Evolutionary rescue theory, antibiotic resistance and the details of bacterial infection

van Eldijk, Timo; Weissing, Franz

Does evolutionary rescue theory predict the evolution of antibiotic resistance?

Timo van Eldijk & Franjo Weissing

MARM-group, Groningen Institute for Evolutionary Life Sciences, University of Groningen, The Netherlands

For correspondence: T.J.B.van.Eldijk@rug.nl

Background & Question

When a population faces a novel (stressful) environment this may cause the population to decline. In such situations **evolutionary rescue theory** aims to predict the probability that a population adapts to the new environment (rescue), instead of facing the otherwise inevitable extinction. Thus, evolutionary rescue theory has the potential to help us understand when to expect the evolution of antibiotic resistance in bacterial populations. Yet, current models of evolutionary rescue fail to account for the mechanisms deployed by bacteria to cope with stressful conditions (like the presence of antibiotics). Here we examine two such mechanisms using stochastic modelling. First we examine the effect of **biofilm formation**, which occurs in the majority of bacterial infections. Biofilms have an explicit spatial structure, whilst standard evolutionary rescue theory assumes well-mixed populations. Secondly we examine the influence of **persister cells**, these are dormant cells that tolerate antibiotics exposure, which are also not modeled in standard evolutionary rescue theory.

How does biofilm formation and the presence of persister cells influence the probability of evolutionary rescue?

Conclusions

1. Spatial structure leads to a decreased rescue probability.
2. This is due to invading mutants locally competing mostly with themselves in spatially structured populations.
3. At high abundance (10 - 100%) the presence of persister cells increases the rescue probability.
4. However, at realistic (0 -10%) abundances persister cells do not influence the rescue probability.
5. Modelling the mechanisms that bacteria use to cope with stressful environments is important for accurately predicting antibiotic resistance.

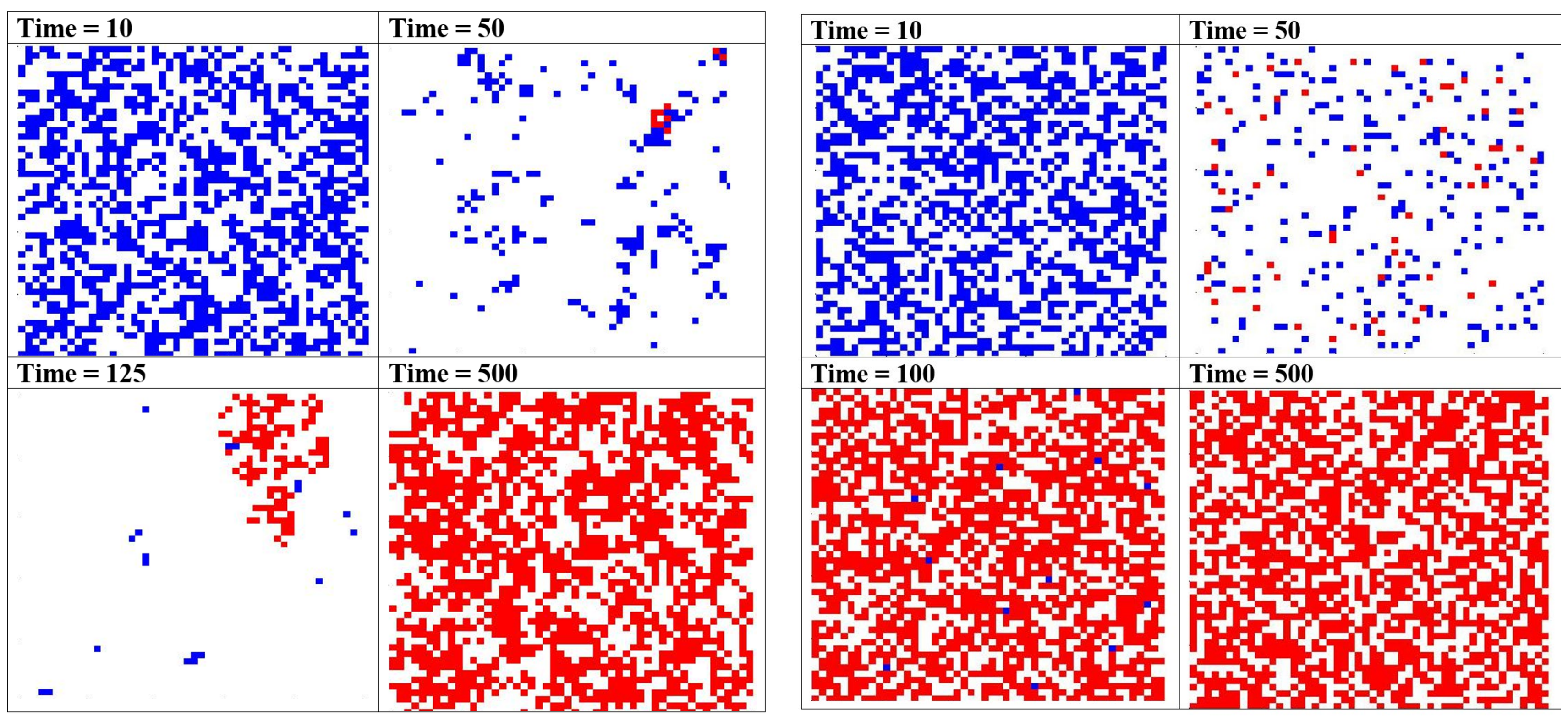
Model biofilm

Assumptions

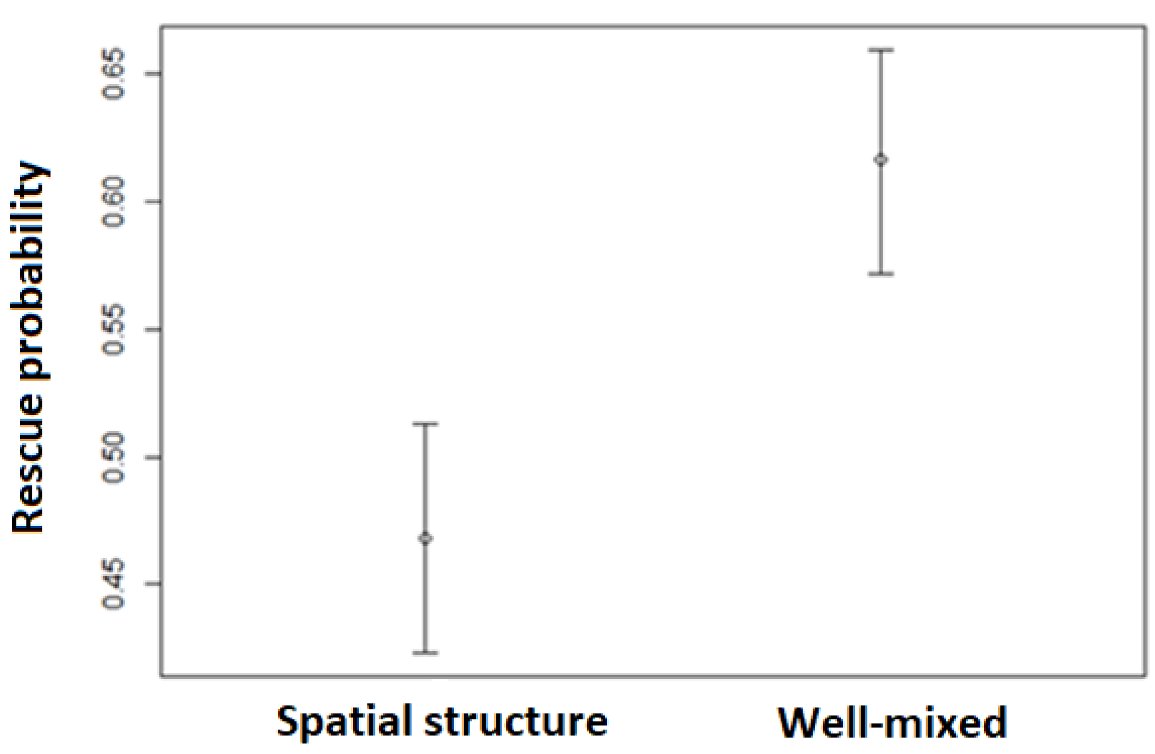
- Cellular automaton
- Susceptibles (negative growth rate, blue)
- Resistants (positive growth rate, red)
- Residents → Resistants (μ)
- 50 X 50 grid, intially filled with suceptibles

Example simulations

Spatial structure, biofilm | **Well-mixed, standard rescue theory**



Summary of results



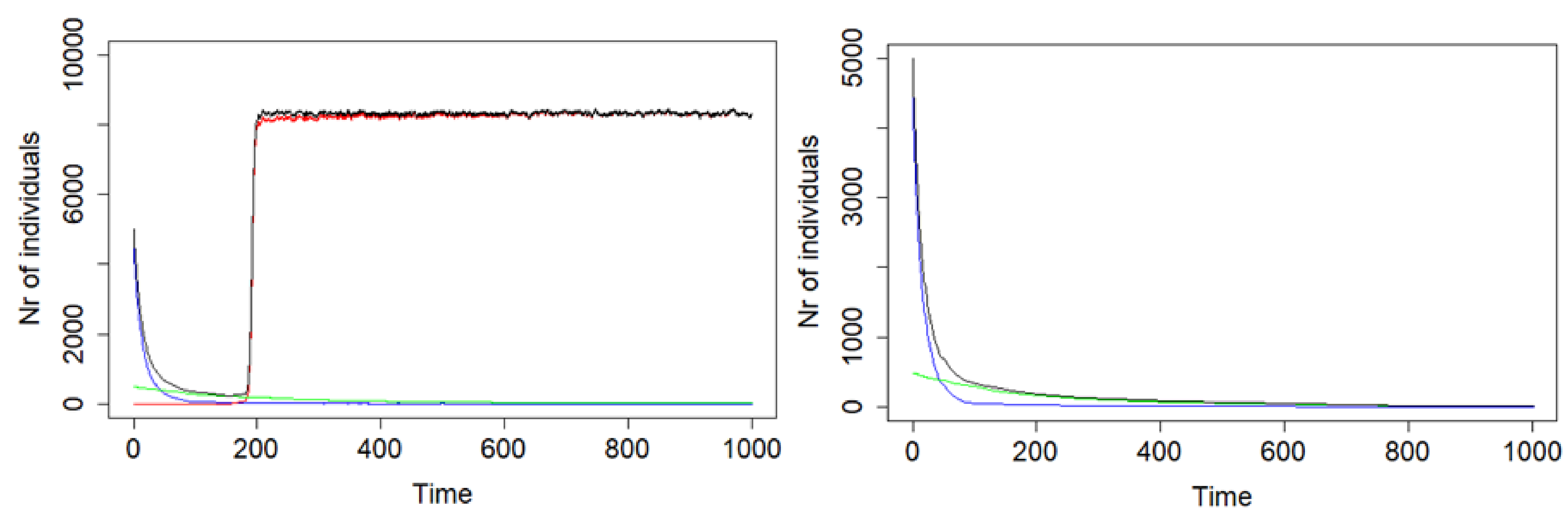
- Significant difference in rescue probability (Fisher's exact test, $p < 0.001$)

Model persister cells

Assumptions

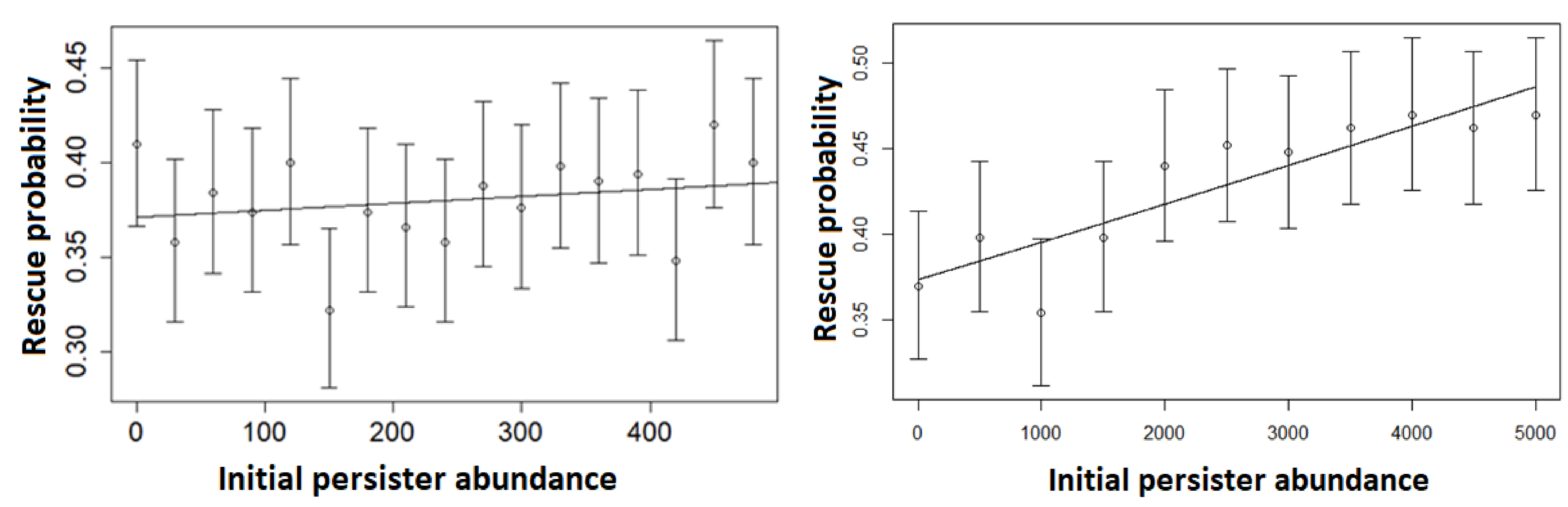
- Susceptibles (negative growth rate, blue)
- Resistants (positive growth rate, red)
- Persisters (no birth or death, green)
- Suceptibles → Persisters (P_{in})
- Suceptibles → Resistants (μ)
- Persisters → Suceptibles (P_{out})

Example simulations



Summary of results

Realistic persister abundance (0-10%) | **High persister abundance (10-100%)**



- No significant effect of initial persister abundance (chi-squared test p=0.303)
- Significant effect of initial persister abundance (chi-squared test $p < 0.001$)

This population is no more! It has ceased to be! 'E's expired and gone to meet 'is maker! 'E's a stiff! Bereft of life, 'e rests in peace! If you hadn't nailed it to the perch 'e'd be pushing up the daisies! 'Is metabolic processes are now 'istory! 'E's off the twig! 'E's kicked the bucket, 'e's shuffled off 'is mortal coil, run down the curtain and joined the bleedin' choir invisible!! THIS IS AN EX-POPULATION!