Nature Reviews Genetics | AOP, published online 4 March 2014; doi:10.1038/nrg3703

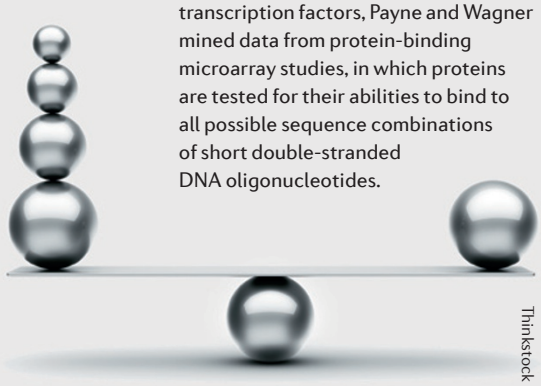
EVOLUTION

Boom and robust

> “systems may be ‘wired’ in both a robust and an evolvable way”

In the face of mutations, biological systems can gain from two seemingly opposite phenomena: robustness, which buffers the effects of otherwise deleterious mutations to preserve phenotypes and survival; and evolvability, in which mutations alter phenotypes to provide potential adaptive benefits. Theoretical modelling studies have suggested that robustness and evolvability can actually be parallel (rather than conflicting) phenomena; a new study now provides experimental support for the simultaneous robustness and evolvability of transcription factor binding sites.

To interrogate the sequence specificities of 104 mouse and 89 yeast transcription factors, Payne and Wagner mined data from protein-binding microarray studies, in which proteins are tested for their abilities to bind to all possible sequence combinations of short double-stranded DNA oligonucleotides.



Thinkstock

For each transcription factor, they assembled genotype–phenotype maps. In these network maps, each bound sequence is depicted by a node, and connections (that is, ‘edges’) between nodes represent one-step mutational routes (single-nucleotide substitutions, insertions or deletions) between different binding sites.

The genotype–phenotype maps revealed various interesting properties. Each map was typically large and highly interconnected (more so than expected by chance). This indicates robustness for transcription factor binding, as many binding-site mutations can be tolerated to maintain this *in vitro* phenotype of transcription factor binding. For example, for the mouse forkhead box protein A2 (FOXA2) transcription factor, bound sites can tolerate on average 37% of all possible single-nucleotide mutations. Additionally, the sequences with highest *in vitro* binding affinity showed the greatest robustness; these high-affinity sites were enriched for transcription factor binding *in vivo* from chromatin immunoprecipitation followed by sequencing (ChIP–seq) data, which implies that *in vivo* binding sites are frequently mutationally robust.

The authors assessed evolvability by integrating maps across different transcription factors. Given that *cis*-regulatory changes underlie various morphological differences between species, the ability of a sequence bound by a given transcription factor to be instead bound by a different transcription factor following a single-nucleotide mutation was used as a proxy for evolvability. The authors found extensive evolvability; for example, for FOXA2-bound sequences, every possible mutation resulted in a binding sequence for at least one other transcription factor.

Crucially, among the transcription factors assessed, as the number of different binding sites increased, so did both robustness and evolvability. Thus, for transcription factor binding sites, robustness and evolvability are intrinsically interconnected, rather than conflicting, and the degree of sequence specificity in transcription factors can ‘fine-tune’ the levels of both robustness and evolvability.

This study shows that, at least for the simple molecular phenotype of transcription factor binding, systems may be ‘wired’ in both a robust and an evolvable way, thus potentially providing the evolutionary benefits of both phenomena. It will be interesting to characterize the interplay of mutational robustness and evolvability for additional phenotypes, particularly those at the organismal level.

Darren J. Burgess

ORIGINAL RESEARCH PAPER Payne, J. L. & Wagner, A. The robustness and evolvability of transcription factor binding sites. *Science* **343**, 875–877 (2014)