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Mutational pathways to drug resistance through a maximally-rugged fitness landscape ADAM PALMER, ERDAL TOPRAK, Department of Systems Biology, Harvard Medical School, Boston, MA, USA, SEUNGSOO KIM, ADRIAN VERES, Faculty of Arts and Sciences, Harvard University, Cambridge, MA, USA, SHIMON BERSHTEIN, Department of Chemistry and Chemical Biology, Harvard University, Cambridge, MA, USA, ROY KISHONY, Department of Systems Biology, Harvard Medical School, Boston, MA, USA — Recent laboratory evolution experiments have identified surprising properties in the evolution of trimethoprim resistance in *E.coli* through mutation of the drug's target, DHFR: (1) mutations are acquired in a reproducibly ordered manner; (2) multiple resistant endpoints exist; and (3) some pathways include mutation reversion or conversion. Here we investigate how these properties emerge from the fitness landscape of DHFR by characterizing all combinations of observed DHFR mutations. We see that the effects of mutations are so profoundly dependent on other mutations that sign-epistasis is nearly maximised, and the distributions of most mutations' effects are indistinguishable from randomly increasing or decreasing resistance. This almost 'maximally-rugged' fitness landscape contains multiple separated peaks in drug resistance, and 20% of favourable mutational steps are the loss or conversion of a previously acquired mutation. Select pathways through the rugged landscape avoid a common tradeoff between growth and resistance. Empirical characterization of this fitness landscape has identified that ordered but sometimes indirect mutational pathways to multiple endpoints arises from near-maximal levels of sign epistasis.

Adam Palmer
Dept of Systems Biology, Harvard Medical School, Boston, MA, USA

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