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The challenge of synthetic biology. Synthetic Darwinism and the aperiodic crystal structure

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'Grand Challenges' offer ways to discover flaws in existing theory without first needing to guess what those flaws are. Our grand challenge here is to reproduce the Darwinism of terran biology, but on molecular platforms different from standard DNA. Access to Darwinism distinguishes the living from the non-living state. However, theory suggests that any biopolymer able to support Darwinism must (a) be able to form Schrödinger's 'aperiodic crystal', where different molecular components pack into a single crystal lattice, and (b) have a polyelectrolyte backbone. In 1953, the descriptive biology of Watson and Crick suggested DNA met Schrödinger's criertion, forming a linear crystal with geometrically similar building blocks supported on a polyelectrolye backbone. At the center of genetics were nucleobase pairs that fit into that crystal lattice by having both size complementarity and hydrogen bonding complementarity to enforce a constant geometry. This review covers experiments that show that by adhering to these two structural rules, the aperiodic crystal structure is maintained in DNA having 6 (or more) components. Further, this molecular system is shown to support Darwinism. Together with a deeper understanding of the role played in crystal formation by the poly-charged backbone and the intervening scaffolding, these results define how we might search for Darwinism, and therefore life, on Mars, Europa, Enceladus, and other watery lagoons in our Solar System.

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Introduction

No detail of chemistry has transfixed the public more than the double helix for DNA, proposed by Watson and Crick 65 years ago [1••]. Today, the double helix is considered elegant enough for public sculptures,[1] novel covers[2] and wearable jewelry.[3] Indeed, given its familiar elegance, many in the community think that DNA may be the *best* way to store and transmit molecular information. Star Trek aliens have DNA. NASA missions seek extraterrestrial DNA. Microsoft plans to use DNA to replace silicon-based information storage [2•].

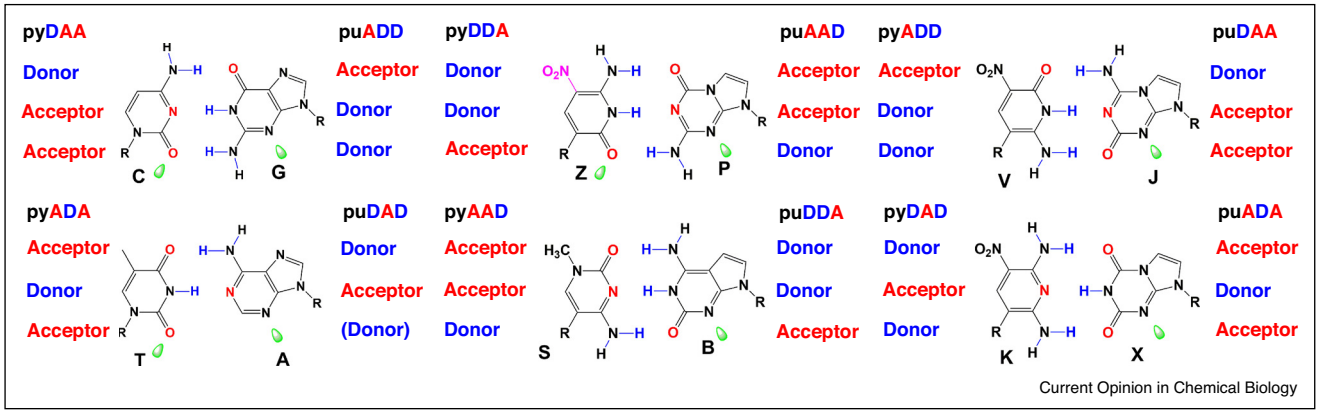
In 1953, however, the double helix had little experimental support. It was accepted nevertheless, in part because it offered an elegant shortcut connecting molecules to heredity. In doing so, it filled a gap in Darwinian biology, which lacked an explanation of heredity [3••]. Elegance came from the simplicity of the Watson–Crick pair, which had just two rules of complementarity: firstly, size, large purines pairing with small pyrimidines, and secondly, hydrogen bonding, hydrogen bond donors on one nucleobase pairing with acceptors on the other. Paper cut-outs illustrated the idea, making chemistry seem unnecessary to do 'molecular' biology.

The model had, of course, been pre-validated by Erwin Chargaff, who found that the A:T and G:C ratios were 1:1. This was not, however, central to the thinking of Watson and Crick. Indeed, they had been ignorant of this (and other) details of nucleic acid chemistry [4•], using, for example, the wrong tautomer for guanine (Figure 2). This mistake was pointed out to them by Jerry Donahue, who was visiting from the laboratory of Linus Pauling.[4]

What impressed Watson and Crick was the similar geometry of the A:T and G:C pairs. They immediately remarked that this similarity allowed information in DNA to be stored as an 'aperiodic crystal' [5••]. Aperiodic crystals had been proposed a decade earlier by physicist Erwin Schrödinger as the only way to transmit information with the needed fidelity.

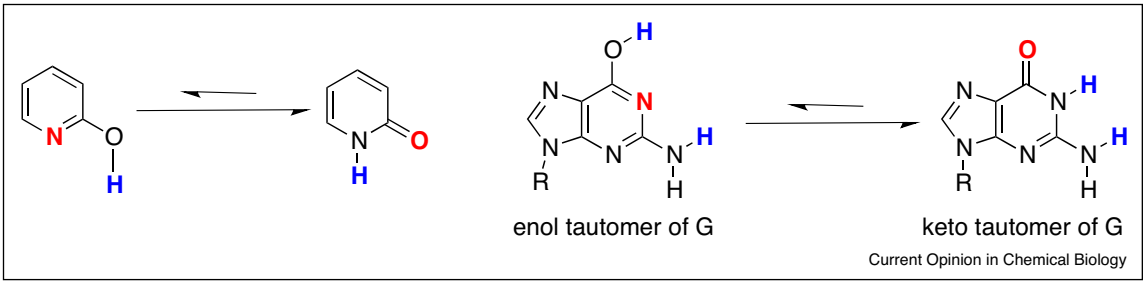
[1] Jencks C: **DNA Double Helix sculpture by in Clare College Memorial Court**. http://clareconferencing.com/news/artwork-at-clare/, 2017.
[2] David P: **Double Helix. Double or Nothing**, NY Simon & Schuster. 1999.
[3] Geek: http://www.thinkgeek.com/product/ee02/, 2017.
[4] Watson and Crick offered Jerry Donohue coauthorship in the paper, which he declined, thinking his contribution too basic. Their acknowledgement ("We thank Jerry Donohue for constant advice and criticism, especially on interatomic distances.") suggests that they might not have appreciated exactly the import of his advice.

Figure 1



'Accepted' theory suggested that rearranging hydrogen bonding donor and acceptor groups on nucleobases will give new pairs, all joined by three hydrogen bonds, all still fitting the aperiodic crystal structure required for Darwinism. Once synthesized, these do 'simple' things, including sequence-specific molecular recognition, transcription, and translation to give proteins with extra amino acids. But can they support 'complex' Darwinism?

Figure 2



(**Left**) The archetypal problem of tautomerism in heterocyclic chemistry, interconverting the enol tautomer (pyridine-2-ol) to the more stable (in water) keto tautomer (pyridine-2-one). (**Right**) The tautomerism of guanosine that so confused James Watson. The enol tautomer, shown in a textbook by Davidson that was widely used in its day, is considerably less stable than the keto tautomer. Donohue, trained by Linus Pauling, pointed out that the keto tautomer dominates perhaps 10000:1 in aqueous solution.

Schrödinger was also no chemist; he did not propose a chemical substance that could actually form an aperiodic crystal. But he realized that millions, if not billions, of 'bytes' must be transferred faithfully for biology to exist. He also knew that simple binding could not allow that fidelity. Schrödinger needed the physics of the phase transition to get that fidelity, known to chemists in the sharp melting points of (very) pure organic crystals.[5]

But pure crystals hold no information. To get information into a crystal, Schrödinger required that different molecular species of (essentially) the same size fit within a crystal lattice. Crick (a physicist) and Watson (an ornithologist) immediately realized that their double helix allowed for this. A:T pair could be exchanged with T:A, G:C, and C:G, without changing the packing of the one-dimensional crystal. By analogy with organic crystals, phase transitions in double helices are called 'melting'; a perfectly matched duplex has a sharp 'melting point'.

Thus, DNA is not special because A binds T and G binds C. Binding is seen throughout chemistry. Nor is DNA special because it stores information. Many biopolymers do; proteins are examples. No, the special property of DNA, the property key for biology, is the ability to support Darwinism. This ability comes from the ability of an aperiodic crystal to be replicated with only a few errors. The errors fit into the aperiodic crystal, meaning that they too can be replicated with few errors, allowing 'fitter' information to emerge. Replication with errors, where the errors are themselves replicable, with selection for fitness, *is* Darwinism.

Synthesis and the grand challenge: create an artificial Darwinian system

'Elegance', 'obviousness', and 'accepted theory' can, however, cause scientists to overlook peculiarities that,

[5] Students remember that their grade in organic chemistry la depended on the sharpness of their melting point.