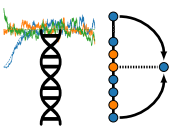
Within-host dynamics of antibiotic resistance

Pete Czuppon
(in collaboration with Troy Day, Florence Débarre & François Blanquart)

BEVAS, Lausanne, April 2023

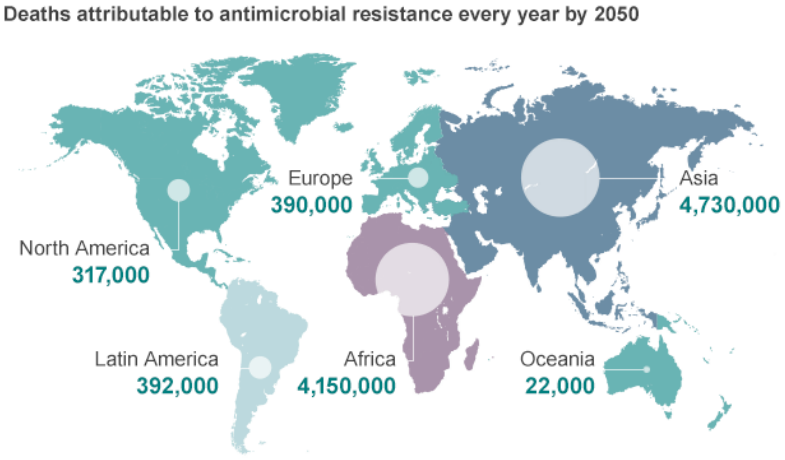


Antibiotic resistance

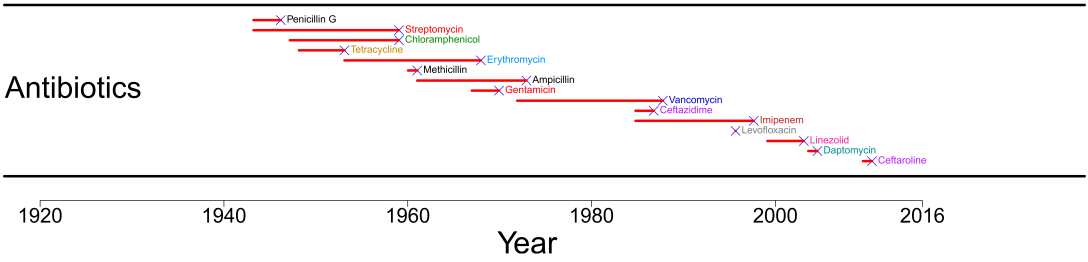
Antibiotic resistance – a public health problem

Currently: $\sim$ 1 million deaths per year

(Murray et al. (2022), Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis, *The Lancet*)

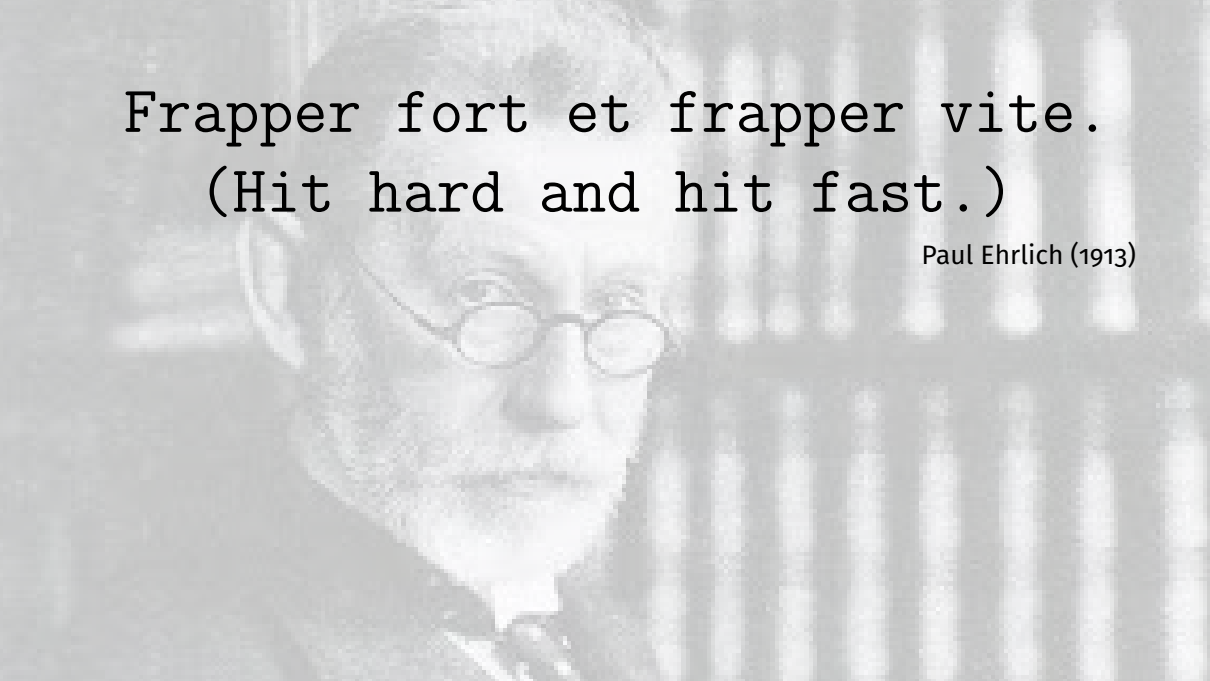


Resistance always evolves



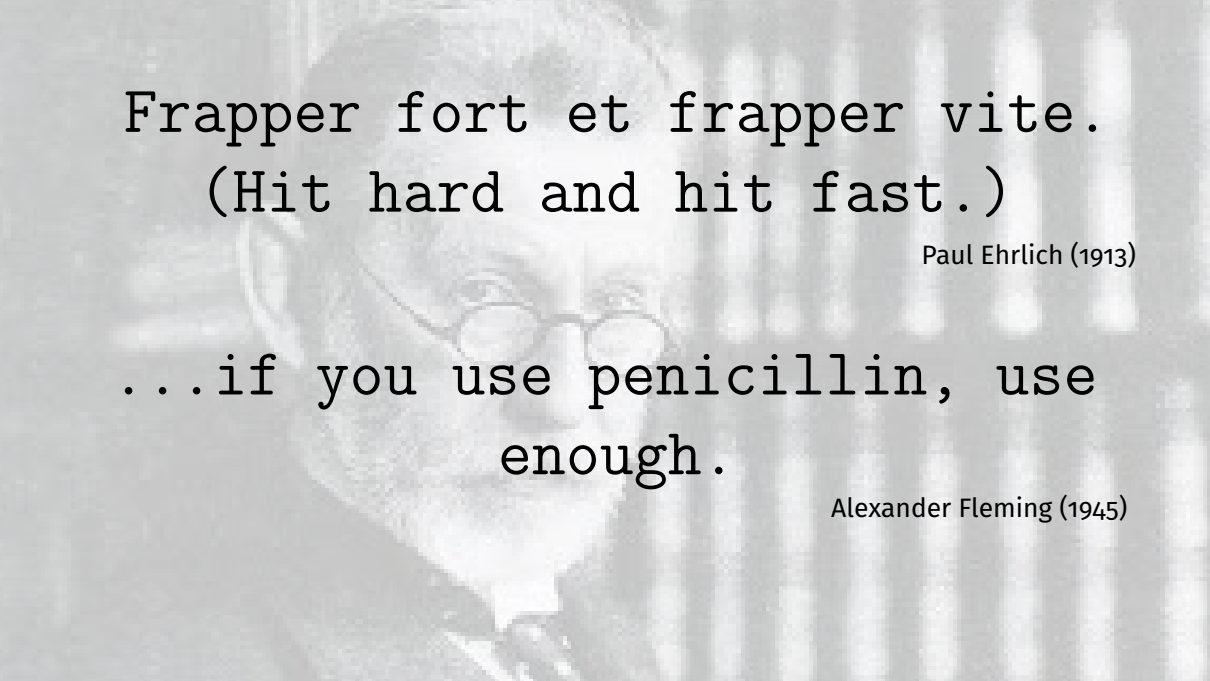
Kennedy et al. (2018), *PNAS*

Crosses indicate the appearance of a resistant strain



Frapper fort et frapper vite.
(Hit hard and hit fast.)

Paul Ehrlich (1913)



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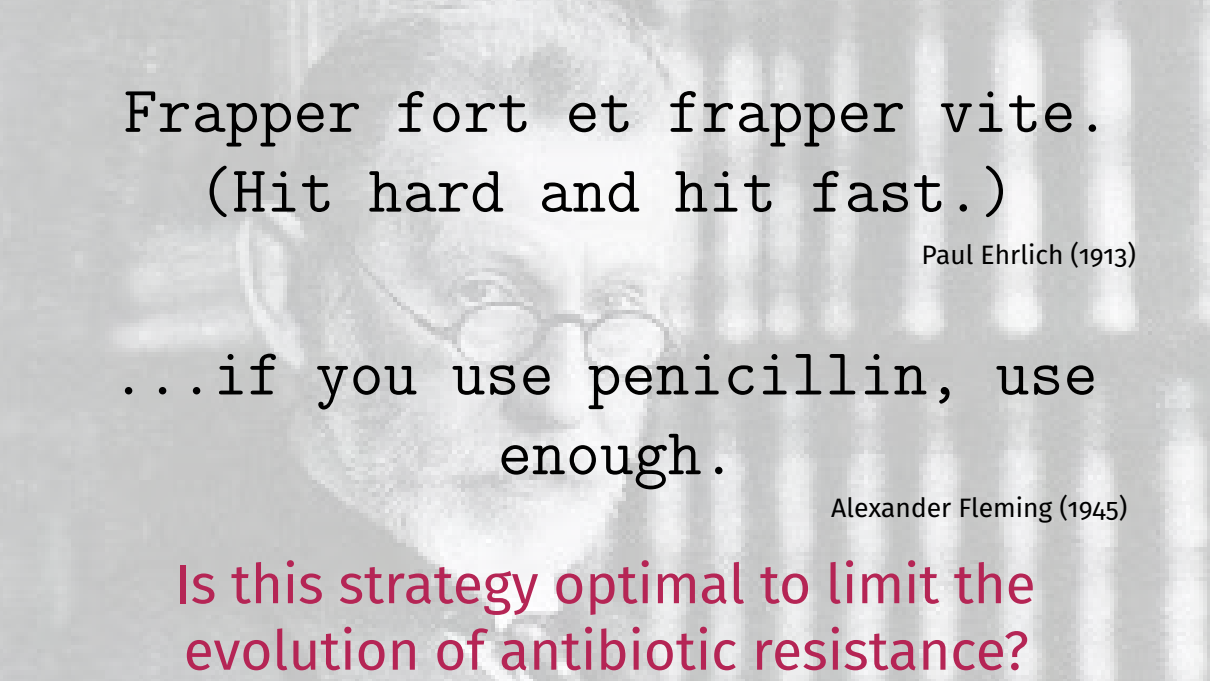
...if you use penicillin, use enough.

Alexander Fleming (1945)



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Is this strategy optimal to limit the evolution of antibiotic resistance?

Arguments exist in favor and against this strategy in the context of resistance evolution

Ankomah & Levin (2014), PNAS

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Day & Read (2016), PLoS CB

‘‘Theory does not support using the highest tolerable dose as a rule of thumb.’’

Predicting the establishment probability of a resistant subcolony during treatment

Modeling antibiotic treatment

deterministic growth rate $= \beta - \delta - \alpha(c)$

antibiotic response $\alpha(c)$ is modeled by a sigmoid (e.g. Regoes et al., 2004)

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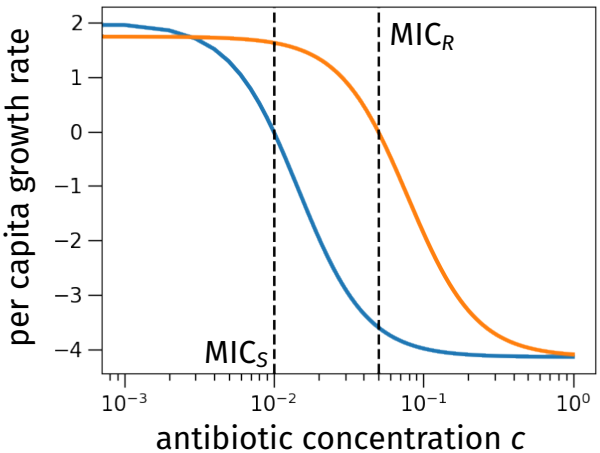

sensitive

resistant

MIC = minimal inhibitory concentration

Modeling bacterial population dynamics

- per capita birth (β) and death rate (δ)
- density regulation of bacteria (through competition, γ)
  - reducing birth rate (resource competition)
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Example: birth competition and biocidal treatment
($x(t)$ = bacterial concentration at time t)

$$\begin{aligned} \text{birth rate:} \quad & \lambda = \max(0, \beta - \gamma x(t)) \\ \text{death rate:} \quad & \mu = \delta + \alpha(c) \end{aligned}$$

Deterministic population dynamics

birth competition + biocidal treatment

$$x_i(t) = \lambda(t) - \mu(t) = x_i(t)\left(\max\left(0, \beta_i - \gamma(x_S(t) + x_R(t))\right) - \delta_i - \alpha_i(c)\right)$$

Assumptions

- **resistance:** $\alpha_R(c) \leq \alpha_S(c)$ for all concentrations $c \geq 0$
- **cost of resistance:** $\beta_S - \delta_S > \beta_R - \delta_R$

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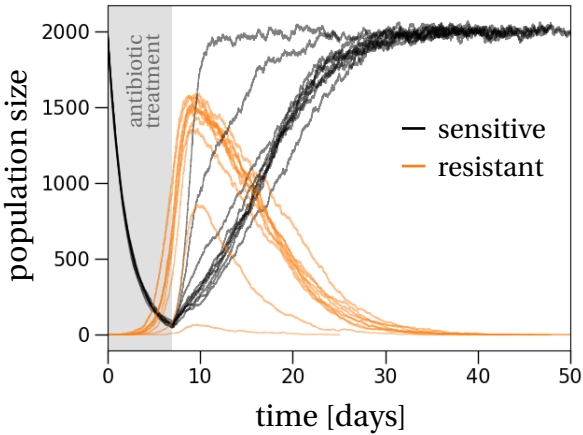

Survival probability until the end of treatment

…continuous-time branching process theory (Kendall, 1948; Uecker & Hermisson, 2011)

Survival probability $\varphi(\tau)$ for a treatment of duration τ when started with a single resistant cell is given by

$$\varphi(\tau) = \frac{1}{1 + \int_0^\tau \mu_R(t) \exp\left(\int_0^t (\lambda_R(t') - \mu_R(t'))dt'\right) dt}$$

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Example: birth regulation and biocidal treatment

Abbreviations

- par capita maximal growth rate of strain k: $\rho_k = \beta_k - \delta_k - \alpha_k(c)$
- selection coefficient: $s = \rho_R - \rho_S > 0$!

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Survival probability ($\tau = \infty$)

$$\varphi = \frac{1}{1 + \frac{\delta_R + \alpha_R}{\rho_R}\left(\frac{x_S(0)\gamma}{s} + 1\right)}$$

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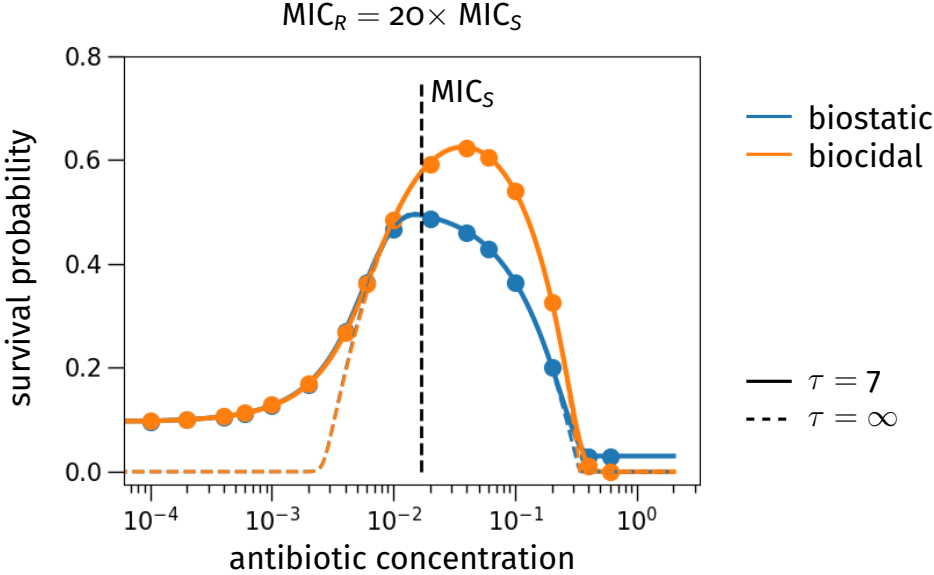
Analogous expressions can be obtained for death competition + biostatic/biocidal treatment
birth competition + biostatic treatment is more complicated

Survival probability

birth competition



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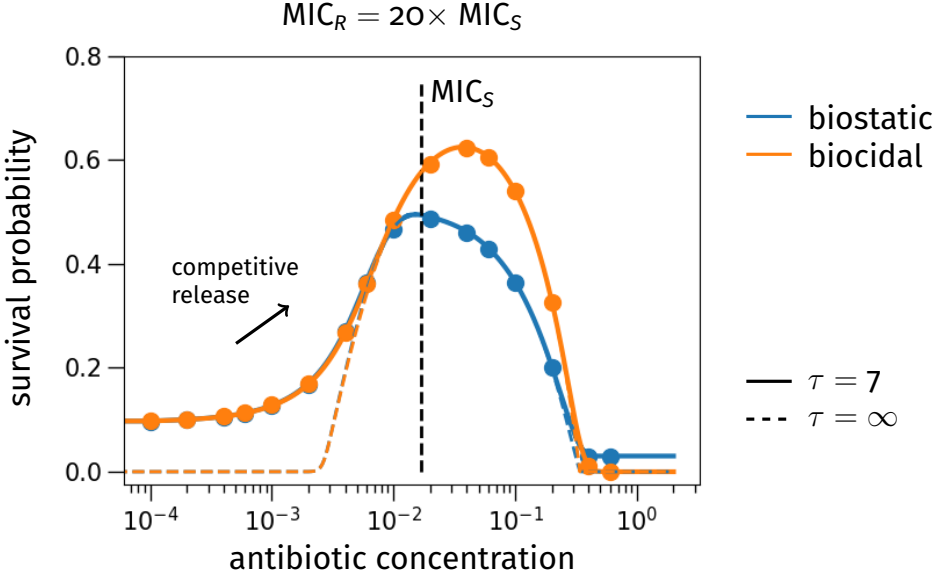

Predicting the location of the maximal risk of resistance establishment

Maximizing the survival probability

$$\varphi(c) = \frac{1}{1 + f(c)} \quad \Rightarrow \quad \varphi'(c) = -\frac{f'(c)}{(1 + f(c))^2}$$

And hence

$$\varphi'(c) = 0 \qquad \Leftrightarrow \qquad f'(c) = 0$$

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Example: birth competition + biocidal treatment

$$\frac{\alpha_S'(c)}{\alpha_R'(c)} = 1 + \frac{\beta_R\, s(c)}{\rho_R(c)(\delta_R + \alpha_R(c))} + \underbrace{\frac{\beta_R\, s(c)^2}{x_S(0)\gamma\rho_R(c)(\delta_R + \alpha_R(c))}}_{\approx 0 \text{ for weak selection}}$$

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Example: death competition + biostatic treatment

…not possible to resolve

But: we can derive a condition for a critical concentration $\tilde{c}$ below which the maximizing concentration has to be!

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$$\tilde{c} = \inf\{c : \beta_S - \alpha_S(c) = 0\}$$

Maximizing the survival probability

death competition + biostatic treatment

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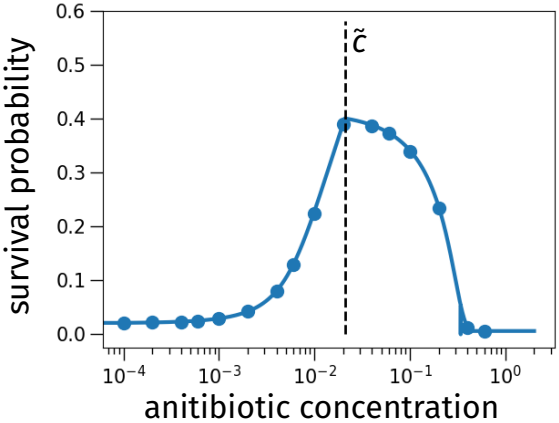
This threshold is independent of the resistant type!



$\text{MIC}_R = 20\times\ \text{MIC}_S$

Maximizing the survival probability

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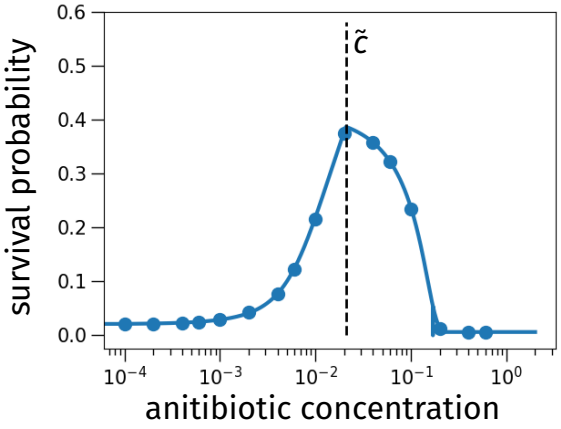


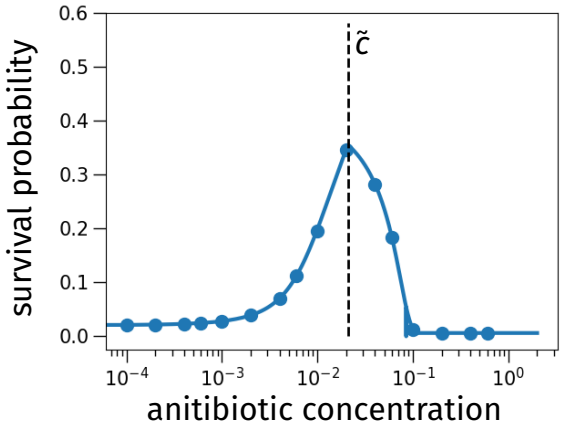
$\text{MIC}_R = 10\times\ \text{MIC}_S$

Maximizing the survival probability

death competition + biostatic treatment

$$\tilde{c} = \inf\{c : \beta_S - \alpha_S(c) = 0\}$$

This threshold is independent of the resistant type!

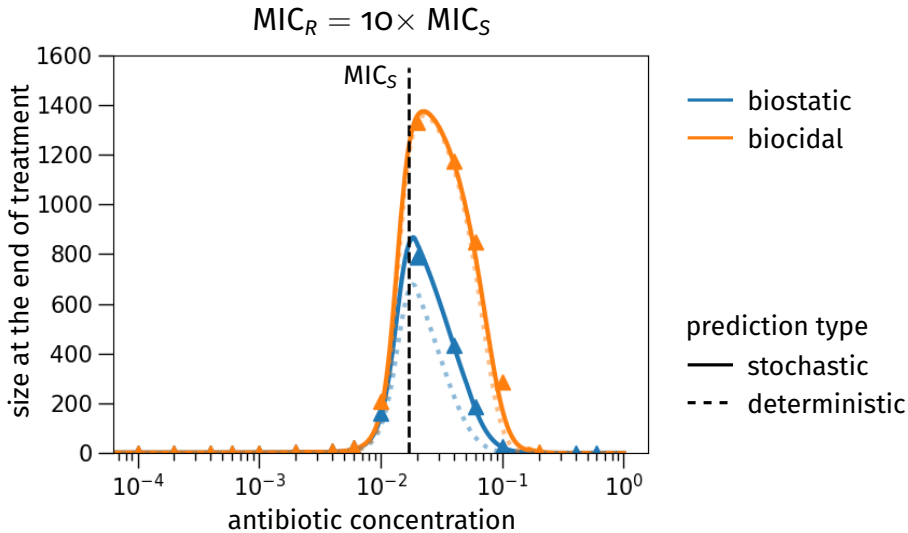


$\text{MIC}_R = 5\times\ \text{MIC}_S$

survival $\neq$ establishment
Does survival matter?

The resistant subpopulation size at the end of treatment

birth competition



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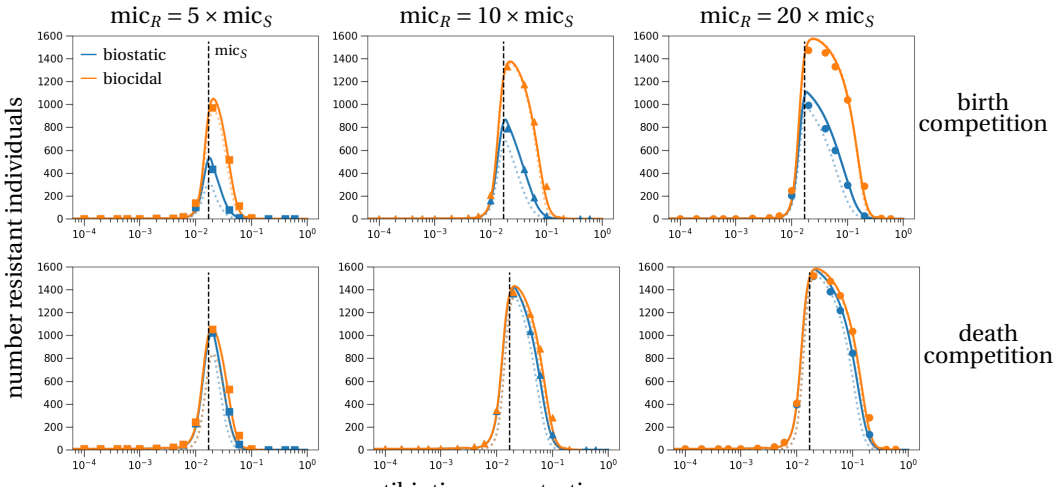

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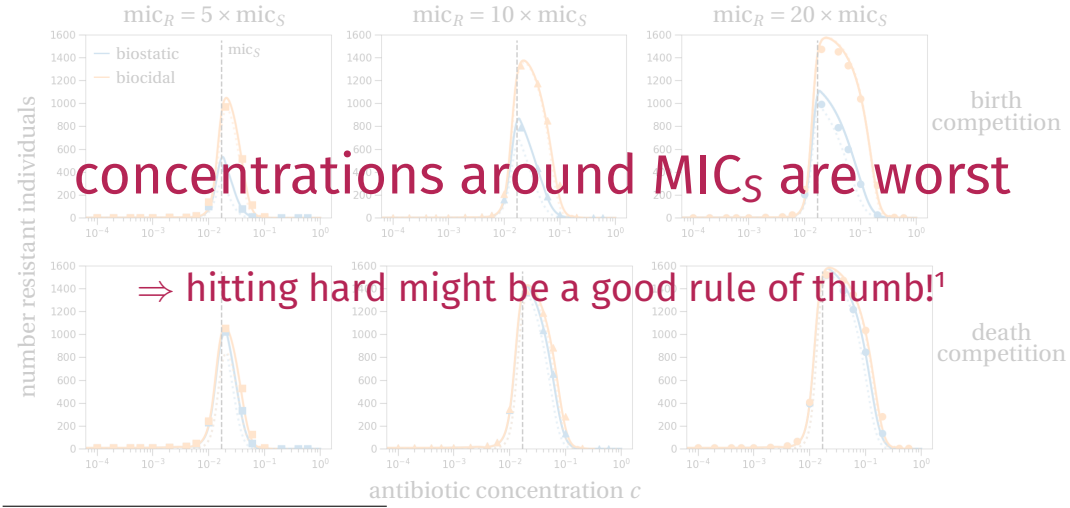

concentrations around MIC_S are worst

$\Rightarrow$ hitting hard might be a good rule of thumb![1]

[1] my personal conclusion, which is not shared by all of my coauthors

Summary & Conclusion

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Summary & Conclusion

- **continuous-time branching processes** allow us to compute the survival probability explicitly for several scenarios of (self-limited) bacterial population dynamics
- …and further helps to derive conditions for the **resistance-survival-maximizing antibiotic concentration**
- survival is not necessarily clinically relevant
  $\rightarrow$ size of the resistant subpopulation
- the **resistant subpopulation size is maximized typically at the MIC$_S$** (in our model)
  we ran a lot of additional scenarios (immune response, different antibiotic response curves, different population dynamical models) and the result is robust (in all of our considered parameter ranges … but we don't have analytical solutions in those cases)

Thank you for your attention!

Collaborators

François Blanquart
(Collège de France)

Troy Day
(Queen's Uni)

Florence Débarre
(Sorbonne Uni)

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MARIE CURIE ACTIONS