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Dynamics of Bacteria and antibiotic

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Numerical Analysis Project

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Abstract

Understanding the dynamics of interactions between antibiotic-resistant bacteria, the immune response, and the presence of antibiotics is crucial for developing effective strategies to combat antibiotic resistance. In this work, we introduce an innovative mathematical model that delves into the complex dynamics between bacteria that are resistant to antibiotics, the immune system, and the administration of antibiotic treatment. Through qualitative analysis, four distinct stable equilibria have been identified, each representing distinct biological scenarios, providing valuable insights for combating antibiotic resistance.

Contents

1 Introduction

Antibiotic resistance constitutes a critical global health threat, with World Health Organization projections indicating potential annual mortality in the millions by 2050 if current trends persist. This project develops a mathematical framework for modeling bacterial population dynamics within the human body, specifically examining the tripartite interaction between pathogenic bacteria, host immune response, and antibiotic interventions.

1.1 Problem Context

Traditional models of bacterial dynamics exhibit a significant limitation: they typically isolate either antibiotic effects *or* immune response mechanisms. This fragmentation neglects the synergistic reality where:

1. **Antibiotic-resistant bacteria (ARB)** employ survival mechanisms including target-site modification and plasmid-mediated resistance gene transfer

2. **Non-resistant bacteria** compete for resources while responding differently to selective pressures

3. **Immune effectors** dynamically interact with both bacterial subpopulations

4. **Antibiotics** simultaneously impose selective pressure while modulating immune activity

The clinical urgency is underscored by resistance drivers such as antibiotic overuse (e.g., inappropriate viral infection treatment), premature therapy

discontinuation, and incorrect dosing—all contributing to evolutionary selection favoring resistant strains.

1.2 Modeling Imperatives

Treatment complexity escalates dramatically with resistance emergence due to:

- Diminished therapeutic options with higher toxicity profiles
- Immune function degradation during severe infections
- **Selective pressure** phenomena where indiscriminate antibiotic use eliminates susceptible bacteria while creating ecological niches for ARB expansion

Epidemiological evidence suggests that modest reductions (e.g., 10%) in unnecessary antibiotic usage could significantly curb resistance propagation. However, predicting intervention outcomes requires sophisticated modeling accounting for:

$$\underbrace{\text{Bacterial growth kinetics}}_{\text{Competition}} + \underbrace{\text{Resistance transmission}}_{\text{Horizontal transfer}} + \underbrace{\text{Immune recruitment}}_{\text{Nonlinear dynamics}}$$

1.3 Proposed Framework

Our novel dynamical system addresses existing gaps by concurrently integrating:

- Dual bacterial subpopulations (resistant vs. susceptible)
- Adaptive immune response dynamics

- Pharmacokinetic/pharmacodynamic antibiotic profiles

This tripartite model enables quantitative investigation of:

- Equilibrium conditions governing pathogen clearance
- Resistance dominance thresholds
- Chronic infection persistence criteria

Through numerical analysis and computational implementation, we examine critical scenarios including:

- Optimal dosing windows minimizing resistance selection
- Immune augmentation strategies complementing antibiotics
- Failure modes under subtherapeutic drug concentrations

1.4 Structural Overview

This paper proceeds as follows: Section 2 formalizes key biological mechanisms; Section 3 develops the governing equations; Section 4 analyzes equilibrium states; Section 5 presents numerical simulations; and Section 6 details the open-source implementation. Our integrated approach provides a critical tool for simulating combination therapies and optimizing antimicrobial stewardship policies.

2 Dynamic Model

In our study, we introduce a detailed mathematical model designed to capture the behavior of bacterial populations, including both non-resistant and resistant strains, along with their interactions with immune cells responsible for host defense, all within the context of antibiotic presence. Our model is built upon several key assumptions, including considerations for bacterial reproduction and death rates, the transfer of antibiotic resistance genes between bacterial strains, the impact of the antibiotic itself, and the response of the immune system. This complex interplay is described by a system of differential equations, which outlines the dynamic relationships between these variables and processes:

$$\begin{cases} \dot{A}(t) = \Lambda - \mu A, \\ \dot{S}(t) = \eta_s \left(1 - \frac{S+R}{K}\right) S - \bar{\alpha} A S - \beta \frac{SR}{N} - \Gamma S P, \\ \dot{R}(t) = \eta_r \left(1 - \frac{S+R}{K}\right) R + \beta \frac{SR}{N} - \Gamma R P, \\ \dot{P}(t) = \Phi(N) P \left(1 - \frac{P}{P_{\max}}\right) - \Psi(N) P, \end{cases} \tag{1}$$

where S represents the population of Non-Antibiotic Resistant Bacteria (NARB), R stands for the population of Antibiotic Resistant Bacteria (ARB), P denotes the population of immune cells and A indicates the concentration of antibiotic.

In biological systems, the proliferation of ARB is frequently reported to exhibit a slower rate compared to NARB, owing to a multitude of underlying reasons. These factors may include the metabolic costs associated with maintaining resistance mechanisms, alterations in cellular physiology resulting from genetic mutations, and potential trade-offs between resistance

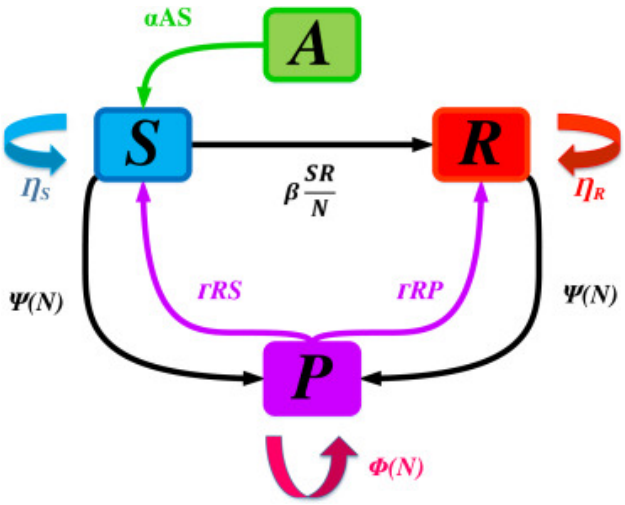


Figure 1: Schematic Diagram

and other cellular functions. This phenomenon is significant as it impacts the overall dynamics of bacterial populations within ecosystems and during infection processes. In our model, we incorporate a logistic growth terms characterized by growth rates η_s for NARB and η_r for ARB, with $\eta_s > \eta_r$, alongside a shared carrying capacity K.

Here, we look at how a resistance plasmid helps antibiotic-resistant genes move from bacteria types that are already resistant to those that are not (susceptible strains). This plasmid serves as a means for the transfer of antibiotic resistance determinants between bacteria. Biologically, this transfer is analogously perceived as analogous to the contagion dynamics observed in disease transmission: a resistant bacterium (acting as the donor) encounters a non-resistant bacterium (the recipient), and the likelihood is that both bacteria acquire resistance traits subsequent to the interaction. In this case, we employ the term: $\beta\frac{SR}{N}$.

The terms ΓSP and ΓRP describe the elimination of (NARB) and (ARB)

by the immune cells. The final equation is supported by the observed relationship between the potency of the immune response and the concentration of bacteria. Specifically, a minor infection initiates an immune reaction, while a major infection dampens the immune response, either through the death of immune cells or by impeding the proliferation of immune cells. P_max is the maximum number of immune cells and the functions $\Phi(N)$ and $\Psi(N)$ are supposed to be positive and belonging to $\mathrm{C}^1(\mathbb{R}_+)$.

Ultimately, the antibiotic is administered at a rate denoted by λ and absorbed at a rate represented by μ.

This model system has 9 parameters in all, which makes mathematical analysis complicated. We are going to review the following transformation of variables:

$$a = \tfrac{A}{\Lambda/\mu},\ \ s = \tfrac{S}{K},\ \ r = \tfrac{R}{K},\ \ p = \tfrac{P}{P_{\max}},\ \ \alpha = \tfrac{\bar{\alpha}A}{\mu},$$
$$\gamma = \Gamma P_{\max},\ \ n = s + r$$

With the scaling, system (1) takes the form

$$\begin{cases} \dot{a}(t) = \mu(1-a) \\ \dot{s}(t) = \eta_s(1-n)s - \alpha a s - \beta\frac{sr}{n} - \gamma s p \\ \dot{r}(t) = \eta_r(1-n)r + \beta\frac{sr}{n} - \gamma r p \\ \dot{p}(t) = \phi(n)p(1-p) - \psi(n)p \end{cases} \tag{2}$$

where

$$\phi(n) = \Phi(Kn)$$

and

$$\psi(n) = \Psi(Kn).$$

3 Equilibria

In this part, we discuss the presence of non-negative equilibrium points for our system. Initially, we consider the function $f(n) = 1 - \frac{\psi(n)}{\phi(n)}$. It is assumed that $f(0) > 0$, with f increasing for relatively small values of n and decreasing as n becomes significantly large. These characteristics of the function mirror the biological phenomenon where a low viral load encourages the growth of immune cells, whereas a high infection level reduces cell proliferation and augments cell mortality. The function f presents two scenarios: (i) it can stay positive across all values of n, or (ii) alternatively, it may turn negative when n reaches a certain threshold. here we focus on the latter scenario.

The equilibrium points coincide with the solutions of :

$$\begin{cases} \mu(1-a) = 0 \\ \eta_s(1-n)s - \alpha as - \beta\frac{sr}{n} - \gamma sp = 0 \\ \eta_r(1-n)r + \beta\frac{sr}{n} - \gamma rp = 0 \\ \phi(n)p(f(n)-p) = 0 \end{cases} \tag{3}$$

which is equivalent to:

$$\begin{cases} a = 1 \\ s = 0 \quad \text{or} \quad \eta_s(1-n) - \alpha - \beta\frac{r}{n} - \gamma p = 0 \\ r = 0 \quad \text{or} \quad \eta_r(1-n) + \beta\frac{s}{n} - \gamma p = 0 \\ p = 0 \quad \text{or} \quad p = f(n) \end{cases} \tag{4}$$

- Case 1: $r = s = p = 0$

  We have the equilibrium $E_0(1, 0, 0, 0)$.

- Case 2: $r = s = 0\ ,\ p \neq 0$

  We obtain the equilibrium $E_1(1, 0, 0, f(0))$.

- Case 3: $s = p = 0\ ,\ r \neq 0$

  The equilibrium state is denoted as $E_2(1, 0, 1, 0)$.

- Case 4: $s = 0\ ,\ r \neq 0\ ,\ p \neq 0$

  In this case, we have $r = \lambda_+$ and $p = f(\lambda_+)$ with λ_+ being the solution of the following equation:

$$f(r) = \eta_r \frac{1 - r}{\gamma} \tag{5}$$

  λ_+ is identified at the points where the function f intersects with the line $y = \eta_r \frac{1-r}{\gamma}$. Therefor, if $f(0) < \frac{\eta_r}{\gamma}$ we will have a unique solution $0 < \lambda_+ < 1$ that satisfies our equation.

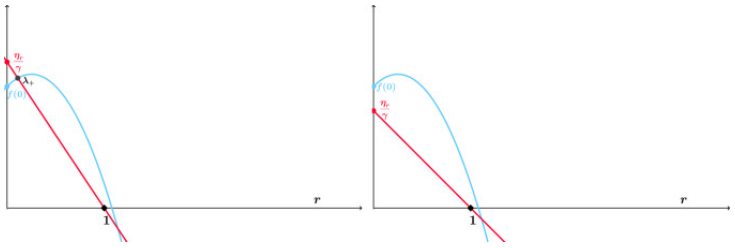


Figure 2: f and λ_+

- Case 5: $s \neq 0\ ,\ r = 0\ ,\ p = 0$

  Here, we have the equilibrium $E_3(1, 1 - \frac{\alpha}{\eta_s}, 0, 0)$ which exists if $\alpha < \eta_s$.

- Case 6: $s \neq 0$, $r = 0$, $p \neq 0$

  In this scenario, $s = \lambda_-$ and $p = f(\lambda_-)$, where $0 < \lambda_- < 1$ is the unique solution of this equation:

$$f(s) = \frac{\eta_s - \alpha}{\gamma} - \frac{\eta_s}{\gamma} s \tag{6}$$

  which exists for $f(0) < \frac{\eta_s - \alpha}{\gamma}$.

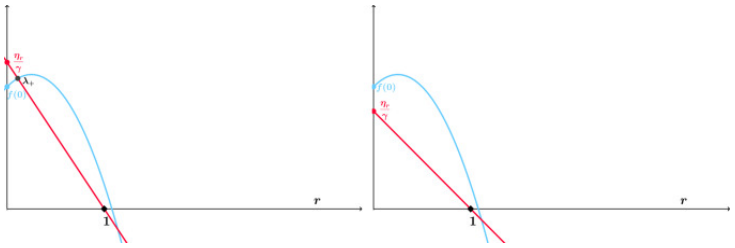


Figure 3: f and λ_-

- Case 7: $s \neq 0$, $r \neq 0$, $p \neq 0$ In this case, we obtain $n_* = s + r = 1 - \frac{\alpha+\beta}{\eta_s - \eta_r}$.

  This value of n_* is positive under the condition that $\alpha + \beta + \eta_r < \eta_s$, hence, we have $p_* = f(n_*)$. Furthermore, the equations for s_* and r_* are given by:

$$s_* = \frac{n_*}{\beta}\left(\gamma f(n_*) - \eta_r \frac{\alpha + \beta}{\eta_s - \eta_r}\right)$$

$$r_* = \frac{n_*}{\beta}\left(\eta_s \frac{\alpha + \beta}{\eta_s - \eta_r} - \alpha - \gamma f(n_*)\right)$$

  and these values are positive under the condition

$$\eta_r \frac{\alpha + \beta}{\eta_s - \eta_r} < \gamma f(n_*) < \frac{\alpha \eta_r + \beta \eta_s}{\eta_s - \eta_r}.$$

4 Stability Analysis

Local stability is determined by the signs of the eigenvalues of the Jacobian matrix obtained by linearizing our system around the steady state. This is given at any point $J(a, s, r, p)$ by

$$\begin{pmatrix} -\mu & 0 & 0 & 0 \\ -\alpha s & \eta_s(1-n) - \eta_s s - \alpha a - \beta\frac{r^2}{n^2} - \gamma p & -\eta_s s - \beta\frac{s^2}{n^2} & -\gamma s \\ 0 & -\eta_r r + \beta\frac{r^2}{n^2} & \eta_r(1-n) - \eta_r r + \beta\frac{s^2}{n^2} - \gamma p & -\gamma r \\ 0 & \phi(n)(f(n)-p) + \dot{f}(n)p\phi(n) & p\dot{\phi}(n)(f(n)-p) + \dot{f}(n)p\phi(n) & \phi(n)(f(n)-2p) \end{pmatrix}.$$

We denote Locally Asymptotically Stable as LAS. Moreover, we use the notations below

$$C_+ = \eta_s\left(1-\lambda_+\right) - \alpha - \beta$$

$$C_- = \eta_r\left(1-\lambda_-\right) + \beta$$

$$C_* = -\frac{\left(\eta_s s_* + \eta_r r_*\right)\beta s_* r_*\left(\eta_s - \eta_r\right)}{f(n_*)\phi(n_*)(n_*)^2\left(\eta_s s_* + \eta_r r_* + f(n_*)\phi(n_*)\right)} - \frac{\eta_s s_* - \eta_r r_*}{\eta_*}.$$

Theorem 1.

1. The equilibrium E_2 $(1, 0, 1, 0)$ is unstable.
2. The equilibrium E_3 $\left(1, 1-\frac{\alpha}{\eta_s}, 0, 0\right)$ is unstable.
3. The equilibrium E_+ $(1, 0, \lambda_+, f(\lambda_+))$ is LAS iff $\gamma f(\lambda_+) > C_+$ and $\gamma\dot{f}(\lambda_+) > \eta_r$.
4. The equilibrium E_- $(1, \lambda_-, 0, f(\lambda_-))$ is LAS iff $\gamma f(\lambda_-) > C_-$ and $\gamma\dot{f}(\lambda_-) > \eta_s$.
5. The equilibrium E_* $(1, s_*, r_*, f(n_*))$ is LAS iff $\gamma\dot{f}(n_*) > C_*$.

Proof.

1. Equilibrium $E_2(1,0,1,0)$: The Jacobian matrix of the equilibrium E_2 is given by

$$J(E_2) = \begin{pmatrix} -\mu & 0 & 0 & 0 \\ 0 & -a-\beta & 0 & 0 \\ 0 & -\eta_r+\beta & -\eta_r & -\gamma \\ 0 & 0 & 0 & \phi(1)f(1) \end{pmatrix}.$$

   Given that $\phi(1)f(1) > 0$, it follows that E_2 is an unstable point.

2. Equilibrium $E_3\left(1, 1-\frac{\alpha}{\eta_s}, 0, 0\right)$: The Jacobian matrix corresponding to the equilibrium point E_3 is represented as

$$J(E_3) = \begin{pmatrix} -\mu & 0 & 0 & 0 \\ \frac{\alpha^2}{\eta_s}-\alpha & \alpha-\eta_s & \alpha-\eta_s-\beta & -\gamma+\frac{\gamma\alpha}{\eta_s} \\ 0 & 0 & \frac{\eta_r\alpha}{\eta_s}+\beta & 0 \\ 0 & 0 & 0 & \phi\left(1-\frac{\alpha}{\eta_s}\right) f\left(1-\frac{\alpha}{\eta_s}\right) \end{pmatrix}.$$

   Since $\phi\left(1-\frac{\alpha}{\eta_s}\right) f\left(1-\frac{\alpha}{\eta_s}\right) > 0$, this indicates that the equilibrium E_3 is unstable.

3. Equilibrium $E_+(1,0,\lambda_+, f(\lambda_+))$: The Jacobian matrix associated with

the equilibrium point E_+ is expressed as

$$J(E_+) = \begin{pmatrix} -\mu & 0 & 0 & 0 \\ 0 & \eta_s(1-\lambda_+) - \alpha - \beta - \gamma f(\lambda_+) & 0 & 0 \\ 0 & -\eta_r\lambda_+ + \beta & -\eta_r\lambda_+ & -\gamma\lambda_+ \\ 0 & f(\lambda_+)f(\lambda_+)\phi(\lambda_+) & f(\lambda_+)f(\lambda_+)\phi(\lambda_+) & -f(\lambda_+)\phi(\lambda_+) \end{pmatrix}.$$

The eigenvalues of the Jacobian matrix $J(E_+)$ are expressed as:

$$\lambda_1 = -\mu,$$

$$\lambda_2 = \eta_s(1-\lambda_+) - \alpha - \beta - \gamma f(\lambda_+).$$

The remaining eigenvalues, λ_3 and λ_4, are given from the matrix B:

$$B = \begin{pmatrix} -\eta_r\lambda_+ & -\gamma\lambda_+ \\ \dot{f}(\lambda_+)f(\lambda_+)\phi(\lambda_+) & -f(\lambda_+)\phi(\lambda_+) \end{pmatrix}.$$

We have

$$\mathrm{tr}(B) = -\eta_r\lambda_+ - f(\lambda_+)\phi(\lambda_+) < 0$$

and

$$\det(B) = \lambda_+ f(\lambda_+)\phi(\lambda_+)(\eta_r + \gamma f(\lambda_+)).$$

Consequently, the eigenvalues have a negative real part if and only if

$$(\eta_s - \eta_r)(1-\lambda_+) < \alpha + \beta, \quad f(\lambda_+) > -\frac{\eta_r}{\gamma}.$$

4. Equilibrium $E_-(1, \lambda_-, 0, f(\lambda_-))$: The Jacobian matrix corresponding

to the equilibrium point E_- is

$$J(E_-) = \begin{pmatrix} -\mu & 0 & 0 & 0 \\ -\alpha\lambda_- & -\eta_s\lambda_- & -\eta_s\lambda_- - \beta & -\gamma\lambda_- \\ 0 & 0 & \eta_r(1-\lambda_-) + \beta - \gamma f(\lambda_-) & 0 \\ 0 & f(\lambda_-)f(\lambda_-)\phi(\lambda_-) & f(\lambda_-)f(\lambda_-)\phi(\lambda_-) & -f(\lambda_-)\phi(\lambda_-) \end{pmatrix}.$$

The eigenvalues of the Jacobian matrix $J(E_-)$ are determined as follows:

$$\lambda_1 = -\mu,$$

$$\lambda_2 = \eta_s(1-\lambda_-) + \beta - \gamma f(\lambda_-).$$

For the additional eigenvalues, λ_3 and λ_4, they are calculated from matrix C:

$$C = \begin{pmatrix} -\eta_s\lambda_- & -\gamma\lambda_- \\ \dot{f}(\lambda_-)f(\lambda_-)\phi(\lambda_-) & -f(\lambda_-)\phi(\lambda_-) \end{pmatrix}.$$

Since

$$\mathrm{tr}(C) = -\eta_s\lambda_- - f(\lambda_-)\phi(\lambda_-) < 0$$

and

$$\det(C) = \lambda_- f(\lambda_-)\phi(\lambda_-)(\eta_s + \gamma f(\lambda_-)),$$

then, the eigenvalues have a negative real part if and only if

$$(\eta_s - \eta_r)(1-\lambda_-) > a + \beta, \quad f(\lambda_-) > \frac{\eta_s}{\gamma}.$$

5. Equilibrium $E_*(1, s_*, r_*, f(n_*))$: We investigate below the local stability of E_*. The Jacobian matrix of our system at E_* takes the form

$$J(E_*) = \begin{pmatrix} -\mu & 0 & 0 & 0 \\ -\alpha s_* & -\eta_s s_* + \beta \dfrac{s_* r_*}{n_*^2} & -\eta_s s_* - \beta \dfrac{s_*}{n_*} + \beta \dfrac{s_* r_*}{n_*^2} & -\gamma s_* \\ 0 & -\eta_r r_* + \beta \dfrac{r_*}{n_*} - \beta \dfrac{s_* r_*}{n_*^2} & -\eta_r r_* - \beta \dfrac{s_* r_*}{n_*^2} & -\gamma r_* \\ 0 & f(n_*) f(n_*) \phi(n_*) & f(n_*) f(n_*) \phi(n_*) & -f(n_*) \phi(n_*) \end{pmatrix}.$$

The characteristic polynomial of $J(E_*)$ is given by

$$P(\lambda) = -(\lambda + \mu) \left(\lambda^3 - \operatorname{tr}(D) \lambda^2 - \frac{1}{2} \left[\operatorname{tr}(D^2) - (\operatorname{tr}(D))^2 \right] \lambda - \det(D) \right),$$

where D is the following matrix:

$$D = \begin{pmatrix} -\eta_s s_* + \beta \dfrac{s_* r_*}{n_*^2} & -\eta_s s_* - \beta \dfrac{s_*}{n_*} + \beta \dfrac{s_* r_*}{n_*^2} & -\gamma s_* \\ -\eta_r r_* + \beta \dfrac{r_*}{n_*} - \beta \dfrac{s_* r_*}{n_*^2} & -\eta_r r_* - \beta \dfrac{s_* r_*}{n_*^2} & -\gamma r_* \\ f(n_*) f(n_*) \phi(n_*) & f(n_*) f(n_*) \phi(n_*) & -f(n_*) \phi(n_*) \end{pmatrix}.$$

Therefore, the primary eigenvalue is $\lambda_1 = -\mu$, while the remaining eigenvalues are solutions to the cubic equation

$$\lambda^3 + a_2 \lambda^2 + a_1 \lambda + a_0 = 0, \tag{10}$$

with coefficients defined as follows:

$$a_2 = -\operatorname{tr}(D), \quad a_1 = -\frac{1}{2} \left[\operatorname{tr}(D^2) - (\operatorname{tr}(D))^2 \right], \quad a_0 = -\det(D).$$

Per the Routh-Hurwitz criterion for third-order polynomials, all solutions of the equation are situated in the left half of the complex plane if and only if $a_2 > 0$, $a_0 > 0$, and $a_2 a_1 > a_0$. Detailed computations yield

$$a_0 = f(n_*)\phi(n_*)\beta\frac{s_* r_*}{n_*}(\eta_s - \eta_r) > 0$$
$$a_2 = \eta_s s_* + \eta_r r_* + f(n_*)\phi(n_*) > 0,$$

and

$$a_1 a_2 - a_0 = f(n_*)\phi(n_*)(\eta_s s_* + \eta_r r_*)(\eta_s s_* + \eta_r r_* + f(n_*)\phi(n_*))$$
$$+ (\eta_s s_* + \eta_r r_*)\beta\frac{s_* r_*}{n_*}(\eta_s - \eta_r) > 0 \quad \square$$

$\square$

Proposition 1. The equilibrium $E_0(1, 0, 0, 0)$ is unstable.

Proof. Assume, by way of contradiction, that for an initial condition $(a(0), s(0), r(0), p(0))$ near E_0, it holds that

$$\lim_{t\to+\infty} s(t) = \lim_{t\to+\infty} r(t) = \lim_{t\to+\infty} p(t) = 0.$$

Since f and ϕ are continuous functions, we have

$$\lim_{t\to+\infty} f(u(t)) = f(0), \quad \lim_{t\to+\infty} \phi(u(t)) = \phi(0).$$

Thus, for any $\epsilon > 0$, there exists $\tilde{t} > 0$ such that for all $t \geq \tilde{t}$, the following

conditions are satisfied:

$$f(u(t)) \geq f(0) - \epsilon \quad \text{and} \quad \phi(u(t)) \geq \phi(0) - \epsilon.$$

For all $t \geq \tilde{t}$, the function $p(t)$ satisfies

$$\begin{aligned} p(t) &= p\phi(n)(f(n) - p) \\ &\geq p\phi(n)(f(0) - \epsilon - p) \\ &\geq p(\phi(0) - \epsilon)(f(0) - \epsilon)\left(1 - \frac{p}{f(0) - \epsilon}\right). \end{aligned}$$

This yields

$$\liminf_{t \to +\infty} p(t) \geq f(0) - \epsilon.$$

As $\epsilon > 0$ was chosen arbitrarily, we conclude that $\liminf_{t \to +\infty} p(t) \geq f(0)$, which contradicts our initial assumption. □

Theorem 2. The equilibrium E_1 is LAS if $\alpha > \eta_s$ and $\gamma f(0) > \eta_r$.

Proof. First, $\lim_{t \to +\infty} a(t) = 1$. Substituting this value into the second equation of our system we obtain the asymptotically equivalent system given by

$$\begin{cases} \dot{s}(t) &= \eta_s(1-n)s - as - \beta\frac{sr}{n} - ysp, \\ \dot{r}(t) &= \eta_r(1-n)r + \beta\frac{sr}{n} - yrp, \\ \dot{p}(t) &= \phi(n)p(f(n) - p), \\ n &= s + r. \end{cases} \tag{7}$$

The first equation gives

$$\begin{aligned}\dot{s}(t) &= \eta_s(1-n)s - as - \beta\frac{sr}{n} - ysp \\ &\leq (\eta_s - a)s\end{aligned}$$

which implies that $\lim_{t\to+\infty} s(t) = 0$. Substituting this value into the second equation we obtain the asymptotically equivalent system as follows

$$\begin{cases}\dot{r}(t) &= \eta_r(1-r)r - yrp, \\ \dot{p}(t) &= \phi(r)p(f(r)-p).\end{cases} \tag{8}$$

The Jacobian matrix associated with the point $(0, f(0))$ of this planar system is given by

$$\begin{pmatrix}\eta_r - yf(0) & 0 \\ f(0)f(0)\phi(0) & -f(0)\phi(0)\end{pmatrix}$$

which completes our proof. □

Table 1: Conditions for the stability of equilibria.

Equilibrium	**Biological existence**	**Stability**
$E_0\ (1,0,0,0)$	Always exists	Always unstable
$E_1\ (1,0,0,f(0))$	Always exists	$\alpha > \eta_s$ and $\gamma f(0) > \eta_r$
$E_2\ (1,0,1,0)$	Always exists	Always unstable
$E_3\left(1, 1-\frac{\alpha}{\eta_s}, 0, 0\right)$	$\eta_s > \alpha$	Always unstable
$E_+\ (1,0,\lambda_+,f(\lambda_+))$	$\eta_r > \gamma f(0)$	$\gamma f(\lambda_+) > C_+$ and $\gamma f(\lambda_+) > \eta_r$
$E_-\ (1,\lambda_-,0,f(\lambda_-))$	$\eta_s - \alpha > \gamma f(0)$	$\gamma f(\lambda_-) > C_-$ and $\gamma f(\lambda_-) > \eta_s$
$E_*\ (1,s_*,r_*,f(n_*))$	$\begin{cases}\eta_r\frac{\alpha+\beta}{\eta_s-\eta_r} < \gamma f(n_*) < \frac{\eta_r\alpha+\eta_s\beta}{\eta_s-\eta_r} \\ \text{and} \\ \eta_s > \eta_r + \alpha + \beta\end{cases}$	$\gamma f(n_*) > C_*$

5 Numerical Computation and Results

gut

August 6, 2025

1 Modeling Bacteria, Antibiotics and Immune System

This notebook is to accompany the Report file Computation and Code section. Figures and Simulations are generated here.

1.1 Parameter Selection

Our Invarient Set $\mathcal{A}$ implied some restriction on parameters which alligned with our biological and mathematical intuition.

[32]:
```
import numpy as np
import matplotlib.pyplot as plt
plt.rcParams['text.usetex'] = True
```

1.2 Symbolic Calculation

Here is a Calculation of Jacoubian of the system without numerical computation. Using Python Symbolic library.

[13]:
```
import sympy as sp

a, s, r, p = sp.symbols('a s r p')
mu, eta_r, eta_s, alpha, beta, gamma = sp.symbols('mu eta_r eta_s alpha beta␣
 ↪gamma')

vars_params = [a, s, r, p , alpha, beta, gamma, eta_s, eta_r, mu]

def f(x):
    return x - x**2 + 3/4

n = s + r

f1 = mu * (1 - a)
f2 = eta_s*(1 - n)*s - alpha * a * s - (beta * s * r )/n - gamma * s * p
f3 = eta_r*(1 - n)*r + (beta * s * r )/n - gamma * r * p
f4 = p * ( f(n) - p )

dyn = sp.Matrix([f1,f2,f3,f4])
```

```
J = dyn.jacobian([a,s,r,p])
```

[14]:
```
## for E1
li = [1 , 0, 0 , f(0) , 1,0.1, 1,1,0.3,3]

dic = dict(zip(vars_params, li))

res = J.subs(dic).evalf()
res
```

[14]:
$$\begin{bmatrix} -3.0 & 0 & 0 & 0 \\ 0 & -0.75 & -0.1 & 0 \\ 0 & 0 & -0.35 & 0 \\ 0 & 0.75 & 0.75 & -0.75 \end{bmatrix}$$

1.3 Numerical Solver

Our solver is in `odeint` function of `scipy.integrate` module, which actualy is a wrapper for LSODE in ODEPACK in Fortran.

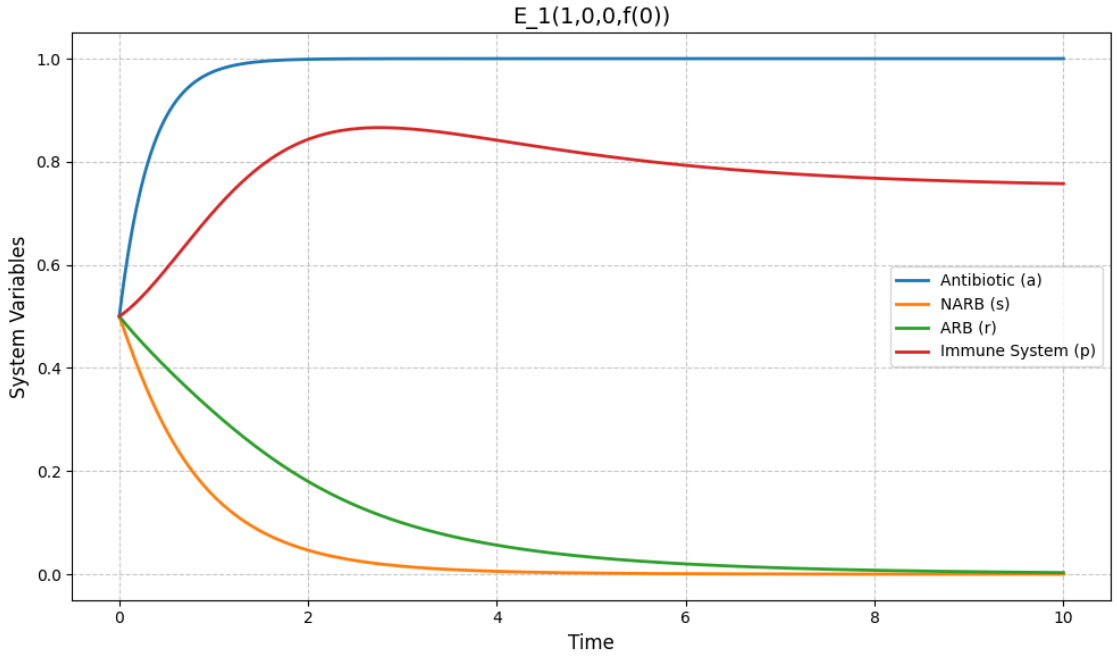
[ ]:
```
from scipy.integrate import odeint

def evaluate_dyn(y , t, alpha, beta, gamma, eta_s, eta_r, mu) -> tuple:
    a, s, r, p = y
    state_vars = [a, s, r, p , alpha, beta, gamma, eta_s, eta_r, mu]
    dic = dict(zip(vars_params, state_vars))
    res = dyn.subs(dic).evalf()
    res = sp.matrix2numpy(res, dtype=np.float64)
    return res.flatten()
```

[ ]:
```
def plot_solutions(sol, t, title:str, save=False) -> None:

    fig, ax = plt.subplots(figsize=(10, 6))

    variable_names = ['Antibiotic (a)', 'NARB (s)', 'ARB (r)', 'Immune System␣
 ↪(p)']
    colors = ['#1f77b4', '#ff7f0e', '#2ca02c', '#d62728']  # Professional color␣
 ↪scheme

    for i in range(4):
        ax.plot(t, sol[:, i],
                color=colors[i],
                linewidth=2,
                label=variable_names[i])

    ax.set_title(title, fontsize=14)
    ax.set_xlabel('Time', fontsize=12)
    ax.set_ylabel('System Variables', fontsize=12)
```

```
    ax.grid(True, linestyle='--', alpha=0.7)
    ax.legend(loc='best')

    if save:
        fig.savefig("figs/{title}.png")

    plt.tight_layout()
    plt.show()
```

1.3.1 For $E_1(1, 0, 0, f(0))$

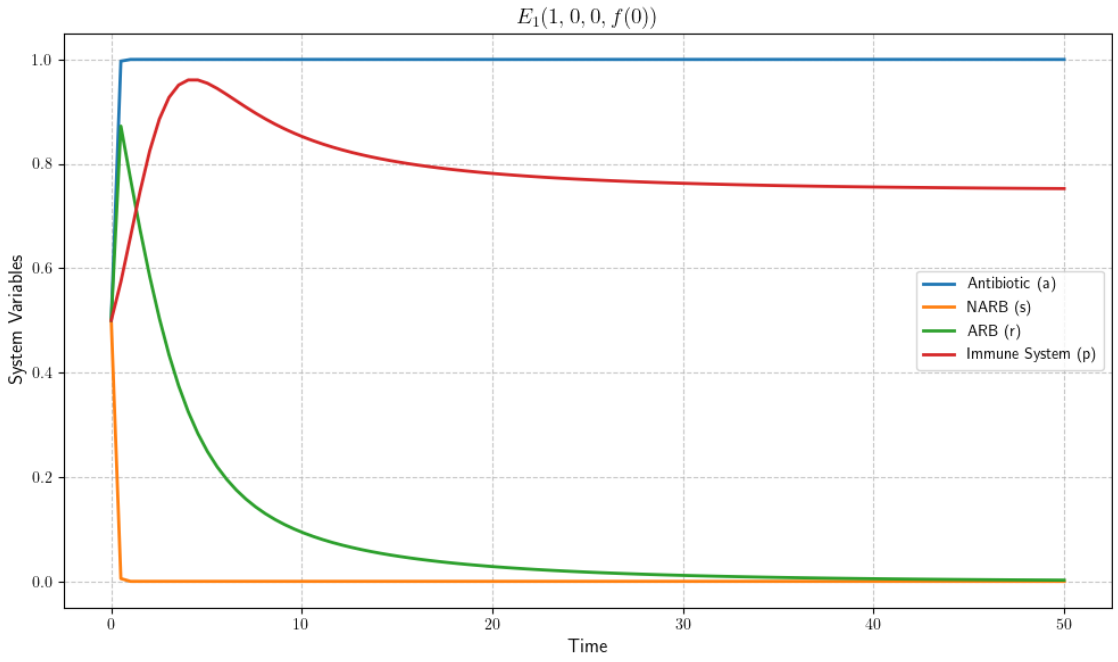
[ ]:
```
parset =  (1, 0.1, 1, 1, 0.3, 3)

if parset[vars_params.index(alpha) - 4] > parset[vars_params.index(eta_s) - 4]:
    print("E1")


y0 = np.repeat(0.5, 4)

t = np.linspace(0, 10, 1000)

sol = odeint(evaluate_dyn, y0 , t, args=parset)

plot_solutions(sol, t, r"Trajectory path for $E_1(1,0,0,f(0))$")
```



[28]:
```
vars_params
```

[28]:
```
[a, s, r, p, alpha, beta, gamma, eta_s, eta_r, mu]
```

[ ]:
```
parset =  np.random.randint(0, 10)

if parset[vars_params.index(alpha) - 4] > parset[vars_params.index(eta_s) - 4]:
    print("E1")


y0 = np.repeat(0.5, 4)

t = np.linspace(0, 50, 100)

sol = odeint(evaluate_dyn, y0 , t, args=parset)

plot_solutions(sol, t, r"Trajectory path for $E_1(1,0,0,f(0))$")
```



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