

Center for Theoretical Biological Physics



SEMINAR

“Genotype to Phenotype? How about Physicochemical to Fitness Instead?”

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BRC, 10th Floor, Rm 1060 A/B

Abstract: In principle, evolutionary outcomes could be largely predicted if all the relevant physicochemical variants of a particular protein function under selection were known and integrated into an appropriate physiological model. We have tested this principle by generating a family of variants of the tetracycline resistance protein TetX2 and identified the physicochemical properties most correlated with organismal fitness. Surprisingly, small changes in the $K_{m(MCN)}$, less than 2-fold, were sufficient to produce highly successful adaptive mutants over clinically relevant drug concentrations. We then built a quantitative model directly relating the *in vitro* physicochemical properties of the mutant enzymes to the growth rates of bacteria. Using experimental evolution and deep sequencing to monitor the allelic frequencies of the seven most biochemically efficient TetX2 mutants in independently evolving populations, we showed that the model correctly predicted the evolutionary outcomes. Our findings support an important role for readily accessible small steps in protein evolution that can, in turn, greatly increase the fitness of an organism during natural selection.