

Influence of network dynamics on evolutionary rates of domains within proteins

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Summary

Each protein has a characteristic rate of evolution, and these rates vary dramatically. Studies of protein evolutionary rate typically take a very coarse view of protein function. Here we take a much finer view, using detailed mechanistic models to measure the influence of each constituent protein on its network's dynamics.

We show that a protein's dynamical influence and its evolutionary rate are negatively correlated, implying purifying selection on network dynamics. Moreover, this correlation is independent of and stronger than the correlation between evolutionary rate and knock-out essentiality, the most common measure of protein functional importance. We have begun to further refine this analysis by measuring evolutionary rate at the protein domain level.

Dynamical influence

χ^2 is an inclusive measure of change in network dynamics due to change in parameters k . It sums and integrates over all dynamical species y in the network [Gutenkunst (2007)]:

$$\chi^2(k) \propto \sum_{\text{species } y} \int \left(\frac{y(t, k) - y(t, k^*)}{\sigma_y} \right)^2 dt.$$

Figure 1 - Dynamical influence

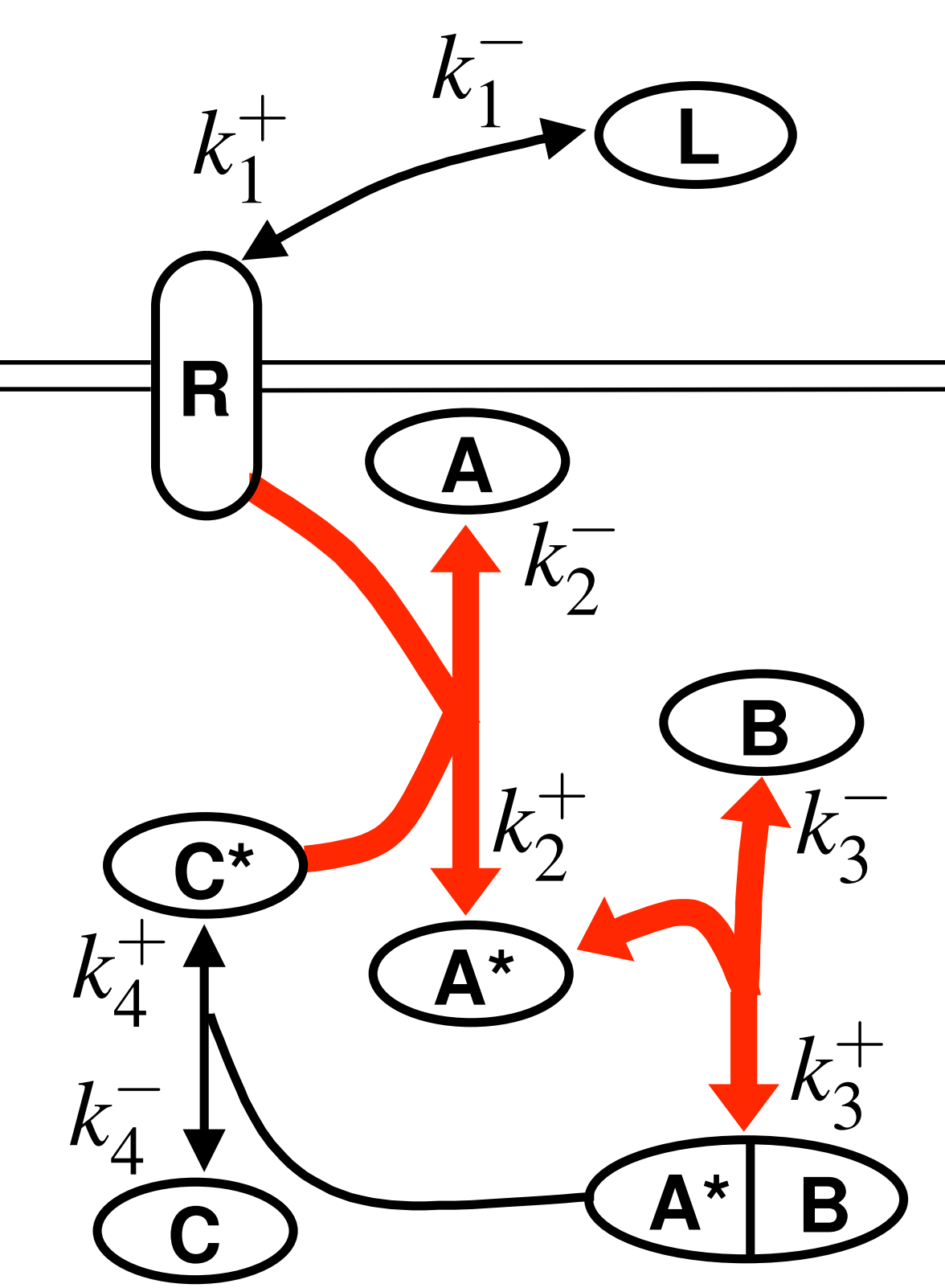
The dynamical influence κ_i of parameter k_i is

$$\kappa_i = \sqrt{\frac{\partial^2 \chi^2}{\partial^2 \log k_i}}.$$

The dynamical influence D of a protein is the mean influence of parameters governing reactions the uncomplexed protein participates in:

$$D = \langle \kappa_i \rangle_{\text{geom}}.$$

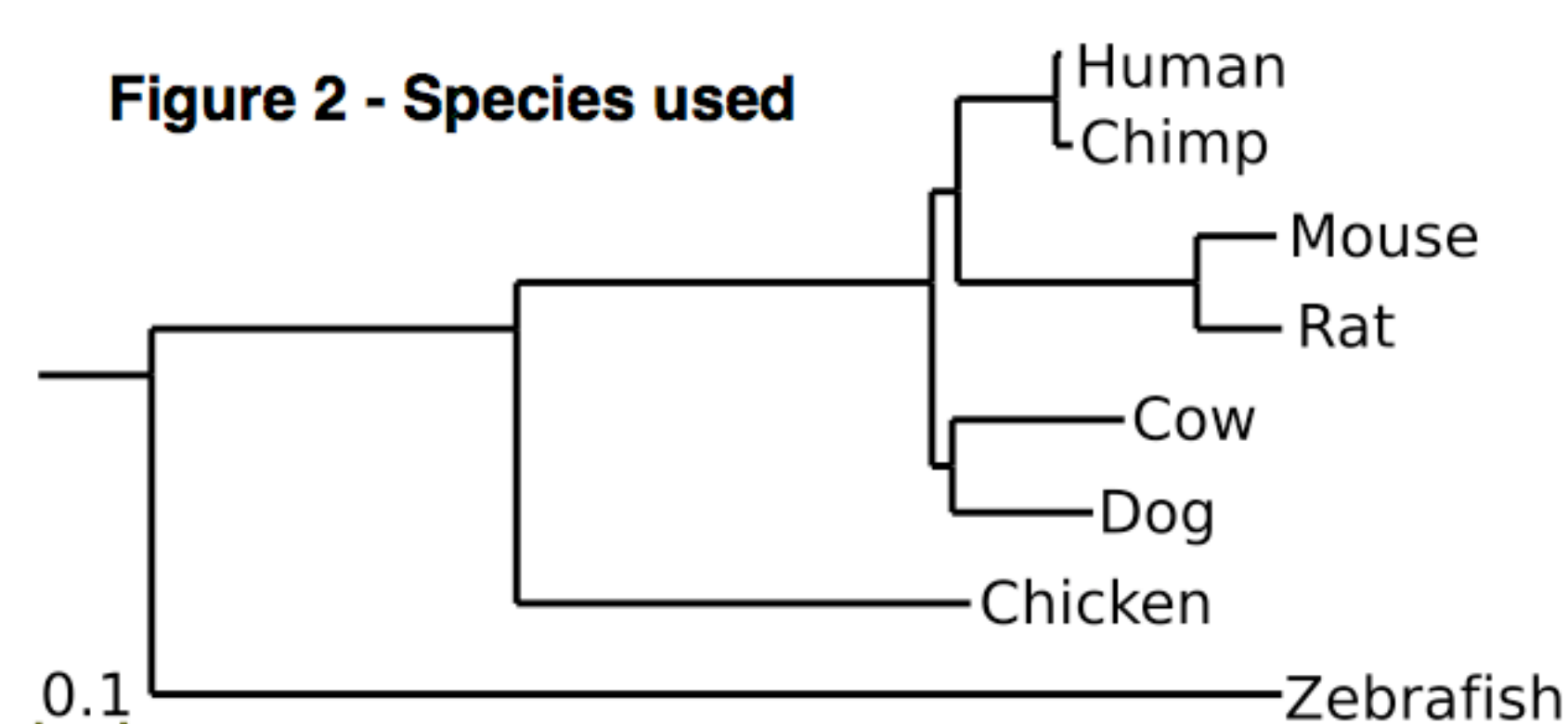
For example, in the network shown in **Figure 1**, the influence of protein A incorporates the highlighted reactions.



Evolutionary rate

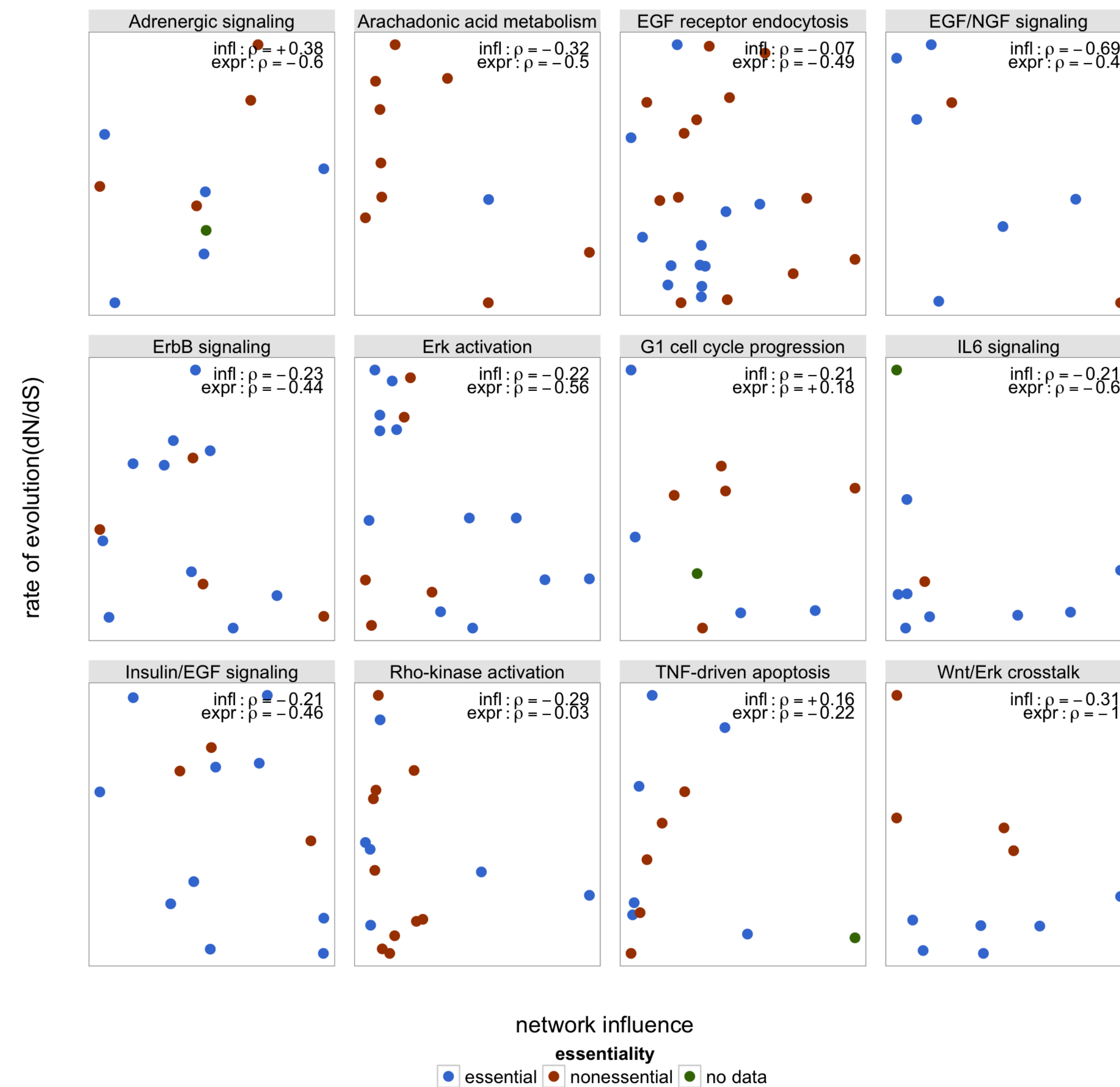
Maximum-likelihood estimates of the rate of nonsynonymous to synonymous substitution (dN/dS) were inferred with PAML, using alignments and sequences from Homologene and GenBank. The species tree used is shown in **Figure 2**.

Figure 2 - Species used



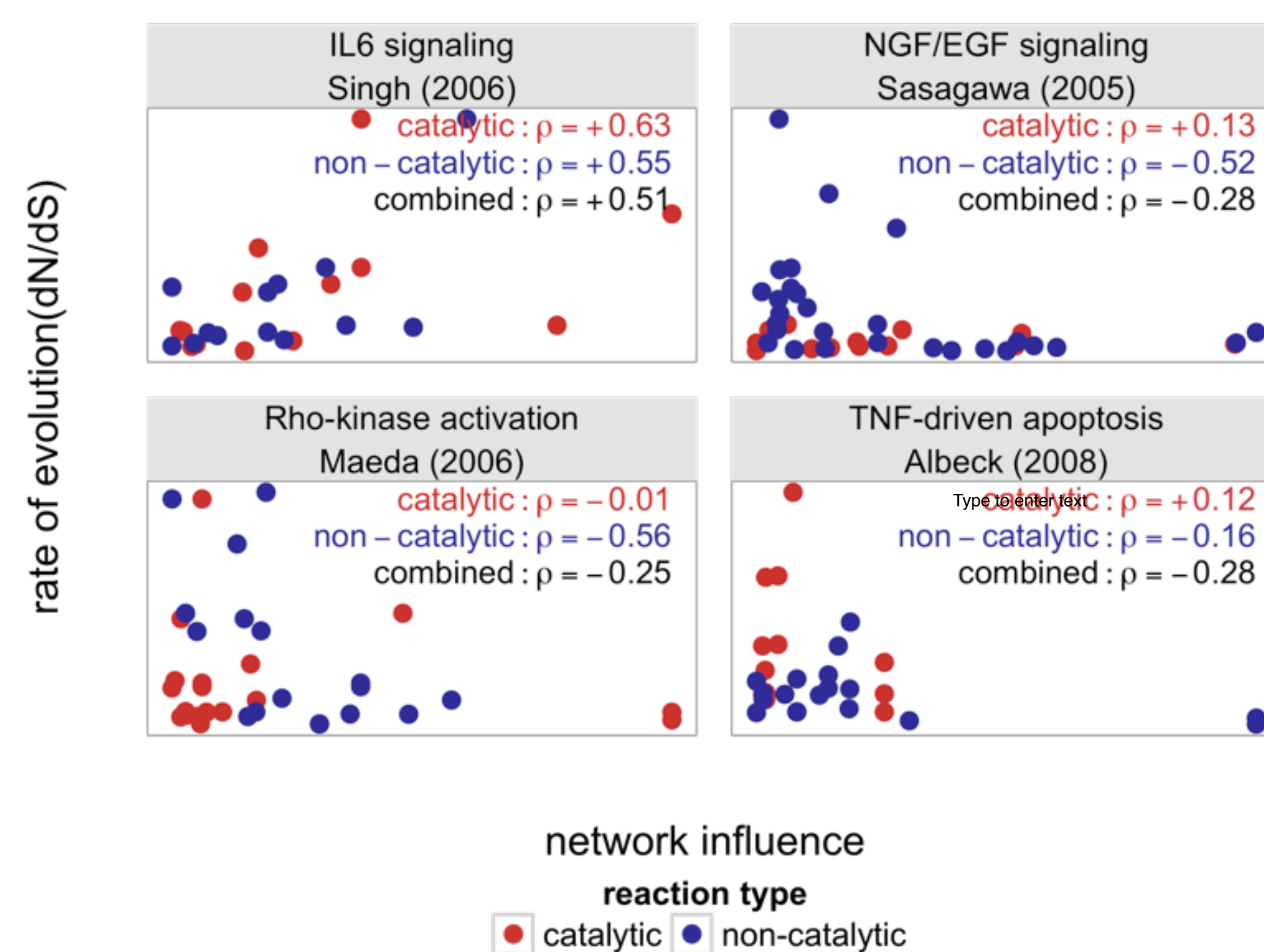
Data

Figure 3 - Correlation in real biochemical networks



We tested all models in the BioModels database possessing 8 or more species annotated with UniProt identifiers. Results are shown in **Figure 3**. For 10 out of 12 models we see a negative correlation between evolutionary rate dN/dS and dynamical influence D . Individual p -values (from one-sided permutation tests) are not dramatic, but the probability that 10 of 12 systems would show a negative correlation by chance is less than 4%. As shown in **Figure 4** below, we have analyzed four of these models at the protein domain level and find that the correlation between dynamical influence and evolutionary rate increases. Additionally, we find evidence suggesting that catalytic domains and protein-protein interaction domains may be subject to different selective constraints and evolve in different ways.

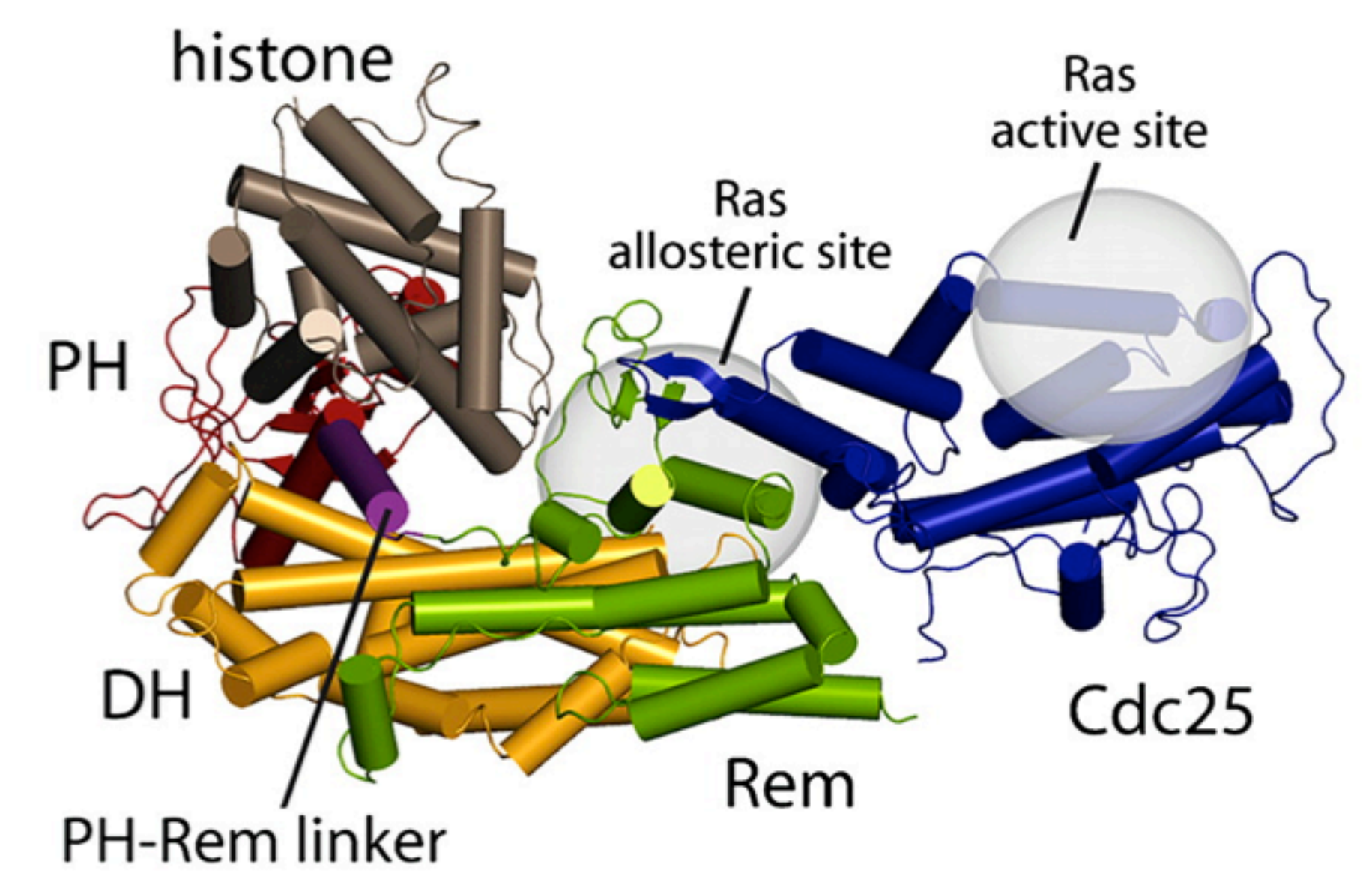
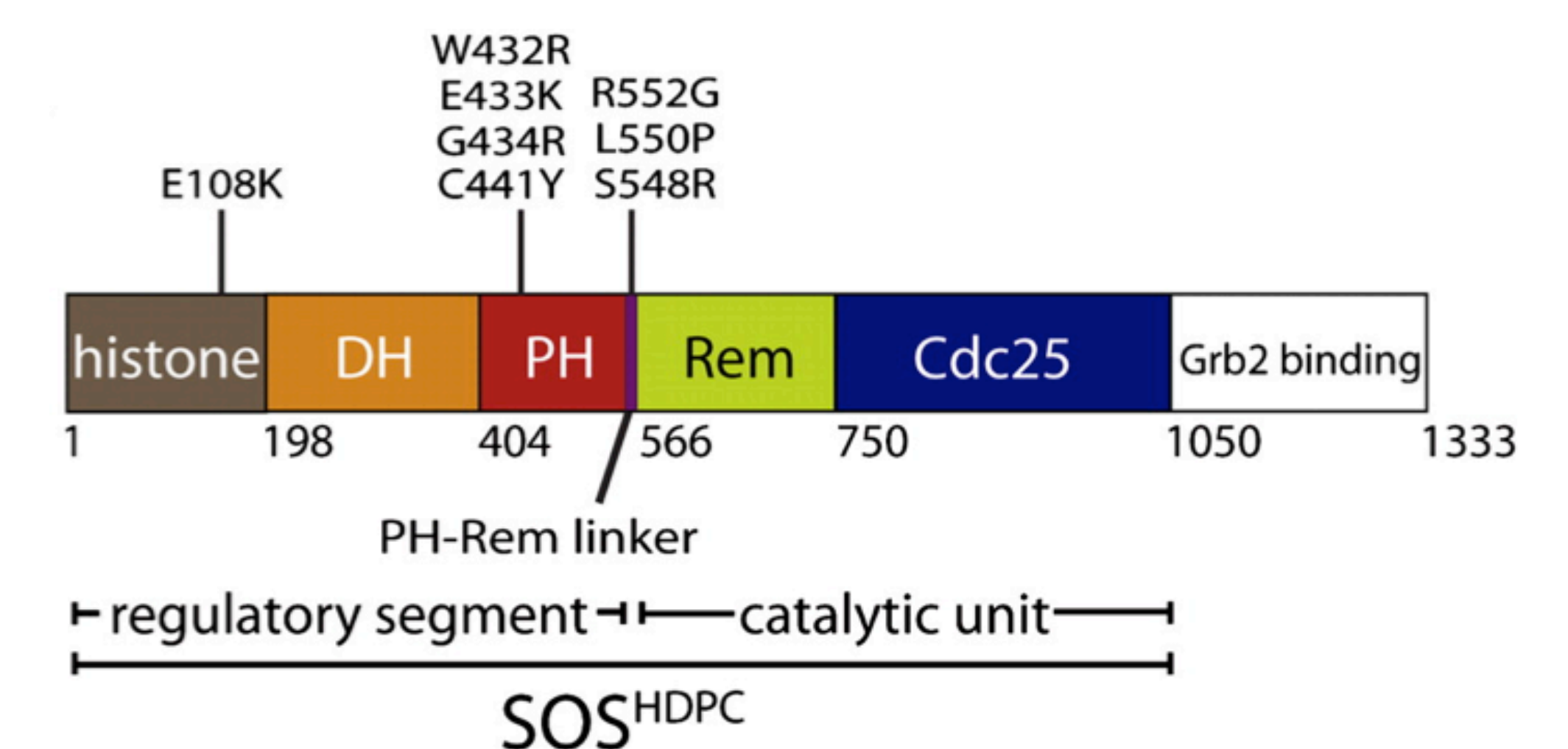
Figure 4 - Correlation at the domain level - Preliminary Results



Protein structure

Proteins are organized into domains which comprise separate functional units, as we see in **Figure 5**. In many cases there are several domains serving both catalytic and protein binding functions. In our analysis presented in **Figure 3** we average all of the reactions in which the protein takes part to calculate its dynamical influence, and we use the evolutionary rate for the entire protein. This averaging causes us to lose information and gives us an opportunity to further refine our analysis. Presently, we are combining bioinformatics with extensive biochemical literature review to identify the domains in each protein and attach each reaction in a biological model to the domain at which it occurs. We have developed a Python package called DynEvol which allows us to curate and analyze this data.

Figure 5- Son of Sevenless domain architecture



SOS^{HDPC} Image: Gureasko et. al. PNAS(2010)

Correlation with essentiality and expression

Figure 3 demonstrates that dynamical influence D shows no correlation with knock-out essentiality E . It is thus an independent (and stronger) functional correlate of evolutionary rate.

Like many factors, dynamical influence is positively correlated with expression level. Tests of the partial correlations between dynamical influence and evolutionary rate, controlling for expression level, suggest that dynamical influence exerts an independent effect.

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