Thesis Summary: Mathematical Modelling of the Evolution of Antibiotic resistance and Pathogenicity in commensal bacteria

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Abstract—The evolution of resistance to antibiotics is a major public health problem, causing more than a million deaths per year [13]. In the human body, almost every bacteria are in the digestive tract [15]. Part of genetic evolution occurs within the gut; such an evolution can create antibiotic resistance. The gut microbiota, along with a specific spatial structure of the gut may play an important role in its evolution in this natural environment of these bacteria. Based on [1], where the authors study the proliferation and behavior of neutral mutants bacteria within a minimal model of the gut that includes hydrodynamic flow and resulting gradients of food and bacterial concentrations, we will try to expand their results in a broader context, in which there is the presence of antibiotics and the mutants are now considered the drug-resistant bacteria.

Keywords— microbial evolution, spatially structured populations, gut microbiota, Antibiotic resistance, concentration gradient, mathematical modeling

I. Introduction

This thesis will be the mathematical modeling of the evolution of antibiotic resistance and pathogenicity in commensal bacteria. Many commensal bacteria like Escherichia coli and Klebsiella pneumoniae are important opportunistic pathogens. They live a commensal lifestyle and do not harm their host the vast majority of the time. However, they sometimes cause severe infections (urinary tract infections, bloodstream infections). The capacity to cause infection (pathogenicity) is under the partial genetic control of the bacteria, as it depends on a large number of virulence genes with diverse functions (adhesins, iron capture systems). Some clones are much more pathogenic than others, like the so-called hypervirulent Klebsiella. In parallel, many species carry resistance genes which allow them to resist antibiotics. Commensal bacteria are most of the time exposed to antibiotics for reasons unrelated to their presence or action ('bystander exposure'). Some emerging clones are both pathogenic and resistant. This project aims to explore the evolving association between pathogenicity and resistance with mathematical modeling. This model will describe both several known effects of virulence genes, such as conferring longer bacterial carriage duration, larger within-host growth rate, and larger pathogenicity, and a drug resistance gene.
We focus on the commensal bacteria within the gut, specifically a minimal model of it, which feature a process that includes a flow of its content along the gut's main axis as well as the associated gradients of concentrations of food and bacteria; along this axis to downstream, food is absorbed and is decomposed by bacteria, and finally the remains exit the system, along with many bacteria constitutes up to half of the fecal mass [1] [17]. These traits lead to a particular spatial structure that can impact the bacteria's evolution.
We will use tools of mathematical analyses, specifically in ordinary differential equations as well as partial differential equations to describe the dynamics of the model and study the existence of the solution with its behavior, then analyze the numerical resolution of the model using R.

II. Brief plan

The analysis strategy will be based on [1], with some extension due to the difference in the equations that describes a broader system (Appendix, section 1).
We will first constitute the partial differential equations that depict the dynamics of the model, then test the plausibility of the equations by solving it with a set of values of parameters, then compare the result with the epidemiological data and modify the equations until it satisfies a certain tolerance. The following steps include obtaining the stationary profile, with and without mutants; studying the dependence of the solutions on the spatial position and the dynamic of antibiotic-resistant bacteria appearing in the gut. Finally, we will analyze to determine whether or not there is a relation between the fixation probability characterized by the ratio of the steady-state concentrations of mutants and bacteria and the spatial dependence of food, antibiotic, and bacterial concentrations in the gut. A possible stochastic simulation could be added if does exist such a relation.

III. Model and Methods

We focus our study on the colon, where the majority of bacteria in the human digestive tract are placed [16]. Since mucus-associated bacteria constitute a small minority in the colon and since their spatial structure and migration patterns are not well characterized [1], we focus on the bacteria present in the big volume of the colon lumen and do not model the mucus layer. Therefore we simply called the colon lumen "gut".

Based on the model of [1], in which the dynamics of wild-type bacteria, neutral mutant bacteria i.e the mutants is not differentiated from wild-type bacteria, and food in the gut, is described through three concentration fields, of food F, wild-type bacteria B, and neutral mutants bacteria M; we now extend it with the presence of drug (antibiotic); the wild-type bacteria B now is considered the sensitive with the drug A, and mutant bacteria M is resistant bacteria. The gut is represented by a tube of length L and cross-section with surface area S (Fig. 1A). We neglect radial variations and are left with a one-dimensional model along the x-axis, specifically a segment of length L [1]. We assume a constant inflow of nutrients and drugs at the entrance of the gut with no inflow of bacteria; at the exit of the gut, we assume that there is a free flow of nutrients, bacteria, and drugs. The dynamic of the system is a mixed mechanism that can be described by Convection-Diffusion Equations combined with the Monod model and maximum growth rate r_{B} , r_{M} (Appendix, section 1).

$$\frac{\partial F}{\partial t} = D_{\mathrm{F}} \frac{\partial^2 F}{\partial x^2} - v_{\mathrm{F}} \frac{\partial F}{\partial x} - \frac{r_{\mathrm{B}}}{\alpha_{\mathrm{B}}} \frac{FB}{k+F} - \frac{r_{\mathrm{M}}}{\alpha_{\mathrm{M}}} \frac{FM}{k+F}, \quad (1a)$$

$$\frac{\partial A}{\partial t} = D_{\mathrm{A}} \frac{\partial^2 A}{\partial x^2} - v_{\mathrm{A}} \frac{\partial A}{\partial x} - \frac{\delta_{\max}}{\beta_{\mathrm{B}}} \frac{A^k B}{A_{50\mathrm{B}}^k + A^k} - \frac{\delta_{\max}}{\beta_{\mathrm{M}}} \frac{A^k M}{A_{50\mathrm{M}}^k + A^k} \quad (1b)$$

$$\frac{\partial B}{\partial t} = D_{\mathrm{B}} \frac{\partial^2 B}{\partial x^2} - v_{\mathrm{B}} \frac{\partial B}{\partial x} + r_{\mathrm{B}} \frac{FB}{k+F} - \delta_{\max} \frac{A^k B}{A_{50\mathrm{B}}^k + A^k}, \quad (1c)$$

$$\frac{\partial M}{\partial t} = D_{\mathrm{M}} \frac{\partial^2 M}{\partial x^2} - v_{\mathrm{M}} \frac{\partial M}{\partial x} + r_{\mathrm{M}} \frac{FM}{k+F} - \delta_{\max} \frac{A^k M}{A_{50\mathrm{M}}^k + A^k}, \quad (1d)$$

with boundary conditions

$$-D_{\mathrm{F}} \frac{\partial F}{\partial x}(x=0) + v_{\mathrm{F}} F(x=0) = v_{\mathrm{F}} F_{\mathrm{in}}, \quad (2a)$$

$$-D_{\mathrm{A}} \frac{\partial A}{\partial x}(x=0) + v_{\mathrm{A}} A(x=0) = v_{\mathrm{A}} A_{\mathrm{in}}, \quad (2b)$$

$$-D_{\mathrm{B}} \frac{\partial B}{\partial x}(x=0) + v_{\mathrm{B}} B(x=0) = 0, \quad (2c)$$

$$-D_{\mathrm{M}} \frac{\partial M}{\partial x}(x=0) + v_{\mathrm{M}} M(x=0) = 0, \quad (2d)$$

and

$$-D_{\mathrm{I}} \frac{\partial I}{\partial x}(x=L) = 0, \ \mathrm{I} \in \{F,A,B,M\}, \quad (2e)$$

Here, $v_{\mathrm{F}}F_{\mathrm{in}}(v_{\mathrm{A}}A_{\mathrm{in}})$ is the food (drug respectively) inflow at the entrance of the gut segment. Diffusion coefficient of i, D_{i} and flow velocity v_{i} , i$\in \{F,A,B,M\}$; while α_{B} , α_{M} denotes the yield of the conversion from food to bacteria, mutant. $\delta_{\max}$ is the maximum killing rate of drug; $A_{50\mathrm{B}}^k$, $A_{50\mathrm{M}}^k$ are the concentration of drug corresponding to a half of elimination efficiency on bacteria and mutants. Finally, β_{B} , β_{M} represents consumption rate of drug killing bacteria and mutants.

In order to study the fate of mutants appearing in the gut, we solve the system without mutants (Appendix, section 2), then take its stationary solution as the initial condition for Eq.1

$$F(t=0,x) = F^*(x), \quad (3a)$$

$$A(t=0,x) = A^*(x), \quad (3b)$$

$$B(t=0,x) = B^*(x), \quad (3c)$$

$$M(t=0,x) = \begin{cases} M_0, & |\mathrm{x} - \mathrm{x_M}| \leq \triangle x/2. \\ 0, & |\mathrm{x} - \mathrm{x_M}| > \triangle x/2. \end{cases} \quad (3d)$$

Where F^*, A^* and B^* represent the steady state of the system (1) without mutants bacteria; $x_{\mathrm{M}} \in (0,L)$ is the position in the gut where the mutants appear, $\triangle x$ is a short length, taken equal to the spatial discrete step in our numerical resolutions (Appendix, section3), (My Code R, section 1), and $M0 << B(x_{\mathrm{M}})$, is the initial local concentration of mutant at this position. As in [1], we set the M_0 through the equation :

$$N_{\mathrm{M}} = M_0 S \triangle x, \quad (4)$$

Where S is the surface area of the section of the gut, and set to be 1 cm^2 in the entire Thesis. The partial differential equations in Eq.1 with and without mutants, with boundary conditions in Eq.2 and initial conditions in Eq.3 can be solved numerically with the code in (My Code R, section 4).

IV. Stationary profile of the system in the free-mutant gut

In order to study the fate of resistant bacteria (mutants) in our system, we will first solve Eq.1 in a free-mutant regime and examine its behavior at steady-state. We will take variation of values of the parameters, to check if as in [1], the solution could be strongly dependent on the position x, with some specific values of the parameters.

Our aim will also be to study a limit where antibiotics are large excess and are not too much affected by B (and M in the full system profile), i.e in the case $\beta_{\mathrm{B}} >>$ (and $\beta_{\mathrm{M}} >>$ also in the full system). In this limit, the antibiotic concentration would be approximately constant over the length of the gut. Therefore, in this limit, the system could behave similarly to the original model [1]. This limit is reminiscent of the wash-out limit in [1], at which either the velocity flow is too fast that bacteria exit the system before reproducing, or for the small diffusion coefficients and the characteristic length of flow is larger than that of diffusion, bacteria are washed out.

Additionally, We will try to convert the steady-state equation that describes our system to a well-known equation that has already been studied, such as traveling wave in a Fisher-Kolmogorov-PetrovskyPiskunov (Fisher-KPP) equation ([8],[10]) as in [1], to compare and study existence of a monotonic solution the behavior of Phase space of the system, but now more complex with the presence of antibiotic in our model (Appendix, section 2).

V. Dynamics and Fate of Resistant bacteria Appearing in the Gut

The initial local concentration of mutants is assumed to be much smaller than that of the wild type at the position x_M where the mutants appear (Eq. 3). We now solve the partial differential equations describing the full system (with the code represented in My code R, section 1,3), and obtain the early dynamics of mutant concentration, which is governed by the fluid dynamics in the gut [1].
We noticed that not like in [1], in which mutants concentration satisfies the same partial differential equation as wild-type bacteria concentration; the equations depict bacteria and mutant (Eq.1 c,d) are now different, hence the ratio of the steady-state concentrations of mutant and wild-type bacteria would not be constant; except in the case that all parameters values of M and B are proportional, but this would rarelt happens since $r_B >> r_M$ [3]. Therefore, in order to study the relation of fixation probability and the spatial dependence of food, antibiotic and bacterial concentrations in the gut, we will draw the ratio of mutants and bacteria concentration at the stationary state, as well as the Reproductions per unit volume and unit time, R at x_M where R can be obtained through the equation :

$$R(x_M) = B(x_M)p(x_M) \quad (5)$$

Where

$$p(x) = r_B \frac{F(x)}{k+F(x)} - \delta_{max} \frac{A^k(x)}{A_{50B}^k + A^k(x)} \quad (6)$$

With all notations as in Eq.1. If such a relation exists, we should obtain the stationary solution of the ratio of M/B and R, typically after the time elapses 500 hours.

VI. Possible study on Fixation Probability of Mutants and stochastic simulation

If the ratio of Mutants and Bacteria does stable when the model has involved in time by at least 500 hours, we can study the probability P_M that mutants fix in the gut.

$$P_M = \frac{\int_0^L R(x_M) \frac{M(x_M)}{B(x_M)} dx_M}{\int_0^L R(x_M) dx_M}$$

Afterward, we can verify the fixation probability by compare the stochastic simulation with our deterministic steady state solution.

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