

TEMPO AND MODE OF COMPENSATORY EVOLUTION

Ana Sousa¹, Isabel Gordo¹

¹*Instituto Gulbenkian de Ciencia, Oeiras, Portugal*

amsousa@igc.gulbenkian.pt

How does a perfectly adapted genome deal with a single alteration in its code? Here we address this question by studying the distribution of compensatory mutations of a bacterium that carries a single nucleotide substitution that confers antibiotic resistance. Reducing antibiotic therapy to the minimum has long been a main policy to decrease resistance in microbial populations since the fitness cost that chromosomal resistance mutations often confer to the cells makes them less competitive. Counteracting this is selection for a decreased cost of resistance. This can be accomplished by reversion of the resistance mutation or acquisition of a second site compensatory mutation, restoring fitness close or equal to the sensitive strains level. Under most conditions compensation rather than reversion is a more frequent event. Given the importance of compensation in general and in the context of antibiotic resistance prevalence, accurate measurements of the tempo and mode of its evolution is an urgent necessity. We assessed the rate and distribution of compensatory mutations using a powerful technique, based on a neutral marker that enables the quantification of very small effect mutations arising and sweeping to fixation in bacterial populations. Importantly this method is unique in its power of detection at a very small time scale. Our results show that adaptation depends on the starting point on the fitness landscape and that compensatory mutations can be detected in tenths of generations. Furthermore, for some resistant clones, compensatory mutations sweep to fixation in only ~100 generations. This observation is in accordance with the theoretical prediction that “at least half the gain in fitness that occurs during adaptation is due to a single substitution”.