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# Multi-scale ecological modeling of plasmid-borne multi drug resistance in hospital-like heterogeneous environments

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## Abstract

**Background** - Plasmid-borne multi-drug resistance (MDR) can result from the accumulation in a bacterial cell of multiple resistance plasmids, or from larger plasmids carrying multiple resistance genes. These MDR genotypes yield similar resistance phenotypes, yet they entail distinct evolutionary strategies promoting either stability (few, larger plasmids) or local adaptation (distinct, smaller plasmids that can be gained or lost independently). We hypothesize that the optimal evolutionary strategy depends on environmental structure. Using a simulation approach, we explore how hospital-like structures influence the competitive spread of plasmid-borne MDR bacterial strains with stable or adaptable genotypes.

**Methods** - We developed *msevol*, a multi-scale, stochastic simulation framework adapted to the setting of large metapopulations of resistant bacteria sharing plasmids by horizontal transfer. A hospital-like structure was modeled as a set of interconnected niches, mimicking wards, with variable antibiotic pressures and connectivity patterns. Analyses were focused on three actionable parameters representing antimicrobial stewardship and infection control strategies, namely total antibiotic pressure, between-ward heterogeneity of antibiotic use, and between-ward transmission rate. Biological events such as plasmid fitness cost or conjugation rate were parameterized from previous studies.

**Results** - In a spatially structured environment, we identified the conditions favoring the survival and spread of a locally adaptable, two-plasmid bacterial lineage over a stable, one-plasmid lineage. These conditions, that reduced the overall prevalence of MDR, met three key criteria: (1) selective pressures exhibited sufficient between-ward heterogeneity to ensure that the loss of a costly and non-essential resistance trait confers a fitness advantage across all wards; (2) bacterial transmission between wards was slow enough to prevent the stable MDR lineage from compensating for their fitness disadvantage through high transmission

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rates; (3) transmission was fast enough to avoid the locally adapted lineages to be trapped locally during bacterial colonization and competition.

**Conclusions** - Our simulations predict that, in spatially structured environments such as hospitals, antibiotic stewardship and infection control have a synergistic influence on antimicrobial resistance. Simulations of hospital-like ecosystems may provide a new framework for the construction of evolution-informed strategies against antimicrobial resistance.

**Keywords:** multidrug resistance, plasmids, stochastic simulations