the immune system exemplifies this with somatic hypermutation and IgH class switch recombination. Both modify immunoglobulin encoding DNA in response to events at the cell surface (membrane bound IgM binding to antigen to "activate" the encoding B cell). The events at the cell surface must therefore trigger messaging to the nucleus. The scale of the problem is best illustrated by imagining magnifying a cell to the scale at which a single nucleotide sitting in the nucleus would be the size of a golf ball. To be specific, let's place that 'golf ball' somewhere in Saint Petersburg. Where would the surface of the cell be?

I encountered this problem of imagining the vast difference between molecular and cellular scales when I was a student at University College London in the 1950s. Hugh Huxley (Huxley, Hanson 1954) was using an electron microscope to visualise the actin and myosin filaments in muscle. Working at the very limit of the resolution of his microscope, he could see (if only just!) the tiny cross-bridges between the filaments, and, to give us students an idea of the magnification, he explained that, at that scale, the muscle fibre itself would be around the size of a large part of the city of London. Well, I am imagining a scale one or two orders of magnitude larger than he was working with.

If we imagine a single nucleotide to be the size of a golf ball, the cell surface would be somewhere around 700 Km away in Moscow! That is how large cells can be on such a scale.

How then do cell surfaces connect with their nuclei? They do so via the vast network of tubules and filaments forming the cytoskeleton. The filaments made of tubulin enable a very important means of communication. They are like roadways. Tiny molecular motors charge along them. Label those molecules with a fluorescent chemical and you will then see them dart around the cell. Yet, on the scale I am imagining, those roadways are not more than the width of a small footpath. In Paleolithic times, humans would have made the journey between Saint Petersburg and Moscow by laboriously walking, or riding horses, along footpaths, snaking their way through the forests and hills. Resizing our scale back to that of a real cell, the molecular motors can make that kind of journey in just a matter of seconds.

How do living cells communicate to their nuclei?

Now, I come to the work of two physiologists who have shown how such 'roadway molecular

motors' carry signals from the cell surface to the nucleus. I refer to the work of Dick Tsien (one of my former students at Oxford in the work on the heart's pacemaker mechanisms, now working at New York University) and Anant Parekh (now working in my department at Oxford University). In a recent article in *Experimental Physiology* (Noble 2022a) here is how I described their work:

"Yet accurate and targeted transport of messenger molecules over these tiny cell 'roadways' have been discovered in living cells. Examples of recent physiological studies that demonstrate this process can be found in the papers of Ma et al. (2014) and Kar et al. (2016), working on the transmission of signals from calcium concentration changes that control the relevant gene activity in the nucleus. The molecular motors can achieve this transport at a speed of up to 2 μm/s. The nucleus can therefore be reached within just a few seconds. Visualising these processes using fluorescent markers reveals a vast trafficking system with messenger molecules moving rapidly in all directions between the cell and its nucleus. The work of Kar et al. is groundbreaking in showing the dependence on two calcium compartments (Kar et al. 2016). Multiple causation must surely be the norm in physiological control systems.

Tsien's team (Ma et al. 2014) showed how the signalling molecule γCaMKII is critical for rapid phosphorylation and gene transcription of CREB (a cellular transcription factor), so unravelling a mechanism for Electro-Transcription (ET) coupling. The diagram from their article showing the stages involved is reproduced here as Figure 4. Their work is a phenomenal achievement. Who can doubt that similar communication processes must exist to complement Electro-Transcription coupling with Electro-Genetic-engineering (EG) coupling? The immune system, and the other living systems I have highlighted in this article, must be able to do it. I surmise that EG coupling uses similar pathways that have yet to be identified.

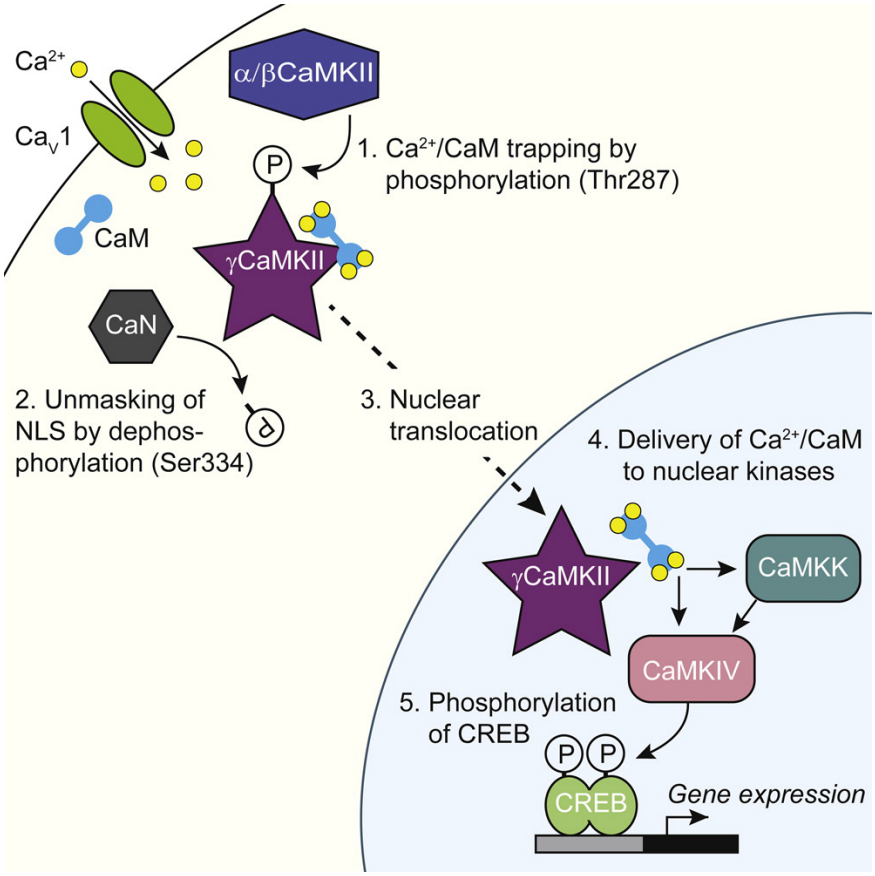

Fig. 4. The mechanism that mediates long-distance communication within cells: "a shuttle that transports Ca^{2+}/calmodulin from the surface membrane to the nucleus. The shuttle protein is γCaMKII, its phosphorylation at Thr287 by βCaMKII protects the Ca^{2+}/CaM signal, and CaN triggers its nuclear translocation. Both βCaMKII and CaN act in close proximity to CaV1 channels, supporting their dominance, whereas γCaMKII operates as a carrier, not as a kinase. Upon arrival within the nucleus, Ca^{2+}/CaM activates CaMKK and its substrate CaMKIV, the CREB kinase. This mechanism resolves long-standing puzzles about CaM/CaMK-dependent signaling to the nucleus." (from Ma et al. 2014)

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Parekh's team (Kar et al. 2016) went one stage further in showing how *two* calcium-dependent signals can communicate simultaneously with the nucleus. That is important since multi-factorial causation must be very common in living control processes. The logic must be multi-conditional. Unravelling such multi-conditional logic in physiological control systems will be difficult, but the cutting edge experiments I have described here show that it is, in principle, possible.

What remains to be done?

So what remains to be done? Both experiments I have described here concern Electro-Transcription (ET) coupling. Electro-Gene-engineering (EG) coupling must also exist, as emphasized also in the recent book *Transformer: The Deep Chemistry of Life and Death* by Nick Lane (2022, 277–284), and as I have proposed in Figure 3. What I call Hodgkin Cycles (Noble 2022b), coupling membrane potentials to the control of molecular networks, must exist everywhere in living systems.

This article celebrates being awarded the highly prestigious Lomonosov Grand Medal for my work on modelling the heart's pacemaker mechanisms. For this I am extremely grateful to the Russian Academy of Sciences. I am now 86 years old. In my remaining years I look forward to physiologists somewhere in the world—and why not here in Russia?—clarifying the processes I have imagined must exist to enable functional physiological networks to control the genome. Those EG coupling processes, when they are discovered, will become a cornerstone for our understanding of how physiology controls the evolution of genomes, which will forever change the fundamental nature of biology.

The word "physiology" means the "Logic of Life". By showing how physiology drives evolution, we bring back the scientific interpretation, the logic, of purpose in life, without which it is impossible to understand it (Noble, Noble 2022). Hence my quotation from Tolstoy at the top of this article. We cannot understand ourselves as humans without understanding who we are. Being alive is definitively purposeful. That is true of all organisms.

Commitment

As the former President of the International Union of Physiological Sciences, I am totally devoted to ensuring that this happens. I showed the way forward in a large Cultural Festival in the UK, the Festival of the Institute of Art and Ideas, held in Hay-on-Wye in June 2022, where I was invited to debate with the author of *The Selfish Gene* and populariser of the Modern Synthesis, Richard Dawkins (1976; 2016). Readers of this article may view that debate on the IAI website in the reference list (Institute of Art and Ideas 2022), or from my website (Denis Noble. The music of life 2022). In addition to explaining that DNA cannot accurately self-replicate "like a crystal", I also referred to the fact that physiologists have now discovered Darwin's "gemmules" (Noble 2019, 2022b), so completing his explanation of Lamarckian inheritance.

The assumed molecular biological foundations of the Modern Synthesis, which led to its hardening in 1963, are now revealed as illusions (Noble 2021). They do not support the isolation of the genome, nor do they support the exclusion of organisms controlling their genomes. No longer is it possible to exclude physiology from the centre of biology.

Conflict of Interest

The author declares that there is no conflict of interest, either existing or potential.

Acknowledgements

I thank my brother, Raymond Noble, for many discussions and collaborative articles on evolution. I thank Dick Tsien and Anant Parekh and their teams for their brilliant work on ET coupling. Dick Tsien was also a great collaborator as a research student in my laboratory in the 1960s, when some of the work was done for which the Lomonosov Grand Medal was awarded. I am deeply grateful to Perry Marshall, James Shapiro and Geoffrey Bamford for comments and corrections on a draft of the article. James Shapiro was also responsible for first drawing my attention to the genome sequencing evidence in Figure 2.

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