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Digital and Analog Chemical Evolution

JAY T. GOODWIN, ANIL K. MEHTA, AND DAVID G. LYNN*

Center for Fundamental and Applied Molecular Evolution, NSF/NASA Center for Chemical Evolution, Departments of Chemistry and Biology, Emory University, Atlanta, Georgia, United States

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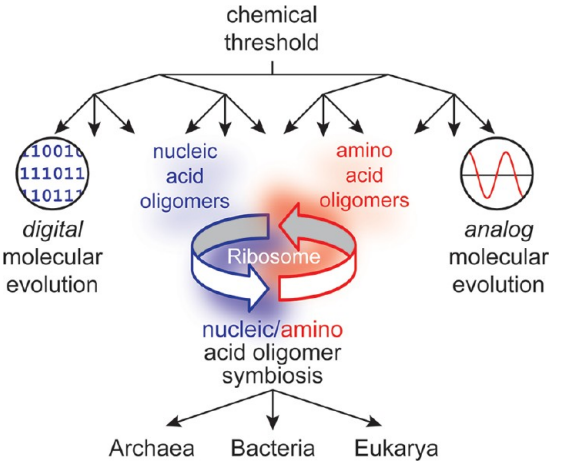
CONSPECTUS

Living matter is the most elaborate, elegant, and complex hierarchical material known and is consequently the natural target for an ever-expanding scientific and technological effort to unlock and deconvolute its marvelous forms and functions. Our current understanding suggests that biological materials are derived from a bottom-up process, a spontaneous emergence of molecular networks in the course of chemical evolution. Polymer cooperation, so beautifully manifested in the ribosome, appeared in these dynamic networks, and the special physicochemical properties of the nucleic and amino acid polymers made possible the critical threshold for the emergence of extant cellular life.



These properties include the precise and geometrically discrete hydrogen bonding patterns that dominate the complementary interactions of nucleic acid base-pairing that guide replication and ensure replication fidelity. In contrast, complex and highly context-dependent sets of intra- and intermolecular interactions guide protein folding. These diverse interactions allow the more analog environmental chemical potential fluctuations to dictate conformational template-directed propagation. When these two different strategies converged in the remarkable synergistic ribonucleoprotein that is the ribosome, this resulting molecular digital-to-analog converter achieved the capacity for both persistent information storage and adaptive responses to an ever-changing environment.

The ancestral chemical networks that preceded the Central Dogma of Earth's biology must reflect the dynamic chemical evolutionary landscapes that allowed for selection, propagation, and diversification and ultimately the demarcation and specialization of function that modern biopolymers manifest. Not only should modern biopolymers contain molecular fossils of this earlier age, but it should be possible to use this information to reinvent these dynamic functional networks. In this Account, we review the first dynamic network created by modification of a nucleic acid backbone and show how it has exploited the digital-like base pairing for reversible polymer construction and information transfer. We further review how these lessons have been extended to the complex folding landscapes of templated peptide assembly. These insights have allowed for the construction of molecular hybrids of each biopolymer class and made possible the reimagining of chemical evolution.

Such elaboration of biopolymer chimeras has already led to applications in therapeutics and diagnostics, to the construction of novel nanostructured materials, and toward orthogonal biochemical pathways that expand the evolution of existing biochemical systems. The ability to look beyond the primordial emergence of the ribosome may allow us to better define the origins of chemical evolution, to extend its horizons beyond the biology of today and ask whether evolution is an inherent property of matter unbounded by physical limitations imposed by our planet's diverse environments.

Introduction

Biology is a marvelously dynamic cooperative built on complex chemical networks. First described more than 50 years ago as the Central Dogma,[1] biopolymer specialization and collaboration underpins a diverse and interdependent chemical system where proteins and nucleic acids cooperate to optimize for the continuous capture, mutation, selection, and propagation of structural forms and replicative success. Environmental fluctuations (physical and chemical gradients) drive the selection of specific nucleic acid sequences, and these

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purine/pyrimidine pairings are translated into the more conformationally diverse and environmentally responsive proteins through the ribosome. This universal ribonucleoprotein is itself a cooperative multicomponent supramolecular assembly, containing 3−4 RNA subunits and more than 70 ribosomal proteins,[2] and is the manifestation of a coevolutionary event that coordinated the special properties of two distinct biopolymer classes as a mutualistic symbiosis.[3] The emergence of such remarkable biopolymer collaboration indeed seeded the evolutionary radiation of the three biological domains, Bacteria, Archaea, and Eukarya, serving as a Darwinian Threshold for cellular life.[4] But evidence for cellular forms may extend almost a billion years before the emergence of the ribosome,[5,6] raising questions as to how connections between the rich chemical and physical gradients of the environment and digital strategies for chemical information processing may have appeared.

Chemical evolution strategies currently exist for both the digital molecular information inherent in nucleic acids and the more analog molecular information embodied in the recently recognized infectious prion proteins.[7] In the simplest cases of viral evolution (Figure 1A), structural information is encoded as linear sequences of nucleobases that are replicated in high fidelity by discrete and canonical hydrogen-bonding associations. This base-pairing interaction dominates all other conformations, and diversity is achieved through host-resourced copying errors. In the epigenetic prion strategy (Figure 1B), a cross-β architecture,[8−10] containing stacks of H-bonded peptide β-sheets, provides the template for replication, and diversity is generated at the level of protein conformation. Protein folding and assembly are modulated by integration of a myriad of context-dependent physicochemical forces, including van der Waals, ionic, aromatic, and hydrogen-bonding interactions presented by the amino acid side chains and polyamide backbone, and the cross-β form is acutely responsive to such continuously variable properties.[11] While cross-β templated propagation is now widely recognized in infectious protein diseases, where different strains can spread within and across traditional species barriers,[12−14] cross-β partitioning is non-Mendelian. The phenotype, as mediated by the assembled structure, is reversible, and conformational diversity is controlled by many strongly context-dependent physicochemical interactions that direct protein folding, following a pattern most analogous to an analog response.

In this Account, we argue that this molecular digital-to-analog converter (DAC) function of the ribosome, uniting separate biopolymer species, emerged from a unification of the two basic strategies outlined in Figure 1. Any chemical network from which the ribosome emerged must have been composed of a diverse population of functional polymer scaffolds, and likewise, the archeological signatures for these diverse ancestral networks must remain in extant biopolymers. Therefore, structural hybrids can now be constructed from existing nucleic acid and cross-β protein biopolymers to reconstitute such functional chemical networks. The design of these materials can benefit greatly from our growing understanding of biopolymer function and an expanding repertoire of methods capable of structural analysis of ordered supramolecular assemblies. Accordingly, we review both the construction of such biopolymer chimeras and the analysis of their structural and chemical behaviors in light of the requirements for chemical evolution.

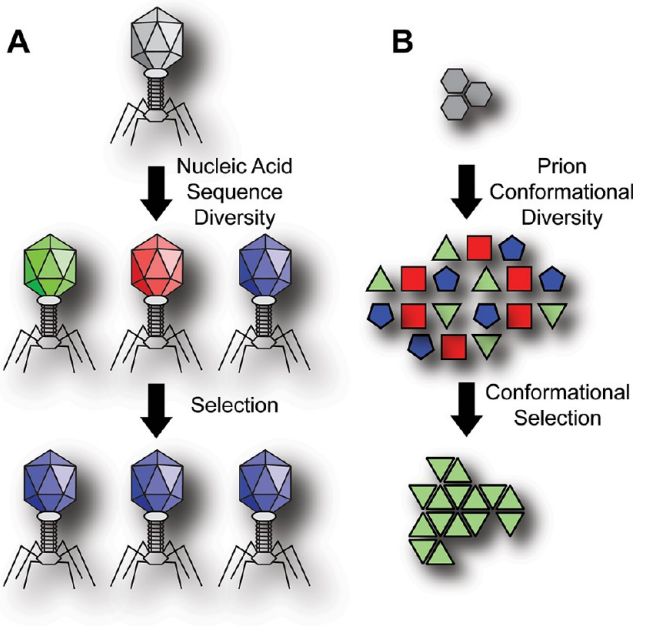

FIGURE 1. In the propagation of chemical information, viral evolution (A) is nucleic acid sequence dependent and therefore digital, whereas prion evolution (B) is dependent on protein conformation and more analog in its behavior. Colors indicate distinct species resulting from mutation in DNA sequence or change in protein conformation.

Digital Chimeras

Discrete purine/pyrimidine nucleobase associations that define digital molecular recognition registry dominate nucleic acid folding. DNA and RNA polymers use essentially the same sugar backbone, recognition moieties, and phosphate linkages but are distinguished by significant differences in hydrolytic stability, a factor critical to their biological roles in biological information processing.[15,16] When one compares nucleic and amino acid polymers, the most significant structural and functional difference resides in the chemistry of the

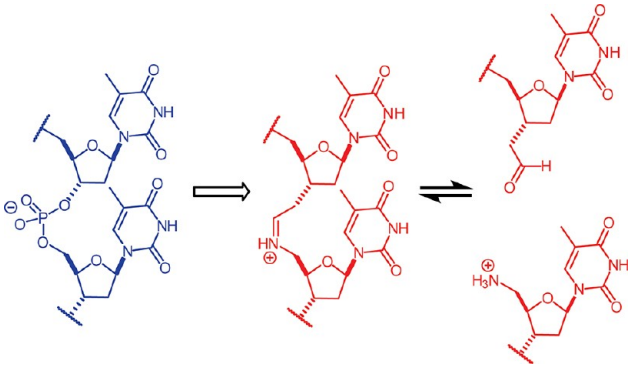

FIGURE 2. The iminium ion linkage serves as an isostructural and kinetically dynamic replacement for phosphate.

phosphate linkage. The phosphodiester is thermodynamically unstable to hydrolysis, but the kinetic barrier is sufficiently high that oligomeric DNA is remarkably stable at neutral pH without enzymatic catalysis.[17] Direct substitution of the phosphodiester for an alkyl iminium ion maintains both backbone solubility and charge (Figure 2) but switches the anionic backbone[15,18−20] to a cationic linkage. Imine formation through amine/aldehyde condensation is analogous to peptide bond formation but greatly attenuates the kinetic condensation/hydrolysis barrier for functional coupling and rapid dynamic exchange on a molecular template. This feature has been used to great advantage in the thermodynamic and catalytic cycles shown in Figure 3.[21]

Like the phosphodiester, imine condensation[22] releases water and is thermodynamically disfavored in aqueous environments, but the lower activation barrier has been exploited in the creation of one of the earliest examples of a synthetic dynamic chemical network (Figure 3).[21,23−32] The network responds to a complementary template, and hydride reagents are used to chemospecifically trap only the template-bound imine. The binding affinity of the resulting secondary amine-linked DNA oligomers to the DNA template (K_5) is 10^6-fold lower than the ternary substrate/template complex (K_3),[33] leading to isothermal dissociation of the product strand from the template and catalytic turnover (Figure 3).[21,23,24,33] When sequence-complementary templates are introduced to this dynamic network at a 1% molar equivalent relative to substrate, efficient product turnover reveals a long-sought strategy to overcome the critical product inhibition limitation of digital molecular information storage in nucleic acids.[23]

Templated growth of amine nucleoside oligomers is remarkably geometric, and the mechanism ensures the sequence specificity of template-associated substrates to accurately translate the template sequence (Figure 4).[34]

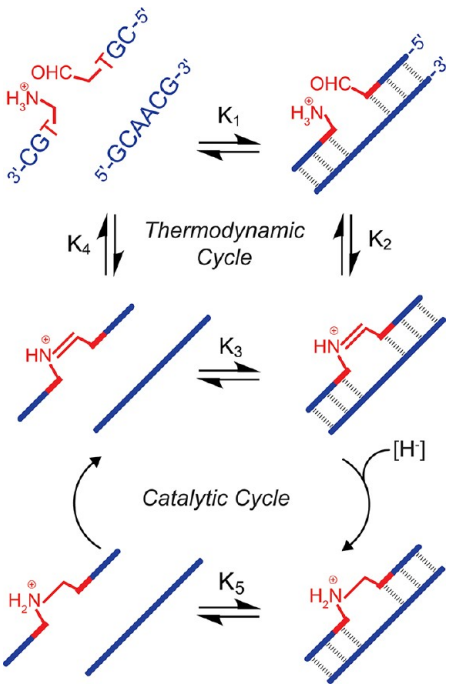

FIGURE 3. Coupled thermodynamic and catalytic cycles with measured equilibrium constants, highlighting imine-linked intermediates, template association energetics, and reductive amination.[21,23,24]

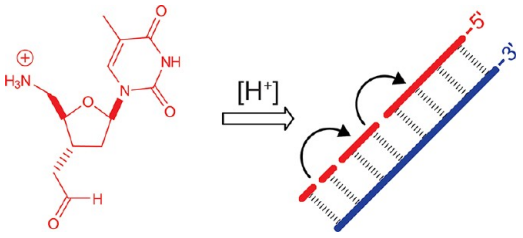

FIGURE 4. Template-directed polymerization of the amine nucleoside oligomer follows power-of-2 kinetics, resulting in both sequence and chain length specific growth on the template.[34]

The overall process has been modeled as a balance of the strength of base-pairing interactions and duplex destabilization incurred by the ammonium linker within the oligomeric products (Figure 4).[35] Therefore, the unique power-of-2 polymerization mechanism offers a very simple approach to achieving chain length- and sequence-specific template-directed polymerization, and indeed, this reaction is sufficiently robust to translate DNA sequences of at least 32 base-pairs in length into amine nucleoside polymers (ANPs) in high yield.[35] With templates ligated to solid supports,[36] ANP synthesis can achieve many of the advantages of PCR reactions in stepwise mitigation of product inhibition.

The resulting ANP/DNA hybrid assemblies show remarkable thermal stability,[24,35] highlighting the strength of base-pairing and the potential for digital associations. However,

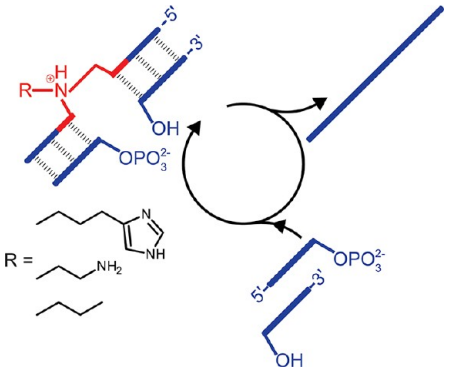

FIGURE 5. Approaching a two-stage replication cycle. Ligation of a complementary DNA catalyzed at the amine linkage site in the template strand.[37]

NMR analyses of the amine linkage provide evidence for significant conformational flexibility and suggest that other associations may contribute to folding.[24] Given the global stability and local dynamics of the hybrid duplex, the potential to control new chemical reactivity has been explored through synthetic modifications of the amine linkage site (Figure 5). In one example, a variety of alkyl side chains, with or without basic functionality, have been surveyed for their ability to enhance the ligation of complementary DNA primers.[37] Simple alkyl chains on the linking amine give assemblies that indeed catalyze ligation, presumably via enhanced dehydration of the nicked phosphate backbone, and this result provides an important step toward developing a two-stage replication cycle.[37] Moreover, the use of imine condensation coupling, embedded within digital molecular systems of DNA and PNA, has now been leveraged to expand the utility of DNA-templated imine chemistry to the formation of novel chemical reactions[38] and to dynamically assemble DNA primers.[39]

The discovery of the power-of-2 mechanism for template-directed polymerization[35] of the ANPs represents a robust process for transferring molecular information and, maybe of more conceptual relevance, suggests that other simpler mechanisms for digital molecular processing are possible even as the polymers become more protein-like. Therefore, in the context of ribosome emergence, we realized that the dominant role of base pairing in the folding landscape need not limit the morphological forms of nucleic acid polymers to digitally directed assemblies, opening the potential for new structures and functionality to emerge even within the same skeleton. Moreover, given the potential for structural diversity being far greater within polypeptides, we elected to explore the nature of this diversity within the cross-β architecture, a structure that offers potential for both template-directed propagation and morphological diversity.

Access to Morphological Diversity

The cross-β architecture of natural polypeptides achieves both the long-range order of surfactant phase behavior[11] and the conformational richness of folded proteins.[40] The role of cross-β assemblies in prion diseases[12−14] reveals a mechanism for infection that involves nucleation and propagation of networks of environmentally responsive ordered phases. Current evidence suggests that the complex environment of the host cell provides an environment for the nucleated growth of diverse conformational populations from which selected prion assemblies propagate.[7,14] Like a virus, selected forms are subject to amplification in their host via template-directed propagation,[7,13,14] but unlike a virus where the digitally encoded oligonucleotide sequences undergo selection, the prion forms have identical sequences and are selected based on survival of molecular conformations of the propagated phase.[41,42] While the functions of the native proteins associated with prion forms range from metal homeostasis[43,44] to translation,[45] neither the role of the cross-β assemblies in compromising cellular function nor their precise contribution to disease etiology are understood.

Indeed, one of the major challenges in connecting disease to amyloid is the degree of cross-β polymorphism. This structural polymorphism is a direct consequence of its analog behavior, and structural insights into the many forms have emerged largely from studies of simpler model peptide phases.[46−48] In the past decade alone, a remarkable range of cross-β architectures have been revealed, but nowhere has this diversity been more obvious than in peptides containing the nucleating core, LVFFA, of the Aβ peptide associated with Alzheimer's disease. Interrogation of intra- and intermolecular interactions directing cross-β assembly of the Aβ(16−22) peptide Ac-KLVFFAE-NH_2 has benefited greatly from computational simulations,[49−52] which predict initial collapse into disordered dynamic particle phases prior to paracrystalline assembly.

Real-time optical analyses with fluorescently labeled Aβ-(16−22) identified an initial micrometer-sized particle phase that was integral to the assembly pathway.[53] The particles contain a highly concentrated and largely unstructured molten phase in equilibrium with dilute peptides in solution. They serve as the primary, if not exclusive, site for nucleation of the paracrystalline phases,[53] which give a "sea urchin-like" transitional appearance to the particles when multiple nucleation events occur. The emergence of these filament-like

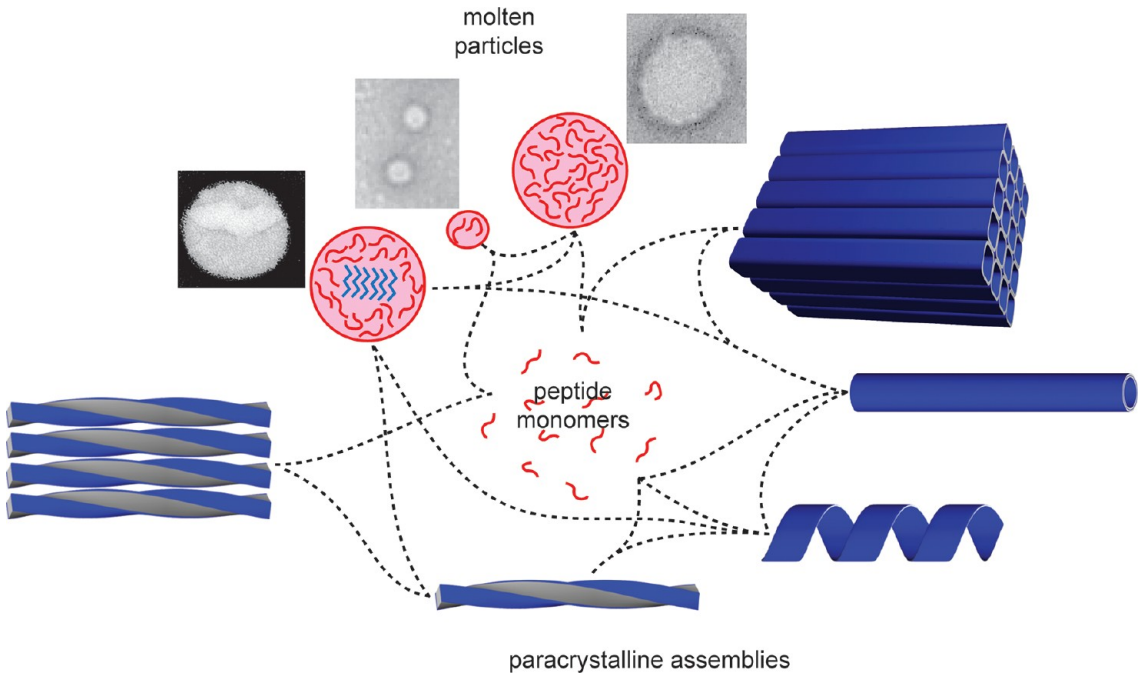

FIGURE 6. Aβ(16−22) assembly phase networks. Dashed lines indicate transitions that have been observed between each phase. Negatively stained uranyl acetate TEMs of Aβ(16−22) assemblies[11] are shown for particle phases. The micrograph with the darker background is contrast enhanced to visualize the structures within individual particles. Both pH and temperature adjustments can initiate emergence of paracrystalline assemblies from these particles.[11]

structures within the particles (Figure 6)[11] seem analogous to the metastable liquid−liquid phases[54] proposed for the intermediates in protein crystallization,[47,54−56] but once emerging beyond the particle surface, template-directed propagation occurs at the exposed ends of the assemblies where peptides can be added at rates of at least 2000 monomers/s.

These Aβ(16−22) assemblies then achieve a wide range of morphologies, some similar to known amyloidogenic proteins,[46,57,61,63−65] but all part of a diverse network of ordered, context-dependent phases.[11,61,62,66] Highlighted in Figure 6 are conditional nodes containing monodisperse assemblies, but a continuous change from one assembly to another reflects a gradient change through many environmentally responsive nuclei, all responsive to variations in the physical environment. The individual nodes represent low-energy states, but even the nodes are context dependent. Acidic media drives the conversion of Aβ(16−22) fibers (Figure 7G) into hollow nanotubes (Figure 7F), and neutral media induces the reverse transition.[11,64] While both fiber and nanotube assemblies contain antiparallel β-sheets, the fibers have in-register strands and the nanotubes are shifted out-of-register by one residue (Figure 8). Clearly, subtle changes in peptide arrangement can result in large changes in morphology.[61] And even more importantly, each phase remains suspended in solution and is robust in its response to the environment, and the structural differences appear to be derived from an initial nucleus that competes for free peptide to create the final assemblies through template-directed conformational propagation.

In addition, this morphological diversity is certainly sensitive to changes in the amino acid sequence, and such sequence substitutions may contribute to the species barrier for many infectious prions.[67] We have therefore surveyed a variety of these substitutions to better define the landscape of possible cross-β assemblies. For example, specific homogeneous diameter nanotubes, ranging from tens to hundreds of nanometers, have been prepared by simple changes in peptide structure.[60,61,64,66,68] Nowhere are these single site constraints on cross-β assembly more apparent than in the acute sensitivity observed in the presence of metals. Metal ions have been shown to exert dramatic control over nucleation events,[57] strand registry,[59] stability,[59,60] and surface patterning[59] through subtle alterations in their specific binding sites. Accordingly, it appears that specific energetic constraints that narrow accessible conformational space and achieve increasing digital-like assembly behavior can be introduced within these analog systems.

Analog Chimeras

Building stronger interactions that dominate the more analog folding behaviors of the cross-β assemblies provides another approach to probing the dynamic networks and

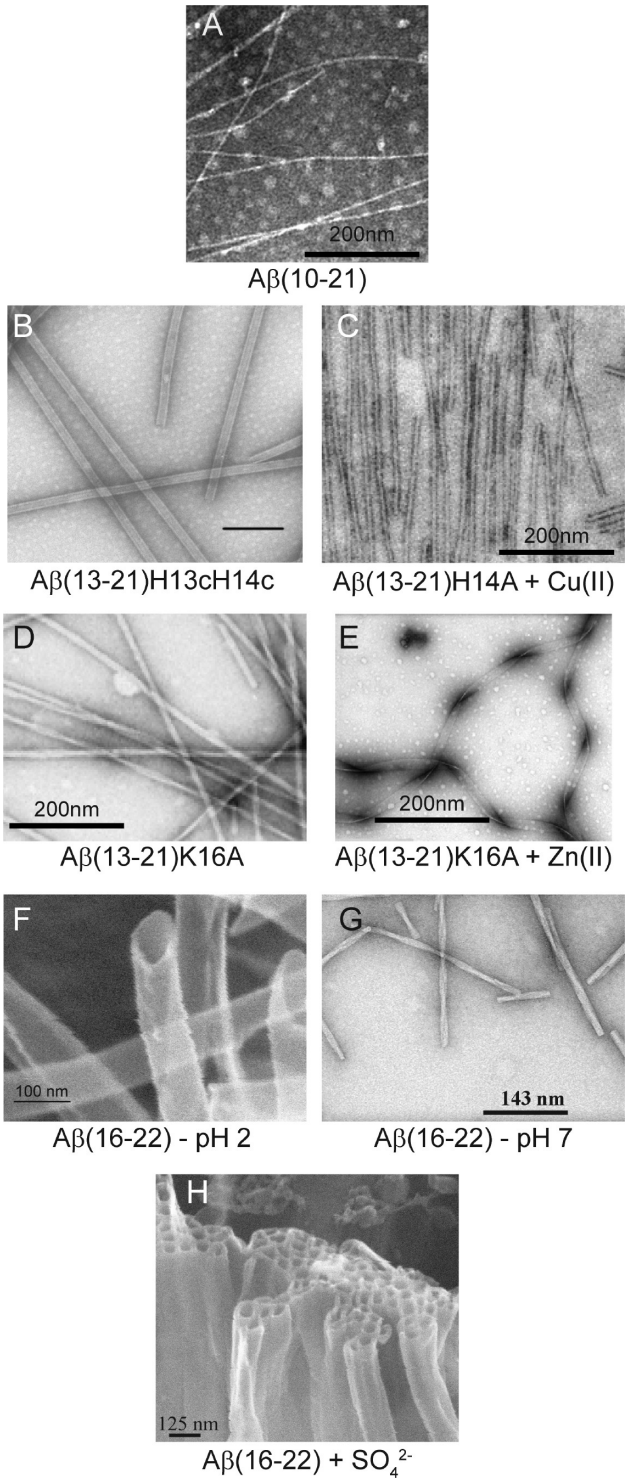

FIGURE 7. Electron micrographs of the peptide assemblies containing the LVFFA nucleating core of Aβ. The peptides are derived from Aβ residues 10−21, ^{10}YEV^{13}HHQ^{16}KLVFFA^{22}E: (A) Aβ(10−21) fibers,[57] (***B***) Aβ(13−21)-H13cH14c tubes,[58] (C) Aβ(13−21) + Cu(II) fibers,[59] (D) Aβ(13−21)K16A fibers,[59,60] (E) Aβ(13−21)K16A + Zn(II) ribbons,[60] (F) Aβ(16−22) tubes,[61] (G) Aβ(16−22) fibers,[61] and (H) Aβ(16−22) tube bundles.[62]

may have provided the foundation for the emergence of DAC-like cooperation. Our current understanding suggests

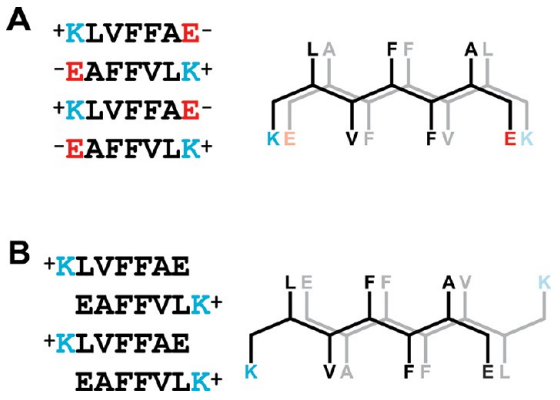

FIGURE 8. Aβ(16−22), ^{16}KLVFFA^{22}E, β-sheet registry formed under (A) neutral[61,63] and (B) acidic pH[61] conditions. Each panel contains the β-sheet registry (left) and two H-bonded peptides, viewed along the H-bond axis with the peptide in the back colored gray (right).

that cross-β self-assembly is controlled by many weak noncovalent interactions that direct growth along both the β-sheet[66] and sheet−sheet stacking (lamination) planes.[69] However the emerging structural evidence for peptide bilayer architecture, at least within the simpler peptide assemblies,[70] have also identified the bilayer leaflet interface as a critical determinant of cross-β morphology. Combining this information with the recognition that prions are generally rich in asparagine (N) and glutamine (Q) focused our attention on the specific roles these residues play in cross-β assemblies. In the context of the Aβ peptide, substitutions of E22 for glycine (Arctic mutant),[71] lysine (Italian mutant), and glutamate (Dutch mutant)[72,73] all significantly impact the etiology of Alzheimer's disease. We therefore began investigating the E22Q substitution, a residue located at the C-terminus of the Ac-KLVFFAE-NH_2 peptide and specifically within the leaflet interface.

Remarkably, the E22Q substitution in Aβ(16−22) switched the assembly from nanotubes with antiparallel β-sheets to fibers with parallel β-sheets.[74] That a single Q substitution can overcome so many competing interactions implicates a specific and energetically dominant interaction. The cooperative Q-track structure (Figure 9), previously observed in peptide crystal structures,[75] provides such a dominant energetic contributor to β-sheet registry. Energetic simulations[76] indeed suggest that these Q-tracks flatten sheet topology, but the E22Q substitution in Aβ(16−22) appears to reinforce sheet twisting, stabilizing fibrils and destabilizing the helical ribbon and nanotube morphologies. While the complete energetic landscape for the Q association will require further analysis, such Q-tracks could setup long-range order, similar to the H-bonding in nucleic acid duplexes, and impose a specific amino acid constraint on

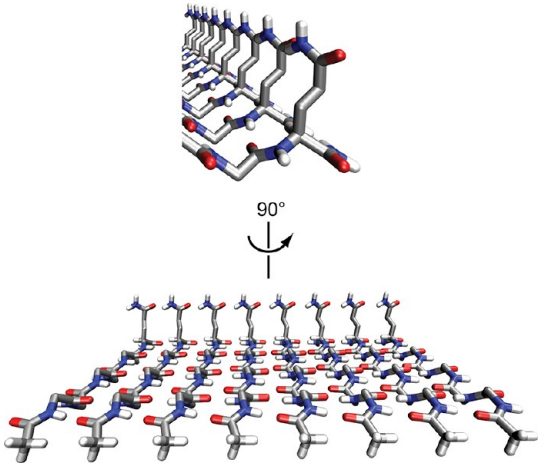

FIGURE 9. Model of Aβ(16−22)E22Q assembly highlighting the cross-strand pairing Q-tracks. Distance measurements constrain the β-strands to the parallel and in-register assemblies as shown.[74]

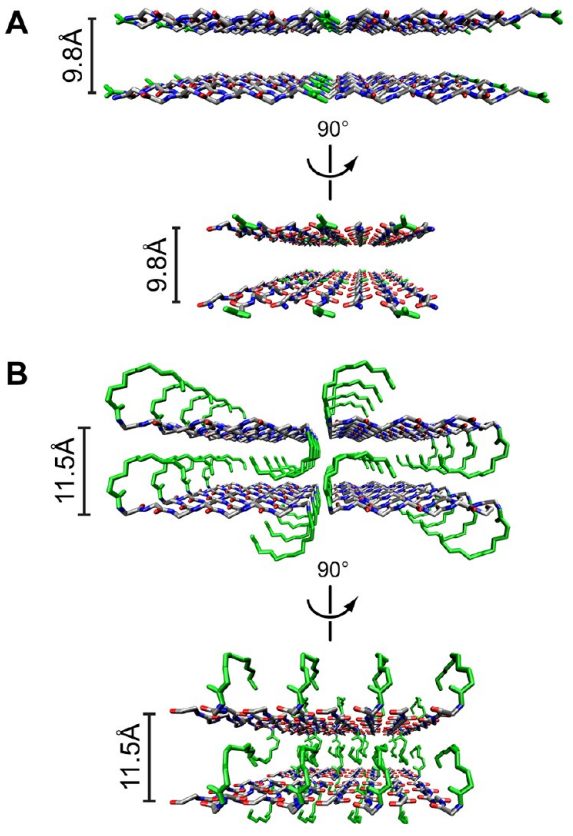

FIGURE 10. Molecular dynamic simulation results for models of the cross-β structure of (A) *N*-acetyl[61] and (B) *N*-lauroyl[68] KLVFFAE tubes showing two laminated, H-bonded, antiparallel, out-of-register β-sheets. For clarity, the side chains are not shown and the respective *N*-acetyl and *N*-lauroyl acyl chains are colored green. The experimental distance constraints, including the different lamination distances and the position of the *N*-lauroyl chains as shown, are maintained throughout these simulations.

assembly that selects for organization and assembly of complementary Q-containing sequences.

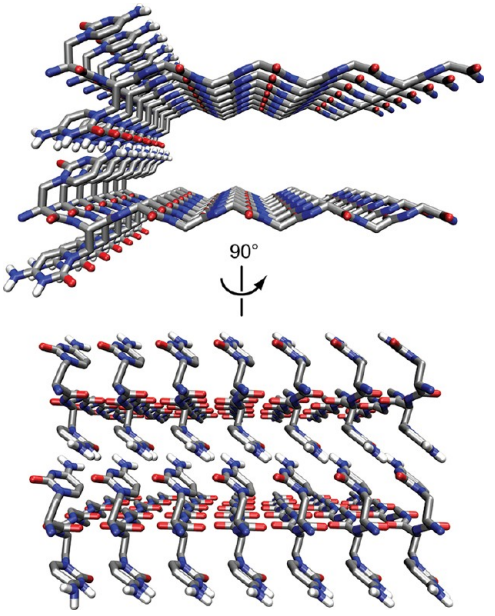

FIGURE 11. Structure model for cytosine self-pairing in the Aβ(13-21)H13cH14c amyloid fibril derived by using experimental distance measurements to constrain molecular dynamic simulations.[58] Only cytosine (c) side chains are shown for clarity.

Structural modifications at the peptide N-terminus have also been shown to significantly impact assembly. Lipid/cross-β amphiphile chimeras had been reported to change sheet orientation;[65] however more detailed structural analyses have revealed a complex array of accessible assemblies, including a completely unexpected new phase. N-Acylation of KLVFFAE-NH_2 with a 12-carbon fatty acid gives a peptide amphiphile that assembles with the hydrophobic chain inserted within the interior of the β-sheet laminate (Figure 10B).[68] Not only does this alternative arrangement expand the sheet lamination distance by almost 2 Å, but also solid-state NMR analyses place the fatty acid chain precisely along the peptide backbone (Figure 10B). This new phase greatly expands our understanding of the plasticity of the sheet laminate in the cross-β fold,[59,77−79] a region already known to serve as the binding site for small molecules[80] and metal ions (Figure 7C,F),[60] and offers new opportunities for engineering specific molecular recognition elements into the peptide assemblies.

This cross-β plasticity has already been exploited for engineering digital registry.[57,59,60] Assembly of Aβ(13−21), the N-terminal homologated peptide HHQALVFFA-NH_2 (Figure 7D),[59,60] was shown to be conformationally controlled by Zn^{2+} chelation to histidine side chains across the laminate interface.[57,60] When the histidines are substituted with the nucleobase-derived β-(cytosine-1-yl)-alanine (c) to give ccQALVFFA-NH_2, the resulting nucleobase/peptide chimera assembles (Figure 7B) to create the only defined

single-walled peptide nanotube with parallel β-sheets.[58] Further, structural analyses indicate that the bases are positioned perpendicular to the β-sheet H-bonding direction, as an i-motif-like base-pairing array (Figure 11), consistent with the pH-dependence of its assembly. This even more specific digital pairing constraint in this nucleic/amino acid chimera can be used in dynamic combinatorial networks with other peptides, nucleic acids, and hybrid materials to elaborate an ever greater landscape of robust and cooperative functional assembly networks.

Summary

If the ribosome emerged as a ribonucleoprotein via synergistic collaboration of nucleic and amino acid polymers to achieve polymer translation functions,[3] thereby providing the foundations for the Central Dogma of Biology, then it should be possible to construct a diverse pool of oligomers, operating within a dynamic network containing both digital associations and diverse analog folding landscapes, which are capable of mutualistic molecular symbiosis (Figure 12). Certainly the existence of such a network necessitates a separate evolutionary transition (Figure 12), a dynamic chemical threshold, allowing for the production of many polymer species capable of chemical evolution. The two biopolymers found in the ribosome likely emerged from such a network. To explore this idea, we have taken the separate evolutionary mechanisms of nucleic acids and proteins and used the functional aspects of those processes to construct and investigate structural hybrids. We predict that some of these hybrids will have greater chemical evolutionary potential than either of the individual biopolymer species but function less effectively than the collaborative assembly that created the ribosome.

On the digital side of the network shown in Figure 12, we have replaced the phosphate ester of the nucleic acids with a partially reduced amide, and this simple change indeed creates a dynamic network that operates without biological enzymes. Polymer translation is achieved simply through template-directed polymerization, and sequence information is efficiently processed between nucleic acids and the amine-containing ANPs.[35,37] This system provides a generalizable and robust mechanism to replicate sequence information in biopolymer chimeras.[35,37] The flexibility of the simple amine linkage of the ANP product then creates a dynamic chemical network with a broader folding landscape, greater analog-like behavior, and increased chemical functionality for chemical evolution.

Within the analog domain of the network, the cross-β fold assemblies connect directly to environmental chemical

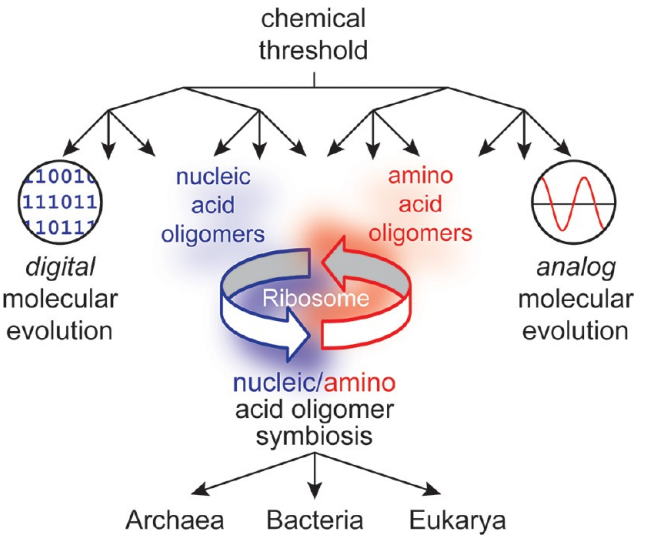

FIGURE 12. Polymer mutualistic symbiosis as the threshold for the three domains of life. The cooperation of nucleic and amino acids to create the ribosome requires a diverse polymer network capable of chemical evolution. The network is shown as bounded by both chemical and Darwinian thresholds.

potential fluctuations and context-dependent forces to mediate replication through conformational template-directed propagation.[81] The broad morphological diversity that can be achieved with these cross-β assemblies, their responsiveness to environmental inputs, and the identified constraints that bridge the higher ordered phases with more digitally responsive assemblies have greatly extended this chemical evolutionary strategy. The glutamine side chains and more dramatically the metal binding and cytosine chimeras represent major steps in transitioning to greater digital folding landscapes for enhancing replication fidelity.

The model presented in Figure 12 is further built on the prediction that other symbiotic and parasitic polymer associations must emerge from these networks. Indeed, supramolecular aggregates,[4] coacervates,[82] and proteinoids[83] from mixed assemblies have for many years been considered phases of matter that contributed to the emergence of more complex cells, but the preparation of such complexes, with multiple components as found in the ribosome, remains challenging. Further, significant challenges remain in the structural analysis of higher order cooperative assemblies, particularly when they exist in dynamic networks. And the assessment of cooperative functions that might emerge from these assemblies is also challenging. But again, the existence of the ribosome provides a blueprint for what might be possible. The cross-β fold is known to create surfaces capable of binding to nucleic acid polymers,[84] and these associations are increasingly implicated in disease

etiology.[12,14,48] The oldest protein folds may be rich in β-structure and interleaved β-sheets,[85] and the primordial ribosomal proteins that are involved in critical ribosomal functions, including mRNA binding, tRNA translocation, and subunit association,[3] all maintain β-sheet rich folds. The ribosome then provides an obvious guide and rich structural prototype for exploring the larger functional potentials that may be possible for discovering entirely new remarkable functions.

Indeed, the construction of biopolymer chimeras has already offered important spinoff applications in therapeutics and diagnostics,[86] in the construction of novel nanostructured materials (DNA/RNA[87,88] and peptides[89]), and toward orthogonal biochemical pathways that expand the evolution of extant biochemical systems.[90] A functional approach that looks beyond the phylogenetic event horizon of ribosome emergence may allow us to fundamentally reinvent chemical evolution, and address an issue that dates back at least to Charles Darwin's suggestion of the warm pond where living matter first emerged.[91] His speculation implied that evolution was an inherent property of matter and that by deciphering the chemical thresholds and physical limitations necessary for the emergence of molecular order, we can unlock and deconvolute the most elaborate, elegant, and complex hierarchical forms of matter through chemical evolution.[92] Uncovering this power of chemical evolution should change forever the way we do chemistry research and impact the critical constraints on life's existence.

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ABBREVIATIONS

DAC, digital-to-analog converter; ANP, amine nucleoside polymers;

BIOGRAPHICAL INFORMATION

Jay Goodwin received his Ph.D. in bioorganic chemistry with David Lynn in the Department of Chemistry at the University of Chicago, and after a sojourn into industrial and entrepreneurial drug discovery, he is now a Senior Research Fellow in the Department of Chemistry at Emory. His scientific focus is on dynamic chemical networks and chemical evolution as they inform our understanding of the potential origins of living matter and the design and implementation of intelligent materials and novel therapeutic systems.

Anil Mehta received his Ph.D. in physical chemistry at Yale University and during this and his postdoctoral training at Washington University developed novel solid-state NMR methods for atomic-level structural characterization. He is now a Faculty Fellow at Emory University where he has focused on understanding the rules and forces directing molecular and supramolecular assembly and how these assemblies can be harnessed to store information and gain novel function.

David Lynn is the Asa Griggs Candler Professor of Chemistry and Biology at Emory University, Chair of the Department of Chemistry, and a Howard Hughes Medical Institute Professor. His interests have focused on understanding the structures and forces that enable supramolecular self-assembly, determining how chemical information can be stored and translated into new molecular entities, and discovering how the forces of evolution can be harnessed in new structures with new function.

FOOTNOTES

*Corresponding author. E-mail: david.lynn@emory.edu.
The authors declare no competing financial interest.

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