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From underwear to non-equilibrium thermodynamics: physical chemistry informs the origin of life

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Children learn that all living things come from other living things ('*Omne vivum ex vivo*'). But this dictum is misleading: at some point, life must have arisen from non-living matter. Indeed, the idea that life could be spontaneously generated under ordinary conditions was seriously investigated in past centuries. For example:[1]

''If you press a piece of underwear soiled with sweat together with some wheat in an open mouth jar, after about 21 days the odor changes and the ferment, coming out of the underwear and penetrating through the husks of wheat, changes the wheat into mice''.

The author of this statement was in fact a historically important figure in physical chemistry, Jan Baptista van Helmont (1580–1644). This Belgian chemist aided the transition from alchemy to chemistry in several ways, including realizing that air is composed of several gases and coining the term 'gas' (from *chaos*).[2] While his interpretation that mice were spontaneously generated in the jar was erroneous, van Helmont, who believed strongly in experimentation at a time when the scientific revolution was just taking hold, did outline a testable synthetic scheme for life. The idea that life could be made from non-living matter was actually controversial, as many scientists believed in a 'vital force' that only biological matter possessed. However, the quest to synthesize molecules of life from inorganic compounds later inspired Friedrich Wöhler to synthesize urea in 1828, thus disproving vitalism.

For a while, studies of the origin of life were largely dominated by the discipline of organic chemistry, from which such champions of the field as Albert Eschenmoser and Stanley Miller hailed. The perspective that the origin of life is an organic synthesis problem is embodied in this contemporary monologue:

''You see this? This is you. I'm serious! Right here, life is about to form on this planet for the very first time. A group of amino acids are about to combine to form the first protein – the building blocks of what you call 'life'. Strange, isn't it? Everything you know, your entire civilization, it all begins right here in this little pond of goo''.

The omnipotent alien Q (*Star Trek: The Next Generation*[3]) thus invokes Darwin's 'warm little pond', an incubator for organic molecules on the primitive Earth. Indeed, an important line of work has been the development of abiotic syntheses of organic compounds under conditions thought to mimic the early Earth. Approaching from the other direction are analytical chemists, who have shown that meteoritic samples, among others, do contain various organic compounds associated with known life, strongly suggesting that they were present in the early solar system.[4] As the field has grown, scientists from disciplines outside chemistry have been drawn in as well, from astronomers hunting for exoplanets to biologists resurrecting ancient proteins. Physical chemistry in particular is uniquely important, because lessons learned about the fundamental nature of molecular mechanisms provide a bridge from work in specific model systems to other possible molecular systems.

The articles in this special issue illustrate the growing importance of physical chemistry in addressing major issues for our understanding of the origin of life. If life is defined as a self-sustained chemical system capable of undergoing Darwinian evolution (NASA's working definition[5]), then the synthesis of self-replicating molecular systems is crucial. We know of only one independent example of such an origin of life, in which, roughly speaking, DNA carries genetic material, proteins act as enzymes, and RNA carries messages between them. But what other chemistries might work as the basis for living systems?

A first question concerns the properties of the building blocks of life. Much attention focuses on nucleic acids, because ribonucleic acid (RNA) in particular is believed to be the foundation for our origin of life. Many features of biology, such as the centrality of ATP in metabolism, appear to harken back to a simpler

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version of life that was based on RNA (the 'RNA World', as named by Walter Gilbert commenting on the discovery of catalytic RNA[6]). Regardless of whether an RNA World indeed existed, the fact that RNA can serve as both genetic material (*e.g.*, the retroviruses) and as catalysts for chemical reactions (*i.e.*, ribozymes) indicates that RNA could be the basis for a kind of simple life. But is RNA unusual, or could other life conceivably be based on other (xeno-) nucleic acids, perhaps having different nucleobases? Seven articles in this issue focus on expanding our view of genetic polymers, from two perspectives: understanding the physical stability of the canonical nucleobases *vs.* alternatives (Brister *et al.*, DOI: 10.1039/C6CP00639F; Pino *et al.*, DOI: 10.1039/C6CP01345G; Yu *et al.*, DOI: 10.1039/C6CP01790H; Marchetti *et al.*, DOI: 10.1039/C6CP00165C; and Nguyen *et al.*, DOI: 10.1039/C6CP01559J) and testing the potential of alternative building blocks to form supramolecular assemblies (Li *et al.*, DOI: 10.1039/C6CP03047E) or even polymers (Mungi *et al.*, DOI: 10.1039/C6CP03047E) under relatively gentle conditions.

The nucleic acids are one part of the puzzle, but a second issue is that the environment must also be conducive to the chemical mechanisms leading to life. Further expanding our view of plausible environments are six studies in this issue. Akoopie *et al.* (DOI: 10.1039/C6CP00672H) and La Cruz *et al.* (DOI: 10.1039/C6CP00836D) examine environmental conditions that could enable chemical activation through phosphorylation. McGuire *et al.* (DOI: 10.1039/C6CP00632A) turn our view outward to find interstellar ices that could provide what many consider to be a prerequisite for life: water. Belmonte *et al.* (DOI: 10.1039/C6CP00608F) study the consequences of the specific composition of seawater, and Chatterjee (DOI: 10.1039/C6CP00550K) considers possible chemistry at hydrothermal impact crater lakes. Even water is not a given, however; Bada *et al.* (DOI: 10.1039/C6CP03290G) analyze the suggestion that formamide might be an alternative solvent to water.

A third major issue for research on the origin of life is a question that is often the elephant in the room: how would early life escape equilibrium? To maintain life, the system must be open, accepting energetic input constantly or periodically, to be driven away from chemical equilibrium. Our current understanding of this critical issue is quite poor. Many experimentalists rely on chemical activation of substrates in a separate reaction. In this issue, three articles address this thorny physical problem. Rapf *et al.* (DOI: 10.1039/C6CP00980H) review work on the idea that organic synthesis could be driven by sunlight, storing solar energy in chemical bonds. Keil *et al.* (DOI: 10.1039/C6CP00577B) and Göppel *et al.* (DOI: 10.1039/C6CP01034B) study how the non-equilibrium environment of thermal gradients could drive molecular evolution.

Finally, physical chemistry plays a crucial role in addressing questions of mechanisms. Four articles address various parts of this issue (Jeilani *et al.*, DOI: 10.1039/C6CP02686A; Nhlabatsi *et al.*, DOI: 10.1039/C5CP07124K; Šponer *et al.*, DOI: 10.1039/C6CP01391K; and Raggi *et al.*, DOI: 10.1039/C6CP00793G). It is worth noting that several articles use very high level theoretical simulation (Göppel *et al.*, Marchetti *et al.*, Jeilani *et al.*, and Nguyen *et al.*, Nhlabatsi *et al.*, Belmonte *et al.*). Not only is computation sometimes faster than experimentation, but simulations can also verify our understanding of experimental results. As Feynman wrote, 'What I cannot create, I cannot understand', we might also suggest that 'What I cannot simulate, I cannot understand'. Šponer *et al.* (DOI: 10.1039/C6CP00670A) step back to review the role of simulations in the field, focusing on nucleic acids.

The study of the origin of life has endured its share of growing pains; the related field of exobiology was famously derided as a 'science without a subject' by prominent paleontologist George Gaylord Simpson in the 1960s. But science has never been constrained to study only that which exists. Scientists also wonder what is possible. Understanding the rules of the game of life under the conditions of an early Earth (or an exoplanet) may help us model those possibilities. Conversely, testing such models against real systems, such as the chemical properties of today's biomolecules, may help constrain possible prebiotic conditions. Physical chemistry has a central role to play in evaluating possibilities for how life could begin and whether life might exist elsewhere.

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