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Preview

Toward computationally guided design of bespoke protein-based materials

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Designer protein-based materials with bespoke properties for technical and biomedical applications might seem like a distant goal, but a recent report by Gregorio et al. in *Cell Biomaterials* brings us closer to that reality. Harnessing computationally guided *de novo* design of homo-oligomerizing protein subunits, the authors produced hydrogel materials and fluid condensates with tunable properties via rapamycin-triggered self-assembly.

Recent advances in computationally guided *de novo* design of proteins are rapidly transforming the fields of biotechnology and bioengineering. Accelerated protein engineering powered by machine learning holds promise to supercharge research areas such as drug discovery, vaccine development, enzyme design, biomedical engineering, and more.[1] Design of new functional materials, however, is perhaps not the first thing that springs to mind when considering possible applications. Yet, as a recent article by Gregorio et al.[2] in *Cell Biomaterials* demonstrates, it is an extremely exciting avenue for developing new materials with properties that are determined by the computationally designed protein sequence, which determines its folded structure and its pre-programmed assembly behavior. This study represents an important step on a journey toward engineering bespoke, high-performance protein-based materials from scratch – however, to fully appreciate the relevance of this breakthrough, it is worth looking briefly to naturally occurring protein-based materials found in biology.

Certain living organisms—such as spiders and mussels—are renowned for their ability to use protein building blocks to fabricate remarkable materials that outperform the best synthetic materials, while also being biocompatible, sustainably produced, and biodegradable.[3] For instance, spider silk is more than three times tougher than Kevlar (a synthetic polymeric material that can stop bullets), while mussel byssus exhibits underwater adhesion unmatched by human-designed glues.[3] Studies reveal that these properties arise from the sequence of the proteins that make these materials and their hierarchical organization across length scales.[3–5] Furthermore, this structure arises from specialized fabrication processes performed by the organism, often involving protein fluid condensates formed via liquid-liquid phase separation (LLPS) as a precursor phase and the stimuli-responsiveness of the proteins to physicochemical cues.[3,4,6]

Efforts to understand the relationships between protein sequence, structure, processing, and function of biological materials has revealed extractable design principles that have been adapted by humans for the development of novel bio-inspired materials. For instance, artificial spider silk fibers possessing native-like properties are now mass produced using recombinantly produced proteins as a feedstock.[3,4] Similarly, recombinant and peptide-based mimics of mussel glue proteins are used in applications ranging from implant coatings and tissue scaffolds to surgical glues and dental cements.[3,6,7]

The sequences of proteins comprising biological materials like silk and byssus have evolved through natural selection over hundreds of millions of years (Figure 1).[5] Many small changes in protein sequence over eons have honed material properties such as stiffness, strength, and toughness, but also economy in resource use and energy consumption during fabrication.[5] Given the immense timescales and the selective pressures at play, evolution arrived at specific protein sequences that, with proper processing, yield fibers, coatings, glues, and composites that are beyond the state-of-the-art in human-designed materials.[3–5]

Yet, despite all this time and tinkering, biological materials could be even better. For instance, the emergence of new protein designs from scratch is not observed because natural proteins must always evolve from an existing predecessor through random genetic mutations.[5] Moreover, biological materials are almost always multifunctional, and their properties are often adapted to numerous conflicting needs simultaneously often unrelated to mechanical performance, which necessitates a compromise in performance of specific properties. Thus, it is conceivable that tougher silk fibers or more effective underwater glues could one day evolve naturally. However, waiting for the next generations of these super materials to emerge spontaneously would likely require timescales far beyond the life span of any human. This is a clear limitation of strictly relying on natural protein sequences to inspire new materials—one which can be addressed through biotechnology.

Protein engineering enables development of new protein designs divorced from evolution and natural selection, capable of moving beyond nature.[4] Indeed, protein engineers are not beholden to the evolutionary baggage that every living organism carries with it. Instead of making minute, random changes on an existing template as occurs with natural selection, protein engineers have the freedom to invent new protein sequences *de novo*.

But with this great freedom comes a massive challenge—the design space available for protein sequences is enormous (there are more possible sequences in a 100 amino acid protein than atoms in the universe![8]). How does one decide where to focus? To tackle this problem of limitless possibilities, researchers have a new tool to play with—computationally guided protein design supported by machine learning and modeling. In such approaches, computers are employed to survey unexplored design space, targeting specific folds with the capacity to oligomerize and self-organize into complex higher-order assemblies.[1] In this way, computational approaches can enable rapid design of novel proteins intended specifically for fabricating materials (Figure 1).

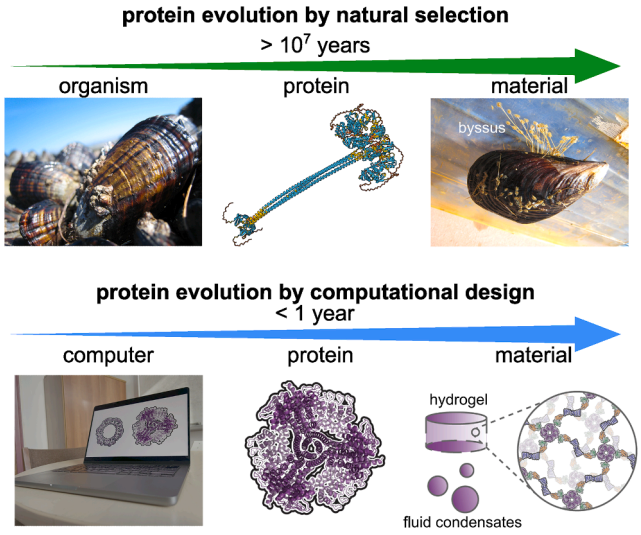

Figure 1. Relative timelines for evolution of protein-based materials by natural selection vis-à-vis computational design

Along these lines, in the current article, Gregorio et al.[2] used computational methods to develop—largely from scratch—a protein-based system capable of self-assembling into a mechanically tunable hydrogel using the small molecule rapamycin as an assembly trigger. Specifically, protein sequences were designed *de novo* with the capacity to self-oligomerize into higher-order assemblies with different numbers of subunits ranging from dimers to 12-mers. Different oligomerizing protein subunits were then tethered to the naturally occurring proteins FRB and FKBP, which form strong interactions with one another in the presence of the small molecule rapamycin.[2] By controlling the local conditions, the authors demonstrated the ability to form hydrogel materials with mechanically tunable rheological properties controlled by the "valency" of the homo-oligomerizing designer proteins (i.e., the number of subunits in the assembly) and by the concentration of rapamycin.[2] Notably, the ability to tune viscoelastic properties of hydrogels is important in tissue engineering applications in which living cells respond to the relaxation behavior of the substrates, promoting cell spreading, proliferation, and even differentiation.[9]

In addition to hydrogel formation, the authors explored the formation of fluid condensate phases by the designer proteins via LLPS, also revealing a dependence of the phase diagrams on the valency of the subunits and the concentration of rapamycin, as well as a tendency under some conditions toward solidification.[2] Notably, this *de novo* designed capacity to trigger fluid condensate formation and solidification via environmental triggers superficially mimics the fabrication pathways that organisms such as spiders, mussels, velvet worms, squids, sandcastle worms, ticks, and even humans use to make materials.[3,6] While the engineered system still relies on existing biologically derived protein sequences to initiate rapamycin-dependent cross-linking, this study provides an exciting preview of a new era of computationally guided "evolution" of new materials.

While quite promising, there are many challenges that need to be overcome to fully realize *de novo* designed protein materials with bespoke properties and thus, functions. Here, the authors relied on an existing biological protein system to initiate rapamycin-based self-assembly rather than designing one *de novo*. This stems in part from existing challenges with computationally designing dynamically responsive proteins.[10] Indeed, computational models often struggle to predict and control the dynamic responsiveness of proteins to environmental cues such as pH, salt concentration, redox conditions, and even mechanical forces.[3,10] Importantly, these same physicochemical parameters are employed as effective triggers for fabrication of biological materials such as spider silk and mussel byssus by shaping protein folding, oligomerization, and cross-linking,[3,6] crucial for transitioning from a dense fluid condensate phase into a hierarchically structured functional material. Thus, integrating dynamic responsiveness of proteins to environmental conditions represents a critical challenge and opportunity for *de novo* design of protein building blocks toward designer materials. Nonetheless, given the rapid rate of progress in this burgeoning field, this challenge will likely be overcome shortly.[10] As a final point, despite the new possibilities endowed through computational protein design, nature still provides an invaluable sounding board for design of novel systems. Perhaps informed computational design based on what we have learned from the proteins comprising existing biological materials could yield results more rapidly than completely reinventing everything from scratch. After all, biology has had a head start of a few billion years.

DECLARATION OF INTERESTS

The author declares no conflict of interest.

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