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A FRAMEWORK FOR EVOLUTIONARY SYSTEMS BIOLOGY

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Many hard problems in evolutionary genomics are related to mutations that have weak effects on fitness, as the consequences of mutations with large effects are often simple to predict. Current systems biology has accumulated much data on mutations with large effects and can predict the properties of knockout mutants in some systems. However experimental methods are too insensitive to observe small effects. Here I propose a novel framework that brings together evolutionary theory and current systems biology approaches in order to determine small effects of mutations and their epistatic interactions *in silico*. Central to this approach is the definition of fitness correlates that can be computed in some current systems biology models employing the rigorous algorithms that are at the core of much work in computational systems biology. The framework exploits synergies between the realism of such models and the need to understand real systems in evolutionary theory. Using these fitness correlates one can address many longstanding questions in evolutionary biology, including the nature of advantageous mutations, the distribution of mutational effects on fitness, epistasis and robustness. A combination of evolutionary and systems biology analyses is expected to benefit both branches of biology as has been already the case with molecular biology and genomics.