The mesoscopic approach to structural biology: an inspiring frontier of research of thermodynamics applied to molecular bioengineering

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The world of biotechnology demands a robust quantitative framework, largely provided by chemical engineering—ranging from large-scale processes to molecular-level bioengineering. Within this context, molecular bioengineering heavily relies on the thermodynamic characterization of biomolecular systems. Since the early days of experimental structural biology, thermodynamics has proven to be a powerful tool for assessing biomolecular stability and tracking key properties such as allosteric regulation driven by conformational changes.However, the traditional thermodynamic approach, centered on Gibbs free energy, has limitations. It is computationally intensive and not ideally suited for high-throughput screening. Furthermore, it lacks resolution in certain key areas, such as generating structure-function fingerprints and offering a detailed residue-level description of protein function and dynamics.

To address these gaps, the application of complex systems theory to protein structure analysis has opened new perspectives. Protein Contact Networks (PCNs)—which map intramolecular interactions in proteins—offer an effective means to relate local and global topological features of a protein to its stability and function. When combined with Molecular Dynamics (MD) simulations, this approach allows for the investigation of subtle dynamic properties and their topological underpinnings.

In this work, I present several applications of this integrative framework. These include identifying functional regions relevant to drug discovery and design (e.g., the spike proteins and protease of SARS-CoV-2), exploring allosteric regulation in oligomeric proteins (e.g., TRAF2), and advancing enzyme engineering.

The implications of this paradigm extend beyond individual case studies. Adopting a system-thinking, molecule-centered approach in chemical engineering could inspire novel solutions to both new and longstanding challenges—such as interpreting complex series-parallel reaction networks through the lens of complex network theory.

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