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Yin and Yang: Polypeptide and Polynucleotide

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Two biopolymers have come to dominate the enzymatic and encoding machinery of contemporary life: polypeptides and polynucleotides. These molecules both exhibit exquisitely well-adapted self-assembly characteristics, albeit employing orthogonal self-assembly strategies. In contemporary life, the ribosome enables the flow of information between these two divergent, yet correlated biopolymers. This review discusses the relationship between these two biopolymers, with a focus on the early evolution of the ribosome.

Charles Darwin famously observed [1] that "…from so simple a beginning, endless forms most beautiful and most wonderful have been, and are being, evolved". We now know that biodiversity on earth waxes and wanes. Forms are being evolved and forms are being extinguished, but not at steady state. The Cambrian explosion, around 540 million years ago, marked a relatively rapid increase in diversity. Cataclysms, especially the Permian–Triassic (251 Mya) and Cretaceous–Paleogene (65 Mya) extinctions, diminished diversity.

Life is Simple. If one looks at molecules, Darwin's breadth of diversity is seen to be illusory. Forms are not endless, and they have remained essentially constant over the last few billion years of evolution. Early biology narrowed the diversity of molecules, rather than escalating it. Chemical complexity, integrated over all biological systems on earth, is lower than the diversity of even a small confined abiotic system such as a chondritic meteorite [2,3] or one of Stanley Miller's spark discharge experiments [4]. On the level of biopolymers, diversity is even more withered. Just two polymer backbones, polynucleotide (DNA/RNA) and polypeptide (protein), dominate life and are universal to it. The unparalleled self-assembly properties of polynucleotides and polypeptides have driven competing polymers [5] from the biosphere.
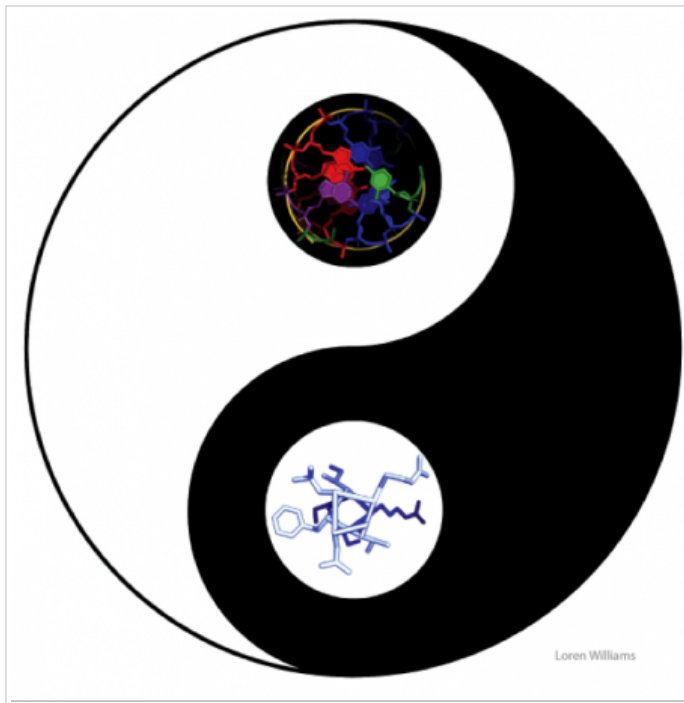
Figure 1. Polypeptide and polynucleotide polymers are the Yin and the Yang of biological structure. Both polymers are masters of self-assembly. Polynucleotides (top) assemble predominantly by sidechain-sidechain interactions to form helices with internally directed sidechains. Polypeptides (bottom) assemble predominantly by backbone-backbone interactions to form α-helices and β-sheets, with externally directed sidechains.

Why two polymer backbones? Why not one, or three? What are the distinguishing features of our biopolymers? These two form a Yin and a Yang of biomolecular structure (Figure 1). The assembly scheme used by polynucleotides is the direct converse of the scheme used by polypeptides. Polynucleotides are polypeptides through the looking glass, and vice versa.
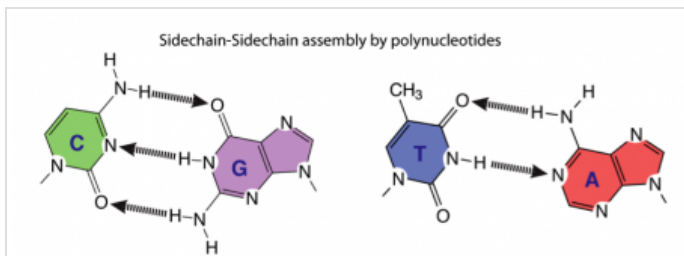

Figure 2. Polynucleotides self-assemble by sidechain-sidechain interactions (base pairing) to form helical structures. Hydrogen bonds are indicated by dashed arrows.
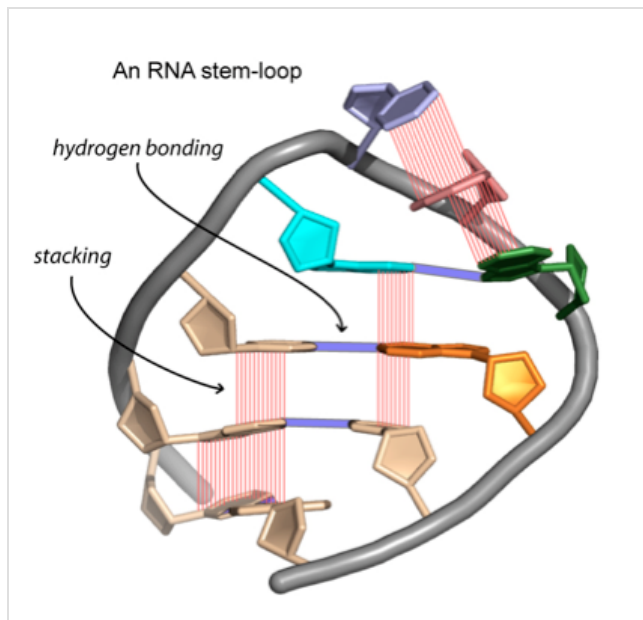
Figure 3. Stacking interactions and hydrogen bonds between sidechains (bases) stabilize an RNA stem-loop. The backbone is on the outside of the assembly. The bases are in the core.

Polynucleotides assemble by hydrogen bonding interactions between sidechains (i.e., between bases, Figure 2). The backbone is self-repulsive, and is on the outside of the sidechain core, exposed to the aqueous environment (Figure 3). In Watson-Crick pairing between bases [6], the spatial arrangement of hydrogen bond donors/acceptors of cytosine is complementary to that of guanine. Adenine is complementary to thymine/uracil. The planarities of the nucleotide bases are also critical to their assembly. Base-base stacking (Figure 3) is at least as important to stability as base pairing [7,8]. RNA is more complex than DNA, with many 'non- canonical' base pairs.
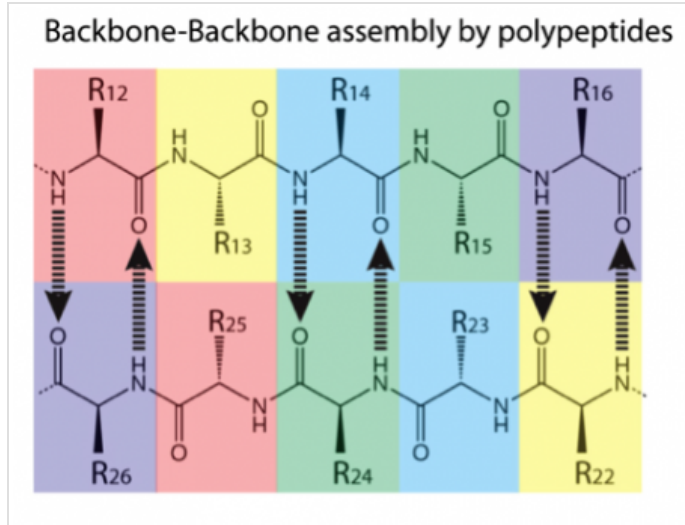

Figure 4. Polypeptides self-assemble by backbone-backbone interactions to form β-sheets and α-helices (not shown). Side-chains are indicated by R12, R13, etc. H-bonds are indicated by dashed arrows.

Polypeptides assemble by hydrogen bonding interactions between atoms of the backbone (Figure 4). The polypeptide backbone is self-complementary and cohesive, with appropriately spaced hydrogen bonding donors and acceptors. The self-complementarity of polypeptide applies in both α-helices or β-sheets, which are the dominant assembly elements of folded proteins. For both α-helices and β-sheets, all hydrogen bonding donors and acceptors are satisfied and the sidechains are directed outwards, away from the backbone core. Therefore, the polypeptide backbone contains an inherent switch: helices and sheets can interconvert.

We can ask if biology as we know it requires exactly two converse types of dominating biopolymers, a Yin and a Yang of self-assembly (Figure 1). I would say yes. The functional polypeptide and the informational polynucleotide gave

rise to each other in an extravagant dance of co-evolution. There was no RNA World, as conventionally described [9], in my view. These polar opposite polymers are interconnected and interdependent in their deepest evolutionary roots. The distinctive and necessary functions of biology's two dominant polymers are directly indicated by their schemes of self-assembly. As expressed by Watson and Crick [6], "[…] the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material." The folded structures of fibrous and globular proteins, which are composed primarily of α-helices and β-sheets, similarly signal their functions.

Translation and the Ribosome. In translation, information is transduced from polynucleotide to polypeptide. During translation, the Yin of biology connects directly with the Yang. Since the assembly principles of these two polymers are converses of each other (sidechain-sidechain versus backbone-backbone), an elaborate process of indirect templating is required for the transduction process. The macromolecular assemblies of translation, composed of both polynucleotide and polypeptide, perform this task, and in doing so, define life and distinguish life from non-life.

The ribosome is composed of a small subunit (SSU) that decodes the message and a large subunit (LSU) that catalyzes peptidyl transfer. The ribosome and translation are some of our most direct connections to the deep evolutionary past [16,18-20] and to the origin of life. This coterie of macromolecules and ions is the best preserved of life's ancient molecular machines, and it is composed of primordial, frozen polymer backbones, sequences, and assemblies.

The Cooption Model of Ribosomal Evolution. The most widely accepted model of ribosomal evolution is the "cooption model" [16,20,21]. In this model, (a) ancestors of the SSU and LSU originated and evolved independently of each other, with autonomous functionalities, (b) an ancestor of the LSU, incompetent for assembly with the SSU, contained the PTC (Peptidyl Transferase Center), and catalyzed non-coded production of heterogeneous oligomers of peptides, esters, thioesters, and potentially other polymers [22], © an ancestor of the SSU had a function that was more tentative but may have involved RNA polymerization, (d) some of the non-coded oligomer products of the PTC bound to the nascent LSU, conferring advantage, (e) ancestral LSU and SSU functions linked, in a cooption process, enabling coded protein synthesis, and (f) the non-coded oligomers of synthesized polymers associated with the ancestral LSU fossilized into the tails of ribosomal proteins that penetrate deep within the extant LSU. In the cooption model, and other models of ribosomal evolution, changes over evolution are restricted to those that maintain PTC and decoding structure and function. The catalytic core of the LSU, and the decoding center of the SSU, are frozen assemblies that predate the cooperative relationship between LSU and the SSU.

An Ancient "Enzyme." The translation machinery catalyzes condensation, one of biology's oldest and most enduring chemical transformations [23]. Two amino acids are joined, forming a peptide bond and releasing a water molecule, in an ancient chemical transformation that predates biology. If one strips away or overrides more modern translational components such as the aminoacyl tRNA synthetases and the small ribosomal subunit, the catalytic core of the ribosome, the PTC, is seen to display all the hallmarks of an ancient enzyme. Here, the word "enzyme" is intended to denote a biological catalyst and does not imply it was made of protein. The extant PTC retains a capability for non-specific condensation. It is a crude entropy trap [24] that, unlike modern enzymes, is incapable of specifically stabilizing a transition state [25]. The PTC has retained the ability to form a wide variety of condensation products including peptides, esters, thioesters, etc. [26-33]. The ancestral PTC was a "sausage maker," producing a non-coded mixture of short heterogeneous oligomers by condensation.

Resisting Change. Life, at its biochemical essence, is the most resilient and robust chemical system in the known universe. Small-molecule metabolites, polymer backbones, chemical transformations and complex biochemical systems that we observe in the biological world today are traceable to early biotic and even prebiotic chemical systems [10-17]. Many of the molecules and processes of life are deeply frozen, and have remained invariant over vast timescales. On a chemical level, the biological world around us contains "living fossils" that are easily over 3 billion years old. We conceptually partition these into molecular fossils (amino acids, polypeptides, base pairs, nucleosides, phosphates, polynucleotides, iron-sulfur centers, and some polymer sequences) and process fossils (condensation, hydrolysis, phosphorylation,

translation, and gluconeogenesis).

Extant life allows us to infer molecules, pathways, structures, and assemblies of ancient life. Life maintains its own history and can teach us that history. Mining the molecular and process fossils of life is one of our best approaches to understanding ancient biology and the origin of life.
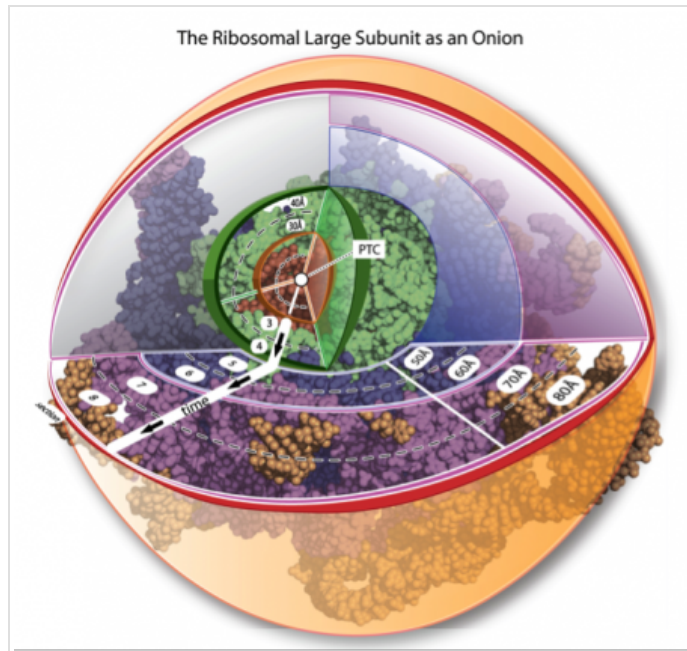

Figure 5. The ribosome as onion. The H. marismortui LSU was carved into concentric shells, with the origin at the site of peptidyl transfer. The 23S rRNA is red in the central shells (1 and 2), green in shells 3 and 4, blue in shells 5 and 6, and purple in shells 7 and 8. More remote shells are shown in orange. Atoms are represented in spacefill. Ribosomal proteins, ions and water molecules are omitted for clarity. The oldest RNA is at the center of the onion.

A Molecular Time Machine. Important information about the ribosome has been revealed by high-resolution, three-dimensional structures from disparate regions of the evolutionary tree [34-39]. We created a molecular time machine by computationally carving the LSU into an onion (Figure 5), with the PTC at the core [19]. We approximate the process of ribosomal evolution as accretion of shells of the onion. One can walk backwards or forwards in time, by moving from shell to shell in the onion. The oldest part of the ribosomal onion is the center (the PTC).
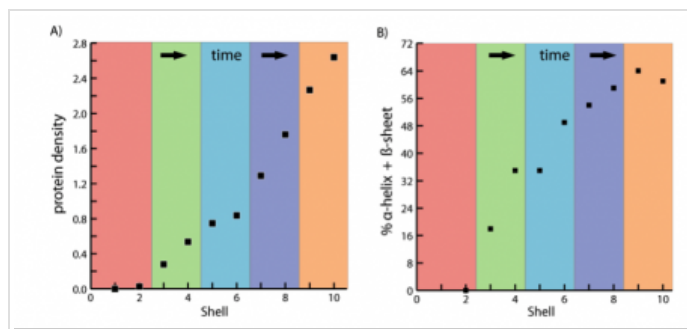

Figure 6. A) The center of the onion is older than protein. Ribosomal protein density increases with distance from the PTC. Ribosomal protein density is given by the number of amino acids normalized to the number of nucleotides. B) The oldest protein segments predate canonical protein folding. Ribosomal protein segments near the core of the onion are infrequently form canonical secondary structure (α-helices and β-sheets). The fraction of protein in involved in canonical secondary structure increases with distance from the PTC. The color-coding on the graphs corresponds to that on the ribosomal onion in Figure 5.

The ribosomal onion provides a detailed and self-consistent story of ancient biological transitions. The density of ribosomal proteins is low in the center of the onion and is high in the outer shells (Figure 6A). Thus, the ribosome contains a record of the introduction and incorporation of coded protein into biology, and the development of the DNA/RNA/Protein World. Ribosomal protein segments near the center of the onion are in unusual 'non-canonical'

conformations, but in the outer shells of the onion are folded into conventional globular forms composed of α-helices and β-sheets (Figure 6B). The ribosome recorded the history of the protein folding.

The ribosome as onion is a device for collecting and interpreting a massive amount of detailed information on ancient biochemistry. Here we have touched on the introduction of polypeptides to biology and on development of folded proteins. The ribosome is a rich repository of diverse information for those interested in ancient evolutionary processes and the origin of life.

Summary. Biochemistry is commonly taught as isolated facts, structures and reactions, taken out of their explanatory context. A reasonable understanding of the deepest and broadest questions in biology requires an integrated approach. Protein structure can be understood only in the context of DNA/RNA structure, and vice versa. The converse relationship of polypeptide to polynucleotide assembly is only clear by comparison, and directly informs our understanding of form, function and evolution. The current poor state of integration in biochemistry is illustrated in modern textbooks, which generally continue to propagate the organization scheme of Lehninger's first biochemistry textbook (1975). Protein structure is taught as irrelevant to and fully disconnected from nucleic acid structure.

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