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The Natural Selection of 'Fitness Chemistry' in Darwin's Warm Little Pond.

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Abstract

'Fitness Chemistry' is proposed as an extension to the concept of natural selection, providing an environment for the emergence and sustenance of life.

Key Words

fitness chemistry, ribose,de-oxyribose, porphryins, autocatalysis, chemosynthesis.

Introduction.

Charles Darwin fondly suggested that life most likely originated in a 'warm little pond', containing the much under characterised 'primordial soup'.

Is it possible that living organisms have developed as a continuum from a pre-biotic world of chemical soup?

If there was a continuum from the pre-biotic to biotic world, life on earth would appear to be a logical progression of chemical processes that conform with the laws of physics, such as thermodynamics.

However, thermodynamic properties such as entropy, leads to disorder as a continuum with respect to time, but life processes require the maintenance of order as a continuum with time .

Living systems appear to have developed from simple chemical entities. However, these chemical feedstocks operate largely under thermodynamic control and cannot in themselves exhibit or develop the new and more complex properties characteristic of living systems. This represents an example of the more general concept of *emergence,* where the initial building blocks develop novel complexity by the emergence and interplay of local interactions. (see: Corning 2002).

How do the new properties of order and complexity of living systems arise from the chaos and noise of the disordered and random nature of the pre-biotic chemical world?

Life on earth in the primitive form of Archaea and prokaryotic cells, has been traced back to the Archaean eon beginning ~ 4 billion years ago . Stromatolites are among the oldest fossils, dating back to ~3.7 billion years. They appear as rock bound laminates containing the remains of small prokaryotic cells of cyanobacteria. Larger and more complex cells with a nucleus ,eukaryotic cells, appeared around just over 2 billion years ago .

Vertibrates appeared at around 530 million years ago and homosapiens perhaps greater than 200,000 years ago. The Holocene age beginning ~11,500 years ago has provided a relatively stable climate on earth which has greatly facilitated the cultural development of humans.

Chemistry in Darwin's warm little pond.

The main issue of this article addresses the conundrum : what was going on for all these aeons of time in Darwin's warm little pond that took so long to initiate life as we know it ?

During this time there were virtually endless interactions of chemical compounds in the primordial soup. It has been suggested that the processes involved were more akin to 'tinkering' rather than by some kind of 'invention from scratch'.

Several models of ' evolutionary chemistry' have been put forward that support the concept that the randomness and disorder of a primitive chemical world can spontaneously emerge into order .

The presence of chemicals in a reaction – diffusion environment such as a 'Darwin pond', can indeed elicit change from the randomness and disorder of an unstable homogeneous solution into a stable heterogeneous pattern. This process of spontaneous symmetry breaking can lead to the production of order, as exemplified by 'Turing patterns'. (Turing, 1952).

Alan Turing referred to these chemicals as morphogens. The counterpart of the effect of Turing patterns in living systems is known as morphogenesis. This is consistent with the observed cell- cell communication that has been demonstrated during development of the stripes of zebrafish, and perhaps explains how leopards got their spots and zebras got their stripes!

'Turing patterns' may find application in providing positional information in cell development research.

Pattern formation in solution can also be produced by chemical reactivity alone. This is illustrated by an autocatalytic redox reaction known as the Belousov-Zhabotinsky reaction, discovered by Boris Belousov in the early 1950's.

been described as an example of non-equilibrium thermodynamics . (see ;Winfree: 1984).The rate of this reaction appears to depend on the rate of the loss of gaseous carbon dioxide bubbles from the aqueous solution.

The chemical 'brew' (soup!) that brings about this reaction consists of a mixture of Cerium (IV) sulphate, potassium bromate, and malonic acid or citric acid, in a solution of dilute sulphuric acid. The complex redox process is initiated by the oxidation of the malonic acid by bromate. The latent period requires gaseous carbon dioxide to diffuse from the solution. This produces an oscillating visual change between the yellow colour of Ce (IV) and colourless Ce (III).

Use of the redox indicator ferroin accentuates the colour changes in this reaction, producing an deep blue colour involving the ferroin complexed Fe(III) ion, alternating with the bright red colour of complexed Fe(II) ions in solution.

Fitness Chemistry

Physico-chemical properties warranted that specific naturally selected chemicals in the primordial soup would emerge as agents able display characteristics, and occupy functionally relevant chemical space, that initiated and eventually sustained life.

In the context of the process of natural selection of species , Darwin used the term fitness as a requirement to propagate a trait that '*if useful, is preserved'*.

Fitness, in the sense of this article, is a composite of factors that allow an entity, whether a chemical or a living cell, to increase its population pool to a sustainable level . It is immaterial what or how fitness is attained, as long as it allows formation of a population of the entity that can survive the environment pertaining at the time .

I propose the term 'Fitness Chemistry' to describe the types of chemistry that have initiated and become integrated with the functions of living organisms

Fitness Chemistry is described in terms of physical and chemical properties of molecules that relate to their role in biological systems , whereas biochemistry emphasises the function of the molecules in living systems.

The evidence for fitness chemistry is contained by the chemical structures of molecules that are utilised by biological sytems to maintain their viability. Evolution has dictated that these molecules have survived and are useful .

The history of the survival of fitness chemistry has been interwoven together with the development of complexity of biological systems. It is hoped that this term may help towards a better description of the overall process of the origin and evolution of life on earth.

The wave mechanical model that is currently used in chemistry provides for a description of the electronic distribution and orientation of atomic and molecular orbitals , controlling both covalent and non- covalent reactivity of molecules , and as a result are indeed therefore ' *selected naturally'*. (see: Pross, 2011).

Fitness chemistry may be illustrated by the characteristics of the naturally selected chemical, D-ribose, the de novo precursor to both RNA and DNA.

In aqueous solution D-ribose exists as an equilibrium mixture of 5 different forms. These are the β- D-ribopyranose (59%), α- D-ribopyranose (20%), the two puckered 5 membered ring furanose forms , β-D-ribofuranose (13%) , α-D-ribofuranose (7%) and the linear/ open chain form (0.1%) .

Interestingly, the furanose ribose ring in ribonucleotides and the furanose deoxyribose ring in deoxyribonucleotides in solution both display a surprisingly similar degree of flexibility of the ring pucker. The angles of ring 'pseudorotation' enable formation of a pathway with relatively low energy barriers, where the 'North – South' conformations above and below the furanose ring appear to be at the energy minima.

It is a consequence of the Law of Mass Action that the mixture in water is able to re- equilibrate producing more molecules of the 'chemically fit' furanose form, during a process where its active mass may become depleted from the aqueous solution.

Only amino derivatives of the β- D- (-) ribofuranose form has been selected by nature as suitable for de novo elaboration to the chemical structures of RNA and DNA.

The anomeric α-1 -OH hemiacetal group of the 5- phosphorylated derivative of α- D-(-) ribofuranose is further phosphorylated by the enzyme Ribose -5- phosphate pyrophosphokinase (PRPP). This activated α- pyrophosphate derivative is then converted to its primary β- amino hemiaminal analogue, 5-

phosphoribosyl –β- amine (PRA), by inversion at the anomeric C-1 carbon atom of the ribose, using the nucleophilic primary amino moiety produced by conversion of glutamine to glutamic acid by the enzyme Glutamine phosphoribosylpyrophosphate amidotransferase (GPAT) (AT-ase).

The primary hemiaminal (PRA) has, not too surprisingly, an extremely short ½ life and is rapidly converted to a more stable amide derivative (GAR) by condensation with glycine, catalysed by the enzyme Glycineamideribonucleotide synthetase (GAR synthetase) . GAR is then further elaborated to the purine and pyrimidine nucleotide bases found in both RNA and DNA.

It is interesting to note that life on earth has relied on the tenuous conversion of D-ribose to PRA as the universal key to the de novo nucleotide building blocks of RNA and DNA . It is perhaps not surprising that additional salvage pathways have evolved that are able to recover both purine and pyrimidine compounds from cell debris and the diet, in order to supplement the availability of key nucleotides .

A second example of natural selection by chemical fitness is that of role of chirality in the chemistry of living systems.

The genetically coded α-amino-acids can be readily synthesized in the laboratory by a 'Strecker synthesis', but as a 50:50 racemic mixture. This involves reaction of an aldehyde with cyanide to form a cyanohydrin, followed by amination with ammonia and then hydrolysis of the cyano-hydrin by water.

The famous experiment of Miller and Urey in 1952 involved an electric discharge introduced into a flask containing a reducing atmosphere mixture of 'abiotic precursors' including hydrogen, methane and ammonia. Amazingly, among other chemicals, ~20 amino acids were formed , but also as racemates.

The Murchison meteorite which landed in Australia in 1969 has an age estimated as 4.95 billion years. This is most definitely pre-biotic and older than the earth itself .
This meteorite was found to contain many organic compounds, including α- amino acids, present not only as racemates, but in some cases, with an enantiomeric excess of <18 %. Most relevant is that the asymmetric bias was found to be towards the same chiral L- form enantiomer utilised in living cells on earth.
In order to attain chiral asymmetric bias in chemical synthesis, a template such as a solid surface tends to be involved , rather than where the molecules are able to freely tumble such as in solution (Strecker) or in an atmosphere (Miller-Urey).
Some rocks, such as the α- form of Quartz, are composed of separate d- and l- chiral crystal forms. These rock surfaces would have be able to serve as chiral templates to form diastereomers with chiral materials . One of the diastereomers may , for example, exhibit higher water solubility than the other.

Hence the D- and L- enantiomers of racemates could separate under conditions that prevailed in Darwin's little pond .

Amplification to the required concentration of the building blocks of life, and conversion to their corresponding homochiral oligomers, has likely come about by synergy between several mechanisms, including autocatalysis, solution equilibrium , and utilisation of chemical cycles.

In this regard, a fascinating development in the synthetic chemistry of chiral compounds is the Soai reaction discovered in 1995. In this reaction, pyrimidyl aldehydes undergo alkylation with diisopropyl zinc forming the product, a tetrahedral alcohol, with a remarkable degree of autocatalytic chiral amplification. (Kawasaki ,et.al; 2006).

Several reaction cycles were shown to produce asymmetric amplification in the order of 63,000 from the catalytic amount of the chiral alcohol that was added at the start of the reaction.

Furthermore, this reaction produces the autocatalysed product with very high chiral integrity when performed under conditions of either left or right polarised light, or in the presence the d- and l- isomers of crushed α- quartz crystals. Significantly, the product has the same absolute configuration of either the polarised light or the quartz.

Taken together , the discovery of chiral bias in the α- amino-acids found in the Murcheson meteorite and the chiral amplification of the Soai reaction, demonstrate diverse prebiotic and abiotic pathways which are able to naturally select chiral organic compounds .

Applications for fitness chemistry

1 .Applications to Synthetic Organic Chemistry

Biomimetic organic synthesis has not only had a impact on the development of new synthetic methodologies, but also has validated major principles and strategies used in organic synthesis.

Alterations to functional groups in organic compounds , which change their chemical reactivity, has proven a mainstay of synthetic chemistry methodology.

A biological counterpart to this may be exemplified where enzymes utilise such chemical principles as umpolung (reverse polarity) and desymmetrisation.

The enzyme pyruvate decarboxylase catalyses the decarboxylation of pyruvate. This enzyme functions together with a thiamine pyrophosphate cofactor. The unusually acidic C-2 atom (pKa ~13) of the heterocyclic thiazolium ring of the cofactor, reacts in an ‘umpolung’ manner in the form of a resonance stabilised nucleophilic carbene . This carbene attacks the carbonyl group of pyruvic acid to effect ready cleavage of the -C=O and -CO2H carbon-carbon bond into carbon dioxide and acetaldehyde.

This modification allows enhanced reactivity towards decarboxylation comparable with that of a β-keto-acid, rather than the α-keto-acid of pyruvate. The carboxylate end of the intermediate serves as the donor and the positively charged nitrogen atom of the thiazolium heterocyclic ring acts as the acceptor in the reaction mechanism.

This observation has prompted chemists to develop N-alkyl thiazolium and triazolium salts as reagents used in biomimetic acyloin , benzoin and Stetter condensation reactions, under very mild reaction conditions .

A further example is the intriguing desymmetrisation reaction of the pro-chiral molecule , citric acid. The ability of a chiral environment, such as an enzyme, to distinguish the pro-S and pro-R hydrogen atoms in one of the -CH2COOH side chain of citric acid is known as the Ogston effect .

The enzyme Aconitase is able to convert prochiral citric acid into chiral D- iso-citrate, generating two new chiral centres with 2R, 3S absolute stereochemistry.

This reaction occurs via the intermediacy of the desymmetrised tricarboxylic acid molecule, cis-aconitate .

Conceptually, this appears to be a simple dehydration and rehydration reaction.

However, both elimination and addition of water are stereospecific anti- processes. Aconitase removes the pro-R hydrogen atom from the citrate –CH2 COOH group, but then adds water from the opposite side of the cis -aconitate.

Several rationale have been put forward to explain this result. Perhaps favoured is that the enzyme bound citric acid is dehydrated at the active site of the enzyme by a Serine residue (642) acting as the donor, and Histidine residue (101) acting as the acceptor in the ‘’citrate binding mode’’. The cis- aconitate then flips over through 180^0 to the ‘’ iso-citrate binding mode’’ where it is rehydrated by water , but now using the Histidine as the donor and the Serine as the acceptor, to give the observed chirality.

Currently iso-citric acid is used as an analytical reagent to check for adulteration of soft drinks that contain citric acid. It is produced by the fermentation of sunflower oil by yeast, but as a mixture with citric acid, involving several separation and purification steps.

It should be feasible to devise a biomimetic solid phase chemical synthesis of iso-citric acid from citric acid. The potential for differential protection and regioselective epimerisation of this polyfunctional molecule would serve as a welcome addition to the pool of chiral auxiliaries for a range of industrial applications.

It could be argued that the biosynthetic precursors of primary and secondary metabolites are all examples of chemical fitness , because they produce molecules that sustain biological processes.

However, there are molecules where the naturally selected physico -chemical properties of their chemical structure alone illustrate major concepts that have advanced knowledge of chemical reactivity and organic synthetic methodology.

The conversion of 7- dehydrocholesterol to cholecalciferol by UV-B sunlight in the skin, is an example of a photochemically ‘allowed’ pericyclic reaction in accord with the conservation of orbital symmetry elucidated by the celebrated Woodward- Hoffmann rules (Woodward and Hoffmann, 1969). This naturally selected chemical event, involved in the biosynthesis of vitamin D3, is entirely controlled by

the direction and nature of the bonding and anti-bonding orbitals of the participating π- and σ- bonds in ring B of the steroid. This photochemical electrocyclic conrotatory ring opening reaction is followed by a thermal 1,7- hydrogen sigmatropic shift.

It should be noted that the biologically active derivative, calcitriol (1,25- dihydroxy vitaminD3) is then formed by further stepwise metabolism in the liver and other tissues.

It is interesting to speculate on the biological precedent set by the photochemically allowed conversions of 7-dehydrocholesterol to cholecalciferol described above, as well as the photochemically allowed 2 + 2 cycloaddition of Uracil described below.

Armed with this knowledge, would organic chemistry rationale have eventually discovered the most beautifully observed and generalised naturally selected phenomena elucidated by Woodward and Hoffmann as the 'conservation of orbital symmetry' ? Would synthetic chemists have then been able to predict the powerful synthetic utility of, for example, thermally allowed reactions such as the classical 2+4 Diels- Alder cycloaddition or pericyclic sigmatropic reactions such as the Claisen and Cope rearrangements? .

An example of a theoretical concept in synthetic organic chemistry that has emerged from biomimetic studies is known as the Baldwin rules. This provides a set of 'favoured and disfavoured' stereoelectronic principles that have been generalised to guide synthetic strategies to the formation of cyclic molecules from acyclic precursors. (Baldwin, 1976).

These rules emerged initially by an astutely rationalised strategy to effect ring closure of a functionalised azetidine as a key intermediate towards the synthesis of the penam bicyclic ring system of penicillin, using an intramolecular but as it turned out, 'disfavoured' Michael addition approach.

There may well be additional chemical concepts that could be discovered by mining further information from biochemical processes .

2. Application to Drug Discovery .

Fitness chemistry may find novel applications in applied research areas such as drug discovery . Both primary and secondary cell metabolites have served as a fruitful and well recognised starting point for the development of many therapeutically useful drugs, dyestuffs and agro-chemical products.

Although these natural products have properties that enable them to be fit for their primary or secondary role in the development of life, they often require further optimisation in various respects to make them more desirable as drug candidates. This would be to change such properties as their toxicity, water solubility , selectivity, efficacy and pharmacokinetic profile .

a. .Design of Ribozyme inhibitors.

RNA is able, among other functions, to provide catalytic activity in the form of ribozymes . These may provide an entry point for 'designer ribozymes' . Their small molecule furanose counterparts, decorated with appropriate pharmacophores, could serve as transition state analogues of ribozymal ribonucleotides. These could find utility as novel antiviral and anti-retroviral agents.

b. Design of Amino acid Mimetics or Antagonists.

The chemical elaboration of the genetically coded and indeed other amino acids has been utilised as a strategy to design drug candidates .

For example, as a secondary metabolite , the ergot alkaloid ergoline ring system comprises a rigid template of the embedded part skeleton of a primary metabolite , the α- amino acid Tryptophan . Ergoline derivatives have found medicinal utility such as in the treatment of Parkinson's disease and migraine. Methotrexate , a derivative of glutamic acid , has found use in the treatment of breast cancer .

3. Application to Models of Artificial Life.

Fitness chemistry may also find applications in paradigms that simulate artificial life, where the properties of naturally fit chemicals can be regarded as information rich or 'privileged templates'. This would reduce the need for searching less productive 'noisy and fuzzy ' areas of chemical space. The development of tools that enable the correlation between chemical structure and the emergence of biological function presents a worthwhile goal for basic research.

The molecular structures of DNA and RNA have been proven by evolution to be one naturally selected solution that has the ability to generate a code. There may indeed be assemblies of algorithms that could lead to other interesting and useful chemical structures that generate building blocks suitable for the discovery of exciting new paradigms of artificial life .

Physico-chemical processes in cellular function. (see; Pascal. et.al; 2013).

It is estimated that there may well be currently 2 million species on earth. Their evolution suggests they have developed from a common ancestor.

This ancestor is currently envisaged as a single cell known as the last universal common ancestor (LUCA).

A LUCA was probably formed in one of Darwin's warm little ponds , where it would have needed to increase its population by formation of viable colonies of itself. These eventually became specialised into the 3 main cell types, the Achaea, prokaryotes and eukaryotes.

In the early 1950's , the Hungarian theoretical biologist Tibor Ganti developed the concept of a 'Chemoton' . This was a model of a cell composed of the chemical cycles and localised equilibrium processes necessary for life found in a LUCA . The Chemoton consists of a vessel composed of lipid cell wall containing the chemicals found in living cells, such as water, amino acids, sugars, ions, phosphate and the nucleic acid pyrimidine and purine bases (Griesemer , 2015).

Ganti highlighted the criteria that enable formation and maintenance of the complex localised cellular equilibriums found in living cells , which function far from the overall thermodynamic equilibrium.

Key criteria of localised equilibriums include:

1. dynamic kinetic stability

A simple analogue of this phenomenon would be a waterfall.

A waterfall may first appear as an object that is in a state of stable equilibrium. However, equilibrium is essentially dynamic in nature. The stability of a waterfall is due to the continual replacement individual water molecules that cascade through an energy gradient from the top to the bottom of the waterfall. Life also has this same need for continual replacement of components that 'if useful, are preserved'.

2.auto-catalysis

Autocatalysis is the catalysis of a chemical reaction by one of the products of the reaction. This remarkable process is a property found in both chemical and living entities. (Hordijk. et.al; 2010)

Autocatalysis may be illustrated by three varied examples.

Example : Water

Liquid water is a truly remarkable chemical. It is an example of an amphoteric molecule, exhibiting different properties under different physical conditions .

A water molecules that is in contact with acidic media, such as some clays present in Darwin's warm little pond, can generate a proton. A proton is able to catalyse its own production (auto-catalysis) under the right conditions. An example would be where a simple organic compound, such as an ester in aqueous solution comes in contact with a proton. At equilibrium, the products formed by this reaction are an alcohol and an acid, the latter in water dissociating to produce a carboxylate anion and an additional proton. This auto-catalytic chemical process starts with one proton and ends by increasing its population to two protons.

Under these conditions, a proton, a non-living entity , has the inherent property to generate a replica of itself !

A consequence of such a relationship is a sigmoid increase in population over time. The reaction rate starts off slowly and increases with time and plateau's when the reactants become exhausted.

In the case above, when one new proton is generated by autocatalysis , the rate of population increase is doubled. When reaction progresses further, and three protons are present, the rate increase is trebled, and so on.

Example: DNA

DNA (deoxyribose nucleic acid) is perhaps the world's most celebrated fit chemical survivor, and is ubiquitous among all living cells.

In the example above with the proton, autocatalysis occurs under the direct control of thermodynamics and produces an exact copy or replica of itself. A waterfall as an example of dynamic kinetic

equilibrium also replicates itself by a cascade of input and output of unchanged water molecules. The synergy of auto-catalysis, dynamic kinetic equilibrium, a chemical cycle, and compartmentalisation , together provide a 'Ganti- like environment' where local equilibriums can function. Such conditions are necessary, but not wholly sufficient, to mimic the intricate circuitry that controls replication of entities such as RNA and DNA in a living cell.

Consider the analogy of a mountain, like Everest , which has existed for ~60 million years . The original molecules that constitute the mountain are today are largely the same as when they were first formed .

DNA has had the same apparent overall chemical structure for billions of years! Unlike the molecules that comprise Mt.Everest, or a proton , or water , each new molecule of DNA has been continually copied, re-synthesised, and replaced, requiring input of nutrients and energy during the cascade of generations of living cells. This mechanism of replication allows for a new and complex emergent property to occur, such as mutations and repair of the constituent bases of the DNA.

The physico-chemical properties embedded in the chemical structure ensure that DNA is useful and is preserved.

Example : The prey / predator population dynamic. (eg. cheetah vs baboon)

Consider a two species population model of predatory animals such as cheetahs and their prey , baboons, together occupying an area on the African grasslands .This model also follows the population dynamics of auto-catalysis .

When the baboon population increases, more nutrients are made available for the cheetahs to eat , so they also are able to survive and increase their own population . However, a point comes where the baboons are devoured at a rate where both populations may stabilise.

This illustrates another fascinating consequence of auto-catalysis. Over time, the apparent randomness of interacting population curves are able to form new patterns that can themselves become stable .

3. Continual influx and efflux of nutrients .

For cells to function they need energy.

The earth has continuously been endowed with energy from various sources, particularly sunlight, heat, and electrical discharge such as lightning.

How do cells control continual influx and efflux of essential nutrients?

The environment in a cell where these functions have evolved produce an energy gradient maintained by the formation of more and more complex localised and specialised organelles, membranes and enzymes.

Living cells have adapted and evolved chemical processes, an example of so called systems chemistry, which utilise chemical cycles and networks . For example, In aeorobic systems, cycles effectively allow for the controlled storage of chemical energy in molecules such as adenosine triphosphate (ATP). This chemical acts as an 'energy pump' by its stepwise hydrolysis to adenosine diphosphate (ADP)

and then to cyclic- adenosine monophosphate (cyclic –AMP), catalysed by the enzyme adenylyl (adenylate) cyclase.

The hydrolysis of just one phosphate ester group to form the very strong P=O double bond of each phosphate residue yields < - 31 KJ/mol of Gibbs free energy.

The formation of the P=O double bond as a phosphine oxide product is also the driving force in the abiotic (laboratory) synthesis of a C=C double bond from reaction of a phosphorous -ylid with a carbonyl compound, in the Wittig reaction .

However, the production of cyclic –AMP by living tissue provides a 'bonus' because this chemical can act as a secondary messenger . This represents a remarkable example of extracellular communication, signalled by the presence of the secondary messenger cyclic-AMP, occuring with single cells of slime moulds. In the presence of excess of the ' biomarker' cyclic –AMP, indicating a paucity of energy in the immediate environment of the cell, these single eukaryotic cells form multicellular aggregates that then move as a single entity towards a novel environment that provides more food. Due to this transformation, prompted by the chemical cyclic –AMP, slime moulds have been described as 'animals without a brain'.

Natural selection of 'Fit' chemical feedstocks using both dark and light chemical reactions

Darwin was well versed that nature tends to move in very small and controlled steps. An example of this is indeed natural selection of the origin of species, where the generations elicit changes to genes in a gradual manner.

In cells, the production and metabolism of key organic carbon compound feedstocks are exquisitely controlled in small steps by use of enzymes acting within chemical cycles. This enables the organic compound substrates to be made available in both the correct carbon chain length and oxidation state, for provision of the appropriate amount of energy and feedstocks that sustains cell metabolism. An example of such a chemical cycle is well known in biochemistry as the Kreb's, citric acid or tricarboxylic acid cycle (see : Zhang, and Bryant 2011).

Darwin's warm little pond may better be viewed as many ponds, such as those found at the sea shore, volcanoes, fumaroles and hollows of black smokers found around thermal vents deep on the ocean floor.

For example, when the moon was formed from the earth, its orbit was much closer to the earth than at present, leading to much larger tides than today. Millions of warm little ponds may be envisaged bathed in sunlight that have been subjected to continual cycles of variation (fluctuations) in temperature and contact surface with the materials of rocks, as well as diffusion controlled osmosis of the concentrations of single organic molecules together with polymeric components in the primordial soup.

Over the billions of years history of earth, an almost inexhaustible variety of chemical interactions and reactions have taken place leading to the synthesis of an unknown number and variety of organic compounds. These have been driven largely by chemical reactions such as condensation, coupling , oxidation and reduction. These reactions have occurred under a variety of conditions , from the early anaerobic reducing atmosphere to the post oxygen aerobic atmosphere which emerged ~2.4 billion years ago.

Thriving ecosystems have evolved in deep sea thermal vents and 'cold seeps' from the ocean floors. By necessity, these have utilised 'dark chemical' processes known as chemosynthesis , rather than sunlight, as their source of energy.

A key source of energy in thermal vents has been found to involve the reaction between hydrogen gas , hydrogen sulphide and carbon dioxide , producing simple sugars. The cold seeps have provided the environment that has evolved prokaryotic methanotrophs . These are able to convert hydrogen gas and carbon dioxide into methane which is then oxidised catalytically to produce formaldehyde and methanol as precursors to sugars. These bacteria are of considerable interest because they may indeed represent the first form of life on earth. They also offer potential as a means of removing methane from the atmosphere . Methane is a far more potent greenhouse gas than carbon dioxide.

Chlorin and the Porphryins

In the environment at the earth's surface, the photosensitive porphryin derivatives, chlorophyll-a and chlorophyll-b, contain a chlorin ring which plays a key role in the generation of energy from sunlight. These compounds first appeared in Archaean cyanobacteria and later in green plants, in the latter case perhaps as long as 700 million year ago.

Chlorin consists of a chemical complex of a cyclic array of 4 – pyrrole rings, linked by a one carbon methine bridge and where the one D –ring is reduced to a 7,8 dihydro –derivative. The four pyrrole ring nitrogen atoms are chelated by divalent magnesium ions.

The nature of the extended aromatic chromophore found in Chlorophyll –a provides the chemically fit vehicle for electrons to naturally select and capture an appropriate quantum of energy from photons from the visible wavelength of sunlight, in accord with Planck's equation. Chlorophyll-b, captures a higher percentage of light from the lower energy red wavelengths. This primary event then initiates a ' dark' redox reaction. The complete reaction, photosynthesis, results in the oxidation of water, generating free molecular oxygen as a side product, and a reduction which brings about 'fixation' of carbon dioxide molecules. This eventually produces glucose as the store of chemical energy via the concomitant dark (chemical) phase known as the Calvin cycle.

It cannot be over emphasised that this reaction alone transformed the earth's atmosphere from an excess of the global warming 'greenhouse gas' carbon dioxide and at the same time produced free gaseous molecular oxygen . Together, this event in green plants, facilitated the balance of suitable climatic conditions essential for the subsequent development of mammals on earth.

Absorbsion of the photon by chlorophyll in the chloroplasts of plant cells is a complex process, modulated by appropriate stacking of the photosynthetic 'antenna' in the plant Thylakoid membranes. An array of chlorophyll molecules act in conjunction by a process called Förster energy resonance transfer which provides the conversion of light energy into chemical energy.

This occurs in concert with other chemical pigments found in leaves, such as the more green light sensitive chromophores of other classes of extended polyene chemicals called carotinoids and conjugated

linear pyrrole derivatives such as the peptide linked phycocyanobilins, which are found in underwater cyanobacteria and red algae.

These initiate an electron transport mechanism that overall converts light energy collected through the two chlorophyll photosystems-1 (P-700 nm) and 2 (P-680 nm), into chemical energy.

The ease of this incredible series of reactions, is essential to sustain life on the earth's surface as we know it. The extended aromatic nature of the chlorin heterocyclic planar ring system interacts with the wavelengths of visible light shifted from the blue towards the red end spectrum. The wavelengths of green light are the poorest absorbed by chlorophyll and is largely reflected by leaves. Also, the human eye is most sensitive to these wavelengths. These two phenomena together explain why plants largely appear green in colour.

Both porphryin and chlorin may be considered as extended aromatic rings because they are planar and sustain a 'ring current' strength of ~27 nA/T and ~ 21.5 nA/T respectively (cf. Benzene, pyrrole ~ 12 nA/T). In this regard, they conform with Hückel's rule, which states that $(2n + 2)$ π-electrons, where n is an integer, conjugated in a planar ring, provides the property known as 'aromaticity'. Chlorin has a total of 20 π– electrons (n=9) and porphyrin has 22 π– electrons (n=10)conjugated in their respective rings. (Sundholm, et.al; 2016).

However the ring current involved in any one delocalised pathway involves only 18 electron (n=8) of the porphrin and 16 (n=7) of the chlorin ring . The chlorin ring current follows a different pathway than a porphryin ring due to the 'insulating' 7,8- dihydro- moiety on the periphery of the ring -D pyrrole.

The porphryin ring system is found in mammalian haem which exists in the more complex proteins myoglobin, and functions as storage of oxygen. It is produces the red coloured protein haemoglobin in the form of an iron molecular complex, which facilitates the transport of oxygen in more contemporary life, such as mammals.

Haem porphryin displays a intensive red colour because it absorbs visible light at wavelengths shifted towards the blue end of visible spectrum . The extra 2 π- electrons in the extended aromaticity of the porphryin ring increases the energy gap between the four orbitals consistent with the Platt-Gouterman HOMO and LUMO molecular orbital model .

A significant event in the evolution of eukaryotic cells was the apparent ingestion by 'endosymbiosis' of a prokaryotic mitochondrial cell by a eukaryotic cell , estimated to have happened ~ 1.45 billion years ago. This enabled the newly merged cell a 'kick start' in evolution by the synergistic utilisation of the chemical energy stored in the ATP of the mitochondrial prokaryotic cell . In mitochondria the reactions involved in the production of ATP are collectively known as the 'electron transport chain'.

A key enzymes that facilitates electron transport are the super-family of Cytochromes, which also use porphryin derivatives as a cofactor . Characterised first as a iron containing haem pigment extracted from liver tissue, the cytochrome P-450 family of enzymes are now known to exceed 1000 in number and is ubiquitous in the animal kingdom.

The human genome project has characterised 57 genes that encode for the CYP-450 proteins. Furthermore, extensive polymorphism occurs in the CYP- genes with at least 28 common allele variants.

The main role of these porphrin derivatives in sustaining life is their function in mammalian liver to detoxify a wide range of compounds, such as xenobiotics, and other endogenous substances, as well as therapeutically administered drugs . This is achieved by CYP-450 oxidation of the substrate organic molecule R–H group to the R–OH counterpart. In a secondary metabolic event, this R−OH group is further conjugated with agents such as glucuronic acid to form a glucuronide ester. The many free hydroxyl groups present in the conjugate makes the molecule very water soluble and readily excreted in the urine through the kidneys .

Chlorin and Porphryin and are justifiably known as the 'pigments of life' because they are essential to sustain green plants as the net producers , and red blooded animals as the net consumers of chemical energy.

Origin of Ribose, Lipids and Oligomers

How did ribose, the chemical building block precursor to both RNA and DNA , become synthesised in the prebiotic age ?

Ribose comprises a chain of 5- carbon atoms covalently bound to hydrogen and oxygen atoms to form a monosaccharide . This 5- carbon monosaccharide chain can be constructed by chemical synthesis either as a 4 +1 or a 2+3 condensation or coupling reaction .

Modern chemical synthetic methodology in the laboratory has been very successful using condensation reactions to form new carbon- carbon bonds using the 2+ 3 paradigm, but less efficient for the 4+1 paradigm.

The C-2 and C-3 units were not abundant on prebiotic earth , but there were amounts available of the C-1 units , for example, formaldehyde (HCHO) and hydrogen cyanide (HCN). (Noe et.al; 2013; Sutherland , 2017).

Naturally selected chemistry therefore would be expected to use the 4 +1 approach. However, if this was the case, a paradox arises on how the 4- carbon unit originated ?

It would seem plausible that the C-1 units initially reacted together to form a 2-carbon chain .

The C-1 + C-1 coupling of formaldehyde with itself forms the C-2 unit , glycolaldehyde (CHOHCHO). However, the reaction mechanism for this step is still unclear, but may involve formation of a calcium or borate complex,and radical coupling followed by an hydride transfer . The chemical yields of this reaction are low. It is indeed difficult to envisage a low energy reaction mechanism where two strongly identically polarized formaldehyde molecules can form the new carbon-carbon bond found in glycolaldehyde. Alternative synthetic origins to glycoladehyde or an C-2 equivalent building block has been the subject of much speculation.

Further condensation of Glycolaldehyde with another formaldehyde molecule would form, after isomerisation, the C -3 unit, dihydroxyacetone, (CHOHCHOCHOH). This C-3 unit then undergoes

further condensation with another C-2 unit of glycolaldehyde to yield, after isomerisation, the 5- carbon pentose sugar, ribose .

This overall process, known as the formose reaction, was discovered by Aleksander Butlerov in 1861. Although this process provides a chemical route to ribose it may not have dominated as the naturally selected choice.

Cyanide may have also served as a viable C-1 unit. Unlike formaldehyde, the unique resonance stabilised properties of the carbon and nitrogen atoms of cyanide allows for either atom to possess a partial positive or negative charge . This effect allows cyanide to more readily condense with itself forming oligomeric compounds such as the C-4 diaminomaleonitrile, NC(NH2)C=C(NH2)CN which exists as a crystalline solid. This compound has been shown to act as a precursor under laboratory conditions to a range of heterocyclic compounds, including pyrimidine and purine derivatives.

However, it has not been proven that cyanide did act as a prebiotic precursor to ribose or as the source of the purine and pyrimidine bases of RNA or DNA nucleotide monomers.

The prebiotic origin of the lipids represents an even more taxing conundrum. The Fischer-Tropsch reaction between carbon monoxide and hydrogen under high pressure and temperatures catalysed by iron sulphides and other metal complexes could account for the formation of a variety of lipids as well as other of life's building blocks, in ancient volcanic vents.

Oligomers are certain types of short polymeric chains. Peptides are oligomers of amino acids, short strands of RNA are oligomers of ribose nucleotides, DNA is an oligomer of deoxyribose nucleotides, oligomeric starch forms from simple sugars , and lipids are oligomeric derivatives of hydrocarbons.

Lipids in water can form into numerous polymorphic shapes such lipid bilayers, micelles, liposomes and cylinders .

Perhaps in Darwin's ' *muddy'* little pond, it is plausible that these, and other now extinct oligomers, were formed from their respective monomers by chemical catalysed polymerisation. For example, under laboratory conditions, the layered structure of Montmorillonite clays are able to catalyse polymerisation of monomeric ribonucleotides of RNA as mixed 2'3'- and 3'5' - oligomers of <50 units. (Ferris, 2006).

The multiplicity of oligomers were then able to self -assemble, intertwine, envelope, self- organise, capture and exchange nutrients, and finally merge, forming abiotic micelle-like protocells.

The overall reaction –diffusion environment in protocells, would have set up a dynamic system of fluctuations in the concentration of the key chemicals. This would aid formation of stable structures bound to the porous rock surfaces of the pond and able to promote such phenomena as catalysis and osmosis.

Under the conditions attainable in Darwin's warm little ponds would the formation of homochiral peptides and RNA have been possible ?

There appears to be no consensus on how this key 'signature of life' event of the formation of homo-oligomers occurred. The Soai reaction illustrates that amplification of monomeric chirality can occur,

but it would be interesting to identify a plausible symmetry breaking pathway to homochirality that could arise from polymerisation in a pre-biotic chemical environment.

Protocells are perhaps a plausible and direct precursor to the LUCA, where over time continual naturally selected cycles eventually allowed fitness chemistry to integrate with the emergence of life, most likely, and primarily, through evolution of the biocatalytic and eventually enzymatic actions of RNA.

The stepwise formation of an agglomerate → conglomerate → protocell → LUCA provides a viable vector to sustain the necessary conditions to nurture the transition from abiogenesis to biogenesis .

The concept of emergence appears to fill , but not necessarily explain, the chronological gap between the two distinct states of non-life and life on earth .

Origin of catalytic RNA Oligomers

Perhaps progress in finding the 'missing link' in the origins of life would be from more knowledge of the 'virus world'.

Viruses function in all cells and all species. They are involved in horizontal gene transfer in both RNA and DNA genomes, as well as in virtually every cellular metabolic process . Viruses range in size and their length of their 'packages' of RNA oligomers , from non-coding viroids that lack a protein coat, to the numerous bacteriophages ,and to larger entities such as the recently discovered Pandoravirus. Viruses may provide the vehicle which has produced 'larger leaps' in the synthesis of the length and homochirality of RNA. This would enhance the consequent ability of RNA to synthesise even longer polypeptides, and eventually simple protein material , than would appear feasible by chemical polymerisation alone.

Biochemical processes appear to have the capacity, among other functions, to catalyse , or speed up, chemical reactivity. Without this capacity, chemical reactivity alone would not have been able to produce the complexity of living entities found on the earth today.

Biocatalysts appear to have been first evolved from the advent of the 'RNA world' , and subsequently with more fidelity and efficiency by evolution of more complex proteins encoded through the emergence of DNA.

In both organic chemistry and biochemistry, it should be emphasised that a functional group in an organic molecule can display widely different characteristics , depending on the environment in which they are found .

For example, RNA catalytic oligomers such as ribozymes, are formed after the initial molecular recognition event of the chemoselective coupling of ribose 5'-monophosphate in the direction of the primary alcohol 5'-OH → secondary alcohol 3'-OH of an adjacent ribonucleotide residue .

In small hammerhead hepatitis δ -virus (HDV) and hairpin ribozymes, the functional catalytic action involves abstraction of the proton from the 2'-OH group by a general base. Proton transfer to the 3'-OH

group of the ribose moiety generates a 2', 3' – cyclic phosphate during several catalytic cycles . The general base may include the nitrogen atom of an adjacent nucleotide base, such as N-1 from an adenosine or N- 3 from a cytosine moiety. The 3'-OH group is also activated as a phosphate ester and by coordination to a divalent metal cation, such as that of magnesium. The 2'- OH and 3'-OH groups of ribose then essentially engage in 'neighbouring group participation' to form the 5- membered cyclic phosphate.

In the case of some ribozymes, this simple 2'- OH chemical group is able to critically control the outcome of biological function.

Note that the formally covalent 'neutral' 2'- OH alcohol behaves more like an ionic H^+ and O^- species when activated in the 'push' (general base) and 'pull' (3'- O coordinated to Mg ++) that it experiences when in the catalytic environment of a ribozyme. (Doudna and Lorsch, 2005).

Very small differences in the chemical structures of fit molecules can allow for large differences in their properties, and their subsequent utilisation in cell biology. Just the presence , or otherwise of the one hydroxyl group, 2' -OH, for each furanose form of either the ribose or deoxyribose sugar residues in monomeric building blocks of RNA and DNA, ultimately dictates chemical fitness for their critical roles in the processes of life.

Was deoxyribose formed by chemical reduction of the 2'-OH group of ribose ?

Prebiotic molecules of ribose or an activating derivative such as the phosphate ester, may well have been converted to 2'- deoxyribose by a chemical reduction process using hydrogen gas , in the presence of an iron- sulphur metal catalyst found in the earth's crust.

The corresponding reduction process in living cells allows biosynthesis of deoxyribose from ribose by a variety of highly regulated metal containing enzymes, the ribonucleotide reductases. In the bacterial form of these enzymes, a very specific stepwise single electron transfer process occurs from a stabilised tyrosine radical which is deeply embedded in the divalent iron core of the enzyme.

This process transfers an electron in a stepwise manner , through a series of tyrosine , cysteine other amino acid side chains, which ultimately reduces the 2'-OH group of ribose to the deoxy derivative, 2'-deoxyribose.

Several key chemical fitness elements of the vital molecule D-ribose are worthy of notice. Natural selection has identified D-ribose as a chemically fit molecule for an array of key biological utilities. This is highlighted by the bullet points below:

- The puckered shape of the furanose form has been naturally selected for its role as a template which is further elaboration into vital components of living cells.
- It is worthy to note that all four of the alcohol chemical groups in this monosaccharide , C5', C3', C2' and C1' have been differentiated for varied vital utilities in biological functions.

- In ATP, the 5'-OH is selectively phosphorylated and the anomeric 1'-OH has been inverted and replaced by the base, Adenine.
- In cyclic AMP, the 5', 3' –OH's together form a 6- membered ring cyclic phosphate ester .
- The 5'→3' chemoselective direction in adjacent ribose residues is molecularly recognised by RNA synthase, and by DNA polymerase for deoxyribose .
- The 2',3' –OH's form a 5- membered ring cyclic phosphate during ribozyme catalytic cycles, where the formally covalent 2'-OH functions as though it has become ionised during ribozymes catalytic activity.
- The 2'-OH of ribose is reduced to a C-H moiety by the enzyme ribose reductase during the formation of deoxyribose.
- The anomeric C1' hemiacetal alcohol group is epimerised and aminated by the enzyme GPAT (AT-ase) as a vital step in the de novo biosynthesis of RNA and DNA.

An –OH group in an organic molecule invariably allows it to be more hydrophilic, (water soluble) than it's -H counterpart. Deoxyribose is a more lipophilic molecule than ribose , and hence is less water soluble. It is also less chemically reactive, due to lack of the 2'- hydroxy group.

Emergence of the genetic code using the B- polymorph of DNA.

2'- Deoxyribose contributes to the stability of double stranded DNA. The DNA motif is ideally suited for encapsulation of the Watson – Crick base pairs, the key storage medium for genetic information. The non-covalent stacking interactions between adjacent bases comprise of electrostatic and hydrophobic forces collectively known as van der Waals interactions.

The Watson-Crick purine and pyrimidine base pairs are then able to be neatly accommodated within the double helix of the B- polymorphic form of DNA, where Adenine forms 2 hydrogen bonds with Thymine, and Guanine forms 3 H- bonds with Cytosine .

An unwound portion or 'bubble' of DNA is able to expose a portion of a single strand of DNA sequence to the enzyme RNA polymerase. This enzyme adds the RNA monomeric nucleotides in the complementary order, which is known as the transcription process. This provides for the synthesis of short strands of the more water soluble and shorter longevity messenger (m)-RNA. mRNA is better suited to be transferred though the aqueous medium of the cell to a ribosome . It is in the ribosome that the triple codon message is translated by the cooperative roles of enzyme families of transfer (t)-RNA and ribosomal (r)- RNA. These remarkable enzymes are able to assemble the correct coded amino acid sequence, and couple them into the corresponding polypeptide chain. The polypeptides are then often further processed by 'post translational modification' into functional proteins.

The 4^3 or 4x 4 x 4 = 64 combinations that arise in this mathematical 'set' allow for the code that corresponds to the 20 amino acids found in cellular proteins .This set allows for the triple codon required for recognition of each amino-acid, the start and stop signals, and redundancy that further encodes for the more rare amino acids .

The advent of this (genetic) code represents highly pertinent example of how emergence is able to produce new properties and complexity not shown by the simple chemical constituents.

However, the key property of the naturally selected furanose form of deoxyribose may have provided the initial chemical fitness necessary for the emergence of the supramolecular events that led to the formation of the structure of DNA.

A further significant single chemical change concerns the chemical structures of the base Thymine, which is found exclusively in DNA . Uracil is the corresponding base found in RNA. Uracil is quite promiscuous in its ability to hydrogen bond with the other bases and even with itself . Uracil also readily dimerises when exposed to UV light .

In DNA, thymine presumably has replaced uracil during evolution by the mechanism of mutation and repair. Abiotic and enzymatic synthesis of thymine from uracil by 5-methylation occurs due to the regioselective chemical reactivity of the enamide moiety found in the heterocyclic uracil ring. This single chemical change from a 5-H atom of uracil to the 5-methyl group of thymine (5-methyl uracil) has profound consequences to evolution.It reduces the ability of the parent uracil ring to form a dimer by a UV light induced 2+2 cycloaddition reaction. This is largely due to the steric hindrance produced by the methyl group. The 5- methyl group also allows a clearer code in DNA as a distinct entity that is not biosynthesised merely from the hydrolytic de-amination of cytosine . Indeed, the replacement of coding uracil in RNA to the coding thymine of DNA represents a key event in evolution, and supports the hypothesis that the RNA world preceded the DNA world.

James Watson famously described the outcome of the genetic code ensures that 'DNA makes RNA make proteins'.

This flow of information allows for the overall replication, transcription and translation consequence of gene expression.

The enzyme DNA polymerase is able to polymerise the monomeric nucleotide precursors into single stranded DNA because of its exquisitely chemoselective molecular recognition of one residue of deoxyribose in the direction of the 5' – primary alcohol group → 3'secondary alcohol of the adjacent residue of deoxyribose, in an analogous way to the oligomerisation of RNA described above.

The DNA double helix consist of one strand of ''right screw'' α -helix inter-twined with a second strand of the same right hand screw but threaded in an anti-parallel manner.

This forms the major and minor grooves of the resulting double helix . These grooves naturally form their own helical shapes along the surface of the encoding length of DNA. The major groove of the B-polymorphic form of DNA has the dimension comparable with the α- helix peptide backbone motif of DNA major groove binding proteins . These proteins are thus molecularly recognised by the B-polymorphic form of DNA and are enabled to slide along the major groove and serve to indentify the location of 'wobbles' in the helix caused by mutated base pairs. This allows initiation of further enzymatic events that enable their repair . The A- polymorphic form of DNA has a deeper and more narrow groove and does not accommodate the binding proteins as well.

The inorganic phosphate group also plays an essential structural and functional role .

As well as key to both spacing and flexibility of the overall structure of the various polymorphs of DNA, this phosphate moiety carries a negative charge on the phosphate oxygen atom which provides the whole DNA backbone with an overall negative charge. This aids facilitation of hydration and utility of metal cations in both structure and function.

A functional role of the phosphate group is attributed to its susceptibility for highly selective attack by phosphatases as a key step in opening the helix at specific junctures , which allows for the access to further enzymatic repair of mutated DNA bases.

It is difficult to envisage an alternative mechanism other than the natural selection of fit chemicals such as the base paired purine and pyrimidine rings that could mimic such a spectacular and pertinent molecular ensemble as DNA (see : Parker and Tullius2011).

These chemical building blocks are both fit for structural requirements and fit for their role in biological function.

Protein Folding and the formation of catalytic domains

Proteins are formed by folding polypeptide chains into a remarkable complexity of shapes. In particular, is the formation of 3- dimensional functional domains .

In some cases domains can be formed and activated by recruitment of amino acid residues that are far apart in the primary polypeptide sequence .

Anfinsen's Dogma suggests that this folding process is solely a consequence of the originating polypeptide sequence. However, Levinthal's paradox points out that for an unfolded protein containing < 100 amino acid residues, it would take longer than the age of the universe to explore all the chemical space made available by the constituent freely rotating bonds !

Protein folding is a physical process, determined by the overall environment composed of both intramolecular and supramolecular events.

These include a multiplicity of local phenomena, mainly using non-covalent interactions , such as intra-molecular hydrogen bonding, hydrophobic collapse, lipophilicity, π-π stacking, dipole-dipole and induced dipole interactions, metal co-ordination,and side chain/ peptide backbone interactions, as well as stabilisation by side chain covalent bond disulphide bridges formed by oxidative coupling of two cysteine residues .

Models of the protein folding sequence from 1er→2er→ 3er structure have suggested formation of a funnel - like energetics 'landscape' , involving a stepwise Origami-like folding process, which would indeed maximise utilisation of multiple local interactions (Daggett and Fersht , 2003).

The supra-molecular events, in particular the solvation and displacement of local water molecules, need to be better quantified and included to the description of the global as well as local energetics of the protein folding landscape.

The amino acids proline and glycine display physico- chemical properties that enable fitness to form turns in secondary protein structures, a sequence of 4 amino acids form the β-turn, and lipophilic amino acids statistically are found more in the (more hydrophobic) core rather than the surfaces of globular proteins. One mutation alone can lead to the formation a tertiary structure domain of the protein with greatly altered characteristics, in particular with the catalytic function of enzymes.

Protein domains are able to combine with other proteins using local and non-covalent interactions at the tertiary structure level, and with different stoichiometries, each acting as sub-units for the formation of new and larger protein complexes.

This mechanism allows formation of a quaternary structure for proteins that provides new co-operativity and biological functions, encoded from a minimal number of genes.

Examples of this more efficient and the consequence of the emergence of proteins in the 'DNA world ' in eukaryotic cells are profound and numerous.

Two varied examples are illustrated below.

1.The function of the protein Haemoglobin relies on co-operativity at the quaternary level , using two copies of the alpha-2 and beta-2 subunits acting as a 'hinge', which participates in the well known ability of haemoglobin to acquire and release molecular oxygen.

2. The origin of the rudimentary nervous system involved emergence of the generation of an action potential across the lipid bilayer of neuronal cells. These action potentials are generated and modulated by a remarkable mechanism involving co-operativity between subunits of voltage gated ion channels.

These channels are selective pores that allow the ions to cross an electrochemical gradient in the lipid bilayer. This mechanism transports readily available ions such as the cations of sodium, potassium, calcium and the chloride anion through their respective ion channel pores. This effectively exchanges the ions across the cellular bilayer from the exterior and interior aqueous media. When, for example, a sodium cation is pumped across the sodium channel from the exterior to the interior surface of the bilayer, a temporary negative charge is generated on the outside of the bilayer. This negative charge is subsequently neutralised by a positively charged potassium cation which is pumped across a potassium channel from the interior to exterior of the bilayer.

This provides emergence of a mechanism that, in effect, transports an charge across the outside surface of the lipid bilayer.

In a neuronal cell this charge eventually terminates in the axonal part of the cell where it effects degranulation of storage vesicles of chemical messengers called neurotransmitters. These primary chemical messengers, such as norepinephrine and dopamine, in turn activate membrane bound receptors on both connecting and adjacent cells.

This overall process serves as a major mechanism for cell to cell communication in the nervous system.

It is worthy of note that although DNA codes for, and the three RNA's together decode and synthesise polypeptides, nature relies on physico-chemical properties to produce proteins in their chemically fit structural and bioactive forms .

However, this outcome is quite consistent with the two concepts of natural selection and emergence . Proteins are able to become folded in a bioactive form under control of an emerged complexity of physical processes, but only because the polypeptides have been synthesised by RNA in the correct order of amino acids.

The DNA, RNA and protein worlds function together, and these molecules could perhaps be described as the 'molecular initiators' of life.

Conclusion

The biological sciences have evolved in the form of more and more complex chemistry that have enabled the emergence of new and unique paradigms that we call ' *life* '.

It is suggested that the concept of natural selection can be extended to include fitness chemistry which has both initiated, and become integrated into the functions of living organisms.

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