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Comment

Network models of biological adaptation at the molecular scale Comment on "Dynamic and thermodynamic models of adaptation" by A.N. Gorban et al.

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The inspiring work of Gorban and coworkers [1] highlights how correlation graphs explain connections among a variety of processes from scales of individual organisms to societies. Networks, and correlation graphs in particular, capture relationships among the myriad elements of complex systems [2] (e.g., the structure of social networks - whether digital or not - frames the scale of relevant events in society). The intriguing aspect of networks is their ability to describe very different systems, from the life sciences to finance to technology, with a general language.

Being a matter of definition, the elements in a life network (nodes) span scales from regions of molecules to whole societies. We focus here on a smaller limit of observation with respect to the kinds of systems that were discussed in Ref. [1]: the molecular scale of life, embodied by proteins, a basic element of living systems, albeit one with properties of the non-biological world. Protein science lies at the interface of physics, chemistry and biology [3]; the functional feature addressing their role as biological elements is allostery, the molecular machinery behind homeostatic processes.

The success of structural networks relies on the right choice of scale of interaction they account for. In the case of molecular graphs, representing the structural formula of organic molecules, network links represent π orbitals, responsible for many molecular properties [4]. As such, Protein Contact Networks (PCNs) represent the intramolecular interactions (noncovalent, with a prevalence of hydrophobic interactions) responsible for protein dynamic adaptation to its environment. In a sense, PCNs represent a class of causal correlation graphs, since the intramolecular interactions are a cause of correlations between elements (residues) in the protein dynamics and function.

Allosteric regulation, the control of protein activity by processes, such as ligand binding, that occur at sites often far removed, plays a critical role in cell function. Network analysis has identified regions of proteins and systems of biomolecules involved in signaling contributing to allosteric regulation, including "hot spot" residues that mediate the signal. How protein function, including allostery, adapts to stress such as mutation is currently a major area of study. Recent work [5] suggests that proteins adapt to mutations by developing new allosteric networks satisfying thermo-

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dynamic conditions for allostery. Residues important for structural integrity are highly conserved, while residues that appear as allosteric hot spots are not. There thus appears to be evolutionary pressure for structural stability, whereas allosteric networks exhibit plasticity; signaling does not require a unique pathway and is adaptable to mutation. Upon mutation a "rewiring" of allosteric networks occurs, analogous to adaptation of genetic networks to some diseases [1].

Networks facilitate identifying allosteric regions in protein molecules and complexes through structural and dynamic descriptions. They help to pinpoint residues, or hot spots, that contribute to signal transmission and mechanisms that underlie allostery. Networks have been defined and analyzed both in terms of structural as well as dynamic properties.

Dynamic networks indicate signaling pathways in proteins and protein complexes that facilitate energy transport between binding sites [6–11]. For example, energy transport networks of the homodimeric hemoglobin from *Scapharca inaequivalvis* (HbI), identified by molecular dynamics simulations [12], reveal regions of the protein including water molecules that mediate allosteric transitions. Those networks are altered by mutation, reconfigured to facilitate cooperative ligand binding, albeit by a different mechanism. The dynamic networks obtained in the computational studies of HbI and mutants [12,13] indicate regions that mediate cooperativity of ligand binding previously identified experimentally [14,15].

Those results suggest that allostery adapts to mutation by at least some reorganization of networks, a general picture put forth and supported by a recent study involving mutational scanning of a bacterial tetracycline repressor [5], indicating rearrangement of networks for allostery in response to a variety of mutations. The networks that emerge from adaptation to mutation have to satisfy the thermodynamic constraints for allostery. Small structural adjustments can lead to significant changes in dynamics throughout the protein [16], and corresponding entropy, which can facilitate ligand binding and allostery [17].

Protein contact networks (PCNs) are structural networks whose elements are the protein residues and links between nodes represent the relevant intramolecular interactions (noncovalent) in protein structures [18]. They allow to identify residues active in allosteric regulation through partition of the protein molecules in functional domains [19,20]. For instance, in enzyme systems, PCNs let emerge functional domains and the border regions as responsible for transmission of signals between domains [21].

Recently, we have applied the PCN methodology to verify the presence of allosteric regions in the complex of the spike protein of SARS-CoV2 with the human receptor ACE2. We have followed an integrated dynamic/topological approach comparing results with those obtained through a method that predicts intersubunit affinity (SEPAS) as well as the Elastic Network Model (ENM). There was general agreement between all the methods applied. PCNs have identified residues of an allosteric modulation region (AMR) in charge of allosteric communication between the binding interface and the rest of the protein molecule [20].

All in all, we can say the PCNs and dynamical networks in protein molecular systems represent the molecular scale of (causal) correlation graphs, falling in the same general framework of the work of Gorban [1].

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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