Proteins which have a large influence on their network's dynamics evolve slowly

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Short Abstract — **Understanding why different proteins evolve at different rates is a key challenge at the interface of systems biology and population genetics. Building upon detailed mechanistic models of real-world biochemical systems, I demonstrate that the evolutionary rates of proteins are inversely correlated with their influence on the dynamics of the networks in which they are embedded. The correlation coefficient is typically of order -0.3, among the strongest known network-level correlates of evolutionary rate. This suggests that network dynamics are under strong stabilizing selection not to change and that detailed models can shed light on their evolution.**

I. INTRODUCTION

Combining high-throughput systems biology with population genetics has revealed that protein evolutionary rates depend strongly on their network context and function. For example, proteins evolve slower if they have many interaction partners, are highly transcribed, or have large knock-out effects [1].

Such top-down approaches, however, give only a coarse view of a protein's role. Here I use detailed, bottom-up, mechanistic models to take a much finer view, focusing on the influence proteins have on the dynamics of the networks in which they are embedded.

## II. METHODS AND REPRESENTATIVE RESULT

I study mechanistic biochemical models from the BioModels database [2]. Changes in protein sequence affect network dynamics by changing corresponding kinetic rate parameters. As in [3], I measure changes in network dynamics by χ^2, which sums changes over all molecular species in the model. The influence ϕ_k of a given parameter on the network dynamics is defined as:

$$\phi_k \equiv \sqrt{\frac{\partial^2 \chi}{\partial^2 \log k}}.$$

I define the influence Φ_p of a protein on the network dynamics to be the geometric mean of the influence of all parameters for all reactions in which it is involved:

$$\Phi_p \equiv \left(\prod_k \phi_k \right)^{1/N_k}.$$

A protein's evolutionary rate is measured by the fraction of its amino acids that differ between distantly related species (e.g. humans and zebrafish). For this divergence estimation, I use alignments from the NCBI's Homologene database [4].
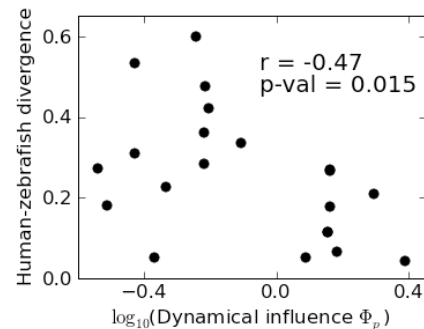
As a representative example, the figure shows the correlation between evolutionary rate and dynamical influence in a 19-protein model of the ErbB growth-factor signaling network [5]. The correlation coefficient of -0.47 is highly significant (permutation test p-value: 0.015).

III. CONCLUSION

The observed negative correlation of protein evolutionary rate with dynamical influence suggests that network dynamics are under strong stabilizing selection. It also quantifies the prevailing wisdom that evolutionary conservation is indicative of functional importance. Finally, it suggests that the models considered, while necessarily incomplete, capture not only the functional properties of networks, but also their evolutionary properties. As biochemical network models grow more complete, future investigations will no doubt shed further light on the connection between network dynamics and evolution.

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