

# Population Dynamics of Bacteria inside Humans

Battle of Bacteria, Antibiotics and Immune system

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# Outline

- 1 Introduction
- 2 Dynamic Model
- 3 Equilibria
- 4 Stability Analysis
- 5 Numerical Computation
- 6 Code
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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



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# 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

$$\dot{A}(t) = \Lambda - \mu A,$$

$$\dot{S}(t) = \eta_s \left( 1 - \frac{S+R}{K} \right) S - \bar{\alpha} AS - \beta \frac{SR}{N} - \Gamma SP,$$

$$\dot{R}(t) = \eta_r \left( 1 - \frac{S+R}{K} \right) R + \beta \frac{SR}{N} - \Gamma RP,$$

$$\dot{P}(t) = \Phi(N)P \left( 1 - \frac{P}{P_{\max}} \right) - \Psi(N)P,$$

# Parameter and Term Definitions

$\Lambda$  : administration rate of Antibiotics

$\mu$  : absorption rate of Antibiotic

$\eta_S$  and  $\eta_R$  : reproduction rate of  $S$  and  $R$

$K$  : carrying capacity (Limiting the reproduction)

$\beta$  : transfer rate of resistant gene

$\Gamma$  : Immune System's activity

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

$\Psi$  and  $\Phi$  : 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  $\Gamma_{SP} \Gamma_{RP}$

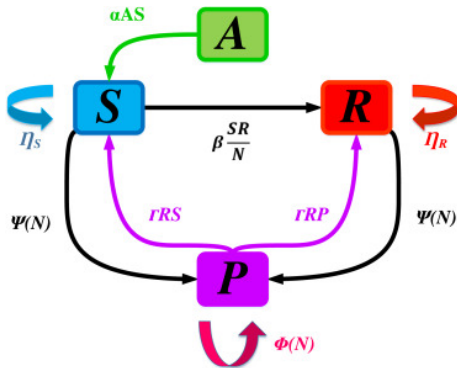


Fig. 1: Schematic Diagram

# Transformation

$$a = \frac{A}{\Lambda/\mu} = \frac{\mu A}{\Lambda} \quad s = \frac{S}{K} \quad r = \frac{R}{K} \quad p = \frac{P}{P_{\max}}$$
$$\alpha = \frac{\bar{\alpha} A}{\mu} \quad \gamma = \Gamma P_{\max} \quad n = s + r \quad \phi(n) = \Phi(Kn) \quad \psi(n) = \Psi(Kn)$$

$$\dot{a}(t) = \mu(1 - a)$$

$$\dot{s}(t) = \eta_s(1 - n)s - \alpha as - \beta \frac{sr}{n} - \gamma sp$$

$$\dot{r}(t) = \eta_r(1 - n)r + \beta \frac{sr}{n} - \gamma rp$$

$$\dot{p}(t) = \phi(n)p(1 - p) - \psi(n)p$$

# Boundedness

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

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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 (remember  $n$  is bounded )

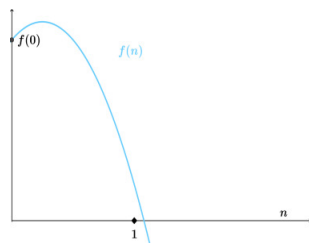


Fig. 2: Schematic Rep. of what  $f$  can be

$$\mu(1-a) = 0$$

$$a = 1$$

$$\eta_s(1-n)s - \alpha as - \beta \frac{sr}{n} - \gamma sp = 0$$

$\Rightarrow$

$$s = 0 \quad \text{or} \quad \eta_s(1-n) - \alpha - \beta \frac{r}{n} - \gamma p = 0$$

$$\eta_r(1-n)r + \beta \frac{sr}{n} - \gamma rp = 0$$

$$r = 0 \quad \text{or} \quad \eta_r(1-n) + \beta \frac{s}{n} - \gamma p = 0$$

$$\phi(n)p(f(n) - p) = 0$$

$$p = 0 \quad \text{or} \quad p = f(n)$$

# Equilibria

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

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

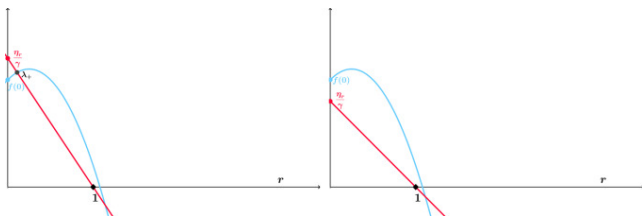


Fig. 3:  $f$  and  $\lambda_+$

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

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

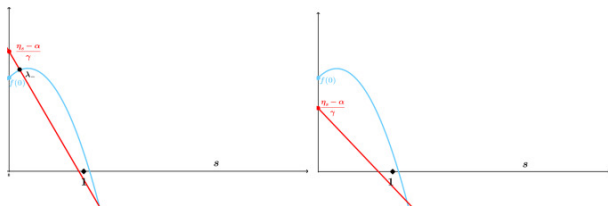


Fig. 4:  $f$  and  $\lambda_-$

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

## Case 7: $E_*$

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

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

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

$$p_* = f(n_*)$$

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

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

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

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

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

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 $\gamma f(\lambda_-) > \eta_s$
$E_* (1, s_*, r_*, f(n_*))$	$\left\{ \begin{array}{l} \eta_r \frac{\alpha + \beta}{\eta_s - \eta_r} < \gamma f(n_*) < \frac{\eta_r \alpha + \eta_s \beta}{\eta_s - \eta_r} \\ \text{and} \\ \eta_s > \eta_r + \alpha + \beta \end{array} \right.$	$\gamma f(n_*) > C_*$

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# Numerical Computation

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

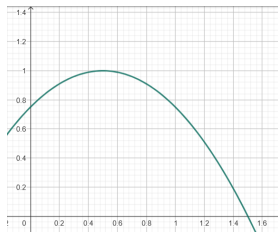


Fig. 5:  $f(n) = -n^2 + n + \frac{3}{4}$

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

# Numerical Computation

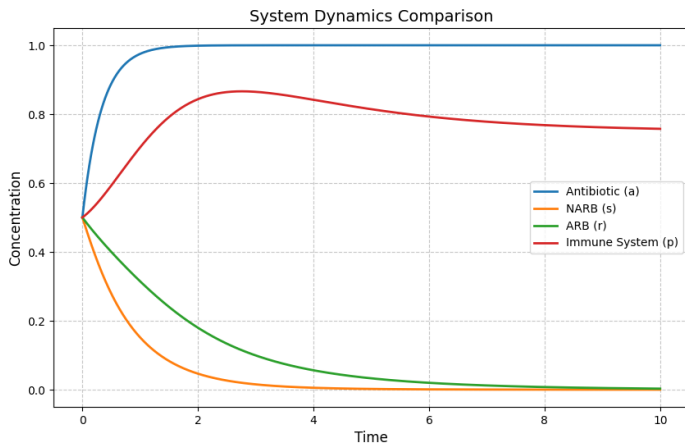


Fig. 6: Stability of  $E_1$

# 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

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# Deriving Jacobian I

```
1  import sympy as sp
2
3  a, s, r, p = sp.symbols('a s r p')
4  mu, eta_r, eta_s, alpha, beta, gamma = sp.symbols(
5      'mu eta_r eta_s alpha beta gamma'
6  )
7
8  vars_params = [a, s, r, p , alpha, beta, gamma, eta_s,
9  eta_r, mu]
```

# Deriving Jacobian II

```
10 def f(x):  
11     return x - x**2 + 3/4  
12  
13 n = s + r  
14  
15 f1 = mu * (1 - a)  
16 f2 = eta_s*(1 - n)*s - alpha * a * s - (beta * s * r )/n  
    - gamma * s * p  
17 f3 = eta_r*(1 - n)*r + (beta * s * r )/n - gamma * r * p  
18 f4 = p * ( f(n) - p )
```



# Deriving Jacobian III

```
19
20     dyn = sp.Matrix([f1,f2,f3,f4])
21
22     J = dyn.jacobian([a,s,r,p])
23
24     ## for E1
25     li = [1 , 0, 0 , f(0) , 1,0.1, 1,1,0.3,3]
26
27     dic = dict(zip(vars_params , li))
28
```

# Deriving Jacobian IV

```
29     res = J.subs(dic).evalf()  
30     res  
31
```

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

# ODE Numeric Solve I

```
1  from scipy.integrate import odeint
2
3  def evaluate_dyn(y , t, alpha, beta, gamma, eta_s, eta_r
4  , mu) -> tuple:
5      a, s, r, p = y
6      state_vars = [a, s, r, p , alpha, beta, gamma, eta_s,
7  eta_r, mu]
8
9      dic = dict(zip(vars_params, state_vars))
10     res = dyn.subs(dic).evalf()
11     res = sp.matrix2numpy(res, dtype=np.float64)
```

# ODE Numeric Solve II

```
9      return res.flatten()
10
11  parset = (1, 0.1, 1, 1, 0.3, 3)
12
13  y0 = np.repeat(0.5, 4)
14
15  t = np.linspace(0, 10, 1000)
16
17  sol = odeint(evaluate_dyn, y0, t, args=parset)
18
```

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# For Your Attention

*Thank You!*