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Evolution of regulatory complexes: a many-body system ARMITA NOUEMOHAMMAD[1], Lewis-Sigler Institute, Princeton University, MICHAEL LAESSIG[2], Institute for theoretical Physics, University of Cologne — In eukaryotes, many genes have complex regulatory input, which is encoded by multiple transcription factor binding sites linked to a common function. Interactions between transcription factors and site complexes on DNA control the production of protein in cells. Here, we present a quantitative evolutionary analysis of binding site complexes in yeast. We show that these complexes have a joint binding phenotype, which is under substantial stabilizing selection and is well conserved within Saccharomyces paradoxus populations and between three species of Saccharomyces. At the same time, individual low-affinity sites evolve near-neutrally and show considerable affinity variation even within one population. Thus, functionality of and selection on regulatory complexes emerge from the entire cloud of sites, but cannot be pinned down to individual sites. Our method is based on a biophysical model, which determines site occupancies and establishes a joint affinity phenotype for binding site complexes. We infer a fitness landscape depending on this phenotype using yeast whole-genome polymorphism data and a new method of quantitative trait analysis. Our fitness landscape predicts the amount of binding phenotype conservation, as well as ubiquitous compensatory changes between sites in the cloud. Our results open a new avenue to understand the regulatory "grammar" of eukaryotic genomes based on quantitative evolution models.

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