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Roles for Thermodynamics and Catalysis in Systems Biology: Case and Point

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The primary challenge in mammalian biology has shifted towards functional relationships between the molecules in cells and tissues and how the individual molecular components function as modules. Systems biology addresses this grand challenge [1] and focuses mainly on synthesizing functional relationships in the form of networks and pathways [2]. In general, the networks represent the relationships between molecules in a cell either as reactions or as activation or inhibition events. The specificity of such cellular responses is decoded by spatial and temporal signals propagating through intracellular signaling pathways. Network analyses tools encode quantitative relationships and decode functional insights into the complex relationships between the stimuli, cellular responses, and cell fate [3-5].

A comprehensive understanding of how molecules interact, however, can be derived only from three-dimensional structures, which provide atomic details about the specificity of binding and molecular recognition. For the most part, structural biology has remained limited in scope in terms of informing systems biology because of challenges in determining macromolecular (protein-protein and protein-nucleic acid) interfaces and in dealing with large protein complexes. However, new techniques in crystal structure determination have recently emerged to predict and model the structures of interacting proteins [2]. These include improvement in over expression and purification procedures to obtain sufficient material for structural analysis, the ability to express the subunits of a complex in model organisms, and improvements in crystallization techniques and synchrotron radiation facilities to utilize smaller sample amounts to solve structures of complexes. Techniques such as cryoelectron microscopy routinely reconstruct structures of large complexes at lower-resolution using much smaller amounts of material. Many efforts have been undertaken to provide comprehensive lists of protein–protein interactions. The yeast two-hybrid system and affinity purification methodologies remain the most widely used systems, although other experimental methods, including chemical cross linking, chemical foot printing, protein arrays, fluorescence resonance energy transfer, and fluorescence cross-correlation spectroscopy, are becoming increasingly popular. Despite the improvements in these experimental systems, there is still a large gap between the number of inferred complexes and those for which 3-dimensional structures are available [2].

Studying molecular complexes and how they propagate at the cellular signaling scale can be complementarily achieved through multiscale computational modeling, which leverages fundamental principles of thermodynamics and catalysis and applies them to systems at the nano- to micro-scale. The task of multiscale modeling is to bridge the scales of structural and systems biology to elucidate the effects of perturbations to macromolecular structure on downstream signaling events initiated by multiprotein complexes. As the robustness of biological systems hinges upon the efficient transfer of information across multiple spatial and temporal scales, the application of multiscale modeling methods is an effective way to bridge the scales and provide more insights than would be gleaned at any single scale [6]. Protein–protein interactions can be predicted computationally, complementing the efforts of high-throughput experiments [5]. On the one front, statistical approaches are based on the comparison of complete genome sequences and the more established criteria of complementarity, as demonstrated by the extensive literature in yeast genetics, or based on co-evolution patterns across several species [2]. Structures of interacting proteins are also modeled computationally through homology modeling (if structures have been previously determined for suitable homologous proteins)[7], In the absence of known structural information, domain or motif-based modeling methods are available. These methods have predicted several domain–domain and domain–motif interactions [2]. On a second front, computational chemistry approaches rooted on fundamentals of statistical mechanics and thermodynamics are based on the potential energy (or force-field) of molecular interactions to predict atomic details for a pair of interacting proteins are also available [8]. Docking techniques attempt to find the best-docked complex on the basis of shape or electrostatic complementarity, or directly on the underlying free energy landscape mediating the protein surfaces [2, 9-11].

Construction of accurate macromolecular complexes remains a challenge, as the orchestrated assembly of such complexes is difficult to capture under most experimental conditions. New hybrid techniques integrating multiple scales for prediction of macromolecular complex structure are becoming increasingly available. Hybrid multiscale methods [12], in which multiple lower-resolution techniques are combined to generate atomic models of protein complexes, represent one approach to molecular complex prediction. These hybrid techniques, which may integrate methods such as X-ray crystallography, cross linking studies, and cryoelectron microscopy, provide a way to combine the accuracy of atomic level models with the computational speed allowed by coarse-grained models[13-18].

Hybrid methods can be divided into two categories [19]: mapping methods, which use information from one scale of representation to inform or create (*e.g.*, through model parameterization) a lower-resolution model, and bridging methods, which involve bidirectional information flow between scales. Mapping methods have been applied

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to study the self-assembly of viral capsids [20, 21], including the HIV capsid [22]. Moreover, simulation results derived from high-resolution models of subunit interactions can help to quantitatively narrow the parameter space, has also been done for models of actin and tubulin dynamics [23].

Bridging methods are more difficult to implement than mapping methods, as it is a challenge to attain high accuracy for each scale of representation. However, several groups have applied bridging techniques to specific biological systems of interest [24,25]. In one study [26], coarse-grained simulations of the immature HIV virion were performed to identify the key molecular interactions responsible for maintaining the capsid structure, and these highlighted interactions then guided high-resolution molecular dynamics simulations of the capsid, in order to provide detailed hypotheses on the effect of perturbations (such as mutation) on the capsid structure.

A more advanced multiscale modeling approach is to semi-automate the iterations of information flow between models, i.e., rather than map the results of a high-resolution molecular dynamics simulation to a coarse-grained simulation, construct the system such that the models inform each other during simulation in real-time [19].

Hence the emerging suite of multiscale modeling approaches for studying functional interactions are getting ever-closer towards constructing models of intracellular signaling networks with the ability to encode the resolution of molecular decisions at key nodes of networks. While network models of cellular signaling pathways represent the highest level of modeling to monitor the global behavior, alterations in network behavior can be predictively inferred based on the application of a multiscale strategy to resolve how key structural differences translate into altered topologies in the network. That is, in the multiscale approach, molecular modeling or structure-based experimentation are adopted to quantify altered topologies of interactions as well as to provide the missing topologies/parameters for network models. Hence, in the near future, multiscale computational methodologies will offer a powerful, quantitative, and complimentary avenue for the study of intracellular signaling, which if utilized correctly can encode molecular-level specificity (i.e. predict effects of mutations in key nodes) while retaining a network or a whole cell level predictability. Exciting applications portending this trend have been successful in describing the signaling specificity in the fibroblast growth factor receptor family [2], in modeling the structural basis of signaling in the Epidermal Growth Factor Receptor (EGFR) family [27], and in the predictive modeling of the ErbB receptor mutational landscape [28-33].

Protein interaction networks provide an abstract view of macromolecular association and signaling, which can be useful for deducing the global features of a cellular network. However, such networks have a limited relationship with physical reality. A more realistic picture of the cell will ultimately develop when pathways and high-resolution structures can be integrated by a near complete repertoire of the three-dimensional structures of protein complexes. This places experimental and computational structural biology in a crucial partnership and on equal footing with systems biology [2]. Principles of thermodynamics and catalysis together with advances in high-performance computing will be the primary agents in establishing this equity and exciting new challenges for the practitioners of thermodynamics are threatening to be explored.

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