Population Dynamics of Bactria inside Humans

Battle of Bacteria, Antibiotics and Immune system

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Outline

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Introduction

- Antibiotic Resistance
- Importance of Immune System
- Selective Pressure and Challenges
- Why Mathematical Modeling is Important

Antibiotic Resistance

- Bacteria becoming resistant

  Why this happens?

- Antibiotic Abuse
- Early Stop of Medication
- Prescription Error (Dosage and Medication)

Importance of Immune System

- Immune System can put up a sturdy defense
- Severe Infection weakens Immune System
- Mild ARB Infection Becomes Fatal When Immune System is Weak
- **WHO** Warns 25 million Death by 2050

Selective Pressure and Challenges

- Difficulties of Curing ARB Infection
- Incorrect Prescription leads to selective pressure
- Small Change of Dosage can make a Considerable Difference
- Epidemiological Models shows less abuse affects growth of resistance in population level

Why Mathematical Modeling is Important

- we ask:
  - In what circumstances Antibiotic solely kills infection?
  - When combined interventions i.e. Immunity enhancement or multi medication–is needed?
- Mathematical models show
  - simulation of various therapeutic scenarios
  - Overdosage and Underdosage effects

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

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 : absorption rate of Antibiotic

η_S and η_R : reproduction rate of S and R

K : carrying capacity (Limiting the reproduction)

β : transfer rate of resistant gene

Γ : Immune System's activity

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

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

Key Assumptions

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

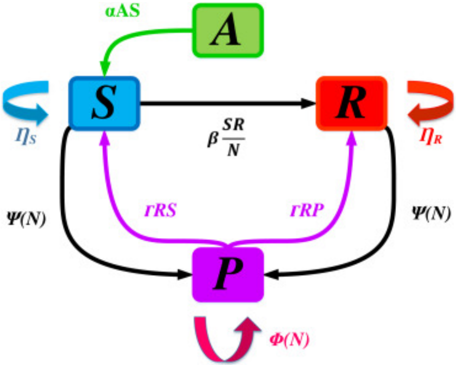

Fig. 1: Schematic Diagram

Transformation

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

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

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

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

Outline

Analyzing reveals 4 Equilibria - stable

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

deriving Equilibria

- Equilibria $\equiv$ 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)

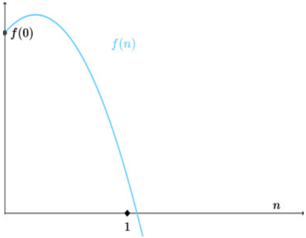

Fig. 2: Schematic Rep. of what f can be

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

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_+ $s = 0$, $r \neq 0$, $p \neq 0$

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

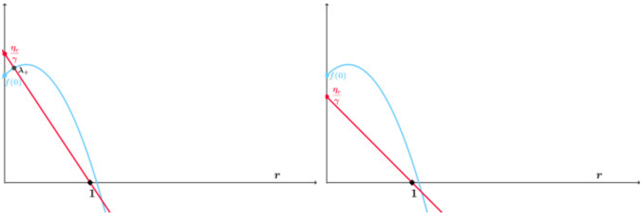

Fig. 3: f and λ_+

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_- $s \neq 0$, $r = 0$, $p \neq 0$

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

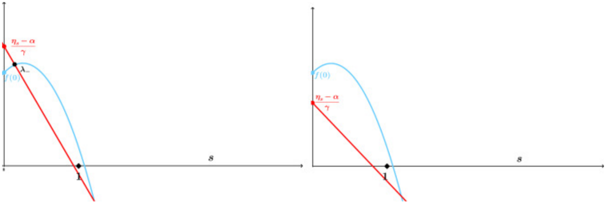

Fig. 4: f and λ_-

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

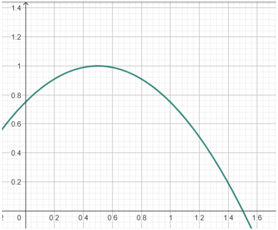

Fig. 5: $f(n) = -n^2 + n + \frac{3}{4}$

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

Numerical Computation

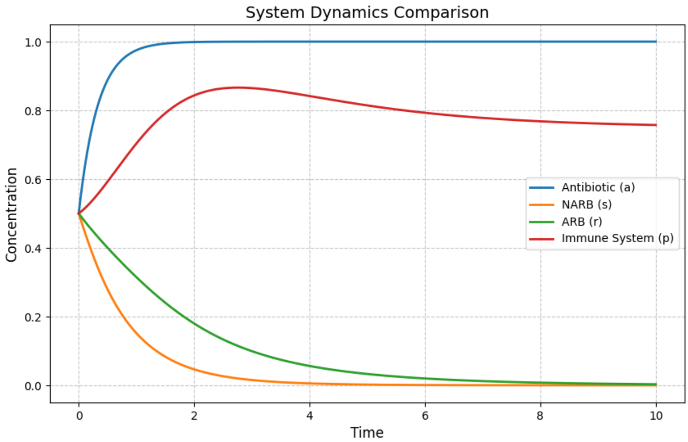

Fig. 6: Stability of E_1

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

Deriving Jacobian I

```python
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]
```

Deriving Jacobian II

```python
    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 )
```

Deriving Jacobian III

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

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

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

dic = dict(zip(vars_params, li))

```

Deriving Jacobian IV

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

```

$$\begin{bmatrix} -3.0 & 0 & 0 & 0 \\ 0 & -0.75 & -0.1 & 0 \\ 0 & 0 & -0.35 & 0 \\ 0 & 0.75 & 0.75 & -0.75 \end{bmatrix}$$

ODE Numeric Solve I

```python
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)
```

ODE Numeric Solve II

```
    return res.flatten()

parset =  (1, 0.1, 1, 1, 0.3, 3)

y0 = np.repeat(0.5, 4)

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

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

```

Outline

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For Your Attention

Thank You!