

MAR11-2010-007028

Abstract for an Invited Paper
for the MAR11 Meeting of
the American Physical Society

Understanding the distribution of fitness effects of mutations by a biophysical-organismal approach

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The distribution of fitness effects of mutations is central to many questions in evolutionary biology. However, it remains poorly understood, primarily due to the fact that a fundamental connection that exists between the fitness of organisms and molecular properties of proteins encoded by their genomes is largely overlooked by traditional research approaches. Past efforts to breach this gap followed the “evolution first” paradigm, whereby populations were subjected to selection under certain conditions, and mutations which emerged in adapted populations were analyzed using genomic approaches. The results obtained in the framework of this approach, while often useful, are not easily interpretable because mutations get fixed due to a convolution of multiple causes. We have undertaken a conceptually opposite strategy: Mutations with known biophysical and biochemical effects on *E. coli*'s essential proteins (based on computational analysis and in vitro measurements) were introduced into the organism's chromosome and the resulted fitness effects were monitored. Studying the distribution of fitness effects of such fully controlled replacements revealed a very complex fitness landscape, where impact of the microscopic properties of the mutated proteins (folding, stability, and function) is modulated on a macroscopic, whole genome level. Furthermore, the magnitude of the cellular response to the introduced mutations seems to depend on the thermodynamic status of the mutant.