

**THE DISTRIBUTION OF FITNESS EFFECTS OF BENEFICIAL MUTATIONS IN
*PSEUDOMONAS AERUGINOSA***

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The distribution of fitness effects of spontaneous beneficial mutations is crucial to our understanding of adaptation by natural selection. Population genetic theory predicts that this distribution is exponential whenever fitness is high, suggesting that a mechanistic understanding of the fitness effects of beneficial mutations derived from systems biology may contribute little to our understanding of the properties of beneficial mutations. To test this idea, we used an experimental evolution approach involving adaptation to the antibiotic rifampicin in the opportunistic human pathogen *Pseudomonas aeruginosa*. As predicted by population genetic theory, the fitness effects of beneficial mutations are exponentially distributed when the fitness of the wild-type is high. However, when the fitness of the wild type is low, the fitness effects of beneficial mutations are no longer exponentially distributed because of a bias towards mutations of large effect. We show that this non-exponential distribution can be explained by a detailed structural understanding of the interactions that occur between rifampicin and RNA polymerase. This work shows how a detailed mechanistic understanding of genes under selection, in this case derived from structural biology, can be integrated with statistical population genetics to understand how beneficial mutations impact fitness. At a more applied level, our results suggest that systems biology approaches are critical for being able to predict the evolution of antibiotic resistance.