Integrating Modeling and Silk-Like Protein Design to Mimic Biological Fiber Spinning

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New scalable computational modelling tools are required to integrate with and guide the experimental design of polymers in order to generate materials with predictable functions. Toward this goal, here we engineer and process spider-silk protein sequence designs coupled with coarse-grained dissipative particle dynamics (DPD) simulations to demonstrate how fiber formation and fiber features can be understood and predicted. We also pursue new
design improvements with longer multiblock copolymer sequences composed of two repeated peptide building blocks of “A” (poly-alanine rich, hydrophobic domain) and “B” (GGX (X = R, L, Y, or Q) rich, hydrophilic domain). This integrated approach provides a path forward to generate well-defined functional materials, in this case, by integrating scalable computational modelling tools, protein polymer bioengineering, and biologically inspired microfluidic shear-flow-focused processing (Fig. 1).

Figure 2. Coarse-grained representations of new silk protein sequence design in the DPD simulation: (a) H(AB$_3$)$_2$ and (b) H(AB$_3$)$_8$. Polymer network of (c) H(AB$_3$)$_2$ and (d) H(AB$_3$)$_8$ after equilibration, as well as structural evolution after shear flow. Although similar protein aggregate sizes are observed for the two sequences in (c) and (d), greatly enhanced polymer network connectivity is observed for the much longer sequence H(AB$_3$)$_8$. Scale bar 10 nm.

We demonstrate here how this integrated set of tools is used to successfully predict sequence designs of protein multiblock copolymers that will or will not generate useful fibers, largely informed by network interactions among the self-assembled protein chains. Specifically, we find that the cluster size of the hydrophobic domains of the protein increases under the shear flow, and that the connections between clusters, linked by the hydrophilic domains, lead to a polymeric network and ultimately, fiber assembly (Fig. 2). The number and alignment of connections (bridges) in the network is more critical than the beta-shear content in the synthetic protein during the fiber formation process. Our study provides a strategy to design synthetic protein sequences for optimal shear-flow induced fiber assembly, as well as insights
into the natural silk spinning mechanism. Furthermore, there are direct implications for these findings for silk fiber generation, with broader impact is in the ability to predict material properties *de novo*.