Mutators drive evolution of multi-resistance to antibiotics

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Intro

Can combination treatment prevent resistance evolution?

- Antibiotics take time to reach effective concentrations
- Mutators (higher mutation rate) are found in infections

Methods

1 | Experimental evolution

- wild-type *E. coli* K-12 BW25113 and mutator Δ*mutS*
- mutator introduced as 0%–30% of initial population
- antibiotics used: rifampicin, nalidixic acid, or combination
- concentrations increased over time

2 | Eco-evolutionary simulations

- interacting logistic growth (like Lotka-Volterra competition)
- stochastic reproduction and mutations
- growth and mutation rates parameterised experimentally

Key results

Where and how did double resistance evolve?

- in all single-drug and combination treatments
- only in the mutator genetic background
- through sequentially acquiring each resistance

Why did double resistance evolve?

- genetic hitch-hiking of mutators in single-drugs
- direct fitness benefit in combination treatment

What effect did mutators have on fitness?

- increased variability in fitness
- weak evidence for build-up of deleterious mutations
- minimal trade-off with antibiotic-free fitness

Discussion

Should we use combinations more widely?

- combinations precipitate spread of high-fitness mutators
- mutators are common in infections
- this may increase the evolvability of resistance

See our preprint on bioRχiv http://doi.org/c6dd
& GitHub: https://github.com/dannagifford/multi-resistance

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Mutators let populations evolve **multiple independent resistance mutations** during single-drug & combination antibiotic treatments.