Population Dynamics of Bactria inside Humans

Battle of Bacteria, Antibiotics and Immune system

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Outline

- Bacteria lives inside us
- Some of them unwanted
- Antibiotics to get rid of them
- interactions lead to different equiliberia

Outline

Variable Definitions

A : Concentration of Antibiotics

S : Biomass of Non-Antibiotic-Resistant Bacteria

R : Biomass of Antibiotic-Resistant Bacteria

P : Immune Cell Population

N : $S + R$ total bacteria

Ψ and Φ : functions in $\mathcal{C}^1(\mathbb{R}_+)$

Model Equations

Modified Logistic Model

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

Parameter and Term Definitions

Λ : administration rate of Antibiotics

μ : absorbtion rate of Antibiotic

η_S and η_R : reproduction rate of S and R

K : carrying capacity (Limiting the reproduction)

Γ : transfer rate of resistant gene

$P_{\max}$: limit of prolifiration of immune cells

Key Assumptions

- $\eta_S > \eta_R$ cost of resistance
- Resistance genes transfer $\beta \frac{SR}{N}$
- Immune response ΓSP ΓRP

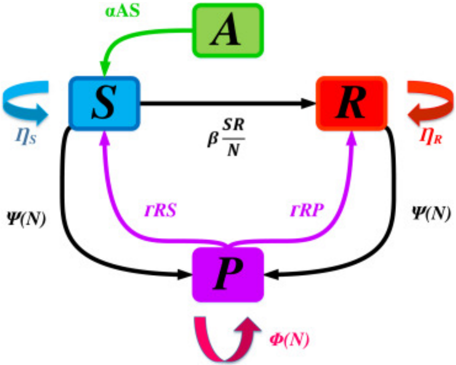

Fig. 1: Schematic Diagram

Transformation

$$a = \frac{A}{A/\mu} \qquad s = \frac{S}{K} \qquad r = \frac{R}{K} \qquad p = \frac{P}{P_{\max}}$$

$$\alpha = \frac{\bar{\alpha} A}{\mu} \quad \gamma = \Gamma P_{\max} \quad n = s + r \quad \phi(n) = \Phi(Kn) \quad \psi(n) = \Psi(Kn)$$

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

Boundedness

- $\mathbb{R}_+^4 = \left\{(a,s,r,p) \in \mathbb{R}^4 \mid a \geq 0 \; s \geq 0 \;,\; r \geq 0 \;,\; p \geq 0\right\}$
- Right hand side of our system $\in \mathcal{C}^1 \left(\text{Int}(\mathbb{R}_+^4), \mathbb{R}_+^4\right)$
- Unique Solution exists $\in [0, T_{\text{max}}]$
- $\mathcal{A} = \left\{(a,s,r,p) \in \text{Int}\left(\mathbb{R}_+^4\right), a \leq 1, s+r \leq 1, p \leq 1\right\}$
- lemma: $\mathcal{A}$ is positively invariant with recpect to 1
- hence mathematically and biologically well posed

Outline

Analysing reveals 4 Equilibria - biologically meaningfull

- clearance of infection
- infection under S
- infection under R
- infection under both

deriving Equilibria

- Equiliberia $\equiv$ Zero Change $\equiv \dot{\mathbf{X}} = \vec{0}$
- let $f(n) = 1 - \frac{\psi(n)}{\phi(n)}$ with $f(0) > 0$ and simplify
- we want $f \uparrow$ for small n and $f \downarrow$ for large n (How Immunity works)
- f either remains $+$ or after a threshold drops < 0
- we focus on 2nd scenario (remmeber n is bounded)

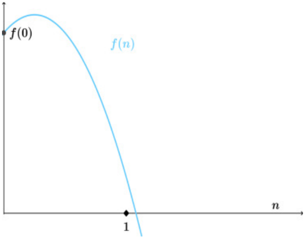

Fig. 2: Schematic Rep. of what f can be

$$
\begin{aligned}
&\mu(1-a) = 0 & & a = 1 \\
&\eta_s(1-n)s - \alpha a s - \beta\frac{sr}{n} - \gamma s p = 0 & & s = 0 \quad \text{or} \quad \eta_s(1-n) - \alpha - \beta\frac{r}{n} - \gamma p = 0 \\
&\eta_r(1-n)r + \beta\frac{sr}{n} - \gamma r p = 0 & \Rightarrow & r = 0 \quad \text{or} \quad \eta_r(1-n) + \beta\frac{s}{n} - \gamma p = 0 \\
&\phi(n)p(f(n) - p) = 0 & & p = 0 \quad \text{or} \quad p = f(n)
\end{aligned}
$$

Equiliberia

7 Cases

- Case 1: $E_0(1,0,0,0)$ $r = s = p = 0$
- Case 2: $E_1(1,0,0,f(0))$ $r = s = 0$, $p \neq 0$
- Case 3: $E_2(1,0,1,0)$ $s = p = 0$, $r \neq 0$

Case 4

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

$$r = \lambda_+ \quad p = f(\lambda_+) \quad \Rightarrow f(r) = \eta_r \frac{1-r}{\gamma}$$

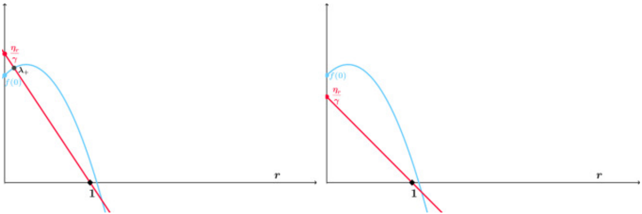

Fig. 3: f and λ_+

if $f(0) < \frac{\eta_r}{\gamma}$ exists Unique $0 < \lambda_+ < 1$

Case 5 an 6

- Case 5 $E_3(1, 1 - \frac{\alpha}{\eta_s}, 0, 0)$ $s \neq 0$, $r = 0$, $p = 0$
- Case 6 E_- $s \neq 0$, $r = 0$, $p \neq 0$

$$s = \lambda_- \quad , \quad p = f(\lambda_-) \Rightarrow f(s) = \frac{\eta_s - \alpha}{\gamma} - \frac{\eta_s}{\gamma} s$$

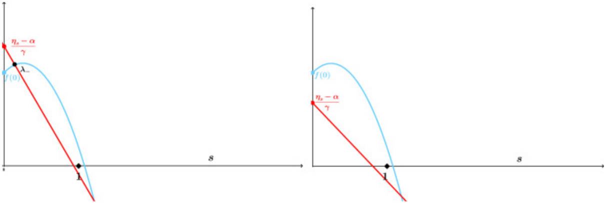

Fig. 4: f and λ_-

Like Case 4 if $f(0) < \frac{\eta_s - \alpha}{\gamma}$ exists Unique $0 < \lambda_- < 1$

Case 7: E_*

$s \neq 0$, $r \neq 0$, $p \neq 0$

$n_* = s + r = 1 - \frac{\alpha+\beta}{\eta_s - \eta_r}$

$n_* > 0$ if $\alpha + \beta + \eta_r < \eta_s$

$$\begin{aligned} p_* &= f(n_*) \\ s_* &= \tfrac{n_*}{\beta}\left(\gamma f(n_*) - \eta_r \tfrac{\alpha+\beta}{\eta_s-\eta_r}\right) \\ r_* &= \tfrac{n_*}{\beta}\left(\eta_s \tfrac{\alpha+\beta}{\eta_s-\eta_r} - \alpha - \gamma f(n_*)\right) \end{aligned}$$

$$p_* \;,\; s_* \;,\; r_* > 0 \qquad \text{if} \qquad \eta_r \frac{\alpha+\beta}{\eta_s-\eta_r} < \gamma f(n_*) < \frac{\alpha\eta_r + \beta\eta_s}{\eta_s - \eta_r}$$

Outline

Linearinzation

- System is non linear,
- Linearinzation around fixed points $\Rightarrow$ Jacobian Matrix
- Signs of the eigenvalues of the Jacobian matrix shall be determined

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

- let $C_+ = \eta_s\left(1-\lambda_+\right) - \alpha - \beta$, $C_- = \eta_r\left(1-\lambda_-\right) + \beta$ and

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

will show up for finding stability criteria

Stability Table

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_* $(1, s_*, r_*, f(n_*))$	$\begin{cases} \eta_r \frac{\alpha+\beta}{\eta_s-\eta_r} < \gamma f(n_*) < \frac{\eta_r\alpha+\eta_s\beta}{\eta_s-\eta_r} \\ \text{and} \\ \eta_s > \eta_r + \alpha + \beta \end{cases}$	$\gamma f(n_*) > C_*$

Outline

Numerical Computation

- we have chosen the function $f(n) = -n^2 + n + \frac{3}{4}$ the aligns with our hypothesis

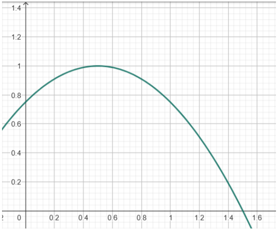

Fig. 5: $f(n) = -n^2 + n + \frac{3}{4}$

- Since E_1 is the equilibria which the system will reach an infection free state we will display it

Numerical Computation

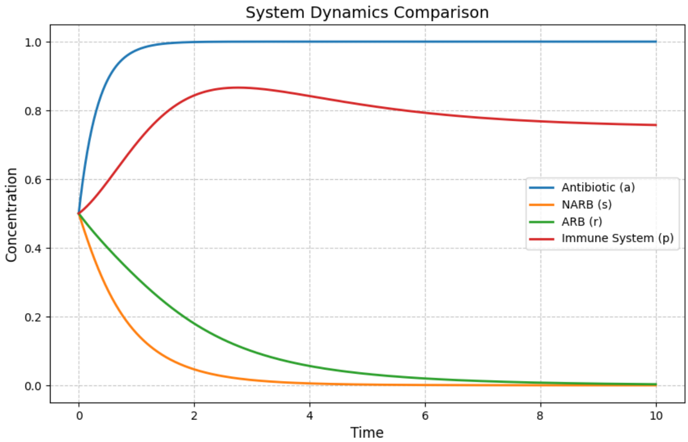

Fig. 6: Stability of E_1

Numerical Computation

Specifically, for E_1 to be stable, two crucial conditions must be met:

- the antibiotic must be administered at a sufficiently high rate compared to the reproduction rate of non-resistant bacteria
- the immune response must be strong enough to outcompete and eliminate resistant bacteria

Outline

Code I

Outline

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For Your Attention

Thank You!