Spatial structure facilitates evolutionary rescue by cost-free drug resistance

Cecilia Fruet
Laboratory of Computational Biology and Theoretical Biophysics

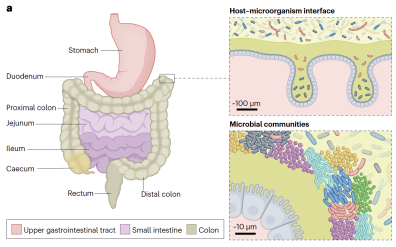
Joint work with: Ella Müller, Claude Loverdo, Anne-Florence Bitbol
Swiss Physical Society meeting - Biophysics section
September 12, 2024

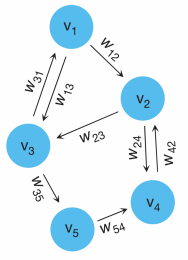
Contents

Contents

Antimicrobial resistance and factors into play

- Mutations $\rightarrow$ **adaptation** to hostile environments (increase in MIC - lowest concentration to inhibit growth);
- Communities and complex **spatial** structures[1,2] $\rightarrow$ **graph** theory[3,4].





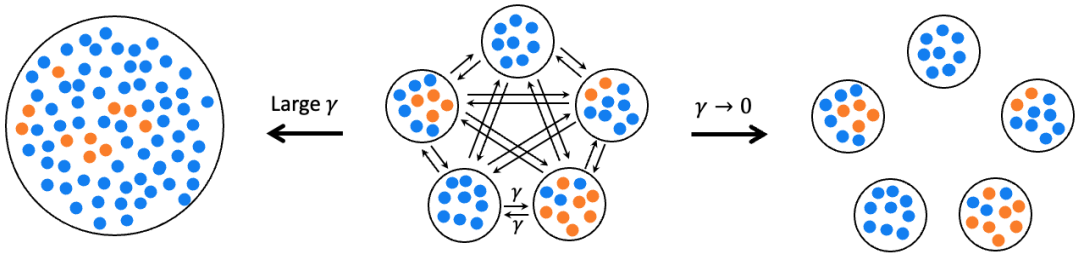
- Environment **changes** in time $\rightarrow$ **timescale** impacts fixation of mutants[5-7].

1. Donaldson, G. P. et al. *Nat. Rev. Microbiol.* (2016)
2. McCallum, G. & Tropini, C. *Nat. Rev. Microbiol.* (2023)
3. Lieberman, E. et al. *Nature* (2005).
4. Allen, B. et al. *Nature* (2017).
5. Marrec, L., & Bitbol, A.-F. *J. Theor. Biol.* (2018).
6. Marrec, L. & Bitbol, A.-F. *PLoS Comput. Biol.* (2020).
7. Morsky, B. & Vural, D. C. *Theor. Ecol.* (2022).

Contents

Model and methods I

Not only the population size matters, but also the **spatial organization**:



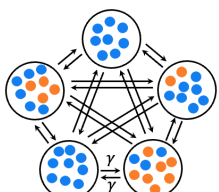
Well-mixed population (WMP)

Clique-structured population

Fully structured population (SP)

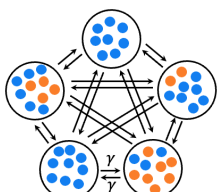
Model and methods II

- System with • (sensitive, S, fitness f_S) and • (resistant, R, fitness f_R) individuals;
- Focus on **neutral** mutants;
- When add biostatic drug: $f_S = 0$;
- Events:



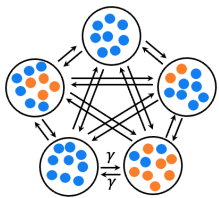
Model and methods II

- System with • (sensitive, S, fitness f_S) and • (resistant, R, fitness f_R) individuals;
- Focus on **neutral** mutants;
- When add biostatic drug: $f_S = 0$;
- Events:
  1. **Birth** with logistic regulation (carrying capacity K, eq. population size N)
     - rate $f_S(1 - N/K)$ for S
     - rate $f_R(1 - N/K)$ for R



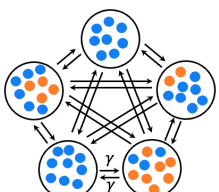
Model and methods II

- System with • (sensitive, S, fitness f_S) and • (resistant, R, fitness f_R) individuals;
- Focus on **neutral** mutants;
- When add biostatic drug: $f_S = 0$;
- Events:
  1. **Birth** with logistic regulation (carrying capacity K, eq. population size N)
     - rate $f_S(1 - N/K)$ for S
     - rate $f_R(1 - N/K)$ for R
  2. **Mutation** to resistant at birth, probability μ



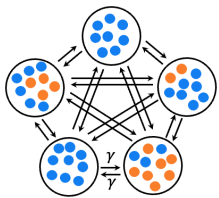
Model and methods II

- System with • (sensitive, S, fitness f_S) and • (resistant, R, fitness f_R) individuals;
- Focus on **neutral** mutants;
- When add biostatic drug: $f_S = 0$;
- Events:
  1. **Birth** with logistic regulation (carrying capacity K, eq. population size N)
     - rate $f_S(1 - N/K)$ for S
     - rate $f_R(1 - N/K)$ for R
  2. **Mutation** to resistant at birth, probability μ
  3. **Death**, rate g



Model and methods II

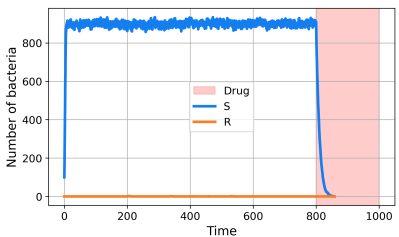
- System with • (sensitive, S, fitness f_S) and • (resistant, R, fitness f_R) individuals;
- Focus on **neutral** mutants;
- When add biostatic drug: $f_S = 0$;
- Events:
  1. **Birth** with logistic regulation (carrying capacity K, eq. population size N)
     - rate $f_S(1 - N/K)$ for S
     - rate $f_R(1 - N/K)$ for R
  2. **Mutation** to resistant at birth, probability μ
  3. **Death**, rate g
  4. **Migration** between demes, rate γ.



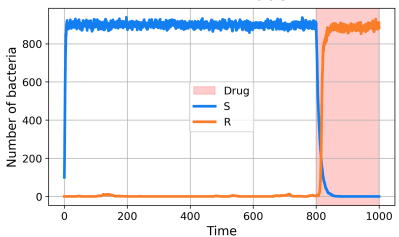
Addition of biostatic drug at T_{add}

In a well-mixed population[5,6]:

Most of the times: extinction.



If at least one R at T_{add}: **rescue**.



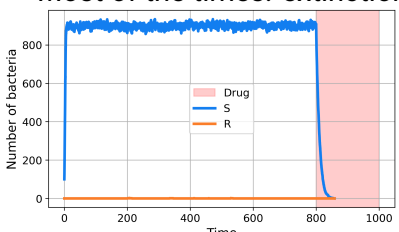
5. Marrec, L., & Bitbol, A.-F. *J. Theor. Biol.* (2018).

6. Marrec, L., & Bitbol, A.-F. *PLoS Comput. Biol.* (2020).

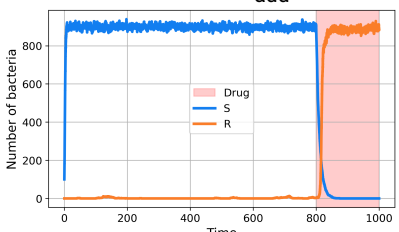
Addition of biostatic drug at T_{add}

In a well-mixed population[5,6]:

Most of the times: extinction.



If at least one R at T_{add}: **rescue**.

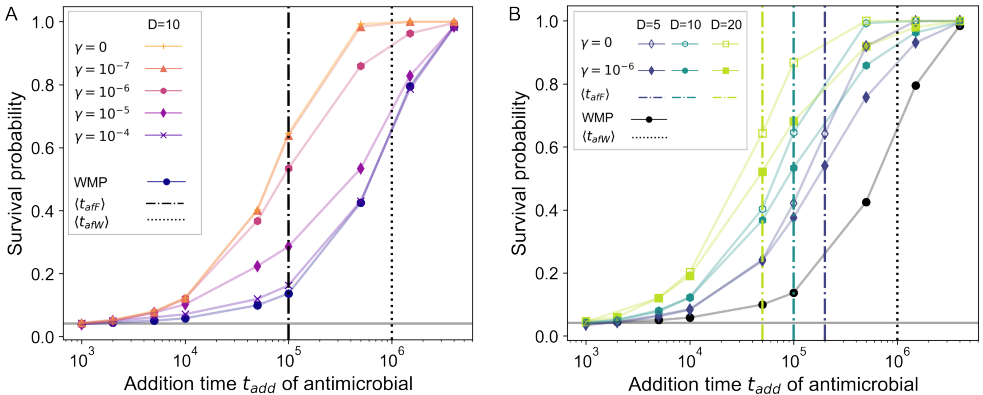


5. Marrec, L., & Bitbol, A.-F. *J. Theor. Biol.* (2018).

6. Marrec, L., & Bitbol, A.-F. *PLoS Comput. Biol.* (2020).

What is the effect of **spatial population structure** when adding a biostatic drug?

Spatial structure increases the survival probability



Varying the migration rate allows interpolation between WMP and SP.

Local fixation of R mutants promotes survival of the SP

App. time of a neutral mutant that fixes, $\langle t_{af} \rangle$, in a WMP:

$$\langle t_{af\,W} \rangle = \frac{1}{N\mu g} \times N = \frac{1}{\mu g} \quad \rightarrow \text{ Independent of N.}$$

At steady-state
growth rate = death rate:
$f(1 - N/K) = g$;
N eq. pop. size;
μ mutation rate;
D demes;
$1/N\mu g$ appearance time of R;
$1/N$ fixation prob. of R.

Local fixation of R mutants promotes survival of the SP

App. time of a neutral mutant that fixes, $\langle t_{af} \rangle$, in a WMP:

$$\langle t_{af\,W} \rangle = \frac{1}{N\mu g} \times N = \frac{1}{\mu g} \quad \rightarrow \text{ Independent of N.}$$

μg rate for appearance of mutant that fixes

↓

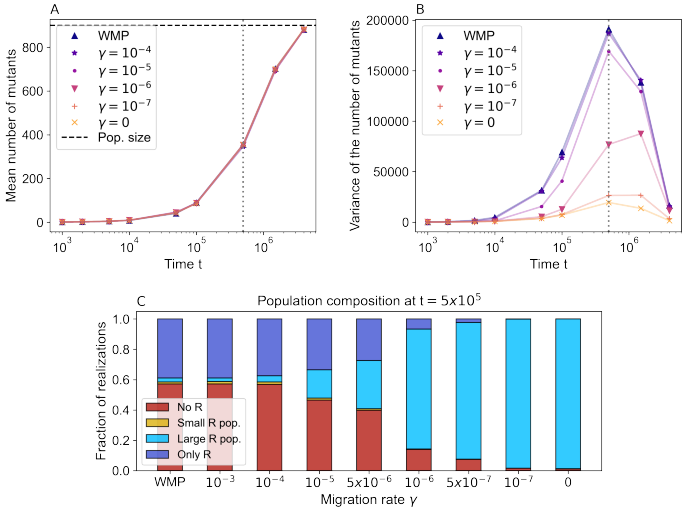
Find prob. density of app. time of mutant that fixes in the fastest deme.

$\langle t_{af} \rangle$ in the Fastest deme of SP:

$$\langle t_{af\,F} \rangle = \frac{1}{D\mu g} < \langle t_{af\,W} \rangle$$

At steady-state
growth rate = death rate:
$f(1 - N/K) = g$;
N eq. pop. size;
μ mutation rate;
D demes;
$1/N\mu g$ appearance time of R;
1/N fixation prob. of R.

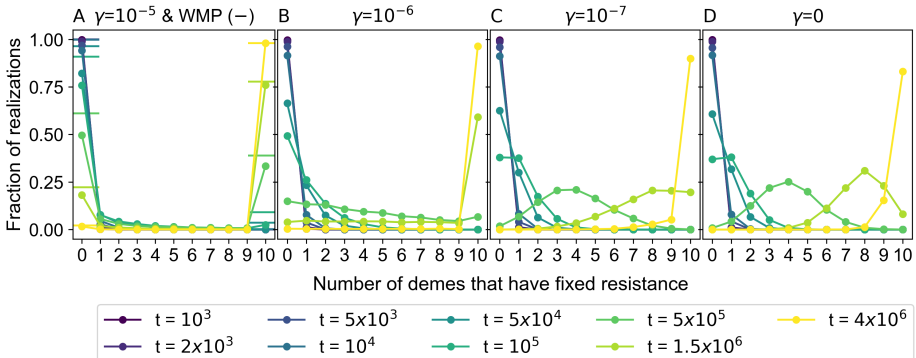
Spatial structure impacts system composition before drug



- Average tot. n. of mutants independent of structure;
- **Variance** of n. of mutants depends on **time** and **structure**.

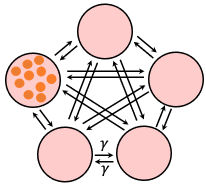
Spatial structure impacts system composition before drug

Demes that have fixed resistance at a specific time, before drug addition:



Populations are **heterogeneous** for intermediate γ.

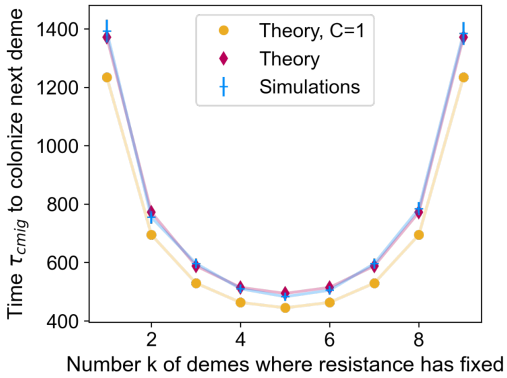
R mutants readily colonize the system after drug addition



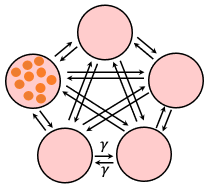
Time to colonization of the next deme:

$$\tau_c(k) = \frac{1}{\gamma N k (D-k)} \times C$$

$C = \frac{1}{1-\frac{g}{f}}$, g death rate, f fitness;
D demes;
N deme eq. pop. size;
γ p. capita migration rate;
k demes where mutants have fixed.



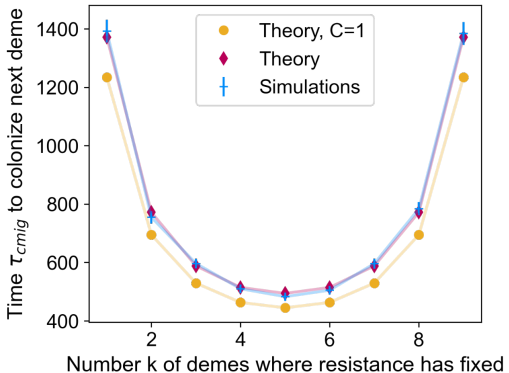
R mutants readily colonize the system after drug addition



Time to colonization of the next deme:

$$\tau_c(k) = \frac{1}{\gamma N k (D-k)} \times C$$

Structure impacts the survival of a population and its spread.



Contents

Conclusions:

- $\langle t_{af\,F} \rangle < \langle t_{af\,W} \rangle \rightarrow$ on average, successful mutants appear **earlier** in the structured population;
- Local fixation of resistant mutants in demes (**refugia**) $\rightarrow$ population survives when drug is added;
- **Migrations** readily allow spread of resistance;
- Conclusions still hold for other **structures** (lattice, star);
- Extension to **biocidal** drugs: local fixation of resistant mutants is not impacted.

Conclusions:

- $\langle t_{af\,F} \rangle < \langle t_{af\,W} \rangle \rightarrow$ on average, successful mutants appear **earlier** in the structured population;
- Local fixation of resistant mutants in demes (**refugia**) $\rightarrow$ population survives when drug is added;
- **Migrations** readily allow spread of resistance;
- Conclusions still hold for other **structures** (lattice, star);
- Extension to **biocidal** drugs: local fixation of resistant mutants is not impacted.

Extensions:

- Add environmental **heterogeneities** (gradients);
- Change framework to **public good** production - extend studies on a well-mixed population;
- Test predictions **experimentally**.

C. Fruet, E. Müller, C. Loverdo, A.-F. Bitbol
Spatial structure facilitates evolutionary rescue by cost-free drug resistance, bioRxiv 10.1101/2024.09.02.610767

Acknowledgments

Joint work with:

- Ella Müller
- Claude Loverdo (CNRS - Sorbonne U.)
- Anne-Florence Bitbol

Thank you for discussions to:

- Alia Abbara
- Arthur Alexandre

The rest of the group & alumni:

- Luca Biggio
- Nicola Dietler
- Cyril Malbranke
- Umberto Lupo
- Alexandre Littiere
- Damien Ribiere
- Richard Servajean
- Damiano Sgarbossa

Swiss National Science Foundation

erc
European Research Council
Established by the European Commission

Thank you for your attention!