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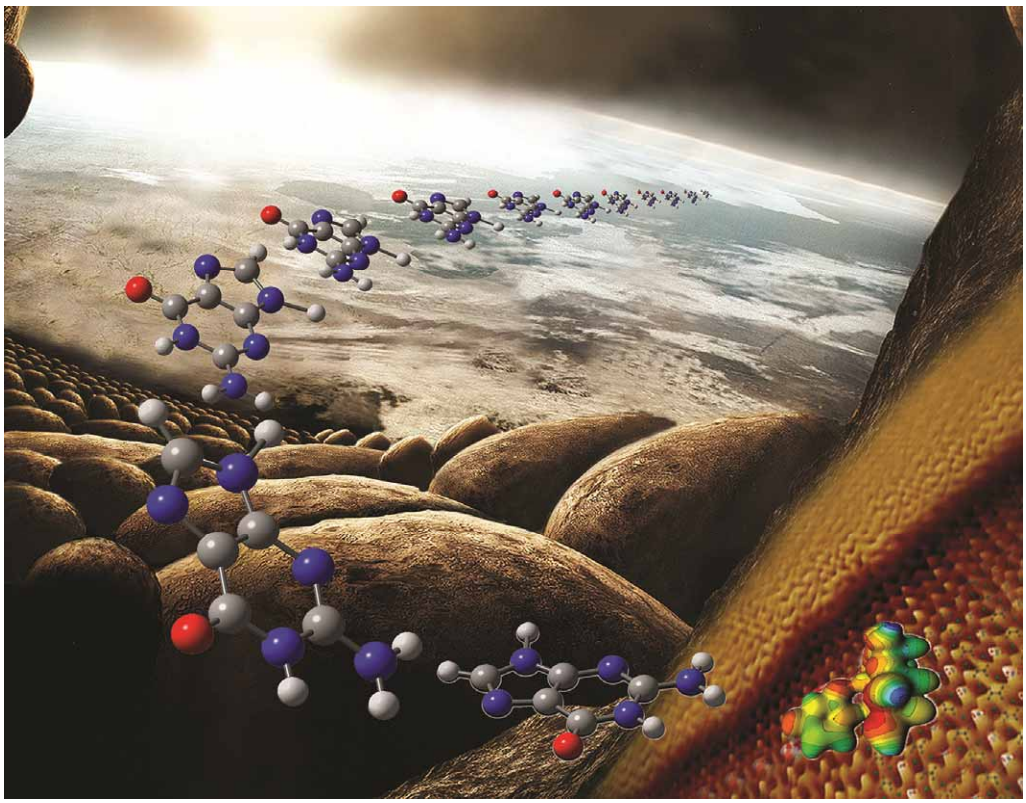

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TUTORIAL REVIEW

Theory, modelling and simulation in origins of life studies†‡

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Origins of life studies represent an exciting and highly multidisciplinary research field. In this review we focus on the contributions made by theory, modelling and simulation to addressing fundamental issues in the domain and the advances these approaches have helped to make in the field. Theoretical approaches will continue to make a major impact at the "systems chemistry" level based on the analysis of the remarkable properties of nonlinear catalytic chemical reaction networks, which arise due to the auto-catalytic and cross-catalytic nature of so many of the putative processes associated with self-replication and self-reproduction. In this way, we describe *inter alia* nonlinear kinetic models of RNA replication within a primordial Darwinian soup, the origins of homochirality and homochiral polymerization. We then discuss state-of-the-art computationally-based molecular modelling techniques that are currently being deployed to investigate various scenarios relevant to the origins of life.

1. Introduction

Few topics with a chemical basis can compete with the origins of life on Earth (and, of course, elsewhere in the Universe) in the popular imagination. The subject is still, today, largely one of theory and conjecture given the vast period in time separating us from those key events. We begin by briefly discussing aspects of current theories in origins of life studies, with particular emphasis on prebiotic chemistry where the chemical species and the fundamental phenomena defining life (including metabolism, information replication, compartmentalisation) arose. Having established the current conceptual position, we provide a review of the theoretical modelling of various key origins of life processes, followed by an introduction to the methods and application of computational chemistry simulation within this area. We show that theory and modelling has, over the years, provided considerable insight into both the physiochemical phenomena of these complex and often nonlinear processes, and elucidated the chemical interactions between biomolecules or proto-biomolecules with mineral surfaces.

The question "How and where did life arise on Earth?" is one which has always attracted widespread attention, and increasingly so in recent years. Origins of life studies represent an exciting and highly multidisciplinary research field that incorporates contributions from geologists, physicists, biologists, mathematicians, chemists and computer scientists, *inter alia*. In this review we focus on the contributions of modelling and simulation to answering origins of life questions as well as the wider advances these techniques have made in this field.

The uniformity of biochemistry in all living organisms indicates that life descended from a single last universal common ancestor (LUCA).[1] If the stages from which LUCA evolved from abiotic components on early Earth were known, in principle we should be able to compile a complete account of the origins of life. Much of the research undertaken in origins of life studies aims to address the question of "what and where were the sources of the organic molecules that made up the first self-replicating systems?" and "how did biological organisation evolve from an abiotic source of organic molecules?"[2]

One of the first origins of life hypotheses to be adopted by the scientific community was the "warm little pond" idea attributed to Charles Darwin. It is difficult to conceive how the traditional concept of a "warm little pond", also-known-as a "prebiotic soup", could have given rise to life, not just because of the absence of geological evidence but because there is no obvious source of free energy in such a system. For the polymerisation required to form RNA (or proteins) to occur two things are essential: energy and a reasonable concentration of ribonucleotides (or amino acids). Moreover, the prebiotic soup as normally conceived is in thermodynamic equilibrium, whereas all life processes are inherently far from

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equilibrium; as a result of any such equilibrium, nucleotides would be reluctant to react further. To counter this a number of approaches where physical and/or chemical gradients impose far from equilibrium conditions have been hypothesised and tested including the use of minerals to concentrate monomers,[3] salt induced peptide formation reactions which mimic tidal pools,[4] and the concentration of monomers in freezing processes.[5]

It is important to begin by scotching a nugatory argument that has been articulated surprisingly often by members of the origins of life community. This argument goes along the lines that the probability of synthesising a mere gram of the 'one' (or a few) particular self-reproducing sequences by a random assembly process would need more mass of substance than exists in its totality on Earth, so cannot have happened.[34] This argument is based on the naïve notion that RNA sequences in a soup form by random synthesis (*i.e.* as if at equilibrium) and entirely ignores the nonlinear nature of their dynamical self-assembly. What it does establish is that not all sequences have been made: nature does not perform a global search for optimality over all possible chemical species. There is a large element of chance in determining which sequences have been produced.

Life is indeed driven by a set of chemical processes taking place far from equilibrium.[6] To maintain these processes, all organisms are open systems; their complexity is founded on feedback involving autocatalytic and crosscatalytic molecules that assist reactions without being destroyed in the process. One metabolic or regulatory pathway may produce a molecule that accelerates other pathways (crosscatalysis) which, through a vast amount of interlinked chemistry, may end up indirectly catalysing the original pathway.

Miller and Urey's seminal contribution to abiotic synthesis addressed many of the shortcomings associated with the prebiotic soup. They passed an electric discharge through a mixture of methane, ammonia and hydrogen producing amino acids, amongst other products. This demonstrated that an energy input could generate biochemicals. Miller continued this research, showing that the major synthetic route to amino acids is through the Strecker reaction.[7] The reactions performed by Miller were suggested some time before by Haldane in his 1929 essay on the origins of life. Haldane proposed that ultra-violet (UV) radiation provided the energy to convert methane, ammonia and water into the first organic compounds in the early ocean.[8] The history of the early Earth's atmosphere has not, as yet, been completely resolved although there is evidence to suggest that the early Earth did not have a strongly reducing atmosphere, making the Miller–Urey experiments less pertinent than originally thought.[9]

The discovery of deep submarine hydrothermal vents in the 1970s eventually led to a further, plausible alternative hypothesis that provided a possible solution to the atmospheric conditions on the early Earth. These vents are out of equilibrium with the surrounding seawater.[10] "Black smokers" were the first type of hydrothermal vent discovered; they arise in part from magma interacting with seawater at ocean spreading zones. However, black smokers present certain challenges as candidates for the origins of life including their extremely high temperatures, low pH, short lifetimes and a lack of three-dimensional compartmentalization,[11] which conceivably would lead to irretrievable dilution of proto-biomolecules in the early ocean.

A second type of hydrothermal vent was discovered at the turn of the millennium.[12] Unlike black smokers, these "alkaline vents" are not volcanic but form through serpentinisation. Serpentization is the oxidation of olivine and consequent reduction of water to hydrogen.[13] The process creates temperatures of around 150–200 °C and strongly alkaline fluids of pH 9–11 rich in hydrogen. Russell *et al.* suggested the role of these alkaline vent systems in prebiotic scenarios in 1993, before their eventual discovery at the "Lost City" of the mid-Atlantic.[14] Russel and co-workers hypothesized alkaline vents are potential candidates for producing life owing to their relatively benign temperature and pressure, apparent ability to incubate proto-metabolism through proton and redox potential gradients within emerging alkaline fluids, and their delicate internal porous structure acting as protocells.

One well-developed theory for the origin of life on Earth is the "RNA World" hypothesis, which states that at some point prior to the present deoxyribonucleic acid (DNA)/protein world, ribonucleic acid (RNA) provided the molecular basis for catalysis and replication.[15] The theory is attractive because it solves the problem of complexity raised by the Miller–Urey experiments: The RNA world requires the synthesis of only one type of biomolecule. Evidence in support of the RNA World hypothesis arose from the work of Cech and Altman who won the 1989 Nobel prize in chemistry for their independent discovery of a group of catalytic RNA molecules known as ribozymes;[16] and further from the discovery, by Stietz and Moore, of the structure of the ribosome, a cellular component which makes proteins.[17] These latter studies aided the demonstration that the ribosome is, in fact, a ribozyme. Recently, Sutherland and co-workers provided an abiotic synthetic route to nucleotides, under near prebiotic conditions (see Fig. 1).[18] However, despite the prevalence and hitherto dominance of the RNA World hypothesis in prebiotic chemistry research, an alternative hypothesis, where proteins emerged initially from readily available amino acids to generate a protein world still receives attention and also makes a strong case.[19]

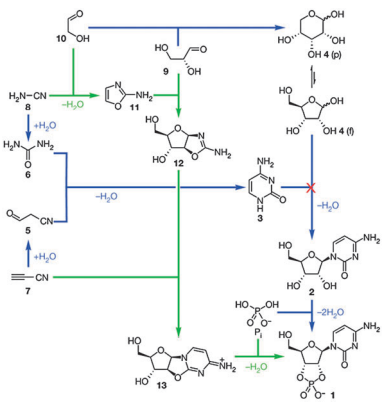

Fig. 1 Pyrimidine ribonucleotide assembly options. Previously assumed synthesis of b-ribocytidine-29,39-cyclic phosphate **1** (blue; note the failure of the step in which cytosine **3** and ribose **4** are proposed to condense together) and the successful new synthesis described in Sutherland *et al.*'s work (green). p, pyranose; f, furanose. Reproduced with permission from ref. 18.

In this review we will highlight the advances made using theoretical modelling and simulation methods within the prebiotic context. In essence, we can divide the modelling methods discussed in to two distinct groups:

(i) those that describe "higher-level" phenomena such as chiral amplification, or vesicle formation kinetics, using the law of mass action without direct chemical structural information;

(ii) those that describe chemical structures and processes at an electronic structure, atomistic or molecular level of detail using computational chemistry methods such as quantum and/or molecular mechanics.

A commonality of both approaches is that they tend to be overlooked by many sections of the experimental prebiotic chemistry community. This is despite the fact that prebiotic chemistry of necessity has had to depend heavily on abstraction and theory, with concepts such as the iron sulphide world of Wächtershaüser[20] having its roots in calculations of the energetics of chemical reactions.

2. Theoretical nonlinear chemical kinetics

What can theory say to guide us in setting parameters to limit the search for the origin of life? For a complex system of interlocking chemical reactions, the second law of thermodynamics is the place to start. It defines a set of thermodynamic potentials whose extrema specify the equilibrium states of matter. In particular, under the usual conditions pertaining in chemical reactions (fixed temperature and pressure, or fixed temperature and volume), the Gibbs and Helmholtz free energies serve as potentials whose global minima completely define the equilibrium state.[21]

If the system is prevented from attaining thermodynamic equilibrium through the imposition of external constraints (*e.g.* temperature or concentration gradients, *etc.*), but is able to get sufficiently close to equilibrium (technically, the thermodynamic forces and fluxes are linear in the displacement from their vanishing equilibrium values), then the appropriate thermodynamic potential is the internal entropy production of the system.[22] That is, its extrema (usually they are minima, but in some cases maxima) define the stationary states of the system.

However, for systems far from equilibrium (that is, for which the thermodynamic forces and fluxes are no longer linearly dependent on the distance from equilibrium), there is no thermodynamic potential that guides the evolution of the system. Although this result was established more than 35 years ago, remarkably little attention has been paid to it.[20,23] Beyond the overriding importance of irreversibility (that is, entropy is always increasing) chemical thermodynamics in the conventional sense has very little to say about the global behaviour of systems far from equilibrium, such as living states of matter and those involved at the origins of life. Instead, for more quantitative insight we must turn to the study of nonlinear dynamics, the formal mathematical domain within which the theoretical basis of complex reaction kinetics resides, all compatible with the second law.

Enormous progress has been made in our understanding of the behaviour of nonlinear dynamical systems over the past forty years or so, much of it traceable to Turing's seminal paper on the chemical basis of morphogenesis.[24] Chemical reactions far from equilibrium provide an example *par excellence*, because many rate processes (including autocatalytic and cross catalytic ones), based on the law of mass action, are nonlinear. Qualitatively, what makes nonlinear systems so fascinating is that they exhibit "unexpected" properties from the standpoint of conventional linear, equilibrium, or steady-state theory. Nonlinear systems are much more reminiscent of the world we inhabit: they can exhibit multiple states for the same equations and parameters (such as multi-stability and hysteresis), various forms of spatial, temporal and spatio-temporal organisation (often referred to as dissipative structures or "self organisation"), chaos (in the technical sense) and its corollary, sensitive dependence on initial conditions.[20] It is through the application of the mathematics of nonlinear dynamical systems that we can expect to better understand the origins of life.[20]

2.1 Hypercycles

Some of the earliest modelling of processes pertaining to the origins of life came in the form of a three part paper by Eigen and Schuster[25] under the title "The Hypercycle: A Principle of Natural Self-Organization". In their paper, the authors discussed the interlocking of reaction cycles as an explanation for the self-organization of prebiotic systems. The authors described this special so called hypercycle type of functional organization and demonstrated its possible relevance with respect to the origin and evolution of life. Eigen and Schuster represented self-replicating macromolecules, such as RNA and DNA, by their concept of "quasi-species". They defined a quasi-species as a distribution of macromolecular species with closely inter-related sequences dominated by one or several master-copies. The external constraints enforce the selection of the best adapted distribution, commonly referred to as the 'wild-type'. Most important for Darwinian behaviour are certain specified criteria for the internal stability of quasi-species. They showed that as a consequence, selection and evolution of RNA or DNA molecules is limited with respect to the amount of information that can be stored in a single replicative unit.

Using the mathematical theory of dynamical systems, Eigen and Schuster showed that there is only one type of mechanism which fulfills the requirement that information stored in each single replicative unit (or reproductive cycle) must be maintained, namely that the respective master copies must compete favourably with their error distributions. Despite their competitive behaviour these units must establish a cooperation that includes all functionally integrated species. On the other hand, the cycle as a whole must continue to compete strongly with any other single entity or linked ensemble, which does not contribute to its integrated function. The requirements that were enunciated by Eigen and Schuster are crucial for the selection of the best adapted, functionally linked ensemble and its evolutionary optimization. Only hypercyclic organization is able to satisfy these requirements (non-cyclic linkages among autonomous reproduction cycles, such as chains or branches, tree-like networks are devoid of such properties).

Eigen and Schuster's work presented a realistic model of a hypercycle of relevance to the origin of the genetic code and of

translational machinery. The models include the following features: the hypercycle has a sufficiently simple structure to admit an origination with finite probability under prebotic conditions; it permits a continuous emergence from closely interrelated (transfer-RNA like) precursors, originally being members of a stable RNA quasi-species, having been amplified to a level of higher abundance. The organizational structure and properties of a single functional unit of this hypercycle are reflected in the genetic code within the translational apparatus of the prokaryotic cell, as well as in certain bacterial viruses.

The hypercycle soon met with criticism: the evolutionary biologist Maynard Smith showed that, in the presence of parasite molecules that subvert the mechanism for their own selfish ends, such hypercycles are unstable.[26] Parasites exploit the crosscatalytic properties of hypercycles to reinforce their own numbers, but give nothing back in return. Therefore, Maynard Smith argued that these hypercycles would die out over any substantial period of time. His analysis was based on an idealised scenario, in which the hypercycle's ingredients are distributed uniformly in space. Eigen and Schuster's original paper written eight years earlier concluded that some form of compartmentalisation (*i.e.*, spatial nonuniformity) was required to keep a hypercycle in business. Indeed, there is a long-standing debate between "compartmentalists" and others in the origin of life community as to whether compartments came before RNA replication, or *vice versa*.[27] Some suggest that as compartmental permeability is essential for material input and growth, parasitism is not merely possible but inevitable. The extent of the infectivity caused by the parasite will then depend on the specifics of the compartmentalisation.

2.2 Recent assessment of the RNA world hypotheses

Although the RNA world is in various ways conceptually attractive, no one has yet produced experimental proof of its viability. As a result, various theoretical issues concerned with the scenario are often subject to analysis.

Szostak *et al.*[28] highlight the potential and the aims of the field of synthetic life and the RNA world in particular. A central challenge is the discovery of a RNA replicase. This problem is also noted by Ma and Wu,[29] who suggest that self-replicating RNA molecules must be the forerunner of the RNA world, the information content coming in later. Even in the presence of a bountiful supply of substrate, the assembly of RNA strands is inefficient; hence Szostak *et al.* suggest that activated nucleotides are probably required. There are no naturally-occurring ribozymes which can catalyse the necessary chemical reactions. A replicase has to function both as a ribozyme template for replication, which suggests that it has a naturally open structure, and to act as an active polymerase, suggesting that it has a stable folded structure.

These apparently contradictory statements can be reconciled by assuming that the environment undergoes some form of regular oscillatory behaviour; for example the tidal cycling resulting in temperature cycling or periodic fluctuations in the concentrations of monomers. The early impact which created the Moon also caused the Earth to undergo rapid rotation, with a periodicity in the range 2–6 h.[30] This caused significant tidal activity in coastal regions, the flooding and drying producing oscillations in salinity and temperature permitting the interstrand interactions between DNA chains to alternately promote association and dissociation. This would allow copying of the templated information in strands. Since there is only a relatively short period of a few hundred million years between the end of the late heavy bombardment and the origin of life, this theory brings with it the concomitant need to explain the origin of life over a rather short time scale of around 300 000 years.

Fernando *et al.*[31] support the idea that systems with templating but no enzymatic catalysis undergo chain lengthening, which causes a reduction in the total concentration of chains and the overall reaction to slow down. They construct a computer-based model of this process and find that tidal cycling significantly increases the rate of elongation.

Another model of replication was studied by Fernando and di Paolo,[32] namely the Chemoton. A definition of life was proposed by Ganti[33] as involving metabolism, regulation, control, being stable and having an informational subsystem. The Chemoton has autocatalysis, a membrane, and an informational subsystem. This advocates the idea that templated replication can occur without the need for enzymatic catalysis. Their model combines replication of cell-like structures, double-stranded polymers and metabolism. They find only rare elongation of the polymer and oscillations in the monomer concentration throughout the cell-cycle.

In addition to the replication of the information-carrying RNA, Szostak *et al.*[28] also note that in order to replicate successfully, cells need to be able to grow and divide their cell membranes. These membranes also need to satisfy key properties, namely that small molecules should be able to diffuse across on a reasonable timescale, yet large macromolecules should be generally confined to their interiors. Furthermore the chemical environment inside the membrane should be simultaneously beneficial to membrane growth and RNA replication.

The various potential mechanisms underlying the RNA-world hypothesis are also discussed by Joyce.[34] In his view the main challenge in the RNA world hypothesis is overcoming the clutter associated with prebiotic chemistry. He notes that although replication is currently carried out in a residue-by-residue fashion, this need not be the case in the prebiotic environment. As long as the production rate exceeds the decay rate, a polymer or cell will proliferate. Furthermore, even had it existed, the RNA world was not necessarily the starting point for life, as there could have been simpler genetic systems prior to it, for example TNA or PNA (threose nucleic acid or peptide nucleic acid; see Fig. 2), which then transformed into the RNA world. Alternatively, there could have been other replicating mechanisms allowing templating, for example involving inorganic clays.[99] Joyce considers more of the details of potential pathways for RNA and protein synthesis catalysed by RNA. Again the issue of compartmentalisation is raised; amongst the advantages of cell-like structures in which such reactions could occur are the maintenance of sufficient concentrations of product species and the suitability of the environment for reactions. Joyce notes that these compartments need not be the phospholipid bilayers common to modern cells; they could be airborn aerosols, rock pores, β-sheets of other polypeptides, or terpenoids. A further unanswered question for

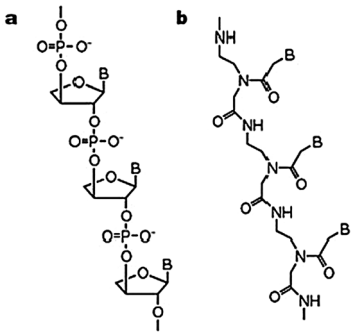

Fig. 2 Chemical structure of (a) threose nucleic acid; (b) peptide nucleic acid, where B is a nucleotide base.

the RNA world is how the transition to the DNA-makes-RNA-makes-protein biochemistry occurred.

The error threshold for the self-replication of a chemical species which acts as both an enzyme and a substrate is analysed by Obermeyer and Frey[35] *via* a model system of equations of the form

$$\frac{dX_i}{dt} = \sum_j M_{i,j} R_j X_j - X_i \sum_j R_j X_j, \qquad (1)$$

where $M_{i,j}$ is a mutation probability, $X_j(t)$ are the concentrations of chemical species j and $R_j = A_j + \sum_i B_{j,i} X_i$ is the replication rate of species j. They note that the potential for nonenzymatic replication is questionable. They find that only weak specificity is required in order for the distribution of species to be localised about the master sequence. Stronger specificity constraints provide stronger localisation and so longer sequences can be replicated, which also furnishes more tolerance against mutations.

2.3 The origin of the RNA world

The work of Eigen and Schuster was taken in new directions in theoretical work done by Wattis and Coveney.[36] Their research concentrated on constructing and analysing a microscopic kinetic model for the emergence of long chains of RNA from monomeric β-D-ribonucleotide precursors in prebiotic circumstances. Wattis and Coveney's theory starts out from similar but more general chemical assumptions to those of Eigen and Schuster, namely, that catalytic replication can lead to a large population of long chains. The models incorporate the possibility of (i) direct chain growth (ii) template assisted synthesis and (iii) catalysis by RNA replicase ribozyme, all with varying degrees of efficiency. However, all chemical processes are "open"; they do not assume the existence of closed hypercycles which sustain a population of long chains, rather it is the feasibility of the initial emergence of a self-sustaining set of RNA chains from monomeric nucleotides that is of concern. Their work confronted directly the nonlinear features of the problem which were previously largely overlooked by Eigen and Schuster. Detailed microscopic kinetic models lead to kinetic equations which are generalisations of the Becker–Döring system for the stepwise growth of clusters or polymer chains; they lie within a general theoretical framework which Coveney and Wattis have successfully applied to a wide range of complex chemical kinetic problems.[37]

The most detailed model Coveney and Wattis considered contains Becker–Döring aggregation terms, together with a general Smoluchowski fragmentation term to model the competing hydrolysis of RNA polymers.[38] This last process is a key one that enables all chemical ingredients to be recycled and leads to the massive amplification of some self-replicating sequences over all others. The main reactions that such growing chains undergo are (i) the basic Becker–Döring rate processes controlling chain growth

$$C_r^\gamma + N_i \overset{\text{slow}}{\rightleftharpoons} C_{r+1}^{\gamma+N_i}. \qquad (2)$$

here, the four nucleotide bases are denoted by N_i (with i = 1, 2, 3 or 4) and oligomeric ribonucleotide sequences by C_r^γ where r signifies the number of bases in the sequence and γ denotes the particular order in which they occur. (ii) Template-based chain synthesis (a form of catalysis mediated by Watson–Crick base pairing of ribonucleotides on complementary chains)

$$C_r^\gamma + N_i + C_s^\theta \overset{\text{fast}}{\rightleftharpoons} C_{r+1}^{\gamma+N_i} + C_s^\theta. \qquad (3)$$

(iii) Hydrolysis, whereby a long chain is split into two shorter chains. Chemically this corresponds to the process

$$C_{r+s}^{\gamma+\theta} \rightarrow C_r^\gamma + C_s^\theta. \qquad (4)$$

This has the form of a general fragmentation process as modelled by the Smoluchowski equations, a mechanism which increases the number of chains but reduces the average chain length. (iv) Enzymatic replication (replicase ribozymal activity), where a third chain aids the growth of a sequence which is already in close contact with another chain acting as a template, is modelled by

$$C_r^\gamma + N_i + C_{r+k}^{\gamma*+\theta*} + C_s^\xi \rightleftharpoons C_{r+1}^{\gamma+N_i} + C_{r+k}^{\gamma*+\theta*} + C_s^\xi. \qquad (5)$$

Here the combination of γ with N_i is a sub-sequence of the chain $\gamma + \theta$, while C_s^ξ plays the part of a replicase ribozyme. Needless to say, some of these replicases will have much higher efficiency than (most) of the others.

Wattis and Coveney demonstrated that it is possible to realise the selection of certain self-replicating RNA polymer chains in a reasonable amount of time starting from plausible assumptions about the chemistry and initial conditions that could have prevailed within a putative prebiotic soup comprised of β-D-ribonucleotide monomers.[36,37]

2.4 Modelling of elements of the RNA-world

All the models developed by Coveney and Wattis are based on deterministic nonlinear dynamics, being derived from macroscopic laws of mass-action. For situations that may frequently pertain at the cellular level, it is by no means clear that this "law" is always valid. With small numbers of molecules involved, more inherently probabilistic models have an important role to play. Thus, Hanel *et al.*[39] consider the kinetics of stochastic minimally nonlinear models, of the form $\dot{x}_i = \sum_j A_{i,j} x_j + J_i + v_i$, where the connectivity matrix A has the form of an Erdos–Renyi network (a network in which edges between nodes are formed independently according to some random variable). Whilst choosing A to be a random matrix, they impose the constraint $x > 0$, which makes the

system nonlinear, hence the Lyapunov exponents may be positive, negative or zero. If all exponents are negative, the system converges to a steady-state or equilibrium solution; if the largest exponent is strictly positive then the system is chaotic and exhibits strong instabilities, sensitive dependence on initial conditions and other 'random' behaviour not conducive to the persistence of living systems. However, if the largest exponent is zero, then the system is at criticality, where a greater range of states can be explored and nonlinear effects are dominant, aiding the control of behaviour; this state is of great interest in the modelling of living systems, wherein the types of behaviour exhibited include oscillations. The average degree of the network $\langle k \rangle = L/N$, where L is the number of links, and N is the number of nodes. There is a considerable range of $\langle k \rangle$ where the largest eigenvalue is close to zero, indicating applicability to living systems.

Lehman[40] proposes that even in the early RNA world self-replication occurred *via* RNA strands breaking into shorter strands which replicated the daughter strands, recombining to form multiple copies of the original RNA molecule. The reasons for this are many: recombination is an energy-neutral process, so would have been common in prebiotic conditions; an RNA replicase ribozyme would have to be long, typically in excess of 100 nucleotides. This is too long to replicate accurately *via* catalysis, whereas shorter RNA strands could easily replicate. One consequence of this hypothesis is a lengthening of RNA in the population over time; this is entirely consistent with the development from simple prebiotic life to more advanced function.

As mentioned earlier, one problem in analysing models of the RNA world is the vast (combinatorially large) number of possible species. In general there is not enough mass for all to be explored, that is, for even one molecule of each to be created, so it is not a question of which has the most stable structure theoretically, but which of those that have been created is best at replicating. A simpler problem, advocated by many authors instead, is to consider a reduced system of species, in which there are only two species competing for a substrate. A good example of the two species are the left- and right-handed chiral structures found in many living systems. Chemically, physically and thermodynamically they have the same stabilities, yet competition and other nonlinear effects cause one to be eliminated and the other to become dominant. Hence in Section 3 we focus in detail on mechanisms which may have caused such a symmetry-breaking bifurcation, in the formation of chiral structures in systems where two species (left- and right-handed) compete, possibly with an achiral state too.

2.5 Compartmentalisation: self-replicating micelles and vesicles

Experimental scenarios leading to self-reproducing vesicles have been successfully developed by Luisi's group.[42] Walde *et al.* describe the conditions under which vesicles formed by caprylic acid and oleic acid in water undergo self-reproduction. The increase in their population number is due to a reaction which takes place within the spherical boundary of the vesicles themselves. This happens by letting caprylic or oleic anhydride hydrolyze at alkaline pH. The initial increase of the concentration of acid/carboxylate is slow, but the presence of vesicles above a critical concentration brings about a rapid second phase leading to more vesicles being formed in an overall autocatalytic process. The process of self-reproduction of caprylic acid and oleic acid vesicles was also studied as a function of temperature by Walde *et al.* They showed that by increasing the temperature (up to 70 °C), the domain of rapid vesicle formation becomes steeper while the long initial slow phase is significantly shortened.

Models of self-replicating vesicles have been proposed and analysed by two of the current authors.[41] Coveney and Wattis constructed a kinetic model based on a novel generalisation of the Becker–Döring cluster equations which describe the stepwise growth and fragmentation of vesicular structures. Their nonlinear kinetic model[41] is complex and involves many microscopic processes; however, by means of a systematic contraction of the complete set of kinetic equations to the macroscopic limit, they showed that the model correctly captures the experimentally observed behaviour of a long slow induction phase, a rapid autocatalytic phase followed by slow convergence to equilibrium. This model was generalised further by Bolton and Wattis[41] to account for the size-templating effect observed by Lonchin *et al.*[42] and Berclaz *et al.*[43] When the systems studied there were initiated with no vesicles, a broad range of vesicle sizes developed slowly; whereas in a system with an initial distribution of vesicles of one particular size (essentially monodisperse), vesicles of the same size are produced more quickly.

3 The origins of homochirality

One area where chiral symmetry-breaking effects occurs is in parity violation in the electroweak interaction of subatomic physics. Mechanisms by which such small differences in energy (10^{-15} kcal mol^{-1}) could cause a symmetry-breaking at the much larger level of polymerisation or crystallisation have been investigated by many authors. See for example, the work of Faglioni *et al.*,[44] and references therein. However, for the remainder of this article we discount this possibility, preferring instead the theory that nonlinear effects cause an instability in the racemic state with random fluctuations selecting one handedness over the other, the nonlinear interactions then driving the system to chiral purity.

The transition from a complex chemistry involving approximately equal numbers of left- and right-handed chiral species into a system involving just one-handedness of chiral molecules was a significant stage in the origins of life. In this section we focus on mathematical models of processes which exhibit this type of symmetry-breaking transition. We consider systems in which this happens during polymerisation, and in the formation of solid crystals. Our aim is to describe the mechanisms responsible for the symmetry-breaking.

In 2001 Sharpless, Noyori and Knowles shared the Nobel Prize for Chemistry for their work on chiral synthesis. The pioneering research originated in the 1970s and included work of a larger group including Kagan.[45] Later important experiments demonstrated the amplification of an initial small imbalance in chirality through a chemical reaction, including

that of Soai *et al.*[46]: In this reaction a small enantiomeric excess in the catalyst at the start of the experiment led to a much larger imbalance in the chiralities of the products at the end of the reaction. An enantiomeric excess exceeding 85% was achieved in the asymmetric autocatalysis of chiral pyrimidyl alkanol. However, the theory and modelling of chiral symmetry-breaking processes has a much longer history.

3.1 Historical background

Over the years, many models have been proposed which explain the emergence of homochirality from an initially racemic mixture. The first was that of Frank,[47] who proposed that two precursors, R and S, combine to form left- or right-handed species, X,Y, through an autocatalytic reaction. The effect of this is to amplify any excess of X over Y or *vice versa* ($ee_{abs} = X - Y$). The two chiral products then combine to form a product P which is removed; thus only the enantiomeric excess of X over Y (or *vice versa*) remains in the system. This stage amplifies the relative chirality, $ee_{rel} = (X - Y)/(X + Y)$.

These processes can be summarised by

$$\begin{aligned} \text{external source} &\rightarrow R, S && \text{input}, k_0, \\ R + S &\rightleftharpoons X && \text{slow}, k_1, \\ R + S &\rightleftharpoons Y && \text{slow}, k_1, \\ R + S + X &\rightleftharpoons 2X && \text{fast, autocatalytic}, k_2 \\ R + S + Y &\rightleftharpoons 2Y && \text{fast, autocatalytic}, k_2 \\ X + Y &\rightarrow P && \text{cross-inhibition}, k_3, \\ P &\rightarrow \text{sink} && \text{removal}, k_4. \end{aligned} \tag{6}$$

We denote the concentrations of each species by variables in lower case which are functions of time. For simplicity, we ignore the reversible reactions and denote time-derivatives by primes. This system is described by the differential equations

$$r' = s' = k_0 - 2k_1rs - k_2rs(x + y) + k_{-1}(x + y) + k_{-2}(x^2 + y^2), \quad p' = k_3xy - k_4p, \tag{7}$$

$$x' = k_1rs + k_2rsx - k_3xy - k_{-1}x - k_{-2}x^2, \tag{8}$$

$$y' = k_1rs + k_2rsy - k_3xy - k_{-1}y - k_{-2}y^2, \tag{9}$$

from which we note that at steady-state we have

$$rs = \frac{k_0 + k_{-1}(x+y) + k_{-1}(x^2+y^2)}{2k_1 + k_2(x+y)}. \tag{10}$$

We write the absolute enantiomeric excess as $ee = x - y$ and the total concentration as $\sigma = x + y$; adding and subtracting the equations for dx/dt and dy/dt, we find $\sigma^2 = 2k_0/k_3 + ee^2$, and

$$ee\left[\frac{k_2(k_{-2}ee^2 + k_{-2}\sigma^2 + 2k_{-1}\sigma + 2k_0)}{2(2k_1 + k_2\sigma)} - k_{-1} - k_{-2}\sigma\right] = 0. \tag{11}$$

Note that $ee = 0$ is always a solution; however, there are other solutions where $ee \neq 0$ provided that the rate constants satisfy certain conditions, including $k_3 > k_{-2}$, and k_0 being sufficiently large.

Here, the important features which produce an asymmetric (*i.e.* chiral) solution are

(i) the open and non-equilibrium nature of the system, that is, a continual input of fresh R, S is necessary; furthermore, to maintain a finite mass of material in the system, we also require the removal of the product P;

(ii) the system has cross-inhibition which removes equal amounts of X and Y, amplifying any differences caused by random fluctuations in the initial data or in the input rates;

(iii) the autocatalytic production of the chiral species X, Y.

That so many special conditions are required to produce asymmetric states can be viewed as a weakness of the Frank model; hence other authors have sought to produce systems which exhibit symmetry breaking without making so many assumptions.

A range of "toy" models were proposed and analysed by Saito and Hyuga.[48] These include varying strengths of non-linear autocatalysis and recycling, summarised by

$$r' = k_r(1 - r - s) - \lambda r, \quad s' = k_s(1 - r - s) - \lambda s, \tag{12}$$

where $r(t)$ and $s(t)$, represent the concentrations of the two enantiomers. Initially they considered the case $k_r = k_s = k$ with $\lambda = 0$ and find that enantiomeric excess, $r - s$, does not increase. In the case $k_r = k_r$, $k_s = k_s$, $\lambda = 0$, the relative enantiomeric excess $r - s/r + s$ is constant; although the absolute $r + s$ excess $r - s$ increases, the total amount of chiral product $r + s$ increases at the same rate. In the more complex case of $k_r = k_r^2$, $k_s = k_s^2$, $\lambda = 0$, the relative enantiomeric excess is amplified, and this amplified excess is maintained in the more general case where $\lambda > 0$. This again demonstrates that strong autocatalysis can cause homochiralisation, but it is not clear which form of rate coefficients (k_r,k_s,λ) should be used in any particular application. In comparison with the model of Frank, these models are closed and have no cross-inhibition, but the autocatalysis has to be strong before symmetry-breaking occurs.

Saito and Hyuga[48] analysed various systems of equations describing polymerisation which include clusters of a wide range of sizes. They observed that a model truncated at tetramers exhibits different behaviour from one truncated at hexamers. In particular, whilst symmetry-breaking is exhibited by the hexamer model, it is not possible within the tetramer model. This serves as a warning to theoreticians who wish to deduce the properties of a complex model simply by analysing a significantly reduced version.

Goldanskii and Kuzmin[49] have considered a 'cold prehistory of life', by which they mean a variety of non-traditional mechanisms by which life could have originated. These include processes occurring in the solid phase, in a cold environment, for example in the 'dirty ice mantles of interstellar dust grains' or an environment which experiences one or a series of 'thermal explosions' during which the temperature is elevated. Reactions occur *via* mechanisms involving molecular tunnelling and 'polycondensation'. Thus the scenario that organic molecules were manufactured in space or on other planets, and brought to Earth *via* meteorites is proposed as a credible possibility. At these low temperatures, entropy plays no role, and such reactions may involve tunnelling mechanisms; they claim timescales of the order of millions of years. A quantum mechanical model of the interconversion of left- and right-handed structures and the interaction with phonons is

proposed by Berlin *et al.*[50] They show that coupling of these effects can lead to a suppression of the interconversion of left- and right-handed structures, stabilising the chiral states. Other simple chemical reaction schemes with autocatalysis, of chiral product destabilising the symmetric state, giving rise to a pitchfork bifurcation are later considered by Goldanskii and coauthors.[51]

Given that life exhibits several key physical properties, namely homochirality, templated-self-replication and evolution, Avetisov *et al.*[52] consider the order in which the properties occurred. They argue that since noncatalysed homochiral polymerisation is almost impossible, enzymatic replication must have preceded the transformation to a chiral world. However, they go on to acknowledge that the interaction of structure and function is not such a simple chicken-and-egg problem; there are levels of chiral dominance, and levels of replication, from simple autocatalysis to the templated self-replication of information-storing polymers such as RNA.

3.2 Experimental observations of homochiral crystallization

The first experiments illustrating symmetry-breaking during crystallisation were those of Kondepudi *et al.*[53] Later Kondepudi *et al.*[53] showed that, with no stirring, approximately equal amounts of left- and right-handed crystals formed. However, when the stirring rate exceeded a critical (threshold) value, the imbalance in the numbers of crystals of each handedness increased; and at large enough stirring rates, total chiral purity was achieved. The final distribution of chiralities of crystals emerging from a supersaturated solution of sodium chlorate could thus be described by treating the stirring rate as a bifurcation parameter.

The reason for homochirality at higher stirring rates is that all crystals are derived from the same 'mother' crystal, which is the first crystal to grow to a supercritical size, such that when it hits the impeller or the wall and fragments fracture off it, all other crystals grow from these fragments (compare with the LUCA). Earlier, Kondepudi and Nelson[53] had worked on the somewhat improbable theory that the parity-violating perturbations could be amplified and cause chiral symmetry-breaking in prebiotic chemistry. Their results suggested that such a process would take approximately 10^4 years. Computer simulations of the chiral structure of solids was carried out by Avetisov *et al.*,[54] leading to a phenomenological description of the formation of homochiral domains.

That grinding a mixture of chiral crystals eventually leads to a homochiral distribution of crystals (that is, all of the same handedness) was first noted by Viedma.[55] He followed Kondepudi *et al.*[53] in using crystalline sodium chlorate maintained in a supersaturated state, with a stirrer and small glass balls to continually crush the crystals. Over time the percentages of left- and right-handed crystals steadily change from approximately racemic to entirely homochiral.

A similar effect has been observed by Noorduin *et al.*[56] with amino acids; these molecules are much more relevant to origins of life studies. The works of Noorduin *et al.* and Viedma have been reviewed by McBride and Tully.[57] Grinding is a dynamic process which results in the conversion of solids of one handedness into the other, through dissolution and recrystallisation. Once the system is in a chirally pure state, the system is 'locked' into that state: it is extremely unlikely that any nuclei of the other handedness could form. The chirally pure state is not the equilibrium state, rather, the imposition of grinding means that energy is continually being fed into the system, which destabilises the equilibrium configuration and instead stabilises asymmetric steady-states.

McBride and Tully[57] go on to describe the growth of one enantiomorph and the dissolution of the other as a type of Ostwald ripening process; the implication being that the stabilisation of an asymmetric steady-state is due to changes in surface area : volume or size:curvature ratios. Whilst small crystals have a rapid dissolution rate due to their large surface area to volume ratio, larger crystals have a lower surface area to volume ratio meaning that, relatively, they dissolve more slowly. Ostwald ripening occurs due to the ratio of dissolution to growth, which depends on the curvature of the crystals, and which varies across the distribution of crystal sizes in a complicated way, since crystals are in general not spherical. However, the models analysed below show it is not necessary to invoke such size-dependent effects to explain how grinding causes homochiralisation.

3.3 Modelling homochiralisation through grinding

Again, before any experimental evidence was published, Uwaha had written down a crude model describing the processes detailed above.[58] We denote the time-dependent concentrations of amorphous (or achiral) monomers by $c(t)$, small left- (right-) handed clusters by $x_1(t)$, $y_1(t)$ respectively, and larger left- (right-) handed crystals by $x_2(t)$, $y_2(t)$.

These rate equations model the processes of:

(i) small chiral crystal clusters (x_1,y_1) nucleating from the pool of achiral monomers (c) at rate k_0;

(ii) small chiral nuclei (x_1, y_1) of the same handedness combining into larger chiral clusters (x_2, y_2) at the rate k_c;

(iii) small and larger clusters of the same handedness combining into larger clusters at the rate k_u;

(iv) large crystals (x_2,y_2) growing through coalescence with achiral monomers (c) at the rate k_1;

(v) the dissolution of larger crystals (x_2,y_2) into smaller clusters (x_1,y_1) at the rate λ_u;

(vi) the dissolution of smaller nuclei (x_1,y_1) into achiral monomers at a rate λ_0;

(vii) the dissolution of larger crystals (x_2,y_2) into achiral monomers at a rate λ_1;

In terms of these quantities, Uwaha's chemical reaction model has the form

$$c' = -2k_0z^2 - k_1c(x_1 + y_1) + \lambda_1(x_2 + y_2) + \lambda_0(x_1 + y_1), \quad (13)$$

$$x_1' = k_0z^2 - k_ux_1x_2 - k_cx_1^2 + \lambda_ux_2 + \lambda_0x_1, \quad (14)$$

$$x_2' = k_1x_2c + k_ux_1x_2 + k_cx_1^2 - \lambda_1x_2 - \lambda_ux_2, \quad (15)$$

$$y_1' = k_0z^2 - k_uy_1y_2 - k_cy_1^2 + \lambda_uy_2 + \lambda_0y_1, \quad (16)$$

$$y_2' = k_1y_2c + k_uy_1y_2 + k_cy_1^2 - \lambda_1y_2 - \lambda_uy_2, \quad (17)$$

The sizes of clusters are not incorporated in this model, since all the variables describe the total mass of material in each state.

Thus surface area to volume ratios are not involved in the analysis. However, symmetry-breaking to a solution in which $x_1 \neq x_2$ and $x_2 \neq y_2$ is still possible in this model. Uwaha notes that the terms involving λ describe the recycling of material and are vital in the formation of a fully homochiral state. When the system is in a chirally asymmetric state, the typical sizes of left- and right-handed crystals may be significantly different. Although the model is not expected to be quantitatively accurate, it should still give a good qualitative description of behaviour.

Wattis[59] quotes a sequence of models starting from a detailed microscopic model which includes standard crystal growth and dissolution. This model is generalised to include the effects of grinding, which removes larger fragments of crystal, and has three species of crystal growing simultaneously, namely amorphous, left-, and right-handed crystals. The left- and right-handed crystals have no direct interaction (no cross-inhibition), although they compete for achiral monomers and small crystal nuclei, which take on the handedness of larger crystals on coalescence. The model is then simplified to show how the basic processes of grinding, stepwise growth, and competition for amorphous material cause symmetry-breaking. As well as microscopic models for the size-distributions of each species, various coarse-graining procedures are used to derive small systems of ordinary differential equations for the total concentration of crystals, the total mass of crystalline material in each handedness and the number of small nuclei of each type.

3.4 Homochiral polymerisation through catalytic feedback

An interesting and novel model of symmetry-breaking in the formation of chiral polymers was proposed by Sandars in 2003.[60] This toy model has many features in common with Frank's 1953 paper on spontaneous asymmetric synthesis[47] (see Section 3.1), but is adapted to an early peptide world. In this model, an achiral substrate (S) splits into chiral monomers L_1,R_1 spontaneously and slowly and, at a faster rate, is catalysed by polymers. As originally proposed, the model has a maximum polymer length (n) and only the longest homochiral chains act as catalysts. The catalytic effect is both autocatalytic and crosscatalytic as follows: long left-handed chains L_n catalyse the production of left-handed monomers L_1 from S, as well as the production of right-handed monomers, R_1

$$\begin{array}{ll} S \rightarrow L_1, S \rightarrow R_1, & \text{slow,} \\ S + L_n \rightarrow L_1 + L_n, & \text{autocatalytic, rate} \propto 1 + f, \\ S + R_n \rightarrow R_1 + R_n, & \text{autocatalytic, rate} \propto 1 + f, \end{array} \quad (18)$$

$$\begin{array}{ll} S + R_n \rightarrow L_1 + R_n, & \text{cross-catalytic, rate} \propto 1 - f, \\ S + L_n \rightarrow R_1 + L_n, & \text{cross-catalytic, rate} \propto 1 - f, \end{array} \quad (19)$$

The polymerisation is assumed to be uncatalysed and hence linear; cross-inhibition, the other mechanism required for symmetry-breaking, is incorporated by allowing a monomer of the opposite handedness to be added to a growing chain. This is assumed to prevent further growth of the chain. Hence

$$\begin{array}{ll} L_j + L_1 \rightarrow L_{j+1}, & \text{chain growth, rate} = a, \\ R_j + R_1 \rightarrow R_{j+1}, & \text{chain growth, rate} = a, \end{array} \quad (20)$$

$$\begin{array}{ll} L_j + R_1 \rightarrow Q_{j+1}, & \text{cross-inhibition, rate} = a\chi, \\ R_j + L_1 \rightarrow P_{j+1}, & \text{cross-inhibition, rate} = a\chi, \end{array} \quad (21)$$

with $j = 1, 2, \ldots, n$. Analyses of the model aim to find the conditions on the parameters k, a, χ, f which destabilise the symmetric steady-state.

As the ratio of autocatalysis to cross-catalysis is increased, that is, by increasing the fidelity parameter f, a pitchfork bifurcation is obtained (at $f = f_c$). The location of the pitchfork can be surprisingly low, for example, $f_c = 0.2$ in the case of large χ. The fact that larger cross inhibition (larger χ) reduces f_c is, at first sight, quite counterintuitive. One way of rationalising this behaviour is to note that if one chirality is to dominate the other, it is more important to stop chains of the other chirality growing, rather than to grow longer chains of the dominating chirality.

Other related but independent work came from Brandenburg *et al.* on the homochirality of an early peptide world[61] and from Wattis and Coveney.[62] In the latter work, the catalytic steps are assumed to hold for all polymer lengths ($n \in N, j \in \mathrm{N}$), allowing an analytical determination of the stability criteria of the symmetric solution. Wattis and Coveney also analysed the kinetics of polymer formation in the case where the system starts from zero concentrations of polymers, which are then formed for a short time. During this time an asymmetry introduced into the system by a random external perturbation may be massively amplified. The system then approaches one of the steady-state solutions in which the product is overwhelmingly homochiral.

Brandenburg *et al.*[63] consider a different variation of Sandars' model in which some reactions are made reversible. They add in $L_n \rightarrow L_m + L_{n-m}$, and $L_nR_1 \rightarrow L_mR_1 + L_{n-m}$. The problem with such systems is that they are dominated by short polymers, and so have an unrealistically short average polymer length. Hence these authors consider other possible modifications, in which fragments are immediately recycled into monomers. Ultimately they find similar results to the original model of Sandars, and a pitchfork bifurcation occurs as f is increased (at about 0.5), leading to an asymmetric steady-state.

Blanco and Hochberg[64] add reversibility to all the reactions in Sandars' model and analyse entropy production at each stage of the reaction. They find that the system undergoes oscillations in the chirality before approaching a steady-state or equilibrium configuration. The rate of entropy production has maxima as the system breaks symmetry (from an initially almost racemic state), or undergoes reversals in its chirality.

Gleiser *et al.*[65] generalise Sandars' model to a spatial domain (both two- and three-dimensional), by replacing the time-derivatives in the governing equations with a diffusion operator ($\mathrm{d}/\mathrm{d}t \rightarrow \partial/\partial t - k\nabla^2$), and adding in Gaussian white noise to simulate the effects of random fluctuations on the system. They find that random initial conditions lead to coarsening behaviour, with regions of homochirality which grow and evolve by surface tension driven kinetics. They also find punctuated equilibria in which noise can wipe the system's memory of its chiral history, and establish a new chirality, thereby extending Eldredge and Gould's notion of punctuated equilibria in evolution.[66]

3.5 Homochiral polymerisation through epimerization

Plasson *et al.* also sought to relax the assumptions of Frank, in particular they wanted a system which was closed and

had no autocatalysis. Their Activation Polymerisation Epimerisation Depolymerisation (APED) scheme[67] has monomers of each chirality (L, R) which can be activated through an input of energy into the system (to L^*,R^*). The four processes of activation, polymerisation, epimerisation and depolymerisation have differing rates depending on whether they act on homopolymers or heteropolymers. An activated monomer can combine with an unactivated one to form a dimer (polymerisation, L_2,R_2,Q_2, the former two being homopolymers, the latter a heteropolymer). In depolymerisation, polymers are split into their component monomers. All of these processes leave the total number of molecules of each chirality the same. Hence there is a new process, epimerisation in which the final monomer in a polymer can change its chirality; this converts homopolymers to heteropolymers and *vice versa* and can be viewed as a replacement for autocatalysis in previous models. Processes have different rates depending on whether they act on homopolymers or heteropolymers.

The processes in Plasson *et al.*'s scheme can be summarised by

$$\begin{aligned} &L \xrightarrow{a} L^*,\quad L^* \xrightarrow{b} L,\quad L^* + L \xrightarrow{p} L_2,\quad L^* + R \xrightarrow{\alpha p} Q_2,\\ &Q_2 \xrightarrow{e} L_2,\quad L_2 \xrightarrow{\gamma e} Q_2,\quad L_2 \xrightarrow{h} L + L,\quad Q_2 \xrightarrow{\beta h} L + R, \end{aligned} \tag{22}$$

with similar reactions replacing L by R and *vice versa*. Although this scheme readily extends to polymers of arbitrary length, Plasson's analysis of this is restricted to the case of monomers and dimers, and yields the interesting result that at low total mass, only a 'dead' state exists, where most matter is in monomeric form and all monomers are activated. There are three other states which exist at larger masses: at large α the system is unstable, and oscillates between the two handednesses; at intermediate values of α the symmetric state is stable; at low values of α the symmetric state is unstable, there are two stable asymmetric states, and the system approaches one of these. Thus Plasson *et al.* succeeded in creating a closed system, with no catalysis and no cross-inhibition of homochiral products. The positive feedback required for homochiralisation is provided by epimerisation instead of autocatalysis. At higher total masses, the overall average effect of epimerisation is to favour the conversion of material from the minority handedness into the dominant enantiomer, destabilising the racemic (symmetric) steady-state.

The analysis of Plasson *et al.* has been extended to investigate the effects of diffusion in a spatially-varying form of the model by Gleiser and Walker.[68] Their motivation was to investigate whether such a model can describe the formation of protocells, that is cellular membranes which enclose a region of particular chirality and so form structures which are thermodynamically separate from their surrounding environment. Gleiser and Walker consider both homogeneous initial conditions in which the system is supersaturated everywhere, and systems in which only localised spatial domains are supersaturated. They find ring-like structures form in which the interior is homochiral and the wall is racemic, with a high concentration of heterodimers. Whilst protocells share many features common to living systems (growth, metabolism, reproduction, an ability to respond to changes in their environment), they are only one component of a living cell. Gleiser and Walker acknowledge that the kinetics of their system cannot describe metabolism or reproduction. Nevertheless, their paper confirms that cell-like structures could have preceded self-replicating genetic molecules, making an important contribution to the wider debate on which came first.

3.6 Accumulation of nucleotides in hydrothermal pore systems

The RNA world requires high concentrations of small prebiotic molecules, whereas geochemical extrapolations suggest the presence of a dilute prebiotic ocean with concentrations comparable with modern day values.[69] Braun *et al.* proposed a potential solution to this discrepancy in concentrations using joint experiment and simulation.[70] Combined solutions of the Navier–Stokes equations, molecular diffusion and heat transfer were simulated in two dimensions using a finite element solver in order to simulate molecular transport in elongated hydrothermal pore systems influenced by a thermal gradient. They found extreme accumulation of molecules in a wide variety of plugged pores. The authors state that the mechanism is able to provide highly concentrated single nucleotides suitable for operation of an RNA world at the origins of life.[70] Accumulation is driven by the thermal gradient across a pore. The fluid is shuttled by thermal convection along the pore, whereas the molecules drift across the pore driven by thermal diffusion. Baaske *et al.* showed that millimetre-sized pores accumulate even single nucleotides more than 10^8-fold into micrometer-sized regions than would be the case without thermal diffusion. An enhanced concentration of molecules is found in the bulk water region near the closed end of the pore. Because the accumulation depends exponentially on the pore length and temperature difference, it is robust with respect to changes in cleft geometry and molecular dimensions. Baaske *et al.*'s findings suggest that, for life to evolve, complicated active membrane transport is not required initially. Instead, interlinked mineral pores in thermal gradients can provide a high concentration starting point for the molecular evolution of life.

4 Molecular modelling

In previous sections, we have been concerned with studying a range of chemical kinetic models, largely based on the macroscopic law of mass action. Now we turn to consider what more microscopic, molecular theory has to say on origins of life. Origins of life studies have hitherto rather rarely used computer simulation based molecular modelling techniques to understand the possible chemical pathways to the formation of the first biomolecules. Simulation methods provide almost unlimited molecular information about systems that are difficult to characterise experimentally because of a lack in measurement resolution and/or the extreme temperature and pressure conditions associated with these origins of life systems. However, it is still very difficult to compute the reaction mechanisms and kinetics of such origins of life systems using first principles techniques. In this section we consider the computational approaches used and the scientific insights gained from these molecular simulation techniques in terms of origins of life studies.

4.1 Molecular simulation methods

Here we give a brief summary of the computational techniques used, in order to familiarise the general reader with these methods. Molecular simulation methods are often classified according to the accuracy with which they compute inter-atomic interactions, and the type of structural data they produce.

4.1.1 Quantum chemical methods. Quantum chemical simulation methods model the interactions between electrons and the nuclei of a system of atoms by attempting to solve the equations of quantum mechanics (based on the Schrödinger equation). Quantum chemical methods allow us to model electrodynamics in processes such as bond-making and bond-breaking as they represent electrons explicitly. One of the advantages of quantum methods is that, in addition to fundamental constants such as the mass and charge of an electron, they only require the input of atomic numbers, the initial configuration of the nuclei and the number of electrons. The major disadvantage of quantum methods is that they are computationally very expensive which currently limits the approach to the study of assemblies of a few hundred atoms. Good introductions to quantum chemical methods can be found in ref. 71.

Quantum chemical calculations, sometimes called *ab initio* or 'first principles' calculations, in the condensed phase often use density functional theory (DFT). DFT uses the Hohenberg–Kohn theorem which states that the electronic ground-state of a molecule or solid is a unique functional of the electron density. The functional is composed of terms for the kinetic energy, coulombic energy, and the electron exchange and correlation energies.

Quantum chemical calculations of interactions between organic molecules and inorganic minerals, like those considered within origins of life studies, provide accurate energies, charge distributions and geometries, but even using large super-computers these models can only be simulated for a few picoseconds with hundreds of atoms. Because of the restriction in model size and simulation length, classical molecular simulation techniques methods (see Section 4.1.2) are better suited to studying the dynamical interactions of large biomolecules. The accuracy of classical molecular simulation techniques is very largely dependent on the validity of the forcefield used. *Ab initio* calculations can be used to determine accurate forcefields for such classical molecular dynamics simulations.

4.1.2 Molecular dynamics. Classical molecular dynamics techniques are based on classical mechanics. Each atom, or group of atoms, is treated as a single entity, and the forces between them are expressed in terms of the gradients of potential energies. Molecular dynamics requires the input of the initial atomic positions as well as the forcefield parameters. These parameters can be derived from experiment or, as discussed in Section 4.1.1, *ab initio* calculations. Molecular dynamics simulations are well suited to modelling systems governed by bonded and non-bonded interactions but without any chemical transformations. The use of interatomic potentials means that it is currently possible to simulate millions of atoms, typically for tens of nanoseconds but in some cases as long as microseconds. Good introductions to the field of molecular dynamics can be found in ref. 72.

Molecular dynamics (MD) describes in detail the individual and collective motion of atoms within a molecular system. MD attempts the *de novo* prediction of all relevant parameters given knowledge of the system's starting structure. Armed with sufficient computational power MD is able to compute the equilibrium description of a classical multi-body system but it also obviously provides dynamical information. It is assumed that the atoms of the system move under the influence of an inter-atomic potential energy. Each atom in the simulation has a mass and a size. Newton's equations of motion are integrated to compute the dynamical behaviour of the N atoms comprising the system. Thus

$$m_i \frac{d^2\mathbf{r}_i}{dt^2} = \mathbf{F}_i, \tag{23}$$

where m_i is the mass of atom i, $\mathbf{r}_i$ is the Cartesian 3-vector of atom i, the second derivative of $\mathbf{r}_i$ is the acceleration of atom i and $\mathbf{F}_i$ is the force vector acting on atom i. The force $\mathbf{F}_i$ is related to the many-body potential V through the equation $\mathbf{F}_i = -\nabla V$, where ∇ represents the gradient operator. We need only specify the initial configuration of the system in terms of an initial set of atomic coordinates while allocating the initial atom velocities randomly from a Maxwell–Boltzmann velocity distribution. One of the principal limitations of molecular dynamics is the time scale that it can reach. For reasons of numerical stability a typical time-step in an MD simulation cannot exceed a few femtoseconds, so billions of timesteps must be integrated to reach the nanosecond domain.

In the context of MD, a force field provides the functional form and parameters used to describe the potential energy of the system of particles. Force field functions and parameter sets are commonly derived from both experiment and computationally expensive quantum mechanical calculations. ''All-atom'' force fields such as the AMBER force field,[73] used to describe the interactions of nucleic acids and proteins, and the ClayFF force field,[74] used to describe the interactions of clays and inorganic minerals, provide parameters for all the atoms in the system.

4.1.3 Computational requirements

In order to perform molecular simulations relevant to the origins of life we require the simulation of realistic size models; although frequently today perhaps only tens of thousands of atoms in size, they may reach hundreds of thousands to millions of atoms. We also aim to simulate these systems in an acceptable amount of wallclock time. In order to perform realistic simulations we therefore need to run the simulations with codes which exhibit excellent speed-up and scaling properties on powerful supercomputers. Classical molecular dynamics codes such as LAMMPS,[75] NAMD[76] and GROMACS[77] display near-linear speed-up with the number of cores used to perform the computations and the ability to simulate systems of increasing size.

4.1.4 Clays and biopolymers. Most clays are composed of continuous two-dimensional sheets stacked in a co-planar way with random in-plane phases.[78] The various types of clays are

characterised by different atomic species in the sheets and the guest species present in the interlayer region. Cationic clays of the smectite kind consist of a combination of tetrahedral and octahedral aluminosilicate sheets. When divalent ions are present in the octahedral sheet all octahedral sites are filled yielding a trioctahedral clay. If trivalent ions are present just two out of three sites are occupied and a dioctahedral clay is obtained. Isomorphic substitutions further diversify the clays. The most common is a partial substitution of silicon in the tetrahedral layer and aluminium in the octahedral layer for atoms of different valency. These substitutions give rise to a net negative charge on the clay layers which is balanced by sorption of charge balancing cations into the interlayer. Anionic clays (more correctly, layered double hydroxides) are structurally related to brucite. Brucite consists of Mg^{2+} ions octahedrally coordinated by hydroxyl groups. In most anionic clays the Mg^{2+} is partially substituted by M^{3+} species such as Al^{3+}, making the clay layers positively charged. Anionic clays are charge balanced by anions resident between the layers.

Modelling of clay minerals in the literature consists mostly of forcefield based classical molecular dynamics simulations. Using the ClayFF forcefield,[74] Kirkpatrick *et al.* interpreted NMR and FTIR data of layered double hydroxides (LDHs) through molecular dynamics simulation.[79] Others, including Coveney and Skipper, have investigated the interlayer structure of water and cations within smectite clays.[80] Greenwell *et al.* have published a review of the application of simulation techniques to clay minerals.[81]

4.2 Use of quantum mechanics simulations in origins of life research

As discussed in the previous sections, quantum mechanical (QM) treatments offer methods of simulating small numbers of atoms at high levels of accuracy. QM studies are also known as *ab initio*, or first principles, methods because, unlike molecular mechanics, they start by solving the ground state electronic structure of the system of interest and, other than the electronic configuration and atomic mass of the atoms present, are essentially entirely parameter free. These methods offer unique insight into bond forming mechanisms, or detailed structural and spectroscopic aspects that depend on small differences in local electronic structure. As such, the primary places that QM is used in origins studies are for probing catalysis (mainly mineral surface mediated) and chiral selectivity by minerals. In order to make QM calculations tractable and applicable to extended structures such as minerals, periodic boundary conditions are often imposed in all three spatial directions so that a small simulation cell is mathematically repeated in all space so as to approximate an infinite system. By far the most commonly employed QM technique is the density functional theory (DFT) approach.

4.2.1 Reactivity at mineral surfaces. In contrast to other research areas within origins of life studies, much of the focus of those involved in QM simulations has been in understanding the process of mineral catalysed peptide bond formation with numerous groups electing to simulate this road to a protein world as compared to those that favour the RNA world approach. One reason for this bias is that the peptide forming reaction involves a relatively simple mechanism, with small reactants, and hence is computationally tractable when compared to many of the reactions involved in nucleic acid synthesis. A comprehensive review of peptide formation on minerals, including both experimental and molecular modelling studies, is presented by Lambert,[82] who identifies a range of simulation studies performed between 1988 and 2007 on silicate, titania, clay and pyrites surfaces.

The peptide forming reaction requires a dehydration and condensation mechanism. It can be readily appreciated that this would be highly disfavoured for amino acids in dilute solution. As such, mineral surfaces[3] and concentrated salt solutions (salt induced peptide formation, SIPF[18]) have been postulated and experimentally shown to promote peptide bond formation, especially where these are coupled to wet/dry cycles as is plausible in a putative tidal lagoon on the Hadean Earth. It is noteworthy that the whole field of research into SIPF arose from Monte Carlo computer simulations of the dehydration of sodium chloride solutions, which showed an unsaturated inner hydration shell of sodium ions above 3M concentration.[83]

Mineral induced peptide formation also has a long research track record. Lahav and co-workers experimented on various ways to activate amino acids from the mid-1970's onward.[84] This was then investigated computationally by Loew *et al.* who used QM (non-DFT) methods to look at the effect of these activating molecules (H_3PO_4, H_2SO_4) and included clusters of atoms to represent clay edges ($Al(OH)_4^-$ and $Si(OH)_4$).[85]

Observing the dearth of mechanistic detail in many of the experimental reports on clay mineral and alumina catalysed peptide bond formation, Aquino *et al.* looked at amide bond formation using DFT, choosing to include explicit and implicit water molecules, though approximating the amino acids in terms of the simpler species acetic acid (CH_3CO_2H) and methylamine (CH_3NH_2) as the reactants.[86] The authors extended the earlier studies of Loew *et al.* by exploiting increasing computing power to simulate a variety of Lewis and Brønsted acid sites, including $Al(OH)_3$, $[Al(H_2O)_5]^{3+}$, H^+, H_3O^+, and H_2O and hence calculate activation energies with commensurate thermodynamic outputs. A key conclusion was the importance of Lewis acid sites and the effect of pH, which the authors saw as a challenge for future advances in the field.

Taking forward the seminal experimental work on SIPF of Rode *et al.*,[87] which showed that Cu^{2+} plays a key role in promoting abiotic peptide bond formation in wetting and drying cycles, Rimola *et al.*[88] used DFT simulation methods to determine that the solvated Cu^{2+} cation with explicit water molecules reduces the activation barrier for peptide bond formation for di-glycine from 55 kJ mol^{-1} to 20 kJ mol^{-1} and therefore favoured the forward dehydration reaction for peptide formation.

4.2.2 Reactivity of amino acids in aqueous solution. In addition to the burgeoning literature on prebiotic peptide bond formation at a variety of mineral surfaces, Nair *et al.* employed first principles molecular dynamics to show that activating agents such as carbonyl sulphide (COS) in tandem with nonequilibrium high pressure and temperature conditions just under the critical point for water could also mediate peptide bond formation without needing to invoke additional

mineral surfaces, though this does not fully address the concentration problem discussed.[89] Experimental evidence for such processes had already been offered by Leman *et al.* in the case of COS activation,[90] and Huber and Wächtershaüser for hydrothermal conditions.[20] The authors identified key constraints in this reaction, including:

(i) extreme conditions stabilise the required neutral forms of the reactants and as such enhance potential reactivity under neutral pH conditions;

(ii) high temperatures ensure increased thermal reactivity;

(iii) high pressure water changes the selectivity to a concerted rather than a stepwise reaction pathway.

4.2.3 Chiral selectivity in minerals. A key area where DFT can add insight is that of understanding the specific binding interactions of chiral proto-biomolecules and biomolecules at chiral surfaces in an effort to elucidate where initial asymmetric imbalances may have seeded kinetic resolution processes. One of the earlier studies using DFT, by Yu *et al.*,[91] probed the structures of the enantiomers of a model di-peptide interacting with the interlayer of nontronite, an iron rich clay. The dipeptide of alanine (Ala) was found to exhibit different structures and different binding energies dependent on the enantiomer. The L-Ala-mineral system was shown to be 6 kcal mol^{-1} more stable than the corresponding D-Ala system, with a readily identifiable conformational structural difference between the two enantiomer-mineral systems. The authors report the compatibility of repeating motifs of the clay structures with structural features of the di-peptides. Such motifs have also been identified by Greenwell and Coveney as important in other layered mineral-biomolecule systems.[92]

4.3 Catalytic nature of mineral surfaces

Mathew and Luthey-Schulten used molecular dynamics, as described in Section 4.1.2, to investigate a proposed origins of life scenario involving clay montmorillonite and its catalytic role in forming oligonucleotides from activated nucleotides.[93] Their simulations provide atomic detail of reactant conformation prior to polynucleotide formation, furnishing insight into reported experimental observations by Huang *et al.*[94] The simulations clarify the catalytic role of metal ions, demonstrate that reactions leading to correct linkages take place primarily in the interlayer, and explain the observed sequence selectivity in the elongation of the chain. Mathew *et al.* went further to compare reaction probabilities involving L- and D-chiral forms of the reactants and found enhancement of homochiral over heterochiral products when catalysed by montmorillonite. The simulations confirmed the synthesis of oligonucleotides should proceed in the 3′–5′ direction when intercalated, just as in template directed synthesis in the RNA polymerase. Interestingly, in terms of origins of life studies, Mathew and Luthey-Schulten's simulations reveal increased regioselectivity for 3′–5′ over competing 2′–5′ linkage formation, as well as an overall increased catalytic effect when the reaction takes place in the interlayer.

4.4 The influence of clay minerals on RNA folding

Swadling *et al.* used molecular dynamics to perform large-scale simulations of various RNAs in bulk water and with an aqueous montmorillonite surface.[95] The simulations reported by Swadling *et al.* elucidated a number of facets of nucleic acid-clay interaction and reactivity that have been observed in previous experimental studies and have hitherto remained unexplained at a molecular level. One prevailing theory in origins of life studies is that RNA in prebiotic conditions may have been confined just as functional RNAs are confined in the ribosome of living cells today. Due to the ubiquitous presence of clay minerals and their associated cations in nature, these aqueous environments may have provided prebiotic habitats for nascent nucleic acid polymers. Indeed, clays may thus have played a key role in the formation and preservation of these polymers and/or their precursors. Swadling *et al.*'s simulations show, through detailed analysis of the RNA dynamics, that the behaviour of RNA interacting with these surfaces is significantly different from that in bulk water. More specifically their simulations show strong electrostatic forces act between the clay surface, the RNA and the cations. The simulations revealed divalent cations are more effective in mediating the interaction between surface and RNA than monovalent cations. The electrostatic attraction and tethering of the RNA strand to the surface causes it to be significantly pinned and hence restricted in movement compared to RNA free in bulk water. Moreover the authors found that RNAs fold at a considerably enhanced rate when a montmorillonite surface is present compared to that in bulk water. Such folding is of importance since early RNA polymers would have needed to produce well defined folds to support enzymatic activity in order to catalyse the self-replicating of RNA strands, essential steps of molecular evolution.

4.5 Stability of free and mineral-protected nucleic acids

Although deep ocean hydrothermal vents have generated particular interest as a possible source of the first life forms, there remains the question of how biopolymers such as RNA could have remained intact at the elevated temperatures and pressures around these vents. One possible explanation is that clay-like particles may have acted as structures which supported and protected nucleic acids once formed. Experimentally, it has been shown that alkanes are formed when methanol reacts with smectites such as montmorillonite under conditions similar to those at hydrothermal seafloor vents. Although layered double hydroxides (LDHs) are not as naturally widespread in present times, evidence suggests that during early ages of the Earth, called the Archean era, minerals such as green rust, $[Fe_2^{II}Fe^{III}(OH)_6]Cl{\cdot}H_2O$, may have been much more common due to the lack of oxygen in the atmosphere.[96]

Due to the nanoscale dimensions of the interlayer region of layered double hydroxides (LDHs), the exact conformation of the intercalated DNA is difficult to elucidate experimentally. Thyveetil *et al.* used molecular dynamics techniques performed on supercomputing grids to carry out large scale simulations of double stranded, linear and plasmid DNA up to 480 base pairs in length intercalated within a magnesium-aluminium LDH (see Fig. 3).[96]

Thyveetil *et al.*'s models were found to be in agreement with experimental observations, according to which hydration is a crucial factor in determining the structural stability of DNA.

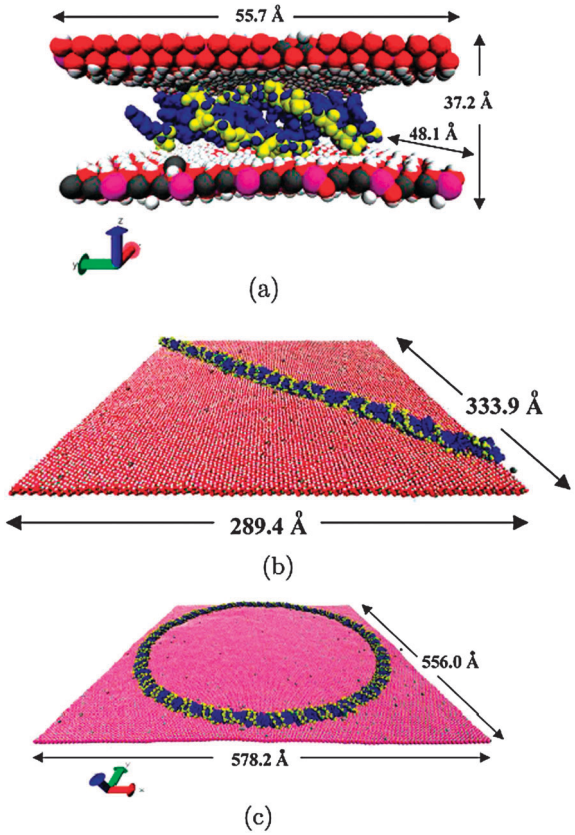

Fig. 3 Visualizations of molecular dynamics simulation snapshots of (a) 12 base-pair DNA intercalated into an LDH; (b) 108bp DNA intercalated into a LDH; (c) 480bp plasmid intercalated into a LDH under ambient conditions (300 K and 1 atm). Magnesium, aluminium, oxygen and hydrogen atoms in the LDH sheets are represented as grey, pink, red and white spheres, respectively. The DNA strand has been coloured yellow to represent the phosphate backbone and blue for the sugar groups and base pairs. Water molecules have not been displayed and only one LDH sheet is visualised for (b) and (c). Figure taken from ref. 96 with permission.

Phosphate backbone groups were shown to align with aluminium lattice positions. At elevated temperatures and pressures, relevant to origins of life studies, some of which maintain that the earliest life forms originated around deep ocean hydrothermal vents (see Section 1), the structural stability of LDH-intercalated DNA is substantially enhanced as compared to DNA in bulk water. Thyveetil *et al.*'s simulations use high temperatures and pressures to observe how the structure and stability of DNA is altered under these conditions when intercalated. The increasing temperature and pressure of the simulations confirmed the DNA is stabilised once intercalated, since the number of Watson–Crick hydrogen bonds rapidly degrades for DNA in bulk water under similar conditions.

In a second set of simulations Swadling *et al.* studied the structural stability of three different nucleic acids intercalated within a magnesium aluminium layered double hydroxide mineral, at varying degrees of hydration, and free in aqueous solution.[97] The nucleotides investigated by Swadling *et al.* were ribonucleic acid (RNA), deoxyribonucleic acid (DNA) and peptide nucleic acid (PNA); see Fig. 4. The simulations show that DNA has enhanced Watson–Crick hydrogen

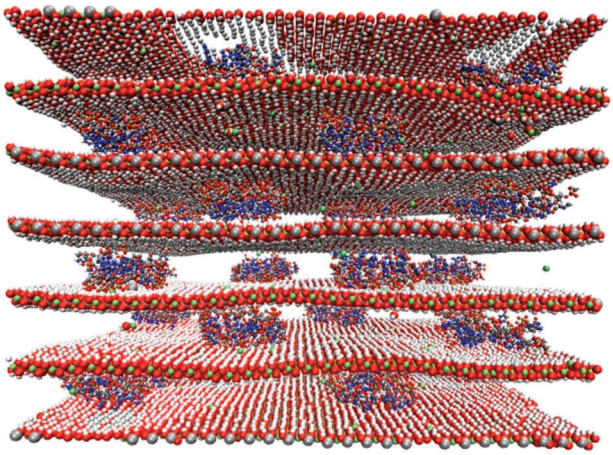

Fig. 4 Mg_2Al LDH intercalated with twenty-four 25mer RNA nucleic acids after 20ns of fully atomistic MD simulation. C, N, O, H, Mg and Al atoms are shown as grey, blue, red, white, green and silver spheres respectively. Reproduced from ref. 97 with permission.

bonding when intercalated within the LDH clay layers compared with intercalated RNA and PNA. The simulations also confirm that hydration plays an important role in determining the structural stability of the three intercalated nucleotides. With regard to Watson–Crick hydrogen bonding, the DNA duplexes retain a greater structural integrity as compared to the intercalated RNA and PNA double strands which manifest significant degradation in base pairing. The uncharged protein backbone of PNA has a detrimental effect on overall stability of the polymer when intercalated as a duplex, as it experiences a greatly reduced electrostatic interaction with the charged layered double hydroxide sheets. The results reported by Swadling *et al.* indicate that a mineral based origin of life may well have been rather different from the aqueous, bulk water based one more commonly considered in origins of life scenarios, DNA being the most stable genetic material in this context. Thus one might conclude that a mineral mediated origin of life may have favoured DNA as the informational storage biomolecule over competing RNA and PNA, providing a driving force for the evolution of biology from the RNA world.

4.6 The role of host layer flexibility in DNA guest intercalation

Another set of simulations performed by Thyveetil *et al.* used the same molecular dynamics techniques to investigate how layered double hydroxides can form staged intermediate structures.[98] These staged intermediates have been observed experimentally, although the mechanism of their formation has not been determined. Thyveetil *et al.* showed that LDHs are flexible enough to corrugate around bulky intercalants such as DNA. The simulations explore three possible intermediate structures that may form during intercalation of DNA into Mg_2Al–LDH and how the models differ energetically. The results showed that when DNA strands are stacked directly on top of each other, the LDH system has a higher potential energy than when they are stacked in a staggered or interstratified manner. The simulations showed that, on average, greater diffusion coefficients arise for DNA strands in the Daumas-Hérold configuration compared to a Rüdorff

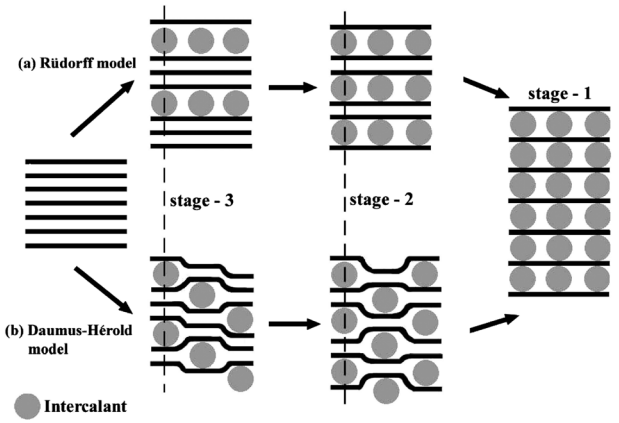

Fig. 5 Schematic representation of the possible pathways by means of which layered materials could intercalate ionic species. LDHs are believed to form stage-2 intermediates through a Rüdorff model (a). More flexible materials such as graphite are believed to follow a Daumas–Hérold pathway (b). Thyveetil *et al.*'s simulations show that Mg_2Al LDHs are able to distort due to the size difference between intercalated DNA and chloride ions, supporting a Daumas–Hérold pathway for intercalation of large biomolecules. The dashed lines indicate similarly staged areas in the two pathways. Figure taken from ref. 98 with permission.

model and Stage-1 structure – Fig. 5 shows a schematic of the various staging structures described.

Peristaltic modes were shown to be more prominent in the Daumas-Hérold structure compared to the Rüdorff and Stage-1 structures and support a mechanism by means of which bulky intercalated molecules such as DNA rapidly diffuse within interlayers.

5 Conclusion

In this review, we have discussed chemical kinetic and molecular modeling approaches that are now throwing very considerable light on numerous challenging issues associated with the origin of life on Earth (and possibly elsewhere in the Universe). The methods available are powerful and wide ranging. They span a host of length and time scales, from the quantum mechanical description of electron dynamics, through the atomistic and molecular levels which are described most often by classical (Newtonian) mechanics, to more mesoscopic and macroscopic levels which represent the collective kinetic behaviour of much larger assemblies of reacting and self-reproducing molecules. As the field continues to gain respectability from within the scientific establishment, we anticipate stronger interactions between such theoretical approaches and related experimental research which can only serve to underpin further advances in our understanding of the momentous events which took place at the dawn of life on Earth.

One area where modelling has become an accepted approach to prebiotic chemistry, and has registered some of its greatest plaudits, is within kinetic modelling of processes such as symmetry breaking, vesicle formation and the origin of the RNA world. The kinetics of such processes are inherently complex and not readily amenable to simple explanations based on reductionist accounts. Kinetic models have illustrated that, for example, small excesses of one enantiomer coupled to chiral amplification feedback loops can result in homochirality arising on time scales far shorter than previously assumed, obviating the need for unfavourable chiral selectivity processes to operate on massively extended temporal scales.

The intrinsic value of modelling approaches cannot be overestimated. Research by numerous experimental groups has shown that many reactions of interest to prebiotic chemists involve reactions between disordered pairs, or groups, of reactant molecules at ordered mineral catalytic surfaces. Such reactions are not amenable to direct chemical or physical analysis, not least as some occur within nanopore or micropore environments deep within the catalytic mineral host. Here, simulations using computational chemistry methodology add insight into, amongst others, peptide bond formation mechanisms and energetics at clay surfaces; carbon monoxide polymerisation at iron sulphide systems; the properties of RNA within clay interlayers; and stability and folding kinetics of nucleic acids at clay surfaces. At present there is something of a discontinuity between the detailed quantum chemical studies of amino acid activation and peptide formation on mineral interfaces and the large-scale molecular simulation of mineral-nucleic acid systems.

Recent advances in computational power have resulted in the large-scale simulation of ever more complex chemical systems. Such simulations have not only added insight to experimental work, but they also inform new directions of study. The recent work by Coveney and co-workers illustrates the potential of charged mineral surfaces to radically alter the kinetics of physico-chemical processes such as nucleic acid folding, which are likely to prove important in future years in underpinning research into one of the great challenges in prebiotic chemistry, namely to identify where and when genetic information first became an important discriminator, and the march of Darwinian evolution began its relentless advance.[95] With increasingly powerful computational resources, and increasingly sophisticated large-scale e-infrastructure environments, simulations will grow in their capacity to address fundamental scientific questions in the prebiotic chemistry domain.

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