Supplementary information: Mathematical Modelling of the evolution of Antibiotic resistance and pathogenicity in commensal bacteria

Hoang Huan Le Ngoc[1]

[1]Ho Chi Minh University of Science, Department of Mathmatical and Computer Science, Ho Chi Minh city, Vietnam

June 2023

1 Constitution of the system of Equations

1.1 Convection-Diffusion Equations

This equation describes physical phenomena where particles, energy, or other physical quantities are transferred inside a physical system due to two processes: diffusion and convection. In our case, it is Food and Antibiotic.

$$\frac{\partial c}{\partial t} = \nabla.(D\nabla c) - \nabla.(vc) + R$$

Where :

c : concentration or density of material

D : Diffusion Coefficient ,

v : flow velocity ,

R : Sources or sinks of the quantity c

Since our model is in a segment of gut, a one-dimensional model along the x-axis, specifically a segment of length L and there are no sources or sinks, we rewrite the Convection-Diffusion equation as :

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} - v\frac{\partial c}{\partial x}$$

1.2 Monod Equations

The Monod model describes the relationship between the specific growth rate of a microbial population and the substrate concentration

$$\mu = \mu_{\max} \frac{c}{k_{50} + c}$$

Where :

μ : Growth rate of considered microorganisms

$\mu_{\max}$: Maximum growth rate of this microorganisms

c : concentration or density of substrate

k_{50} : Concentration corresponding to half of maximum growth rate

.

1.3 Establishing the system that describes the model

We now describe the full system. In this model, We assume a constant inflow of nutrients and antibiotics at the entrance of this gut segment. The system's dynamics are affected by the constant flow velocity, the effective diffusion and by the harvesting of the food by bacteria, and the killing effect of the antibiotic, which is modeled by Convection-Diffusion and Monod Equation.

$$\begin{aligned}
\frac{\partial F}{\partial t} &= D_{\mathrm{F}}\,\frac{\partial^2 F}{\partial x^2} - v_{\mathrm{F}}\,\frac{\partial F}{\partial x} - \frac{r_{\mathrm{B}}}{\alpha_{\mathrm{B}}}\frac{FB}{k+F} - \frac{r_{\mathrm{M}}}{\alpha_{\mathrm{M}}}\frac{FM}{k+F},\\
\frac{\partial A}{\partial t} &= D_{\mathrm{A}}\,\frac{\partial^2 A}{\partial x^2} - v_{\mathrm{A}}\,\frac{\partial A}{\partial x} - \frac{\delta_{\max}}{\beta_{\mathrm{B}}}\frac{A^k B}{A_{50\mathrm{B}}^k + A^k} - \frac{\delta_{\max}}{\beta_{\mathrm{M}}}\frac{A^k M}{A_{50\mathrm{M}}^k + A^k}, \qquad (S1)\\
\frac{\partial B}{\partial t} &= D_{\mathrm{B}}\,\frac{\partial^2 B}{\partial x^2} - v_{\mathrm{B}}\,\frac{\partial B}{\partial x} + r_{\mathrm{B}}\,\frac{FB}{k+F} - \delta_{\max}\,\frac{A^k B}{A_{50\mathrm{B}}^k + A^k},\\
\frac{\partial M}{\partial t} &= D_{\mathrm{M}}\,\frac{\partial^2 M}{\partial x^2} - v_{\mathrm{M}}\,\frac{\partial M}{\partial x} + r_{\mathrm{M}}\,\frac{FM}{k+F} - \delta_{\max}\,\frac{A^k M}{A_{50\mathrm{M}}^k + A^k}
\end{aligned}$$

Where :

k : Monod constant ,

F : Food concentration ,

A : Antibiotic concentration ,

B : Bacteria (sensitive) concentration ,

M : Mutant (resistance) concentration ,

$\delta_{\max}$: maximum elimination rate,

D_{i} : Diffusion coefficient of i, i$\in \{F, A, B, M\}$,

v_{i} : flow velocity of i, i$\in \{F, A, B, M\}$,

r_{B} : growth rate of Bacteria (Sensative) ,

r_{M} : growth rate of Mutant (resistant) ,

α_{B} : yield of the conversion from Food to Bacteria ,

α_{M} : yield of the conversion from Food to Mutant,

β_{B} : the efficiency consumption rate of A in order to kill a unit of B (concentration),

β_{M} : the efficiency consumption rate of A in order to kill a unit of M (concentration),

$A_{50\mathrm{B}}^k$: Concentration of Antibiotic corresponding to a half of elimination efficiency on B ,

$A_{50\mathrm{M}}^k$: Concentration of Antibiotic corresponding to a half of elimination efficiency on M.

2 Stationary profiles without mutants

Without Mutant, at the stationary, the system Eq.1 yields:

$$\begin{aligned}
0 &= D_{\mathrm{F}}\,\frac{\partial^2 F}{\partial x^2} - v_{\mathrm{F}}\,\frac{\partial F}{\partial x} - \frac{r_{\mathrm{B}}}{\alpha_{\mathrm{B}}}\frac{FB}{k+F},\\
0 &= D_{\mathrm{A}}\,\frac{\partial^2 A}{\partial x^2} - v_{\mathrm{A}}\,\frac{\partial A}{\partial x} - \frac{\delta_{\max}}{\beta_{\mathrm{B}}}\frac{A^k B}{A_{50\mathrm{B}}^k + A^k}, \qquad (S2)\\
0 &= D_{\mathrm{B}}\,\frac{\partial^2 B}{\partial x^2} - v_{\mathrm{B}}\,\frac{\partial B}{\partial x} + r_{\mathrm{B}}\,\frac{FB}{k+F} - \delta_{\max}\,\frac{A^k B}{A_{50\mathrm{B}}^k + A^k},
\end{aligned}$$

With initial condition

$$F(t=0,x) = 0.9F_{\text{in}} ,$$
$$A(t=0,x) = A_{\text{in}} ,$$
$$B(t=0,x) = 0.1\alpha F_{\text{in}}$$

3 Washout limits

3.1 Food, drug, and bacteria have the same or proportional diffusion coefficient and flow velocity

(S2) can be written as

$$D\frac{\partial^2 f}{\partial x^2} - v\frac{\partial f}{\partial x} = 0 \quad (S3)$$

Where

$$f = \alpha_{\text{B}}\, F + B - \beta_{\text{B}}\, A$$

The washout limits are the limits where all bacteria get washed out of the system. Mathematically, they correspond to a bifurcation point in the parameter space where the trivial steady state solution $F(x) = F_{\text{in}}$,$A(x) = A_{\text{in}}$ and $B(x) = 0$ becomes stable [1]. It is possible to find analytical estimates for the washout limits in the spatial system by comparing key length scales [1], [10].
In order to calculate the washout limit for δ_{max} , we need to calculate the minimal time in which bacteria can reproduce in this trivial system ($F(x) = F_{\text{in}}$,$A(x) = A_{\text{in}}$)

$$t_{\text{rep}} = \frac{1}{\rho}$$

Where ρ represents the reproduction rate of bacteria in the trivial system and can be obtained by the formula

$$\rho = r_{\text{B}}\frac{F_{\text{in}}}{k + F_{\text{in}}} - \delta_{\text{max}}\,\frac{A_{\text{in}}}{A_{50\text{B}} + A_{\text{in}}}$$

Hence

$$t_{\text{rep}} = \frac{1}{\alpha_1 - \delta_{\text{max}}\,\alpha_2}$$

Where

$$\alpha_1 = \frac{F_{\text{in}}\, r}{k + F_{\text{in}}},$$
$$\alpha_2 = \frac{A_{\text{in}}}{A_{50\text{B}} + A_{\text{in}}}$$

We first compute the velocity limit for the washout of bacteria. Bacteria are washed-out if the time needed to bacterium travels throughout and exit the system smaller than the time required for them to replicate, that is

$$t_{\text{flow}} < t_{\text{rep}}$$

Or

$$\frac{L}{v} < \frac{1}{\alpha_1 - \delta_{\text{max}}\,\alpha_2}$$

So the first estimated washout δ_{max} is

$$\delta_{\text{wo1}} = (\alpha_1 - \frac{v}{L})\frac{1}{\alpha_2}$$

Washout occurs if diffusion characteristic lengths are smaller than flow characteristic lengths at the time of replication, t_{rep} . Moreover,

$$L_{\text{diff}} < L_{\text{rep}}$$

Or

$$\sqrt{4Dt_{\text{rep}}} < vt_{\text{rep}}$$

Hence

$$\delta_{\max} > (\alpha_1 - \frac{v^2}{4D})\frac{1}{\alpha_2}$$

Therefore we have a washout limit for maximum elimination rate

$$\delta_{\text{wo}} = (\alpha_1 - \frac{v^2}{4D})\frac{1}{\alpha_2}$$

3.2 Existence and Uniqueness of the solution

For convenience, we rewrite the notation as:

$$\begin{aligned}
f &= F,\\
f1 &= \frac{\partial F}{\partial x},\\
a &= A,\\
a1 &= \frac{\partial A}{\partial x},\\
b &= B,\\
b1 &= \frac{\partial B}{\partial x},
\end{aligned}$$

Then the ODE system (S2) can be written as:

$$\begin{aligned}
&\frac{\partial f}{\partial x} = f1,\\
&\frac{\partial f1}{\partial x} = \frac{v_{\text{F}}}{D_{\text{F}}} f1 + \frac{r_{\text{B}}}{\alpha_{\text{B}}\ D_{\text{F}}}\frac{fb}{k+f},\\
&\frac{\partial a}{\partial x} = a1,\\
&\frac{\partial a1}{\partial x} = \frac{v_{\text{A}}}{D_{\text{A}}} a1 + \frac{\delta_{\max}}{\beta_{\text{B}}\ D_{\text{A}}}\frac{a^k b}{A_{50\text{B}}^k + a^k}, (S3)\\
&\frac{\partial b}{\partial x} = b1,\\
&\frac{\partial b1}{\partial x} = \frac{v_{\text{B}}}{D_{\text{B}}} b1 - \frac{r_{\text{B}}}{D_{\text{B}}}\frac{fb}{k+f} + \frac{\delta_{\max}}{D_{\text{B}}}\frac{a^k b}{A_{50\text{B}}^k + a^k},
\end{aligned}$$

The Existence and Uniqueness of the solution of S3 can be verified with the below Theorem

Theorem 1 *Given first order system of ordinary differential equations with initial value*

$$\begin{aligned}
&\frac{du_i}{dt} = F_i(t, u_1, ..., u_n)\\
&where\ i \in \{1, ., n\},\\
&F(t, u) = (F_1(t, u_1, ..., u_n), ..., F_n(t, u_1, ..., u_n))^T,\\
&u(t) = (u_1(t), ..., u_n(t))^T,\\
&u(t_0) = a, where\ a = (a_1, a_2, .., a_n) \in R^n,
\end{aligned}$$

If

$$F_i \in C^1, \forall i,$$

Then this system admits a unique solution $u = f(t)$ that is, at least, defined for nearby times, i.e., when $|t - t0| < \delta$ for some $\delta > 0$.

In practice, one always extends a solution to its maximal interval of existence [7].
Easily, we can see that, the right-hand side of equations (S3) satisfies the condition of theorem 1, but notice that, with the boundary condition Eq.2, Eq.3 (Thesis summary), we do not have an implicit initial values of the equations and the space is bounded. Moreover, the boundary condition of (S3) now is

$$\begin{aligned} &- D_{\mathrm{F}}\ f1(x=0) + v_{\mathrm{F}}\ f(x=0) = v_{\mathrm{F}}\ F_{\mathrm{in}}\ , \\ &- D_{\mathrm{A}}\ a1(x=0) + v_{\mathrm{A}}\ a(x=0) = v_{\mathrm{A}}\ A_{\mathrm{in}}\ , \\ &- D_{\mathrm{B}}\ b1(x=0) + v_{\mathrm{B}}\ b(x=0) = 0 \end{aligned}$$

And

$$f1(x=L) = a1(x=L) = b1(x=L) = 0$$

Hence in order to study the existence of the solution, we can first analyze the Phase Space of the system with different types of spatial profiles, i.e. different values of parameters.

3.3 Phase Space Analysis of the System

With the Hartman-Grobman theorem, we can study the Phase Space of the system (S3) by studying its linearization around its Hyperbolic fixed points.

Theorem 2 *(Hartman-Grobman).Consider a system with state $u(t) \in R^n$ that satisfies the differential equation $\frac{du}{dt} = f(u)$ for for some smooth map $f : R^n \to R^n$. suppose the map has a hyperbolic equilibrium state $u^* \in R^n$: that is, $f(u^*) = 0$ and the Jacobian matrix $A = [\partial f_i / \partial x_j]$ of f at state u^* has no eigenvalue with real part equal to zero. Then there exists a neighbourhood N of the equilibrium u^* and a homeomorphism $h : N \to R^n$, such that $h(u^*) = 0$, and in the neighbourhood N the flow of $du/dt = f(u)$ is topologically conjugate to the flow of its linearization U, $dU/dt = AU$ by the continuous map $U = h(u)$.*

References

1. D. Labavi´c, C. Loverdo, and A.-F. Bitbol. Hydrodynamic flow and concentration gradients in the gut enhance neutral bacterial diversity, (Version v1.0.0), http://doi.org/10.5281/zenodo.4704653. Version v1.0.0.Zenodo, 2021.
2. Blanquart F. Evolutionary epidemiology models to predict the dynamics of antibiotic resistance. Evol Appl. 2019;12:365–383. https://doi.org/10.1111/eva.12753.
3. Nguyen TT, Guedj J, Chachaty E, de Gunzburg J, Andremont A, et al. (2014) Mathematical Modeling of Bacterial Kinetics to Predict the Impact of Antibiotic Colonic Exposure and Treatment Duration on the Amount of Resistant Enterobacteria Excreted. PLoS Comput Biol 10(9): e1003840. doi:10.1371/journal.pcbi.1003840. 4. B. Perthame. Parabolic Equations in Biology – Growth, Reaction, Movement and Diffusion. Springer, 2015.
5. G. Birkhoff, E.C. Gartland, R.E. Lynch, Difference methods for solving convection-diffusion equations, Computers Mathematics with Applications, Volume 19, Issue 11, 1990, ISSN 0898-1221, https://doi.org/10.1016/0898-1221(90)90158-G.
6. M. Slatkin, Fixation probabilities and fixation times in a subdivided population. Evolution 35, 477–488 (1981).
7. Peter J. Olver ,University of Minnesota. Nonlinear Ordinary Differential Equations.
8. J.D. Murray, Mathematical Biology:I. An Introduction, Third Edition.
9. Gerald Teschl, Ordinary Differential Equations and Dynamical Systems.
10. J. Cremer, I. Segota, C. Y. Yang, M. Arnoldini, J. T. Sauls, Z. Zhang, E. Gutierrez, A. Groisman, and T.

Hwa. Effect of flow and peristaltic mixing on bacterial growth in a gut-like channel. Proc. Natl. Acad. Sci. USA, 113(41):11414–11419, 2016.