From Structural Genomics to Personalized Medicine

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Abstract

Structural genomics spurred many computational techniques to characterize the function of protein structures and the health impact of their variants. A fundamental difficulty remains, however, that both depend on a surrounding context that is unique, complex and often cryptic. To address these problems we present an integrative framework for propagating structural, functional and evolutionary information *smoothly*. For example, first, smoothness helps elucidate molecular function on a structural proteomic scale [*PNAS* (2013) PMID: 24145433] then, after generalization, on a supergenomic scale spanning genes from hundreds of species. Wet lab experiments validate function and substrate predictions and include the discovery that Exp-1 is a new malarial glutathione-s-transferase that metabolizes hematin and inhibited by Artesunate. This observation opens a new therapeutic window against malaria since Artesunate is the best current malarial drug, but its herbal origin has until now kept its mechanism unknown, even as resistance against it rises [*Cell* (2014) PMID: 25126794]. Another example of the use of smoothness is evolution, in which it suggests that the genotype-phenotype relationship is differentiable and obeys a perturbation equation for the Action of coding mutations on fitness. This Action equation evaluates easily and predicts accurately the effect of protein coding mutations *in vivo* and *in vitro*; the morbidity and mortality of mutations in disease-causing genes; and the frequency distribution of human coding polymorphisms foreseen in 1930 by Fisher [*Genome Research* (2014) PMID: 25217195]. Thus multi-scale evidence spanning molecular, clinical, and population genetics data suggests that an emerging evolutionary calculus can unify structural proteomics and genomics by linking genes to functions and point mutations to fitness perturbations. Although unusual, this quantitative framework for differential equations of biology is consistent with current evolutionary theory and, in practice, already finds clinical and therapeutic applications that complement other efforts towards personalized medicine [*Cancer Research* (2015): PMID:25634208].