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Abstract

Antimicrobial efficacy is traditionally described by a single value, the minimal inhibitory concentration (MIC), which is the lowest concentration that prevents visible growth of the bacterial population. As a consequence, bacteria are classically qualitatively categorized as resistant if therapeutic concentrations are below MIC and susceptible otherwise. However, there is a continuity in the space of the bacterial resistance levels. Here, we introduce a model of within-host evolution of resistance under treatment that considers resistance as a continuous quantitative trait, describing the level of resistance of the bacterial population. The use of integro-differential equations allows to simultaneously track the dynamics of the bacterial population density and the evolution of its level of resistance. We analyze this model to characterize the conditions; in terms of (a) the efficiency of the drug measured by the antimicrobial activity relatively to the host immune response, and (b) the cost-benefit of resistance; that (i) prevents bacterial growth to make the patient healthy, and (ii) ensures the emergence of a bacterial population with a minimal level of resistance in case of treatment failure. We investigate how chemotherapy (*i.e.*, drug treatment) impacts bacterial population structure at equilibrium, focusing on the level of evolved resistance by the bacterial population in presence of antimicrobial pressure. We show that this level is explained by the reproduction number $\mathcal{R}_0$. We also explore the impact of the initial bacterial population size and their average resistance level on the minimal duration of drug administration in preventing bacterial growth and the emergence of resistant bacterial population.

Keywords: Antimicrobial resistance; Evolutionary dynamics; Mathematical modelling; Non-linear dynamical system

1 Introduction

In addition to its impact on ecological dynamics, human activities are major drivers of the evolution of species interacting with us [1]. An example of such impact, the evolution of antimicrobial resistance (AMR) among parasites of medical importance, is a growing concern across the world [2, 3]. An antimicrobial substance is a chemical agent that has the potential to interfere with the physiology of a bacterial cell. Because of their relative size and mechanisms of action (at least for the antimicrobial families currently used to treat infections), a single antimicrobial molecule does not cause any damage to a bacterium, while no bacterial population can survive in a medium fully saturated with antimicrobials. In other words, the negative effect of an antimicrobial substance on a given bacterium's survival, referred to here as the antimicrobial activity and denoted $\mathcal{A}$, is an increasing function of its concentration in the medium (denoted $\mathcal{C}$), with boundaries $\mathcal{A}(\mathcal{C}) = 0$ when $\mathcal{C} = 0$ and $\mathcal{A}(\mathcal{C}) \to \mathcal{A}_{\text{sat}}$ when $\mathcal{C} \to \mathcal{C}_{\text{sat}}$, where $\mathcal{A}_{\text{sat}}$ and $\mathcal{C}_{\text{sat}}$ are saturating threshold levels. Here, $\mathcal{A}$ is measured as the

antimicrobial-related mortality rate. From this intuitive approach, it follows that there exists $\mathcal{C}^\star$ in $(0, \mathcal{C}_{\text{sat}})$ such that $\mathcal{A}(\mathcal{C}^\star)$ is equal to the intrinsic rate of increase and reverses the growth of a bacterial population, all else being equal. This threshold concentration at which a bacterial population does not grow *in vitro* is called the Minimum Inhibitory Concentration (MIC).

Resistance is then a continuous trait by nature referred to as antimicrobial quantitative resistance (qAMR). Indeed, because of their short generation times and large population sizes, bacterial populations show a great intraspecific genetic diversity generated through random mutations. These mutations define distinct strains which therefore can differ by their relative susceptibility to a given antimicrobial [4, 5]. As a consequence, the MIC can be seen as a distributed variable within the same bacterial species, underpinned by a mapping of each strain genome to a unique MIC. These MIC distributions are experimentally assessed on a $\log_2$ -discretised scale (see *e.g.* the EUCAST database [6], usually with a low skewness that spans over two or three order of magnitudes of antimicrobial concentrations). For instance, a recent statistical model of MIC explained by genomic data has shown, in the case of *Neisseria gonorrhoeae*, that independent exponential contributions of distinct substitutions provide a good set of regressors for estimating MIC [7]. Therefore, we here use the log difference in MIC as a phenotypic distance between bacterial strains, with respect to antimicrobial susceptibility. This is particularly suitable because the log scale allows the additivity of independent mutation effects, which will later support symmetric mutation kernels.

Quantitative resistance is key to better understand the within-host evolutionary dynamics of AMR because intermediate resistance can allow bacterial populations to survive drug concentrations below those considered therapeutic [8], and allows the coexistence of multiple strains within the host. Here, we introduce a continuous phenotypic trait $x \in \mathbb{R}$, describing the level of resistance between $-\infty$ and $+\infty$. We also treat this quantitative descriptor x as the label of the bacterial strain with resistance level x. Note that any interval (a, b) with $a < b$ and $x \in (a, b)$ is also valid within the context of the model and results developed here. However, it is important to keep in mind that, intuitively there exist two threshold levels x_0 and x_1 (called reference 'sensitive' and 'resistant' strains) such that each strain with resistance level (labelled by x) can be classified as 'sensitive', 'intermediate', or 'resistant' depending on whether $x < x_0$, $x_0 < x < x_1$, or $x > x_1$ respectively (Figure 1).

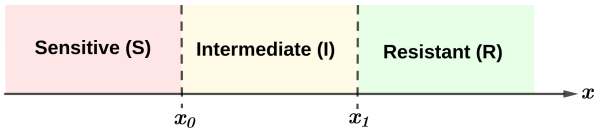

Figure 1: **Classification of the resistance level x.** Here x_0 and x_1 are reference 'sensitive' and 'resistant' strains.

Many mathematical models have been developed to study antimicrobial resistance evolution within a treated host [9–20]. We also think that the literature is so vast that we would not know where to begin since the model used then strongly depends on the question asked. However, most of the modelling approaches devoted to AMR tackling the case of qualitative (or "binary") resistance are generally based on the dynamical interaction between two parasite strains leading to a binary MIC formulation [9]. This analysis ignores the evolutionary short-term transient dynamics which lead to the emergence of resistance.

To our knowledge, no study has considered the continuous nature of AMR as for the approach developed here. However, a similar formalism has been developed in the context of anticancer treatments [21]. There are also parallels with work on linking drug-target binding kinetics with bacterial replication by modelling the number of target molecules per bacterial cell as a positive continuous variable [22]. We use a system of integro-differential equations modeling the dynamics of bacterial population with density $b(\cdot, x)$ and resistance level $x \in \mathbb{R}$. Resistance has a cost and thus growth and death rates depend on the bacterial resistance level x. In addition to those effects on the death and birth rates, bacterial population resistance level also mitigates the antimicrobial efficiency with respect

to that population. From a theoretical point of view, some of the properties of this model build on previous analytical quantitative genetics results developed in [23, 24].

We first describe our model and its main parameters. Next, we investigate how chemotherapy (*i.e.*, drug treatment) impacts bacterial population structure at equilibrium. This includes the characterization of the resistance level acquired by the bacterial population in the presence of antimicrobial pressure. We show that such a characterization is simply based on the reproduction number $\mathcal{R}_0$ [25], which we prove to play the role of the invasion fitness in evolution [26]. Next, we investigate in what conditions of the drug efficiency (measured by the antimicrobial activity relatively to the host immune response) and the cost-benefit of resistance; we can (i) prevent bacterial growth to make the patient healthy, and (ii) ensure the emergence of a bacterial population with a minimal level of resistance in case of treatment failure. This is called thereafter the treatment objective. Finally, we investigate the minimal duration of drug administration to achieve our treatment objective as a function of the initial bacterial population size and their average resistance level.

2 Description

2.1 Scaling considerations and model overview

Of course, anyone can claim to model resistance as a quantitative trait x but this is purely a theoretical thought exercise unless it can be clearly linked with existing nomenclature for sensitive and resistant strains, and with existing quantitative metrics related to drug resistance, especially MIC and growth rate. A bacterial strain is said to be resistant to a given antimicrobial if a treatment, the posology of which does not exceed tolerance limits, is likely to fail [3, 6]. Therefore, each strain can be classified as "sensitive" or "resistant" (R) respectively, depending on whether or not their MIC (*i.e.*, the threshold concentration at which a bacterial population does not grow) is below or above a therapeutic threshold $\mathcal{C}_1$ defined from clinical and pharmacokinetics investigations. Following the EUCAST 2019 nomenclature [6], sensitive strains can be classified as "normal exposure" (S) or "increased exposure" (previously "intermediate", but still denoted by I) depending on whether their MIC is respectively below or above the pharmacologic threshold $\mathcal{C}_0$ corresponding to the antimicrobial concentration reached by a standard posology. They respectively, correspond to the concentration thresholds at usual (*i.e.* normal) and maximum tolerable posologies and are known as the two clinical breakpoints.

Based on these definitions, for any strain of a given bacterial species exposed to a given antimicrobial, we can define a scale-free quantitative descriptor of AMR varying in a symmetric manner at each mutation step such that

$$x := \frac{\log\left(\frac{\mathcal{C}_x}{\mathcal{C}_0}\right)}{\log\left(\frac{\mathcal{C}_1}{\mathcal{C}_0}\right)} \in \mathbb{R},$$

where $\mathcal{C}_x$ is the MIC of the strain with respect to this antimicrobial. With this definition, the EUCAST 2019 typology [6] implies that $S < 0 < I < 1 < R$. With the above equation, notice that having a negative value for the resistance level x (*i.e.* $x < 0$) just means that the given bacterial strain is more sensitive than the reference 'sensitive' strain (*i.e.* $\mathcal{C}_x < \mathcal{C}_0$).

The model follows the dynamics of bacterial population and antimicrobial concentrations. The bacterial population is assumed to be phenotypically (and genetically) diverse, with a structuration through the level of antimicrobial resistance, here defined as a continuous trait x and referred to as quantitative antimicrobial resistance. This quantitative antimicrobial resistance level x ranges from $-\infty$ to $+\infty$, and affects different components of the bacterial population life cycle, such as growth and death rate. Bacterial populations with a resistance level x have a density $b(t, x)$ at time t. The main variables and parameters of the model are listed in Table 1.

Table 1: Model state variables and parameters

State variables	Description	
$b(t,x)$	Density of bacterial population with resistance level x at time t.	
$B(t)$	Total density of bacterial population at time t.	
Functional parameters	**Description (unit)**	
$J(x-y)$	Mutation probability from resistance level x to y per cell division (dimensionless).	
$p(x)$	Intrinsic growth rate of bacterial population with resistance level x (cell/μg).	
$k(x)$	Killing rate of bacterial population with resistance level x due to drug (1/day).	
Fixed parameters	**Description (unit)**	**Value/range**
p_m	Upper bound of the intrinsic growth rate p	10
p_0	Intrinsic growth rate of the reference sensitive strain	$0.95 \times p_m$
$R_0^0(0)$	The reproduction number of the he reference sensitive strain without drug	10
α	Limitation on bacterial growth factor	1
Variable parameters	**Description (unit)**	**range**
m_0	Size of the initial bacterial population	$(0,\infty)$
σ_0^2	Resistance variance of the initial bacterial population	$(0,\infty)$
k_0	Antimicrobial activity on the sensitive reference strain $x=0$	$(0,\infty)$
p_1/p_0	Reference resistant and sensitive growth rate ratio	(0,1)
k_1/k_0	Reference resistant and sensitive drug efficiency ratio	(0,1)

With fixed and variables parameters defined in the table above, other model's parameters are calculated by: $\mu = \frac{p_0}{R_0^0(0)}$, $p_1 = p_0 \times (p_1/p_0)$ and $k_1 = k_0 \times (k_1/k_0)$.

2.2 Model parameters and general hypothesis

For our model formulation and analysis, the killing rate function of the antimicrobial $k(\cdot)$ will be –quite naturally– a decreasing function with respect to the resistance level x. Our primary goal here is to define the function $k(\cdot)$ with two parameters, namely, k_0 and k_1 representing the antimicrobial activity undergone by strains the MIC of which are exactly $\mathcal{C}_0$ and $\mathcal{C}_1$ and hereafter called reference strains 0 and 1. Therefore, we assume that the killing $k(x)$ of the antimicrobial on the bacterial population with resistance level x takes the form

$$k\left(x\right) = k_0 \left(\frac{k_1}{k_0}\right)^x,$$

The qualitative shape of the curve $k(x)$ is shown in Figure 2.

Likewise, one can define a bacterial intrinsic growth rate that incorporates the cost of resistance (for empirical evidence of such costs (e.g., [27]). This intrinsic growth rate, denoted p, should be upper bounded due to physiological constraints, otherwise, a strain not investing at all in AMR would have an infinite growth rate $p\left(-\infty\right) = \infty$, which is biologically unrealistic. Therefore, we set $p\left(-\infty\right) =: p_{\mathrm{m}} < \infty$. On the other side, a strain that takes an infinite concentration of antimicrobial to inhibit would pay an infinite cost then compromising its growth itself, hence $p\left(\infty\right) = 0$. Knowing p_0 and p_1, the intrinsic growth rate of reference strains 0 and 1 (which can be expressed as function of k_0, k_1), a suitable expression for p is

$$p\left(x\right) = \frac{p_{\mathrm{m}}}{1 + \left(\frac{p_{\mathrm{m}}-p_0}{p_0}\right)\left(\frac{p_0}{p_1} \cdot \frac{p_{\mathrm{m}}-p_1}{p_{\mathrm{m}}-p_0}\right)^x},$$

with $0 < p_1 < p_0 < p_m$. The qualitative shape of the curve $p(x)$ is shown in Figure 2. Importantly, the above functional form for p is not strictly important for our model formulation and analysis. The main important property is that p should be a decreasing function with respect to the resistance level x.

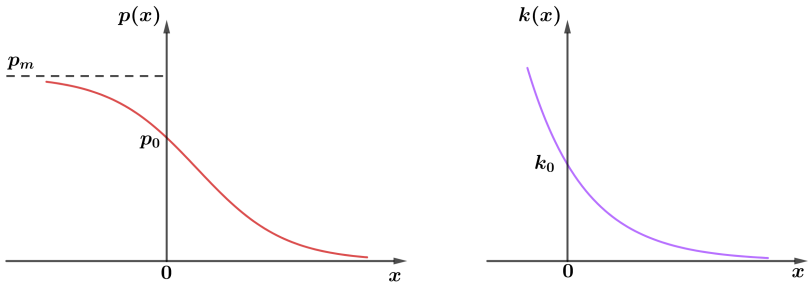

Figure 2: (Left) Intrinsic growth rate $p(x)$ of bacterial population with a level of resistance $x \in \mathbb{R}$. (Right) Drug activity $k(x)$ on bacterial population with resistance level $x \in \mathbb{R}$.

2.3 Bacterial population model with quantitative resistance level

We use an integro-differential equation to model the demographic and evolutionary dynamics of the bacterial population. At any time t, the total bacterial population density is $B(t) = \int_{\mathbb{R}} b(t,y)\mathrm{d}y$. Next, bacterial population with resistance level $y \in \mathbb{R}$ give birth to the bacterial population with resistance level $x \in \mathbb{R}$ at a per-capita rate $J(x-y)\dfrac{p(y)}{(1+B(t))^{\alpha}}b(t,y)$, where $J(x-y)$ is the probability for a bacterial population with resistance level y to mutate towards a level x during the reproduction process, $p(y)$ is the bacterial intrinsic growth rate, $\frac{p(y)}{(1+B(t))^{\alpha}}$ is the effective growth rate, and $\alpha > 0$ is a scaling constant. Thus, the number of bacteria produced at time t with resistance level x is $\frac{1}{(1+B(t))^{\alpha}}\int_{\mathbb{R}} J(x-y)p(y)b(t,y)\mathrm{d}y$. The clearance of the bacterial population with resistance level x due to the immune system occurs at a rate $\mu(x)$. Here, we assume that the immune response μ is constant in time. The presence of antimicrobials generates an additional mortality rate $k(x)$, which depends on the level of bacterial resistance. Therefore, the fraction $\frac{p(y)}{(1+B(t))^{\alpha}}$ accounts for the density dependence of the reproduction rate. Such a formalism is a suitable alternative in regulating the growth of a structured population without reference to the concept of carrying capacity, which we think is not necessarily a measurable factor for this type of population. Thus, the parameter $\alpha > 0$ is introduced only to impose the population homeostasis and does not impact our downstream results. Taking $\alpha = 0$ leads to a population with infinite growth if no effect of the immune response nor of the antimicrobial is taken into account. Overall, the bacterial evolutionary dynamics is described by the following differential equation

$$\begin{cases} \partial_t b(t,x) = \dfrac{1}{(1+B(t))^{\alpha}}\displaystyle\int_{\mathbb{R}} J(x-y)p(y)b(t,y)\mathrm{d}y - (\mu(x)+k(x))b(t,x); \quad t>0, \\ b(t=0,\cdot) = b_0(\cdot). \end{cases} \tag{2.1}$$

The mutation kernel $J = J_\varepsilon$ is such that $J(x-y)$ is the probability of mutation from resistance level y to x. We assume a Gaussian distribution with $J_\varepsilon(x) = \frac{1}{\varepsilon\sqrt{2\pi}}e^{-\frac{1}{2}\left(\frac{x}{\varepsilon}\right)^2}$, where $\varepsilon > 0$ represents the mutation variance in the phenotypic space. Other mutation kernels could be considered provided that they satisfy some general properties such as positivity and symmetry (Appendix A). Preliminary results on the model (2.1), including the existence of a unique maximal bounded dissipative semiflow, are shown in Appendix E.

The formulation of model (2.1) allows to follow evolutionary parameters such as the average level of resistance $\eta(t)$ expressed by the whole bacterial population and the related variance $\sigma^2(t)$ at any time t, as so:

$$\eta(t) = \int_{\mathbb{R}} x\frac{b(t,x)}{B(t)}\mathrm{d}x, \quad \text{and} \quad \sigma^2(t) = \int_{\mathbb{R}} (x-\eta(t))^2\frac{b(t,x)}{B(t)}\mathrm{d}x.$$

Furthermore, the model (2.1) can be used to recover the classical model formulation for the qualitative (or "binary") resistance. Indeed, if we denoted by B_S and B_R the total densities of highly sensitive (i.e. $x = 0$) and resistant (i.e. $x = 1$) bacterial populations, model (2.1) can be rewritten as

$$\begin{cases} \dot{B}_S = \dfrac{1}{(1+B_S+B_R)^\alpha}\left[(1-\varepsilon_0)p(0)B_S + \varepsilon_0 p(1)B_R\right] - (\mu(0)+k(0))B_S, \\ \dot{B}_R = \dfrac{1}{(1+B_S+B_R)^\alpha}\left[\varepsilon_0 p(0)B_S + (1-\varepsilon_0)p(1)B_R\right] - (\mu(1)+k(1))B_R, \end{cases} \tag{2.2}$$

where ε_0 is the mutation probability. We briefly sketch the interpretation of System (2.2), which will also help in better understanding of Model (2.1). Sensitive bacteria B_S growth at effective rate $p(0)/(1 + B_S + B_R)^\alpha$. Furthermore, while a proportion ε_0 corresponds to a mutant growth (*i.e.* mutations away from the sub-population B_S), the remainder $(1-\varepsilon_0)$ corresponds to a faithful growth. Next, the sensitive population B_S is cleared at rate $(\mu(0)+k(0))$ accounting for actions of the immune response $\mu(0)$ and antimicrobial $k(0)$. The same interpretation holds for the resistant population B_R. Finally, we refer to Appendix B for more details on the derivation of System (2.2).

2.4 Initial conditions

The initial bacterial population $b_0(x)$ (at $t = 0$) is assumed to be composed by a sensitive bacterial population, with average resistance level $x = 0$. This population is characterized by two parameters: its size (m_0) and the variance (σ_0^2) of its level of resistance. The higher σ_0^2, the more frequent resistant bacteria are in the initial population. Formally, we set

$$b_0(x) = m_0 \times \mathcal{N}(0, \sigma_0, x),$$

where $\mathcal{N}(0, \sigma_0, x)$ stands for the normalized density function of the Gaussian distribution at x with mean 0 and variance σ_0^2.

3 Results

We illustrate how to use the model to simultaneously capture the bacterial population dynamics and the evolution of antimicrobial resistance. The spread of a bacterial population in a bacteria-free environment is classically determined by calculating the basic reproduction number of this bacterial population. However, the outcome of the evolutionary dynamics of a rare bacterial population with resistance level y in a resident population with resistance level x is determined by the invasion fitness based on standard adaptive dynamics methodology. Furthermore, we show that the level of the bacterial population at the evolutionary equilibrium of Model (2.1) will coincide with the local maximum of the basic reproduction number. We will also show how the outcome of the treatment (success or unsuccess) and the evolutionary bacterial resistance level strongly relies on two parameters: (i) the resistance's cost-benefit ratio, and (ii) the drug efficiency of the reference sensitive strain, quantified relatively to the host immune response. Finally, notice that for all simulations, we randomly set the parameters (Table 1), with the only purpose to illustrate our theoretical results.

3.1 Basic reproduction number $\mathcal{R}_0$ and invasion fitness

Following classical studies, we define the basic reproduction number $\mathcal{R}_0$ as the expected number of bacteria arising from one bacterium in a bacteria-free environment [25, 28]. As shown in Appendix C, for a bacterial population with resistance level x, this basic reproduction number is

$$\mathcal{R}_0(x) = \frac{p(x)}{\mu + k(x)}. \tag{3.3}$$

We use $\mathcal{R}_0(x)$ to measure the fitness (or effective growing capacity) of a bacterial population with resistance level x. This $\mathcal{R}_0$ can be seen as a product between (i) the intrinsic growth rate of new bacterial population during their natural life time, $p(x)$, and (ii) the lifespan of a bacterial population with resistance level x, $1/(\mu+k(x))$. In the following, we denote by $\mathcal{R}_0^0$, the basic reproduction number as in model (2.1) in absence of antimicrobials (*i.e.* when $k \equiv 0$).

As state in the introduction, let us first recall that the quantitative descriptor x for the bacterial resistance level is also treated as the label of the bacterial strain with resistance level x. Then, the spread of a rare bacterial population with resistance level y in a resident population with resistance level x is studied using adaptive dynamics. Quite naturally, we assume $\mathcal{R}_0(x) > 1$, otherwise, the resident population x is not persistent, which a bit contradicts the concept of 'resident population'. Next, to find the evolutionary attractors, we calculate the invasion fitness $f_x(y)$, and the rare population with resistance level y will invade the population x if and only if $f_x(y) > 0$. The sign of this two-dimensional function $f_x(y)$ is classically visualized using Pairwise Invasibility Plot (PIP) [26, 29–31]. As shown in Appendix C, the invasion fitness $f_x(y)$ is written as

$$f_x(y) = \underbrace{\frac{1}{(1+b^x)^\alpha}}_{\substack{\text{feedback of} \\ \text{resident } x}} \times \mathcal{R}_0(y) - 1. \tag{3.4}$$

The environmental feedback of the resident with resistance level x conditions the ability of a rare population with resistance level y to invade the resident population. It depends on the conditions set out by the resident, and by (3.3), the equality (3.4) is rewritten

$$f_x(y) = \frac{1}{(1+b^x)^\alpha} \left(\mathcal{R}_0(y) - \mathcal{R}_0(x)\right). \tag{3.5}$$

It follows that the model (2.1) admits an optimisation principle based on $\mathcal{R}_0$ [26, 29–31]. Indeed, the sign of the invasion fitness $f_x(y)$ is given by the sign of the difference between $\mathcal{R}_0(y)$ and $\mathcal{R}_0(x)$ and thus, the evolutionary attractors of the model (2.1) coincide with the local maxima of the $\mathcal{R}_0$

3.2 Typical dynamics simulated with the model

One of the parameters highlighted through our model's analysis is the ratio

$$c_b = \frac{\log \Delta}{\log(1+\theta)}, \tag{3.6}$$

where $\Delta = \frac{(p_m - p_1)/p_1}{(p_m - p_0)/p_0} > 1$, and $\theta = \frac{k_0 - k_1}{k_1} > 0$. The ratio c_b can be interpreted as the average fitness cost-benefit ratio of the resistance for a given bacterial population. Indeed, the parameter Δ quantifies the relative cost of resistance of a given bacterial population, whereas θ quantifies the fitness advantage of the reference resistant strain ($x = 1$) of that bacterial population. Note that $\Delta \approx 1$ corresponds to cases where the cost of resistance of the given bacterial population is negligible, and $\theta \approx 0$ to cases where the fitness advantage of resistance of that bacterial population is negligible.

Before antimicrobial treatment onset, the fitness of a bacterial population (measured by its basic reproduction number in the absence of antimicrobial, $\mathcal{R}_0^0(x)$) decreases with the level of resistance x, such that wild type sensitive bacteria ($x = 0$) overgrow resistant ones. This is due to the cost Δ (which assumes $\Delta > 0$) of being resistant (Figure 3A).

The initiation of chemotherapy induces an average benefit (measured by θ) in the resistant bacterial population. Indeed, the drug efficiency (k) decreases as the level of bacterial resistance x increases (Figure 3D). Therefore, the treatment can modify the fitness landscape (which obviously will have a very rapid effect on the distribution of x values in the population) by shifting the maximum point of the basic reproduction number $\mathcal{R}_0$ from $x = 0$ to $x = x^* > 0$ (Figure 3A).

The model captures the evolutionary dynamics of the system following treatment onset by tracking, at the same time, the bacterial population dynamics and the evolution of antimicrobial resistance (Figures 3B,C,E). In the first phase, the treatment causes a decrease in the total bacterial population density. At the end of this phase, the infection is seemingly under control (Figure 3B). The second phase begins with an increase in both the population density and the level of resistance. This phase occurs when the average drug resistance reaches an optimum evolutionary threshold x^* that depends on the amount of drug and on the fitness cost. Finally, the bacterial population is not controlled (Figure 3B), and even worse, it completely escapes treatment having evolved a high level of resistance (Figures 3C). Figure 3E illustrates the joint dynamics of bacterial population density and resistance.

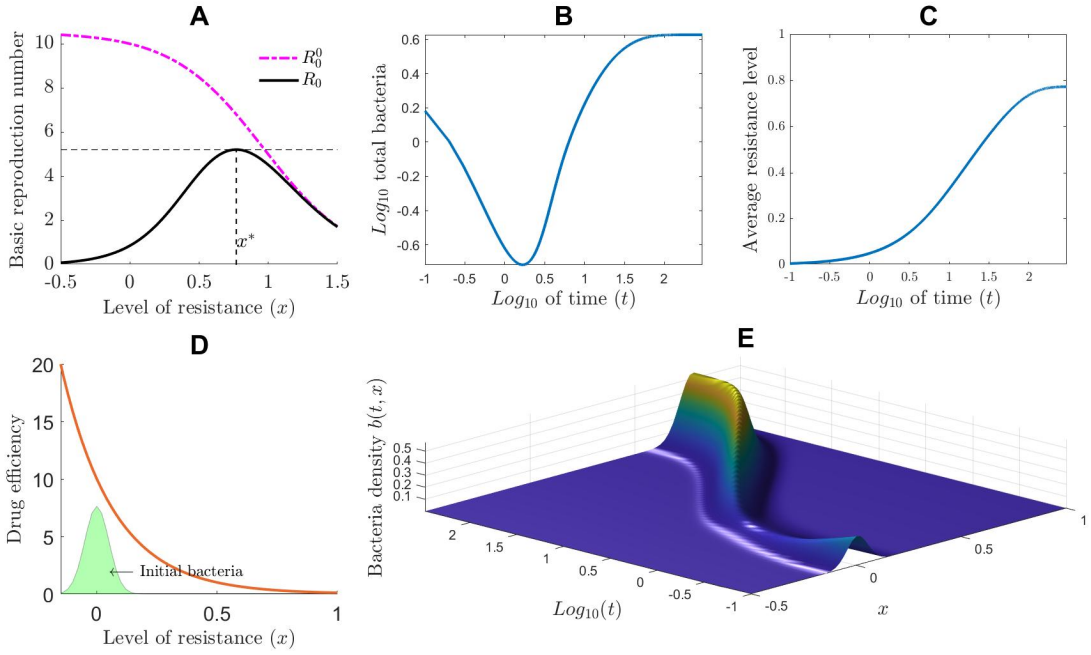

Figure 3: **Typical dynamics simulated with the model.** (A) The basic reproduction numbers $\mathcal{R}_0(x)$ and $\mathcal{R}_0^0(x)$ with and without drug respectively. (D) Drug efficiency $k(x)$ and the initial bacterial population with average level of resistance $x = 0$. (B) Time evolution of the total bacterial population $\int_{\mathbb{R}} b(t,x)\mathrm{d}x$. (C) Distribution of the bacterial population $b(t,x)$ with respect to time t and resistance level x. A logarithmic time scale is used to better highlight transient dynamics of the bacterial population density (B,E), and the increase of the bacterial population resistance level (C). Here, we have set $\sigma_0 = 0.05$, $m_0 = 0.05$, $k_0 = 3$, $p_1/p_0 = 0.5$, $k_1/k_0 = 0.01$ and other parameters are given by Table 1.

3.3 Evolutionary equilibrium and global dynamic

As shown above, the evolutionary attractor (x^*) of the model (2.1), in the set of resistance level $\mathbb{R}$, coincides with the local maximum of the basic reproduction number $\mathcal{R}_0$ (Appendix C). Furthermore, the evolutionary attractor (x^*) characterizes the bacterial evolutionary resistance level, which is the level of the bacterial population at the equilibrium.

An explicit expression of x^* is difficult to obtain with our parameter setting. However, using the EUCAST 2019 nomenclature [6] and defining the cost-benefit ratio c_b by (3.6), we find that low values of cost-benefit ratio (*i.e.* $c_b \leq (1 - p_1/p_m)^{-1}$) can lead to either high resistance levels (*i.e.* $x^* \geq 1$),

intermediate (*i.e.* $0 \leq x^* \leq 1$), or low (*i.e.* $x^* \leq 0$) at the evolutionary attractor. Next, intermediate cost-benefit ratios (*i.e.* $(1-p_1/p_m)^{-1} < c_b < (1-p_0/p_m)^{-1}$) are associated with a low (*i.e.* $x^* \leq 0$) or intermediate (*i.e.* $0 \leq x^* \leq 1$) levels of resistance at the evolutionary attractor. Finally, high cost-benefit ratios (*i.e.* $c_b \geq (1-p_0/p_m)^{-1}$) correspond to a low resistance levels at the evolutionary attractor (*i.e.* $x^* \leq 0$). See figure 4 and we refer to Appendix D for more details.

Next, we simultaneously study the epidemio-evolutionary dynamics of model (2.1) by relaxing the time-scale separation assumption. Indeed, our analysis allows to jointly perform (i) the asymptotic behavior of the model's state variable $b(t,\cdot)$, and (ii) the long-term behavior of the system in relation to the space of resistance level $x \in \mathbb{R}$. We find that the global dynamics of model (2.1) are fully described by $\mathcal{R}_0(x^*)$ as follows:

(i) If $\mathcal{R}_0(x^*) < 1$, all strains asymptotically die out and the bacterial population cannot persist, *i.e.*, $\lim_{t\to\infty} \int_{\mathbb{R}} b(t,x)\mathrm{d}x = 0$ (Appendix F-G).

(ii) If $\mathcal{R}_0(x^*) > 1$, model (2.1) exhibits a unique positive stationary state $b^*(\cdot) = b^*_\varepsilon(\cdot)$ and the bacterial population is persistent, meaning that there exists $\nu > 0$ such that, $\liminf_{t\to\infty} \int_{\mathbb{R}} b(t,x)\mathrm{d}x > \nu$ (Appendix H-I).

(iii) Further, if $\mathcal{R}_0(x^*) > 1$ and the mutation variance ε in the phenotypic space is small, the unique positive stationary state $b^*(\cdot)$ is concentrated around the evolutionary attractor x^* in the space of resistance level $x \in \mathbb{R}$. In other words, the average bacterial resistance level at equilibrium is x^* and we have $b^*(\cdot) \to \delta_{x^*}(\cdot)$ when $\varepsilon \to 0$. This convergence holds for the narrow topology, that is, for any continuous function $u \in \mathcal{C}(\mathbb{R})$ one has $\lim_{\varepsilon\to 0} \int_{\mathbb{R}} u(x)b^*(x)\mathrm{d}x = u(x^*)$.

3.4 Achieving a successful treatment

Combining the asymptotic results described above (Figure 3) with the classification of the evolutionary bacterial resistance level x^* allows us to identify a path to achieve successful treatment, that prevents bacterial growth. In fact, for a given cost-benefit ratio to drug resistance (c_b), our analysis allow us to determine the minimum level of drug activity on the reference strain (k_0/μ), quantified relatively to the host immune response (μ), that is required to achieve a successful treatment. This can be done because we showed that in the plane $(c_b, k_0/\mu)$ it is possible to characterize three level sets $\{(c_b,k_0/\mu) : \mathcal{R}_0(x^*) = 1\}$, $\{(c_b,k_0/\mu) : x^* = 0\}$, $\{(c_b,k_0/\mu) : x^* = 1\}$ that determine the potential persistence of a bacterial population with an evolutionary resistance level x^* (Figure 4).

We find that the threshold value of k_0/μ for which a successful treatment holds increases non-linearly when the cost-benefit ratio c_b becomes small (Figure 4). Interestingly, the treatment is successful if and only if $(c_b,k_0/\mu) > \{\mathcal{R}_0(x^*) = 1\}$, which means this can happen if the evolutionary resistance level x^* is 'sensitive' $(c_b,k_0/\mu) \leq \{x^* = 0\}$, 'intermediate' $\{x^* = 0\} < (c_b,k_0/\mu) < \{x^* = 1\}$ or even 'resistant' $(c_b,k_0/\mu) \geq \{x^* = 1\}$ (Figure 4, gray area). The corresponding evolutionary dynamics are similar to that shown in Figure 5 where the total bacterial population dies out. Note that the treatment results in the acquisition of an intermediate level of resistance x^* by the bacterial population (Figure 5C). However, this population is unable to grow because the treatment imposes, at the evolutionary resistance level x^*, a fitness smaller than unity $\mathcal{R}_0(x^*) < 1$ (Figure 5D).

3.5 Failure in achieving a successful treatment leads to the emergence of a resistant bacterial population whatever the cost-benefit ratio

The treatment is unsuccessful when the point $(c_b,k_0/\mu)$ is below the level set $\{\mathcal{R}_0(x^*) = 1\}$ (Figure 4). Overall, for a given cost-benefit ratio (c_b), therapeutic failure occurs when the drug activity (k_0/μ), quantified relatively to the host immune response (μ), is below a threshold characterized by the level set $\{\mathcal{R}_0(x^*) = 1\}$. Depending on the order of magnitude of c_b, such therapeutic failure leads to the emergence of a bacterial population with high (Figure 4, area R), moderate (Figure 4,

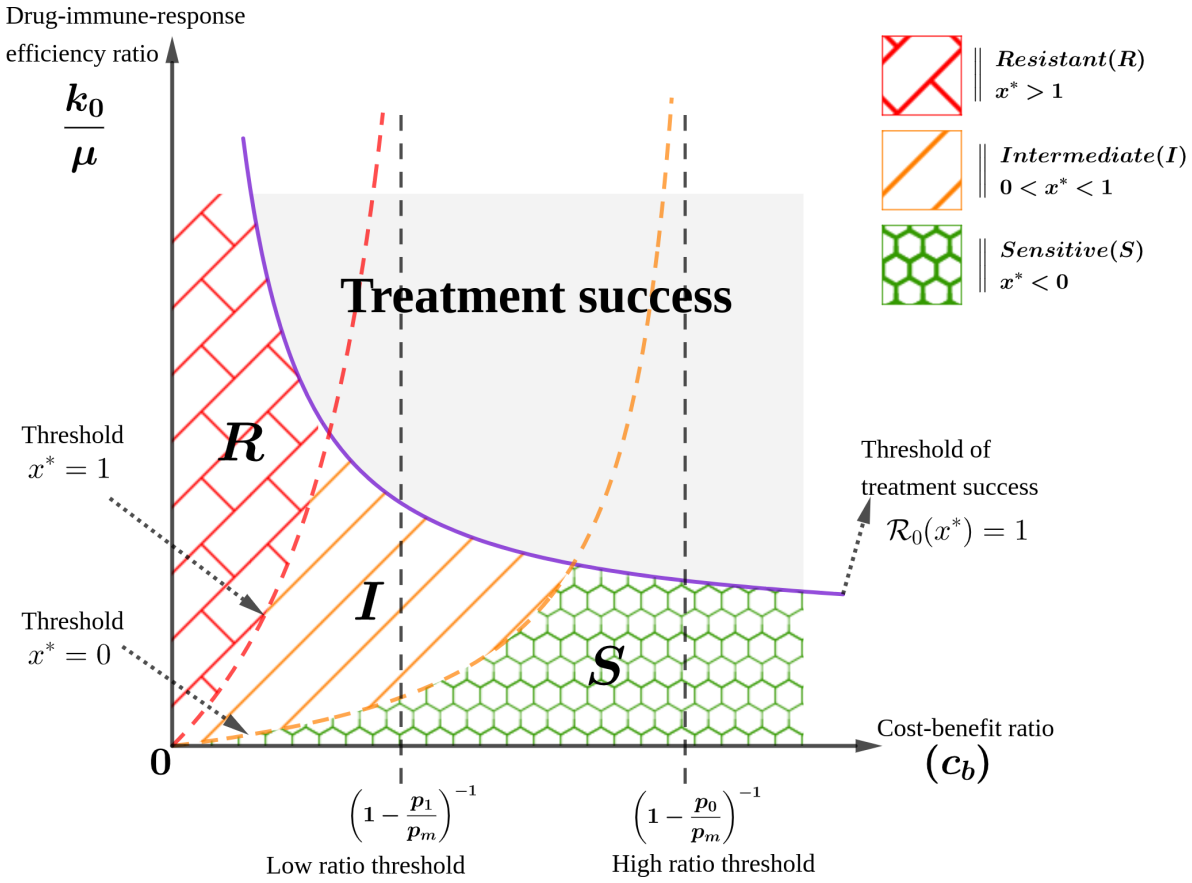

Figure 4: **Evolutionary resistance level (x^*) with respect to the resistance's cost-benefit ratio ($\log(\Delta)/\log(1+\theta)$) and drug efficiency ($k_0/\mu$) on the reference sensitive strain, quantified relatively to the host immune response (μ).** Areas R, I, and S correspond to parameter combinations where the evolutionary level of resistance x^* is such that $x^* \geq 1$, $0 < x^* < 1$, and $x^* \leq 0$ respectively. The treatment success holds above the level set $\{\mathcal{R}_0(x^*) = 1\}$, that is, for the zone in gray. The treatment is unsuccessful below the level set $\{\mathcal{R}_0(x^*) = 1\}$, that is, for zones R, I and S (below the purple curve). The curves labelled '$x^* = 0$' (in yellow) and '$x^* = 1$' (in red) indicate 'sensitive' and 'resistant' thresholds.

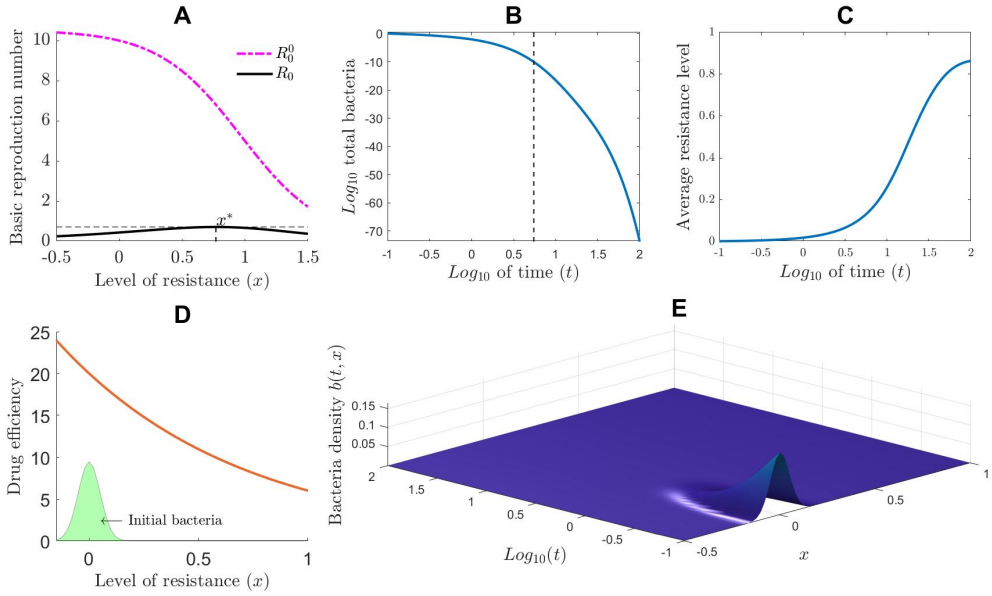

Figure 5: **Evolutionary dynamics with lethal treatment.** Parameter values are $(\sigma_0, m_0, k_0, p_1/p_0, k_1/k_0) = (0.05, 0.05, 20, 0.5, 0.3)$ or default as shown in Table 1. The vertical dashed line in panel (B) shows the time from which the total bacterial population is always $\leq 10^{-10}$.

area I), or low (Figure 4, area S) levels of resistance. Indeed, with high cost-benefit ratio values, $c_b > (1 - p_0/p_m)^{-1}$, therapeutic failures is always associated with the persistence of bacteria with low resistance levels (Figure 6, zone S). A therapeutic failure with intermediate values of cost-benefit ratios, $(1 - p_1/p_m)^{-1} < c_b < (1 - p_0/p_m)^{-1}$, leads to the emergence of bacterial populations with either low resistance level (Figure 6, area S) or intermediate (Figure 6, zone I). Finally, when the cost-benefit ratio is relatively low, $c_b < (1 - p_1/p_m)^{-1}$, a therapeutic failure regimen can lead to the evolution of bacterial population with low (as in Figure 6, area S), intermediate (as in Figure 6, area I), or high (Figure 6, zone R) resistance level.

4 Discussion

Optimizing antimicrobial treatment dosage is important in preventing bacterial growth and the emergence of resistant bacteria (the Twofold Treatment Objective – TTO). Antimicrobial efficacy is traditionally described by a single value, the minimal inhibitory concentration (MIC) for a given bacterial population. The distribution of MICs across bacterial strains is often bimodal and this metric is therefore used to create a qualitative (or 'binary') classification in the two discrete categories sensitive 'S' and resistant 'R'. Most modelling studies model drug resistance as a binary trait but, as shown by the MIC, it is a continuous trait with varying degrees of intermediate resistance. This antimicrobial quantitative resistance (qAMR) is associated with a reduction in the bacterial killing rate of an antimicrobial and fitness cost.

The first achievement of this work is that we introduce a continuous trait $x \in \mathbb{R}$ that describes the normalized level of resistance –using clinical breakpoints– between $-\infty$ and $+\infty$. By simultaneously addressing the population and evolutionary dynamics, the model with qAMR does not ignore the evolutionary and epidemic short-term transient dynamics which lead to the emergence of resistance. Furthermore, such a continuous level of resistance is shown to be strongly linked to the MIC or growth

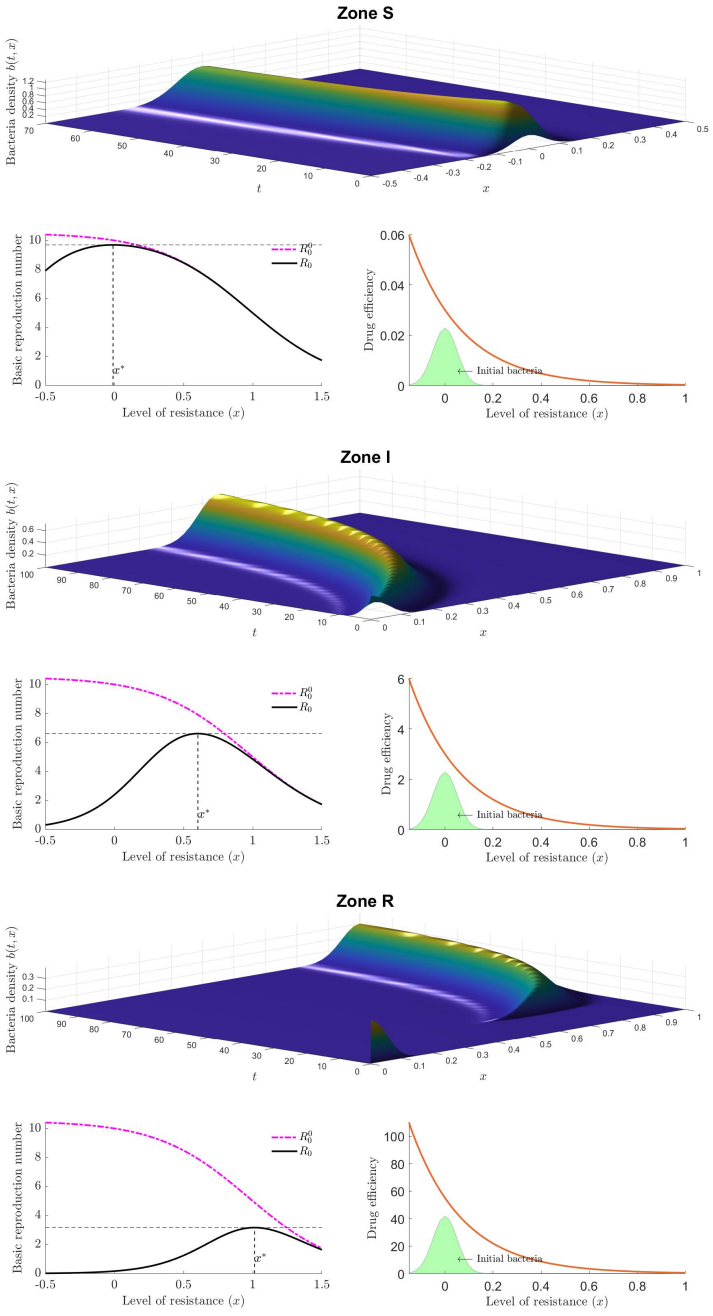

Figure 6: **Evolutionary dynamics under sub-inhibitory drug concentrations.** (Zone S) sub-lethal dose without emergence of resistance in the bacterial population. (Zone I) sub-lethal dose with emergence of intermediate resistance in the bacterial population. (Zone R) sub-lethal dose with emergence of high resistance in the bacterial population. Parameter values are $(\sigma_0, m_0, k_0, p_1/p_0, k_1/k_0) = (0.05, 0.05, 0.03, 0.5, 0.01), (0.05, 0.05, 3, 0.5, 0.01), (0.05, 0.05, 55, 0.5, 0.01)$ for zones S, I, and R respectively. Other parameters are shown by Table 1.

rate, which means it can be informed from actual data.

Using an integro-differential model, we precisely investigate how chemotherapy impacts bacterial population structure at equilibrium. We first characterize the level of acquired evolutionary resistance by bacterial populations in the presence of antimicrobial pressure. We show that this level is governed by a single metric, the reproduction number $\mathcal{R}_0$, which we prove to play the role of invasion fitness in evolution. We then build on our analysis to show which levels of both drug activity on the wild-type sensitive bacterial population and the bacterial resistance cost-benefit ratio are required to achieve our TTO objective. Finally, we compare the effect of lethal and sub-lethal treatments on achieving our TTO objective, and investigate the impact of the initial bacterial population characteristics (*i.e.*, size, initial resistance frequency) on the minimal duration of drug administration to achieve our TTO.

Our analysis emphasizes that the potential success of the treatment does not depend on the antimicrobial activity (k_0) alone but should we assessed with respect to the level of host immunity (μ) as well. These results suggest that treatments with low antimicrobial activity should be limited to infections which elicit a weak immune response (e.g. respiratory infections). They also echoed earlier studies on the synergy between chemotherapy and immune response, *e.g.* [13, 15]. Our model formulation assumes that the immune response μ is constant in time, which allows getting some precise analytical insights into the model's evolutionary dynamics. Furthermore, this assumption of constant immunity is quite plausible in the early moments after the initiation of treatment. However, it is a potential limitation and constitutes one possible extension of the model presented here.

The antimicrobial concentration in the host must not be too low, to clear the bacterial population efficiently, but it cannot be too high without toxic effects in a patient [32]. A sub-lethal treatment is defined here as a treatment where the drug activity k_0/μ is not sufficient to avoid the persistence of bacterial population with the evolutionary resistance level x^*. Mathematically, we have $\mathcal{R}_0(x^*) > 1$. Such a configuration can occurs whatever the value of cost-benefit ratio c_b for which the point $(c_b, k_0/\mu)$ is below the level set $\{\mathcal{R}_0(x^*) = 1\}$ (Figure 4). The corresponding evolutionary dynamics are similar to that shown in Figure 6.

We define a lethal treatment when the drug activity k_0 is enough to ensure that no bacterial population is persistent, *i.e.* that $\mathcal{R}_0(x^*) < 1$. The threshold of this feasible range with respect to the initial drug activity k_0 and cost-benefit ratio of resistance c_b is such that $(c_b, k_0/\mu)$ is above the level set $\{\mathcal{R}_0(x^*) = 1\}$ (Figure 4), and our TTO objective always holds in such configurations. In other words, for any value of cost-benefit ratio c_b (low, intermediate, or high), there exists a minimum drug activity k_0/μ that guarantees a lethal treatment (Figure 4, gray area). The corresponding evolutionary dynamics are similar to that shown in Figure 5 where the total bacterial population dies out.

As pointed by some theoretical studies [12, 33, 34], a high drug dose ('hitting hard' or 'aggressive chemotherapy') is not necessarily the best strategy to limit the spread of resistant strains. We find that a high antimicrobial dose is necessarily to achieve our TTO objective if and only if antibiotic resistance comes with little cost c_b, quantified by the threshold $(1 - p_1/p_m)^{-1}$ (Figures 4, gray zone). However, if the treatment fails for aggressive chemotherapy, it will favor the emergence and spread of a bacterial population with a high resistance level (Figure 4, zone R). This phenomenon is in accordance with the strong relationship between the resistance level of the emerging bacterial population and the antimicrobial dose [10, 11].

The minimal duration of antimicrobial treatment to achieve our TTO objective is a debated question in the literature [13, 33, 35, 36]. Longer treatment duration is associated with a higher frequency of resistance at the end of the experiment [37–40], leading to the suggestion that short antimicrobial courses may limit the evolution of resistance at the population level, and studies to determine whether such short course duration would lead to good infection outcomes [37–40]. We quantify the minimal duration (T_{op}) of drug administration to achieve our TTO objective when cost-benefit ratio c_b and drug activity k_0/μ (relatively to the host immune response μ) on the initial bacterial population lie in the plane $(c_b, k_0/\mu) > \{\mathcal{R}_0(x^*) = 1\}$(Figure 4). We define T_{op} as the time t from which the total bacterial population $\int_{\mathbb{R}} b(t,x)\mathrm{d}x$ is always $\leq 10^{-10}$ (for example the vertical dashed line in Figure 5B). This threshold can be view as the point at which the immune response μ prevents further expansion of the bacterial population. Overall, for a fixed initial bacterial population density, our analysis shows

that the minimal duration of drug administration to achieve our TTO objective is relatively short as soon as $(c_b, k_0/\mu)$ lies in regions that guarantee the TT0 (Figure 4, gray area). This combined effect of the cost-benefit ratio (c_b) and drug activity (k_0/μ) on the time T_{op} is shown Figure 7. We see that, T_{op} is relatively large around threshold values of k_0/μ that guarantee our TTO objective. Next, T_{op} decreases exponentially with a slight increase in k_0/μ compared to the threshold values for our TTO objective. Finally, except around the threshold values of k_0/μ that guarantee our TTO objective, the time T_{op} very short and barely varies with c_b.

The characteristics of the initial bacterial population (size m_0 and the frequency of resistance σ_0) are important for treatment success [10, 13, 36]. We assess the combined effect of m_0 and σ_0 on the minimal duration (T_{op}) of drug administration to achieve our TTO objective (Figure 7). Overall, the size m_0 of the initial bacterial population has a marginal effect on T_{op} as soon as the cost-benefit ratio c_b and the initial drug activity k_0/μ (relatively to the host immune response μ) is such that the pair $(c_b, k_0/\mu)$ lies above the level set $\{\mathcal{R}_0(x^*) = 1\}$ of Figure 4. Whatever the initial population size, our analysis suggests that our TTO objective always holds in a relatively short time period, once the pair $(c_b, k_0/\mu)$ lies above the level set $\{\mathcal{R}_0(x^*) = 1\}$. By contrast, the frequency of resistant strains initially present σ_0 has a strong impact on the minimal duration (T_{op}) of drug administration to achieve our TTO objective (Figure 7). Even if our TTO objective is still achieved as soon as $(c_b, k_0/\mu)$ lies above the level set $\{\mathcal{R}_0(x^*) = 1\}$, the time T_{op} increases nearly exponentially with the frequency of resistance (Figure 7).

The within-host dynamics is often ignored by classifying hosts according to whether they are infected with a given strain or not [19]. A such simplification fails to take into account the genetic diversity of the bacterial resistant population [4, 5] and the short-term evolutionary transient dynamics which lead to the emergence of resistance at the within-host level. Adopting a nested models approach [41–43] is one option to simultaneously track the level of qAMR within the host and the between-host evolutionary epidemiology. Our precise description of the within-host bacterial dynamics, coupled with antimicrobial activity, immune response, and qAMR, can significantly improve the understanding of how bacteria populations adapt to their host at the between-host scale [44].

The concentration property of model (2.1) around the evolutionary attractor x^* is subject to the assumption of a small mutation variance ε in the phenotypic space. More generally, this result holds as soon as the mutation kernel distribution J verifies item 3 of Assumption A. However, that assumption does not mean the mutation kernel has a very fast decay at infinity. We emphasize that the decay of the mutation kernel distribution considered here (namely, Assumption A, item 3.) allows considering the tails of a wide variety of distributions. Indeed, the shape of the distribution of mutational effects can belong to the domain of distributions with exponential tails, truncated tails, or heavy tails that decay as a power law [45].

Finally, in the model proposed here, mutations are assumed to be sufficiently frequent during replication (*i.e.*, new mutants occur during growth), and randomly displace strains into the phenotype space at each generation according to a mutation kernel. However, this constitutes another potential limitation in the model formulation. Indeed, in exponentially growing cells, mutations usually occur during replication [46], but some studies indicate that mutations can be substantially higher in non-growing than growing cultures [47]. Thus, the occurrence of new mutants depends either on the abundance of parental cells or both the abundance and growth rate of the parental cells [48]. Therefore, another potential extension of the model would be to allow both processes for the occurrence of new mutants.

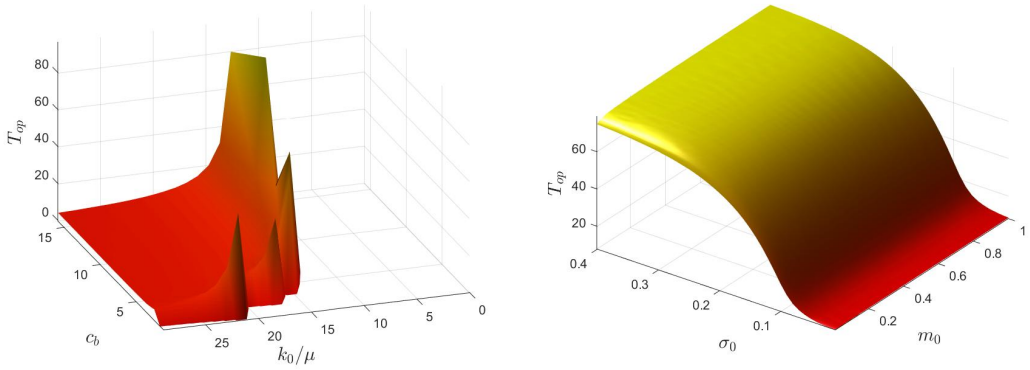

Figure 7: **The minimal duration ($T_{\mathbf{op}}$) of drug administration to achieve our TTO objective.** (Left) Combined effect of the cost-benefit ratio (c_b) and drug activity (k_0/μ), quantified relatively to the host immune response μ, on the time T_{op}. (Right) Combined effect of the initial bacterial population size (m_0) and the initial frequency of resistance (σ_0) on the time T_{op}.

A Model general assumptions

Model (2.1) is defined on the set $L^1(\mathbb{R},\mathbb{R})$ and its parameters satisfy the following general assumptions:

1. Functions μ, k, and p are always positive over $\mathbb{R}$. Furthermore, p is a bounded function on $\mathbb{R}$ and $\alpha > 0$. Finally, the function $\mathcal{R}_0$ defined in (3.3) is continuous on $\mathbb{R}$ and satisfies $\mathcal{R}_0 \not\equiv 0$ and $\lim\limits_{|x|\to\infty} \mathcal{R}_0(x) = 0$.

2. The mutation kernel J is bounded and integrable on $\mathbb{R}^+$, positive almost everywhere, and satisfies $\int_{\mathbb{R}^+} J(x)\mathrm{d}x > 0$, $J(-x) = J(x)$.

3. The mutation kernel J decays rather rapidly towards infinity in the sense that $J(x) = O\left(\frac{1}{\|x\|^\infty}\right)$ as $\|x\| \to \infty$. In other words, $\lim\limits_{|x|\to\infty} |x|^n J(x) = 0$, for all $n \in \mathbb{N}$.

B Model formulation for the qualitative resistance

Recalling that totally sensitive and resistance bacterial levels are respectively $x = 0$ and $x = 1$, we set $b(t,x) = B_S(t)\delta_0(x) + B_R(t)\delta_1(x)$, wherein B_S and B_R are the total densities of highly sensitive and resistance bacterial population. From the b-equation, we have

$$\begin{aligned}\dot{B}_S(t)\delta_0(x) + \dot{B}_R(t)\delta_1(x) = &-(\mu(x)+k(x))(B_S(t)\delta_0(x) + B_R(t)\delta_1(x)) \\ &(1+B_S(t)+B_R(t))^{-\alpha}\left[p(0)B_S(t)J_\varepsilon(x,0) + p(1)B_R(t)J_\varepsilon(x,1)\right].\end{aligned} \tag{B.1}$$

Evaluating the equation (B.1) successively at point $x = 0$ and $x = 1$, we find

$$\begin{cases}\dot{B}_S(t) = (1+B_S(t)+B_R(t))^{-\alpha}\left[p(0)J_\varepsilon(0,0)B_S(t) + p(1)B_R(t)J_\varepsilon(0,1)\right] - (\mu(0)+k(0))B_S(t), \\ \dot{B}_R(t) = (1+B_S(t)+B_R(t))^{-\alpha}\left[p(0)J_\varepsilon(1,0)B_S(t) + p(1)B_R(t)J_\varepsilon(1,1)\right] - (\mu(1)+k(1))B_R(t).\end{cases} \tag{B.2}$$

Since $J_\varepsilon(0,0) + J_\varepsilon(0,1) = 1$ and $J_\varepsilon(1,0) + J_\varepsilon(1,1) = 1$, setting $\varepsilon_0 = J_\varepsilon(1,0) = J_\varepsilon(0,1)$, (B.2) yields

$$\begin{cases}\dot{B}_S(t) = (1+B_S(t)+B_R(t))^{-\alpha}\left[(1-\varepsilon_0)p(0)B_S(t) + \varepsilon_0 p(1)B_R(t)\right] - (\mu(0)+k(0))B_S(t), \\ \dot{B}_R(t) = (1+B_S(t)+B_R(t))^{-\alpha}\left[\varepsilon_0 p(0)B_S(t) + (1-\varepsilon_0)p(1)B_R(t)\right] - (\mu(1)+k(1))B_R(t).\end{cases} \tag{B.3}$$

C The basic reproduction number $\mathcal{R}_0$ and maximization principle

By formally taking the limit $\varepsilon \to 0$ into (2.1), this system becomes

$$\partial_t b(t,x) = \frac{1}{(1+B(t))^\alpha} p(x) b(t,x) - (\mu(x)+k(x)) b(t,x). \tag{C.4}$$

Assume that system (C.4) reaches a monomorphic epidemiological equilibrium $E^z = b^z \delta_z$, for some level of resistance z, before a new mutation with the level y occurs. Note that E^z is the environmental feedback of the resident z. We introduce a small perturbation in (C.4) with level y, such that $b(t,x) = b^z\delta_z(x) + u(t)\delta_y(x)$ and such that the perturbation u is governed by the linearized system of (C.4) around E^z. This reads as

$$\dot{u}(t) = \left[\frac{p(y)}{(1+b^z)^\alpha} - (\mu(y)+k(y)) \right] u(t). \tag{C.5}$$

It follows from the classical adaptive dynamics results [26, 29, 49] that bacterial reproduction number, $\mathcal{R}(y, E^z)$, of a rare mutant strategy, y, in the resident z-population are given by

$$\mathcal{R}(y, E^z) = \frac{1}{(1+b^z)^\alpha} \frac{p(y)}{\mu(y)+k(y)},$$

The invasion fitness $f_z(y)$ of a mutant strategy y in the resident z-population is then given by

$$f_z(y) = \mathcal{R}(y, E^z) - 1. \tag{C.6}$$

When the environmental feedback E^z is reduced to the bacteria-free environment, we have $b^z = 0$. Then, the epidemiological basic reproduction number of the bacterial population with resistance level y is calculated as

$$\mathcal{R}_0(y) = \frac{p(y)}{\mu(y)+k(y)}.$$

Once a bacterial strain has spread and reached a monomorphic equilibrium, the endemic (feedback) environment E^z becomes

$$b^z = (\mathcal{R}_0(z))^{1/\alpha} - 1, \tag{C.7}$$

which is defined when $\mathcal{R}_0(z) > 1$ and satisfies

$$f_z(z) = 0. \tag{C.8}$$

Let us give some details on the derivation of (C.7). At the monomorphic equilibrium E^z, from (C.4) we have,

$$\frac{1}{(1+\int_{\mathbb{R}} b(y)\mathrm{d}y)^\alpha} p(x) b(x) - (\mu(x)+k(x)) b(x) = 0, \quad \forall x \in \mathbb{R}, \tag{C.9}$$

where $b(x) = b^z\delta_z(x)$. Taking $x = z$, (C.9) gives

$$\frac{1}{(1+b^z)^\alpha} p(z) b^z - (\mu(z)+k(z)) b^z = 0.$$

Since $b^z > 0$, it comes

$$(1+b^z)^\alpha = \frac{p(z)}{\mu(z)+k(z)} = \mathcal{R}_0(z),$$

and (C.7) follows.

Next, we show that the model (2.1) admits a maximization principle [30, 31] based on the $\mathcal{R}_0$, such that model's evolutionary attractors (or levels of resistance at equilibrium) are characterized by

local maximums points of $\mathcal{R}_0$. This point is important since, usually, the identification of evolutionary attractors tends more to follow a *mini-max procedure* on an adaptive fitness landscape (see [50] for further discussion). Indeed, by (C.6) and (C.8) we have

$$\begin{aligned} f_z(z) =& \mathcal{R}(y, E^z) - 1 \\ =& \mathcal{R}(y, E^z) - \mathcal{R}(z, E^z) \\ =& \frac{1}{(1+b^z)^\alpha} \frac{p(y)}{\mu(y)+k(y)} - \frac{1}{(1+b^z)^\alpha} \frac{p(z)}{\mu(z)+k(z)} \\ =& \frac{1}{(1+b^z)^\alpha} \left(\mathcal{R}_0(y) - \mathcal{R}_0(z)\right). \end{aligned}$$

The $\mathcal{R}_0$ maximization principle then holds because $\operatorname{sign}(f_z(y)) = \operatorname{sign}\left(\mathcal{R}_0(y) - \mathcal{R}_0(z)\right)$.

D Maximum point of $\mathcal{R}_0$

Recall that $\mathcal{R}_0 = p/(\mu+k)$. From the definition of p and k, it follows that $\operatorname{sgn}(\mathcal{R}_0'(y)) = \operatorname{sgn}\left[f(y) - g(y)\right]$, where f and g are positive function defined on $\mathbb{R}$ by

$$f(x) = \frac{k(x)\ln d}{\mu + k(x)}, \quad \text{and} \quad g(x) = \frac{ba^x \ln a}{1+ba^x},$$

with $d = k_0/k_1$, $b = p_m/p_0 - 1$ and $a = p_0(p_m - p_1)/(p_1(p_m - p_0))$. Functions f, resp. g, are decreasing, resp. nondecreasing, monotonously on $\mathbb{R}$. Therefore, there exists a unique global maximum of $\mathcal{R}_0$ at $x^* \in \mathbb{R}$: $\mathcal{R}_0(x^*) = \max_{x\in\mathbb{R}} \mathcal{R}_0(x)$. Further, we know that $x^* \geq 1$ if and only if $f(1) \geq g(1)$, *i.e.*

$$x^* \geq 1 \quad \text{iff} \quad \left(1 - \frac{p_1}{p_m}\right)\left(1 + \frac{\mu}{k_1}\right) \leq \frac{\log\left(\frac{k_0}{k_1}\right)}{\log\left(\frac{p_0}{p_1}\frac{p_m - p_1}{p_m - p_0}\right)}.$$

Similarly, we also have

$$x^* \geq 0 \quad \text{iff} \quad \left(1 - \frac{p_0}{p_m}\right)\left(1 + \frac{\mu}{k_0}\right) \leq \frac{\log\left(\frac{k_0}{k_1}\right)}{\log\left(\frac{p_0}{p_1}\frac{p_m - p_1}{p_m - p_0}\right)}.$$

We now search for conditions such that $\mathcal{R}_0(x^*) < 1$. Note that

$$\mathcal{R}_0(x^*) = \frac{p(x^*)}{\mu + k(x^*)} = \frac{p_m}{(\mu + k(x^*))(1+ba^{x^*})}.$$

Since $f(x^*) = g(x^*)$ it comes

$$1 + ba^{x^*} = \frac{(\mu + k(x^*))\log(a)}{(\mu + k(x^*))\log(a) - k(x^*)\log(d)}.$$

We then rewrite

$$\mathcal{R}_0(x^*) = p_m \frac{(\mu + k(x^*))\log(a) - \log(d)k(x^*)}{(\mu + k(x^*))^2 \log(a)}.$$

Therefore,

$$\begin{aligned} \mathcal{R}_0(x^*) < 1 \iff & (\mu + k(x^*))^2 \log(a) > p_m(\mu + k(x^*))\log(a) - p_m \log(d) k(x^*) \\ \iff & \frac{\mu + k(x^*)}{p_m} > \frac{1}{2}\left(1 - \frac{\log(d)}{\log(a)}\right) + \sqrt{\frac{1}{4}\left(1 - \frac{\log(d)}{\log(a)}\right)^2 + \frac{\mu}{p_m}\frac{\log(d)}{\log(a)}}. \end{aligned} \tag{D.10}$$

Next, setting $\mathcal{R}_0^0 = \mathcal{R}_0|_{k\equiv 0}$, the basic reproduction number of the model without any treatment, we have $\mathcal{R}_0^0(0) = p_0/\mu$, that is, $\mu = \frac{p_0}{\mathcal{R}_0^0(0)}$ and so, (D.10) becomes

$$\mathcal{R}_0(x^*) < 1 \Longleftrightarrow k(x^*) > \frac{p_m}{2}\left(1 - \frac{\log(d)}{\log(a)}\right) + \sqrt{\frac{p_m^2}{4}\left(1 - \frac{\log(d)}{\log(a)}\right)^2 + \frac{p_0 p_m}{\mathcal{R}_0^0(0)}\frac{\log(d)}{\log(a)}} - \frac{p_0}{\mathcal{R}_0^0(0)}.$$

Setting

$$\gamma = \frac{p_m}{2}\left(1 - \frac{\log(d)}{\log(a)}\right) - \frac{p_0}{\mathcal{R}_0^0(0)},$$

the above condition becomes

$$\mathcal{R}_0(x^*) < 1 \Longleftrightarrow k(x^*) > \gamma + \sqrt{\gamma^2 + \frac{p_0}{\mathcal{R}_0^0(0)}\left(p_m - \frac{p_0}{\mathcal{R}_0^0(0)}\right)}. \tag{D.11}$$

E Dissipativity and positivity

Let $b(t,x)$ be the solution of (2.1) for the initial condition $b(t=0,\cdot) = b_0(\cdot)$. Setting $\zeta(x) = \mu + k$ and introducing the locally Lipschitzian function

$$f(b(t,\cdot))(x) = \frac{1}{(1+B(t))^\alpha}\int_{\mathbb{R}} J(x-y)p(y)b(t,y)\mathrm{d}y,$$

equation (2.1) becomes

$$\partial_t b(t,x) = -\zeta(x)b(t,x) + f(b(t,\cdot))(x). \tag{E.12}$$

Theorem E.1 *Let Assumption A be satisfied. Let $b_0 \in L^1_+$. Then*

1. *There exists a unique global solution $v(\cdot,b_0) : [0,\infty) \to L^1_+(\mathbb{R})$ of (2.1) with $v(0,b_0) = b_0$ and $v(t,b_0) = b(t,\cdot)$ for all $t > 0$.*
2. *The semi-flow defined by $\{v(t,b_0)\}_t$ is bounded dissipative and asymptotically smooth, and hence, it admits a global attractor in $L^+(\mathbb{R})$.*
3. *The semi-flow $\{v(t,b_0)\}_t$ is such that for any $b_0 \in L^1_+(\mathbb{R}) \setminus \{0\}$*

$$b(t,x) > 0, \text{ for all } t > 0, x \in \mathbb{R}.$$

Proof. 1. Since $f : L^1 \to L^1$ is locally Lipschitz, for any $b_0 \in L^1$, there exists $T_M = T_M(b_0) > 0$ such that (2.1) has a unique solution $b \in \mathcal{C}\left([0,T_M)\times\mathbb{R}, L^1\right) \cap \mathcal{C}^1\left([0,T_M)\times\mathbb{R}, L^1\right)$, see [51]. Further, if $b_0 \in L^1_+$, by (E.12), we easily find that $b(t,\cdot) \in L^1_+$ for all $t \in (0,T_M)$. This gives the local well-posedness and positivity of (2.1). Next, we have

$$\dot{B}(t) \le \|J\|_\infty \|p\|_\infty \frac{B(t)}{(1+B(t))^\alpha} - \inf_{\mathbb{R}} \zeta \; B(t),$$

which gives

$$B(t) \le \max\left(\|b_0\|_{L^1}, \left[\frac{\|J\|_\infty\|p\|_\infty}{\inf_{\mathbb{R}}\zeta}\right]^{1/\alpha} - 1\right), \text{ for all } t \in [0,T_M). \tag{E.13}$$

From where we establish the global well-posedness and bounded dissipativity in L^1_+.
2. We now show that the semi-flow is asymptotically smooth, i.e., for any closed, bounded and

positively invariant set $K \subset L^1_+$, there exists a compact set $\Omega \subset L^1_+$ such that $d_h(v(t,K),\Omega) \to 0$ as $t \to \infty$ where $u_K =$ and d_h is the Hausdorff semi-distance [52]. By (E.12) we have

$$b(t,\cdot) = e^{-\zeta(x)t}b_0(\cdot) + \int_0^t e^{-\zeta(x)(t-s)}f(b(s,\cdot))\mathrm{d}s, \quad \text{for } t \geq 0, b_0 \in L^1_+.$$

Then, the compacity of f gives that $\{v(t,\cdot)\}_t$ is asymptotically smooth [53].
3. Let u be the unique solution of

$$\begin{cases} \partial_t u(t,x) = -\zeta(x)u(t,x) + \int_{\mathbb{R}} J(x-y)p(y)u(t,y)\mathrm{d}y, \\ u(0,\cdot) = b_0. \end{cases}$$

By the comparison principle, we have $b(t,x) \geq u(t,x) \geq 0$ for all $t \geq 0$ and $x \in \mathbb{R}$. Therefore, item 3. follow if show $u(t,x) > 0$ for all $t > 0$ and $x \in \mathbb{R}$. Setting $U[u](x) = \int_{\mathbb{R}} J(x-y)p(y)u(y)\mathrm{d}y$ on $L^1(\mathbb{R})$, we find that U is continuous and generates an uniformly continuous and positive semigroup $\{e^{Ut}\}_t$ on $L^1(\mathbb{R})$. Then, for each $t \geq 0$,

$$e^{Ut}[b_0] = \sum_{l=0}^{\infty} \frac{t^l U^l[b_0]}{l!}, \tag{E.14}$$

where the series converges in the operator norm. Since $b_0 \neq 0$, $\int_{\mathbb{R}} J(x)\mathrm{d}x > 0$ and

$$U^{l+1}[b_0](x) = \int_{\mathbb{R}} J(x-y)p(y)U^l[b_0](y)\mathrm{d}y,$$

an iteration argument ensures the existence of l_0 such that $U^l[b_0](x) > 0$ for $x \in \mathbb{R}$ and for all $l \geq l_0$. From where, (E.14) gives that $e^{Ut}[b_0](x) > 0$ for all $x \in \mathbb{R}$. Setting $\bar{\zeta} = \sup_{\mathbb{R}} \zeta(x)$, we then have

$$u(t,\cdot) = e^{-\bar{\zeta}t}e^{Ut}[b_0] + \int_0^t e^{-\bar{\zeta}(t-s)}e^{U(t-s)}[(\bar{\zeta}-\zeta)u(s,\cdot)]\mathrm{d}s \leq e^{-\bar{\zeta}t}e^{Ut}[b_0] > 0.$$

■

F Linearization at the bacteria-free equilibrium

At the bacterial-free equilibrium, the linear system of (2.1) writes

$$\partial_t b(t,x) = L_\varepsilon[b(t,\cdot)](x),$$

with

$$L_\varepsilon = U_\varepsilon + T, \tag{F.15}$$

and $U_\varepsilon[b] = \int_{\mathbb{R}} J_\varepsilon(x-y)p(y)b(y)\mathrm{d}y$, $T[b] = -\zeta b$.

Proposition F.1 *Let $s(L_\varepsilon) = \sup\{R_e\lambda : \lambda \in \sigma(L_\varepsilon)\}$ the spectral bound of L_ε.*

- *If $s(L_\varepsilon) > s(T)$, then $s(L_\varepsilon)$ is an isolated and simple eigenvalue of L_ε, whose eigen-space is spanned by $0 < \phi \in L^1(\mathbb{R})$, and if $\lambda \in \sigma(L_\varepsilon)$ and $\lambda \neq s(L_\varepsilon)$, then $R_e\lambda < s(L_\varepsilon)$.*
- *If there exist $\lambda \in \mathbb{R}$ and $0 < \phi \in L^1(\mathbb{R})$ such that $L_\varepsilon[\phi] = \lambda\phi$, then $s(L_\varepsilon) = \lambda > s(T)$.*
- *$s(L_\varepsilon) > 0$ (resp. $= 0, < 0$) if and only if $r(H_\varepsilon) > 1$ (resp. $= 1, < 1$).*

Proof. By the same argument as in the proof of Lemma H.2, we find the compacity and irreducibility of U, and the first item follows from [54](Theorem 2.2).
For the second item, let $\lambda \in \mathbb{R}$ and $\phi \in {}^1(\mathbb{R})$ such that $L[\phi] = \lambda\phi$. Since T generates a uniformly continuous, positive and uniformly exponentially stable semigroup, by Lemma H.2 and a general perturbation result, note that the semigoup $\{e^{Lt}\}_t$ is positive. Let $v \in L^1(\mathbb{R})$ such that $\|v\|_{L^1} \leq 1$, then for all $t \geq 0$

$$e^{Lt}v \leq \frac{1}{\inf_{\mathbb{R}} \phi} e^{Lt}\phi = \frac{1}{\inf_{\mathbb{R}} \phi} e^{\lambda t}\phi \leq \frac{\sup_{\mathbb{R}} \phi}{\inf_{\mathbb{R}} \phi} e^{\lambda t},$$

from where $\|e^{Lt}\| \leq \frac{\sup_{\mathbb{R}} \phi}{\inf_{\mathbb{R}} \phi} e^{\lambda t}$. Since the growth bound of $\{e^{Lt}\}_t$ coincides with $s(L)$ it comes $s(L) \leq \lambda$ and hence, $s(L) = \lambda$. We now show that $\lambda > s(T)$. Indeed, $\lambda\phi = L[\phi] = H[\phi] - \zeta\phi > -\zeta\phi$ and hence $\lambda > -\sup_{\mathbb{R}} \zeta = s(T)$, from where the second item follows.
It remains to prove the last item. Assume $s(L) = 0$. Then $s(T) = -\sup_{\mathbb{R}} \zeta < 0 = s(L)$. From the first item, we find $\phi > 0$ such that $L[\phi] = 0$. Hence $H[\sqrt{\zeta p}\phi] = \omega L[\phi] + \sqrt{\zeta p}\ \phi = \sqrt{\zeta p}\ \phi$, that is, $(1, \sqrt{\zeta p}\ \phi)$ is an eigen-pair of H. Hence, by Lemma H.2 it comes $r(H) = 1$. Next, assume that $r(H) = 1$. Let $\phi > 0$ such that $H[\phi] = \phi$. Then $L[\phi/\sqrt{\zeta p}] = \omega^{-1/2}(H[\phi] - \phi) = 0$, and the second item gives $s(L) = 0$.
To conclude on the last item of the proposition, it is sufficient to prove that $s(L) > 0$ iff $r(H) > 1$. Assume $s(L) > 0$, then we can find $\phi > 0$ such that $L[\phi] = s(L)\phi$. Hence, $H[\sqrt{\zeta p}\ \phi] = \omega L[\phi] + \sqrt{\zeta p}\ \phi = (s(L)/\zeta + 1)\sqrt{\zeta p}\ \phi \geq (1 + k)\sqrt{\zeta p}\ \phi$, with $k = \inf_{\mathbb{R}} \zeta^{-1} > 0$. By iterating, it comes $H^n[\sqrt{\zeta p}\ \phi] \geq (1 + k)^n\sqrt{\zeta p}\ \phi$ for all $n \geq 1$. This gives that $\|H^n\|^{1/n} \geq (1 + k)$ an hence $r(H) \geq 1 + k > 1$. Conversely, let $r(H) > 1$ and $\phi > 0$ the corresponding eigenfunction. Then $L[\phi/\sqrt{\zeta p}] = \zeta(r(H) - 1)\ \phi/\sqrt{\zeta p} \leq c\phi/\sqrt{\zeta p}$, with $c = (r(H) - 1)\inf_{\mathbb{R}} \zeta > 0$. By contradiction, assume that $s(L) < 0$. Then, $0 \notin \sigma(L)$ and $(-L)^{-1}$ is positive as L generates a positive semigroup. Hence,

$$\phi/\sqrt{\zeta p} = (-L)^{-1}(-L)[\phi/\sqrt{\zeta p}] \leq -c(-L)^{-1}[\phi/\sqrt{\zeta p}].$$

As $(-L)^{-1}[\phi/\sqrt{\zeta p}] \geq 0$, we find $\phi/\sqrt{\zeta p} \leq 0$, which leads to a contradiction. Hence, $s(L) \geq 0$, and so $s(L) > 0$. ∎

G Stability results when $r(H_\varepsilon) < 1$

Theorem G.1 *1. The bacteria-free equilibrium E^0 is asymptotically stable if $r(H_\varepsilon) < 1$ and unstable if $r(H_\varepsilon) > 1$.*

2. When $r(H_\varepsilon) < 1$, the bacteria-free equilibrium E^0 is globally asymptotically stable in $L^1_+(\mathbb{R})$, that is, for any solution $b(t, \cdot)$ with initial $b_0 \in L^1_+(\mathbb{R}) \setminus \{0\}$, we have

$$b(t, \cdot) \to 0 \text{ in } L^1_+(\mathbb{R}) \text{ as } t \to \infty.$$

Proof. 1. Proposition F.1 allows us to derive the following threshold result on the local stability of the bacteria-free equilibrium.
2. By Theorem E.1 it suffices to prove item 2. for any $b_0 \in L^1_+(\mathbb{R}) \setminus \{0\}$ with $\|b(t, \cdot)\|_{L^1} \leq C$ for all $t \geq 0$, where $C \gg 1$. By (2.1), we have $\partial_t b(t, x) \leq L[b(t, \cdot)](x)$, and by comparison principle, we find $0 \leq b(t, \cdot) \leq e^{Lt}b_0$, where $\{e^{Lt}\}_t$ is the positive semigroup generated by L. Next, by Proposition F.1, we have $s(L) < 0$ because $r(H_\varepsilon) < 1$. Furthermore, since the growth bound of $\{e^{Lt}\}_t$ is the same as $s(L)$, we conclude that

$$\|b(t, \cdot)\|_{L^1} \leq c_0 e^{-c_1 t}\|b_0\|_{L^1}, \quad \forall t \geq 0,$$

for the constants $c_0 > 1$ and $c_1 > 0$. This ends the proof of the theorem. ∎

H Equilibrium

The bacteria-free environment $E^0 = 0$ is always an equilibrium of Model (2.1). In this section, we discuss the existence of a nontrivial equilibrium $b^*(\cdot) > 0$. From System (2.1) we find, for all $x \in \mathbb{R}$

$$\omega(x) \int_{\mathbb{R}} J_\varepsilon(x-y)\omega(y)\sqrt{p\zeta}b^*(y)\mathrm{d}y = (1+B^*)^\alpha \sqrt{p\zeta}b^*(x).$$

where $\omega(x) = \sqrt{\mathcal{R}_0(x)}$, and $B^* = \int b^*(x)\mathrm{d}x$. Setting $v^* = \sqrt{p\zeta}b^*$, it comes that v^* is solution of the following system

$$\omega(x) \int_{\mathbb{R}} J_\varepsilon(x-y)\omega v^*(y)\mathrm{d}y = (1+B^*)^\alpha v^*(x). \tag{H.16}$$

Therefore, the existence of $b^*(\cdot) > 0$ is strongly related to the spectral property of the linear integral operator H_ε defined on $L^p(\mathbb{R})$, for any $p \geq 1$, by

$$H_\varepsilon[v](x) = \omega(x) \int_{\mathbb{R}} J_\varepsilon(x-y)\omega(y)v^*(y)\mathrm{d}y. \tag{H.17}$$

We then have the following theorem

Theorem H.1 *Let Assumption A be satisfied. Let $r(H_\varepsilon)$ the spectral radius of operator H_ε and $\phi_\varepsilon > 0$ the associated eigenfunction normalized such that $\|\phi_\varepsilon\|_{L^1} = 1$. Define the quantity*

$$\mathcal{K}_0^\varepsilon = \frac{(r(H_\varepsilon))^{1/\alpha} - 1}{\int_{\mathbb{R}} \frac{\phi_\varepsilon}{\sqrt{p\zeta}}\mathrm{d}y}. \tag{H.18}$$

When $r(H_\varepsilon) \leq 1$, the the bacteria-free equilibrium $E^0 = 0$ is the unique equilibrium of Model (2.1). When $r(H_\varepsilon) > 1$, in addition to E^0, Model (2.1) has a unique nutrient-bacteria equilibrium $E^* > 0$ such that

$$E^*(x) = \mathcal{K}_0^\varepsilon \frac{\phi_\varepsilon(x)}{\sqrt{p(x)\zeta(x)}}. \tag{H.19}$$

Furthermore, an explicit formula for the spectral radius $r(H_\varepsilon)$ of H_ε reads $r(H_\varepsilon) = r_0^\varepsilon$, where

$$r_0^\varepsilon = \sup_{v \in L^2, \|v\|_{L^2}=1} \int_{\mathbb{R}^2} J_\varepsilon(x-y)\omega(x)\omega(y)v(x)v(y)\mathrm{d}x\mathrm{d}y. \tag{H.20}$$

Proof of Theorem H.1. Here, we deal with the existence of the principal eigenpair for the linear operator H_ε, and we proceed by several steps. For simplicity, we do not emphasize the ε-dependency. First, we introduce the following lemma

Lemma H.2 *The following statements hold under Assumption A.*

1. *For each $p \geq 1$, the operator H_ε is compact and irreducible on $L^p(\mathbb{R})$ with positive spectral radius, $r(H_\varepsilon) > 0$. Further, there exists a function $u_p \in L^p(\mathbb{R})$ such that $u_p > 0$ a.e. and $H[u_p] = r(H_\varepsilon)u_p$. Furthermore, if $u \in L^p_+(\mathbb{R}) \setminus \{0\}$ is such that $H[u] = cu$ with $c \in \mathbb{R}$, then $u > 0$ a.e., $u \in span(u_p)$ and $c = r(H)$.*
2. *The common spectral value of the operator H is characterized by $r(H) = r_0$ for all $p \geq 1$; where r_0 is defined by (H.20).*

Before giving details on the proof of Lemma H.2, let us quickly end with the proof of Theorem H.1. Obviously, $E^0 = 0$ is always an equilibrium point of the model. We now check nontrivial solution $b^* > 0$ of system (H.16). Using above notations, (H.16) rewrites $H[v^*](x) = (1+B^*)^\alpha v^*(x)$. From Lemma H.2 we find $r(H) = (1+B^*)^\alpha > 1$ and $v^* \in \mathrm{span}(\phi^*)$, wherein $\phi^* \in L^1(\mathbb{R}) \cap L^\infty(\mathbb{R})$ is the principal eigenfunction of H with $\phi^* > 0$ *a.e.* and normalized by $\|\phi^*\|_{L^1} = 1$. We then write $v^* = \eta\phi^*$, for some constant $\eta > 0$; *i.e.* $b^* = \frac{\eta\phi^*}{\sqrt{p\zeta}}$ and $B^* = \eta \int \frac{\phi^*}{\sqrt{\zeta p}}\mathrm{d}y$. This completes the proof of Theorem H.1. It remains to proof Lemma H.2.

Proof of Lemma H.2. The proof is mostly based on the Frobenius theorem, which generalizes the Krein-Rutmann theorem for positive, irreducible, and compact linear operators in Banach lattices.

H is a bounded operator. Since the kernel operator $J \in L^1(\mathbb{R}) \cap L^\infty(\mathbb{R})$, the operator H is a bounded operator. Indeed,

$$\begin{aligned}\int |H[u](x)|^p \,\mathrm{d}x \leq & \int \left[\omega(x) \int J(x-y)\omega(y)|u(y)|\mathrm{d}y\right]^p \mathrm{d}x \\ \leq & \|\omega\|_\infty^p \|J\|_\infty^p ||u||_{L^p}^p.\end{aligned}$$

H is a compact operator in $L^p(\mathbb{R})$ for any $p \geq 1$. Denote by $\tau_h f$, the translation of $f : \mathbb{R} \to \mathbb{R}$ by h, and defined by $\tau_h f(x) = f(x+h)$ for all $x \in \mathbb{R}$. Let $p \in [1, \infty)$ be given. Let $u \in L^p(\mathbb{R})$ and $h \in \mathbb{R}$ be given. We have

$$\|\tau_h H[u] - H[u]\|_{L^p(\mathbb{R})}^p = \int_{\mathbb{R}} \left| \int_{\mathbb{R}^N} [\tau_h \omega(x) J(x-y) - \omega(x) J(x-y)]\omega(y)u(y)\mathrm{y}\right|^p \mathrm{d}x.$$

Then Young inequality yields

$$\|\tau_h H[u] - H[u]\|_{L^p(\mathbb{R})} \leq \|\tau_h \omega J - \omega J\|_{L^1(\mathbb{R}^N)} \|\Psi\|_\infty \|u\|_{L^p(\mathbb{R})}.$$

Since $\|\tau_h \omega J - \omega J\|_{L^1(\mathbb{R})} \to 0$ as $h \to 0$ one gets that

$$\lim_{h \to 0} \tau_h H[u] = H[u] \text{ in } L^p(\mathbb{R}),$$

wherein the above convergence holds uniformly on bounded sets on $L^p(\mathbb{R})$.

Next, let $u \in L^p(\mathbb{R})$ and $s > 0$ be given. Then we have

$$\int_{|x|>s} |H[u](x)|^p \,\mathrm{d}x \leq \int_{|x|>s} \left[\omega(x) \int_{\mathbb{R}} J(x-y)\omega(y)|u(y)|\mathrm{d}y\right]^p \mathrm{d}x. \tag{H.21}$$

Let $R > 0$ be given. Consider a smooth and nonnegative function χ_R such that $0 \leq \chi_R \leq 1$, $\chi_R(y) = 1$ if $|y| \leq R$ and $\chi_R(y) = 0$ if $|y| \geq R+1$. Then, there exists some constant $C = C_p > 0$, such that equation (H.21) becomes

$$\begin{aligned}\int_{|x|>s} |H[u](x)|^p \,\mathrm{d}x \leq & C_p \int_{|x|>s} \left[\omega(x) \int_{\mathbb{R}} J(x-y)\omega(y)|u(y)|\chi_R(y)\mathrm{d}y\right]^p \mathrm{d}x \\ & + C_p \int_{|x|>s} \left[\omega(x) \int_{\mathbb{R}^N} J(x-y)\omega(y)|u(y)|(1-\chi_R(y))\mathrm{d}y\right]^p \mathrm{d}x.\end{aligned}$$

Now, note that there exists some constant $C > 0$ independent of u (and R) such that

$$\begin{aligned}& \int_{|x|>s} \left[\omega(x) \int_{\mathbb{R}} J(x-y)\omega(y)|u(y)|\chi_R(y)\mathrm{d}y\right]^p \mathrm{d}x \\ & \qquad \leq C\|J\|_\infty^{p-1} ||u||_{L^p(\mathbb{R})}^p \int_{|x|>s} \left[\sup_{|x-y|\leq R+1} J(y)\right] \mathrm{d}x.\end{aligned}$$

Since the function $x \mapsto \sup_{|x-y|\leq R+1} J(y)$ belongs to $L^1(\mathbb{R})$, we then find a constant $C > 0$ such that the previous inequality becomes

$$\int_{|x|>s} \left[\omega(x) \int_{\mathbb{R}} J(x-y)\omega(y)|u(y)|\chi_R(y)\mathrm{d}y\right]^p \mathrm{d}x \leq C\|J\|_\infty^{p-1} ||u||_{L^p(\mathbb{R})}^p.$$

On the other hand, since $\|J\|_{L^1(\mathbb{R})} = 1$, Young inequality ensures that

$$\int_{|x|>s} \left[\omega(x) \int_{\mathbb{R}} J(x-y)\omega(y)|u(y)|(1-\chi_R(y))\mathrm{d}y\right]^p \mathrm{d}x \leq \sup_{|y|\geq R} |\omega(y)|^p ||u||_{L^p(\mathbb{R})}^p.$$

Now, setting $B_p(1)$ the unit ball in $L^p(\mathbb{R})$, it comes that for all $R > 0$

$$\limsup_{s\to+\infty} \sup_{u\in B_p(1)} \int_{|x|>s} |H[u](x)|^p \,\mathrm{d}x \le C_p \sup_{|y|\ge R} |\omega(y)|^p.$$

Finally, by Assumption A, we have $\omega(x) \to 0$ as $|x| \to \infty$. From where

$$\lim_{s\to+\infty} \sup_{u\in B_p(1)} \|H[u]\|_{L^p(\{|x|\ge s\})} = 0.$$

Therefore, the Fréchet-Kolmogorov theorem applies and ensures that H is a compact operator on $L^p(\mathbb{R})$.

The spectral radius of H is positive. By Assumption A, the function ω is positive on $\mathbb{R}$, then the operator H is irreducible on $L^p(\mathbb{R})$, for all $p \ge 1$. Then, Frobenius theorem (Theorem 4.2.13 and Corollary 4.2.15 in [55]) applies and ensures that its spectral radius $r(H)$ is positive and it is a simple eigenvalue associated to an eigenvector $\psi > 0$ *a.e.* in $(0,1)$. Furthermore, if $\zeta \in \mathbb{R}$ is an eigenvalue H associated to an eigenvector $w \in L^p_+(0,1) \setminus \{0\}$ then $\zeta = r(H)$ and $w > 0$ *a.e.* in $(0,1)$. This ends with the proof of Lemma H.2, item 1..

We now prove that for all $p \ge 1$, $r(H) = r_0$, with r_0 defined by (H.20). Denote by $r_p(H)$ the spectral radius of H defined on $L^p(0,1)$, for $p \ge 1$. Then, with $p = 1$, by item 1. there exists a function $u_1 \in L^1(0,1)$ with $u_1 > 0$ *a.e.* such that $r_1(H)u_1 = Hu_1$. Let $q \ge 1$ be given. Again by item 1., to show that $r_q(H) = r_1(H)$, it is sufficient to show that $u_1 \in L^q(0,1)$. Since $u_1 \in L^1(0,1)$ and $J \in L^1(0,1) \cap L^\infty(0,1)$, then the convolution product $\mathcal{F}J * (\mathcal{F}u_1) \in L^1(0,1) \cap L^\infty(0,1)$ and the result follows from Young inequality. Finally, due to the symmetry hypothesis on the mutation kernel J, H is self-adjoint operator and then, the Rayleigh quotient formulation for the principal eigenvalue of H ensures that $r_2(H) = r_0$. This completes the proof of 2. and so the proof of Lemma H.2. ■ ■

I Persistence results when $r(H_\varepsilon) > 1$

Theorem I.1 *Suppose $r(H_\varepsilon) > 1$, then the semi-flow $\{v(t,b_0)\}_t$ is uniformly persistent, that is, there exists a constant $\nu > 0$ such that, for any $b_0 \in L^1_+(\mathbb{R}) \setminus \{0\}$, the unique solution $v(t,b_0) = b(t,\cdot)$ of (2.1) with initial data b_0 satisfies*

$$\liminf_{t\to\infty} \|b(t,\cdot)\|_{L^1} > \nu.$$

Proof. We first establish the weak uniform persistence, that is, there exists $\nu_1 > 0$ such that

$$\limsup_{t\to\infty} \|b(t,\cdot)\|_{L^1} > \nu_1. \tag{I.22}$$

By contradiction, suppose that for $\tau > 0$, there exists $b_0^\tau \in L^1_+(\mathbb{R}) \setminus \{0\}$ such that the unique solution $b^\tau(t,x)$ of (2.1) with initial data b_0^τ satisfies

$$\limsup_{t\to\infty} \|b^\tau(t,\cdot)\|_{L^1} \le 2\tau.$$

Replacing b_0^τ by $b^\tau(t^\tau)$ for some $t^\tau \gg 1$ and applying item 3. of Theorem E.1, without loss of generality, we may assume that $0 < \|b^\tau(t,\cdot)\|_{L^1} < \tau$ for all $t \ge 0$. Then,

$$\partial_t b^\tau(t,\cdot) \ge L^\tau[b^\tau(t,\cdot)], \tag{I.23}$$

where L^τ is the operator defined by $L^\tau[u(\cdot)](x) = -\zeta(x)u(x) + (1+\tau)^{-\alpha} \int_{\mathbb{R}} J(x-y)p(y)u(y)\mathrm{d}y$. We also introduce the operator $H^\tau[u(\cdot)](x) = -\zeta(x)u(x) + (1+\tau)^{-\alpha} \int_{\mathbb{R}} J(x-y)p(y)u(y)\mathrm{d}y$.

Note that $H^\tau \to H$ in the operator norm as $\tau \to 0$ and where H is the operator introduced by (H.17). Since $r(H) > 1$, we can choose τ_0 sufficiently small that $r(H^{\tau_0}) > 1$, as the spectral radius is a continuous function of compact linear operators. By Proposition F.1, $s(L^{\tau_0}) > 0$ and it is an isolated and simple eigenvalue with corresponding eigenfunction $\phi^{\tau_0} > 0$ and normalized such that $\|\phi^{\tau_0}\| = 1$. Let $c > 0$ be a constant such that $c\phi^{\tau_0}(x) \leq b_0^{\tau_0}(x)$ for all $x \in \mathbb{R}$. By Lemma H.2 and general perturbation results, L^{τ_0} the semigroup $\{e^{L^{\tau_0}t}\}$ generated by L^{τ_0} is uniformly continuous and positive. It comes

$$e^{L^{\tau_0}t}b_0^{\tau_0} \geq e^{L^{\tau_0}t}c\phi^{\tau_0} = e^{s(L^{\tau_0})t}c\phi^{\tau_0}.$$

From where $\|e^{L^{\tau_0}t}b_0^{\tau_0}\|_{L^1} \to \infty$ as $t \to \infty$, since $s(L^{\tau_0}) > 0$. By the comparison principle, (I.23) gives $\|b^{\tau_0}(t,\cdot)\|_{L^1} \geq \|e^{L^{\tau_0}t}b_0^{\tau_0}\|_{L^1} \to \infty$ as $t \to \infty$ and leading to a contradiction.

It remains to show that there exists a constant $\nu > 0$

$$\liminf_{t\to\infty} \|b(t,\cdot)\|_{L^1} > \nu.$$

The function $\chi(u) = \|u\|_{L^1}$ is continuous and the compactness assumption to apply Theorem A.34 of [56] is satisfied because the semiflow $v(t, b_0)$ induced by the nonnegative solutions of (2.1) has a compact attractor of bounded sets by Theorem E.1. By Theorem E.1, $\chi(b_0) > 0$ implies $\chi\left(v(t, b_0)\right) > 0$ and the result follows from [56].

■

Code availability. The code (with the MatLab Programming Language) used to simulate the model can be accessed through the Zenodo platform at `http://doi.org/10.5281/zenodo.5508202`

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References

[1] Palumbi SR. Humans as the World's Greatest Evolutionary Force. Science. 2001 Sep;293(5536):1786–1790.

[2] Goossens H, Ferech M, Vander Stichele R, Elseviers M, ESAC Project Group. Outpatient Antibiotic Use in Europe and Association with Resistance: A Cross-National Database Study. Lancet (London, England). 2005 Feb;365(9459):579–587.

[3] Amabile-Cuevas CF. Antibiotics and Antibiotic Resistance in the Environment. CRC Press; 2015.

[4] Lee HH, Molla MN, Cantor CR, Collins JJ. Bacterial Charity Work Leads to Population-Wide Resistance. Nature. 2010 Sep;467(7311):82–85.

[5] Levert M, Zamfir O, Clermont O, Bouvet O, Lespinats S, Hipeaux MC, et al. Molecular and Evolutionary Bases of Within-Patient Genotypic and Phenotypic Diversity in Escherichia Coli Extraintestinal Infections. PLOS Pathogens. 2010 Sep;6(9):e1001125.

[6] EUCAST: Clinical Breakpoints and Dosing of Antibiotics;. https://www.eucast.org/clinical_breakpoints/.

[7] Demczuk W, Martin I, Sawatzky P, Allen V, Lefebvre B, Hoang L, et al. Equations To Predict Antimicrobial MICs in Neisseria Gonorrhoeae Using Molecular Antimicrobial Resistance Determinants. Antimicrobial Agents and Chemotherapy. 2020 Feb;64(3).

[8] Read AF, Day T, Huijben S. The Evolution of Drug Resistance and the Curious Orthodoxy of Aggressive Chemotherapy. Proceedings of the National Academy of Sciences. 2011 Jun;108(Supplement 2):10871–10877.

[9] Blanquart F. Evolutionary Epidemiology Models to Predict the Dynamics of Antibiotic Resistance. Evolutionary Applications. 2019 Jan;12(3):365–383.

[10] Lipsitch M, Levin BR. The Population Dynamics of Antimicrobial Chemotherapy. Antimicrobial Agents and Chemotherapy. 1997 Feb;41(2):363–373.

[11] Kepler TB, Perelson AS. Drug Concentration Heterogeneity Facilitates the Evolution of Drug Resistance. Proceedings of the National Academy of Sciences of the United States of America. 1998 Sep;95(20):11514–11519.

[12] Day T, Read AF. Does High-Dose Antimicrobial Chemotherapy Prevent the Evolution of Resistance? PLOS Computational Biology. 2016 Jan;12(1):e1004689.

[13] Gjini E, Brito PH. Integrating Antimicrobial Therapy with Host Immunity to Fight Drug-Resistant Infections: Classical vs. Adaptive Treatment. PLOS Computational Biology. 2016 Apr;12(4):e1004857.

[14] Handel A, Margolis E, Levin BR. Exploring the Role of the Immune Response in Preventing Antibiotic Resistance. Journal of theoretical biology. 2009 Feb;256(4):655–662.

[15] Hansen E, Woods RJ, Read AF. How to Use a Chemotherapeutic Agent When Resistance to It Threatens the Patient. PLOS Biology. 2017 Feb;15(2):e2001110.

[16] Djidjou-Demasse R, Alizon S, Sofonea MT. Within-Host Bacterial Growth Dynamics with Both Mutation and Horizontal Gene Transfer. Journal of Mathematical Biology. 2021 Feb;82(3):16.

[17] Svara F, Rankin DJ. The Evolution of Plasmid-Carried Antibiotic Resistance. BMC Evolutionary Biology. 2011 Dec;11(1):130.

[18] Tazzyman SJ, Bonhoeffer S. Plasmids and Evolutionary Rescue by Drug Resistance. Evolution. 2014;68(7):2066–2078.

[19] zur Wiesch PA, Kouyos R, Engelstädter J, Regoes RR, Bonhoeffer S. Population Biological Principles of Drug-Resistance Evolution in Infectious Diseases. The Lancet Infectious Diseases. 2011 Mar;11(3):236–247.

[20] Millan AS, Peña-Miller R, Toll-Riera M, Halbert ZV, McLean AR, Cooper BS, et al. Positive Selection and Compensatory Adaptation Interact to Stabilize Non-Transmissible Plasmids. Nature Communications. 2014 Oct;5(1):5208.

[21] Lorz A, Lorenzi T, Clairambault J, Escargueil A, Perthame B. Modeling the Effects of Space Structure and Combination Therapies on Phenotypic Heterogeneity and Drug Resistance in Solid Tumors. Bulletin of Mathematical Biology. 2015 Jan;77(1):1–22.

[22] Clarelli F, Palmer A, Singh B, Storflor M, Lauksund S, Cohen T, et al. Drug-Target Binding Quantitatively Predicts Optimal Antibiotic Dose Levels in Quinolones. PLOS Computational Biology. 2020 Aug;16(8):e1008106.

[23] Djidjou-Demasse R, Ducrot A, Fabre F. Steady State Concentration for a Phenotypic Structured Problem Modeling the Evolutionary Epidemiology of Spore Producing Pathogens. Mathematical Models and Methods in Applied Sciences. 2017 Feb;.

[24] Burie JB, Djidjou-Demasse R, Ducrot A. Asymptotic and Transient Behaviour for a Nonlocal Problem Arising in Population Genetics. European Journal of Applied Mathematics. 2020 Feb;31(1):84–110.

[25] Diekmann O, Heesterbeek JAP, Metz JAJ. On the Definition and the Computation of the Basic Reproduction Ratio R0 in Models for Infectious Diseases in Heterogeneous Populations. Journal of Mathematical Biology. 1990 Jun;28(4):365–382.

[26] Geritz SAH, Metz JAJ, Kisdi É, Meszéna G. Dynamics of Adaptation and Evolutionary Branching. Physical Review Letters. 1997 Mar;78(10):2024–2027.

[27] Gagneux S. The Competitive Cost of Antibiotic Resistance in Mycobacterium Tuberculosis. Science. 2006 Jun;312(5782):1944–1946.

[28] Anderson RM. Populations and Infectious Diseases: Ecology or Epidemiology? Journal of Animal Ecology. 1991;60(1):1–50.

[29] Diekmann O, Jabin PE, Mischler S, Perthame B. The Dynamics of Adaptation: An Illuminating Example and a Hamilton-Jacobi Approach. Theoretical Population Biology. 2005 Jun;67(4):257–271.

[30] Mylius SD, Diekmann O. On Evolutionarily Stable Life Histories, Optimization and the Need to Be Specific about Density Dependence. Oikos. 1995;74(2):218–224.

[31] Metz JaJ, Mylius SD, Diekmann O. When Does Evolution Optimize? Evolutionary Ecology Research. 2008;10(5):629–654.

[32] Olofsson SK, Cars O. Optimizing Drug Exposure to Minimize Selection of Antibiotic Resistance. Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America. 2007 Sep;45 Suppl 2:S129–136.

[33] Geli P, Laxminarayan R, Dunne M, Smith DL. "One-Size-Fits-All"? Optimizing Treatment Duration for Bacterial Infections. PLOS ONE. 2012 Jan;7(1):e29838.

[34] Kouyos RD, Metcalf CJE, Birger R, Klein EY, Abel zur Wiesch P, Ankomah P, et al. The Path of Least Resistance: Aggressive or Moderate Treatment? Proceedings of the Royal Society B: Biological Sciences. 2014 Nov;281(1794):20140566.

[35] Nguyen QH, Contamin L, Nguyen TVA, Bañuls AL. Insights into the Processes That Drive the Evolution of Drug Resistance in Mycobacterium Tuberculosis. Evolutionary Applications. 2018 Jun;11(9):1498–1511.

[36] D'Agata EMC, Dupont-Rouzeyrol M, Magal P, Olivier D, Ruan S. The Impact of Different Antibiotic Regimens on the Emergence of Antimicrobial-Resistant Bacteria. PloS One. 2008;3(12):e4036.

[37] Drusano GL, Liu W, Brown DL, Rice LB, Louie A. Impact of Short-Course Quinolone Therapy on Susceptible and Resistant Populations of Staphylococcus Taureus. The Journal of Infectious Diseases. 2009 Jan;199(2):219–226.

[38] Mouton JW, Ambrose PG, Canton R, Drusano GL, Harbarth S, MacGowan A, et al. Conserving Antibiotics for the Future: New Ways to Use Old and New Drugs from a Pharmacokinetic and Pharmacodynamic Perspective. Drug Resistance Updates: Reviews and Commentaries in Antimicrobial and Anticancer Chemotherapy. 2011 Apr;14(2):107–117.

[39] Nguyen TT, Guedj J, Chachaty E, de Gunzburg J, Andremont A, Mentré F. Mathematical Modeling of Bacterial Kinetics to Predict the Impact of Antibiotic Colonic Exposure and Treatment Duration on the Amount of Resistant Enterobacteria Excreted. PLOS Computational Biology. 2014 Sep;10(9):e1003840.

[40] Martinez MN, Papich MG, Drusano GL. Dosing Regimen Matters: The Importance of Early Intervention and Rapid Attainment of the Pharmacokinetic/Pharmacodynamic Target. Antimicrobial Agents and Chemotherapy. 2012 Jun;56(6):2795–2805.

[41] Mideo N, Alizon S, Day T. Linking Within- and between-Host Dynamics in the Evolutionary Epidemiology of Infectious Diseases. Trends in Ecology & Evolution. 2008 Sep;23(9):511–517.

[42] Lange A, Ferguson NM. Antigenic Diversity, Transmission Mechanisms, and the Evolution of Pathogens. PLOS Computational Biology. 2009 Oct;5(10):e1000536.

[43] Luciani F, Alizon S. The Evolutionary Dynamics of a Rapidly Mutating Virus within and between Hosts: The Case of Hepatitis C Virus. PLoS Computational Biology. 2009 Nov;5(11).

[44] Alizon S, Luciani F, Regoes RR. Epidemiological and Clinical Consequences of Within-Host Evolution. Trends in Microbiology. 2011 Jan;19(1):24–32.

[45] Schenk MF, Szendro IG, Krug J, de Visser JAGM. Quantifying the Adaptive Potential of an Antibiotic Resistance Enzyme. PLOS Genetics. 2012 Jun;8(6):e1002783.

[46] Loewe L. High Deleterious Genomic Mutation Rate in Stationary Phase of Escherichia Coli. Science. 2003 Nov;302(5650):1558–1560.

[47] Sniegowski P. Evolution: Bacterial Mutation in Stationary Phase. Current Biology. 2004 Mar;14(6):R245–R246.

[48] Schulz zur Wiesch P, Engelstadter J, Bonhoeffer S. Compensation of Fitness Costs and Reversibility of Antibiotic Resistance Mutations. Antimicrobial Agents and Chemotherapy. 2010 May;54(5):2085–2095.

[49] Metz JAJ, Geritz SAH, Meszena G, Jacobs FJA, van Heerwaarden JS. Adaptive Dynamics: A Geometrical Study of the Consequences of Nearly Faithful Reproduction [Monograph]; 1995. http://pure.iiasa.ac.at/id/eprint/4497/.

[50] Lion S, Metz JAJ. Beyond R0 Maximisation: On Pathogen Evolution and Environmental Dimensions. Trends in Ecology & Evolution. 2018 Jun;33(6):458–473.

[51] PAZY A. Semigroups of Linear Operators and Applications to Partial Differential Equations. Semigroups of linear operators and applications to partial differential equations. 1983;44:VIII–279 p.

[52] Hale JK. Asymptotic Behavior of Dissipative Systems. American Mathematical Society; 1988.

[53] Webb GF. Compactness of Bounded Trajectories of Dynamical Systems in Infinite Dimensional Spaces†. Proceedings of the Royal Society of Edinburgh Section A: Mathematics. 1979/ed;84(1-2):19–33.

[54] Bürger R. Perturbations of Positive Semigroups and Applications to Population Genetics. Mathematische Zeitschrift. 1988 Jun;197(2):259–272.

[55] Meyer-Nieberg P. Banach Lattices. Universitext. Berlin Heidelberg: Springer-Verlag; 1991.

[56] Thieme HR. Mathematics in Population Biology. Princeton University Press; 2003.