

The Goldilocks Principle and Rapid Evolution of Resistance

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Evolution proceeds via mutations and selective pressure to fix the mutations, and needs the right conditions for optimum rates. We show here that through tuning the spatial gradients of metabolic stress by micro-nanofluidic techniques that there exists a “just right” region on a multidimensional stress landscape where rapid evolution of the resistance of to the antibiotic ciprofloxacin (Cipro) ignites in several hours and rapidly spreads across the entire landscape. Although evolution occurs in well-stirred chemostats without stress gradients, natural environments are rarely well stirred in nature, as Darwin realized on the Galapagos Islands. For complex environments such as the Galapagos Islands, spatial genotoxic stress gradients can be as important as genomic heterogeneity in setting the speed of the evolution of resistance under stress. If the local population of cells in the presence of a high stress gradient is very small it is very unlikely to find locally a resistant persister and the population may be apparently doomed to extinction. However, mutation rates are often greatly increased under conditions of high stress due to the mutagenic SOS response. Further, and paradoxically, if the local mutagenic SOS response succeeds in the creation of a mutant resistant genome within a local small population, since fixing times scale inversely with the population size, a rapid fixation of that resistant genome can occur if the mutants move to the region of higher stress, not lower stress. Thus it is expected that evolution of resistance to genotoxic stress will occur most rapidly along a spatial gradient of the stress in the direction of higher stress if the gradient creates a chain of locally small metapopulations where the combination of SOS induced high mutation rates and rapid fixing times of the small metapopulation overcomes the dreary prospects of extinction.