Mathematical Modelling of antibiotic Interaction on Evolution of Antibiotic Resistance: An Analytical Approach

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**Derivation of Equilibrium Points**

The equilibria of system (5) are given by the solutions of the system of algebraic equations:

|  |  |
| --- | --- |
| $$β\_{s}s\left(1-(s+r)\right)-(q\_{1}c\_{1}+q\_{2}c\_{2})s-\left((α\_{11}c\_{1}+α\_{12}c\_{2}+λ\_{1}α\_{11} α\_{12}c\_{1}c\_{2})+μ\_{s}\right)s=0$$ | (S1a) |
| $$β\_{r}r\left(1-(s+r)\right)+(q\_{1}c\_{1}+q\_{2}c\_{2})s-\left((α\_{21}c\_{1}+α\_{22}c\_{2}+λ\_{2}α\_{21} α\_{22}c\_{1}c\_{2})+μ\_{r}\right)r=0$$ | (S1b) |
| $$μ\_{1}-μ\_{1}c\_{1}=0$$ | (S1c) |
| $μ\_{2}-μ\_{2}c\_{2}=0$. | (S1d) |

 From the equations (S1c) and (S1d), we have *c1 = c2 = 1*. Replacing *c1* and *c2*  in the equations (S1a) and (S1b), we obtain:

|  |  |
| --- | --- |
| $$β\_{s}s\left(1-(s+r)\right)-(q\_{1}+q\_{2})s-\left((α\_{11}+α\_{12}+λ\_{1}α\_{11} α\_{12})+μ\_{s}\right)s=0$$ | (S2a) |
| $β\_{r}r\left(1-(s+r)\right)+(q\_{1}+q\_{2})s-\left((α\_{21}+α\_{22}+λ\_{2}α\_{21} α\_{22})+μ\_{r}\right)r=0$. | (S2b) |

It holds from the equation (S2a) that *s=0* or:

|  |  |
| --- | --- |
| $$β\_{s}\left(1-(s+r)\right)-m-\left(\left(α\_{11}+α\_{12}+λ\_{1}α\_{11} α\_{12}\right)+μ\_{s}\right) =0$$ |  (S3) |

where *m=q1+q2.*

Assume *s=0* replacing this value in the equation (S2b) we obtain:

|  |  |
| --- | --- |
| $$β\_{r}r-β\_{r}r^{2}-\left((α\_{21}+α\_{22}+λ\_{2}α\_{21} α\_{22})+μ\_{r}\right)r=0$$ | (S4) |

which implies $r=0$ or:

|  |  |
| --- | --- |
| $$r=\frac{R\_{r}-1}{R\_{r}}$$ | (S5) |

where

|  |  |
| --- | --- |
| $R\_{r}=\frac{β\_{r}}{(α\_{21}α\_{22}λ\_{2}+ α\_{21}+ α\_{22})+μ\_{r}}$. | (S6) |

Therefore, we obtain the equilibrium solutions

|  |  |
| --- | --- |
| $$P\_{0}=(0,0,1,1)$$ | (S7a) |
| $P\_{1}=\left(0,\frac{R\_{r}-1}{R\_{r}},1,1\right)$. | (S7b) |

From equation (S5), it follows that a necessary and sufficient condition for the biological sense of *P1* is *Rr >1*. Now, for *s≠0* the equation (S2a) is reduced to:

|  |  |
| --- | --- |
| $$s=\frac{R\_{s}-1}{R\_{s}}-r$$ | (S8) |

where

|  |  |
| --- | --- |
| $R\_{s}=\frac{β\_{s}}{m+\left(α\_{11}+α\_{12}+λ\_{1}α\_{11} α\_{12}\right)+μ\_{s}}$. | (S9) |

From equation (S8), it is concluded that a necessary condition for the existence of sensitive and resistant bacteria is *Rs >1* Also, a sufficient condition for $s$ to be positive is:

|  |  |
| --- | --- |
| $\frac{R\_{s}-1}{R\_{s}}>r$. | (S10) |

Substituting equation (S8) in the equation (S2b) and solving for *r* we obtain:

|  |  |
| --- | --- |
| $r=\frac{m\left(\frac{R\_{s}-1}{R\_{s}}\right)}{β\_{r}\left(\frac{1}{R\_{r}}-\frac{1}{R\_{s}}\right)+m}$. | (S11) |

Replacing $r $defined by (S11) in the inequality (S10), it is easy to verify that *s > 0* is equivalent to *Rs > R*r.Further, *r > 0* if 1/*R*r > 1/ *Rs.* Therefore, a necessary condition for *s* and *r* to be positive is *Rs > R*r.

**Stability Analysis of Equilibrium Points**

By evaluating the equation (14) Jacobian *J* in *P0* we obtain:

|  |  |
| --- | --- |
| $J\left(P\_{0}\right)=\left[\begin{matrix}j\_{11}(P\_{0})&0&0&0\\m&j\_{22}(P\_{0})&0&0\\0&0&-μ\_{1}&0\\0&0&0&-μ\_{2}\end{matrix}\right]$. | (S12) |

The eigenvalues of *J(P0)* are given by:

|  |  |
| --- | --- |
| $$φ\_{1}=j\_{11}(P\_{0})=β\_{s}-m-\left(\left(α\_{11}+α\_{12}+λ\_{1}α\_{11}α\_{12}\right)+μ\_{s}\right)=β\_{s}\left(\frac{R\_{s}-1}{R\_{s}}\right)$$ | (S13a) |
| $$φ\_{2}=j\_{22}(P\_{0})=β\_{r}-\left((α\_{21}+α\_{22}+λ\_{2}α\_{21} α\_{22})+μ\_{r}\right)=β\_{r}\left(\frac{R\_{r}-1}{R\_{r}}\right)$$ | (S13b) |
| $$φ\_{3}=-μ\_{1}$$ | (S13c) |
| $φ\_{4}=-μ\_{2}$. | (S13d) |

Since *φ1* and *φ2* are negative for *Rs* < 1 and *Rr* < 1, respectively, then *P0* is locally and asymptotically stable. Since *α11, α12*, *μs, and βs*are positive; there are three conditions for *Rs* < 1 if *λ1* > 0, *λ1* < 0, or *λ1* = 0. If *λ1* > 0, *λ1* < 0 the necessary condition for *Rs* < 1 is:

|  |
| --- |
| $$β\_{s}-μ\_{s}-m<α\_{11}+α\_{12}+λ\_{1}α\_{11} α\_{12}$$ |

and if *λ1* = 0, the necessary condition is:

|  |
| --- |
| $β\_{s}-μ\_{s}-m<α\_{11}+α\_{12}$. |

Analogously, since *α21, α22*, *μr, and βr*are positive, there are three conditions for *Rr* > 1, if *λ2* > 0, *λ2* < 0, or *λ2* = 0. If *λ2* > 0, *λ2* < 0 the necessary condition for *Rr* < 1 is:

|  |
| --- |
| $$β\_{r}-μ\_{r}<α\_{21}+α\_{22}+λ\_{2}α\_{21} α\_{22}$$ |

and if *λ2* = 0 the necessary condition is:

|  |
| --- |
| $β\_{r}-μ\_{r}<α\_{21}+α\_{22}$. |

Now, we determine the conditions for which the equilibrium *P1* is locally and asymptotically stable. To this end, let us observe that the Jacobian given in equation (14) evaluated in *P1* is given by:

|  |  |
| --- | --- |
| $J\left(P\_{1}\right)=\left[\begin{matrix}j\_{11}(P\_{1})&0&0&0\\-β\_{r}\left(\frac{R\_{r}-1}{R\_{r}}\right)+m&j\_{22}(P\_{1})&-(λ\_{2}α\_{21}α\_{22}+α\_{21})\frac{R\_{r}-1}{R\_{r}}&-(λ\_{2}α\_{21}α\_{22}+α\_{22})\frac{R\_{r}-1}{R\_{r}}\\0&0&-μ\_{1}&0\\0&0&0&-μ\_{2}\end{matrix}\right]$. | (S14) |

The eigenvalues of *J(P1)*$ $are given by:

|  |  |
| --- | --- |
| $$ω\_{1}=j\_{11}(P\_{1})= β\_{s}\left(1-\frac{R\_{r}-1}{R\_{r}}\right)-m-μ\_{s}-\left(α\_{11}+α\_{12}+λ\_{1}α\_{11}α\_{12}\right)=β\_{s}\left(\frac{1}{R\_{r}}-\frac{1}{R\_{s}}\right)$$ | (S15a) |
| $$ω\_{2}=j\_{22}(P\_{1})= β\_{r}\left(1-\frac{R\_{r}-1}{R\_{r}}\right)-β\_{r}\left(\frac{R\_{r}-1}{R\_{r}}\right)-μ\_{r}-(α\_{21}+α\_{22}+λ\_{2}α\_{21} α\_{22})=β\_{r}\left(\frac{1-R\_{r}}{R\_{r}}\right)$$ | (S15b) |
| $$ω\_{3}=-μ\_{1}$$ | (S15c) |
| $ω\_{4}=-μ\_{2}$. | (S15d) |

We see that *ω1* < 0 if and only if *Rr* > *Rs* and that *ω2* < 0 if and only if *Rr* >1. Since $α\_{21}$, $α\_{21}$, $μ\_{r}$, and $β\_{r}$ are positive, there are three conditions for *Rr* > 1, if *λ2* > 0, *λ2* < 0, or *λ2* = 0. If *λ2* > 0, *λ2* < 0 the necessary condition for *Rr* > 1 is:

|  |
| --- |
| $$β\_{r}-μ\_{r}>α\_{21}+α\_{22}+λ\_{2}α\_{21} α\_{22}$$ |

and if *λ2* = 0 the necessary condition is:

|  |
| --- |
| $β\_{r}-μ\_{r}>α\_{21}+α\_{22}$. |

Now, we determine the conditions for which the equilibrium *P2* is locally and asymptotically stable. To this end, let us observe that the Jacobian given in equation (14) evaluated in *P2* is given by:

|  |  |
| --- | --- |
| $$J\left(P\_{2}\right)=\left[\begin{matrix}j\_{11}(P\_{2})&-β\_{s}\overbar{s}&-(λ\_{1}α\_{11}α\_{12}+α\_{11})\overbar{s}&-(λ\_{1}α\_{11}α\_{12}+α\_{12})\overbar{s}\\-β\_{r}\overbar{r}+m&j\_{22}(P\_{2})&-(λ\_{2}α\_{21}α\_{22}+α\_{21})\overbar{r}&-(λ\_{2}α\_{21}α\_{22}+α\_{22})\overbar{r}\\0&0&-μ\_{1}&0\\0&0&0&-μ\_{2}\end{matrix}\right]$$ | (S16) |

where

|  |  |
| --- | --- |
| $$j\_{11}\left(P\_{2}\right)=β\_{s}\left(1-\left(\overbar{s}+\overbar{r}\right)\right)-β\_{s}\overbar{s}-m-μ\_{s}-\left(α\_{11}+α\_{12}+λ\_{1}α\_{11}α\_{12}\right)$$ | (S17a) |
| $j\_{22}(P\_{2})=β\_{r}\left(1-(\overbar{s}+\overbar{r})\right)-β\_{r}\overbar{r}-μ\_{r}-(α\_{21}+α\_{22}+λ\_{2}α\_{21} α\_{22})$. | (S17b) |

From (S3), it follows:

|  |  |
| --- | --- |
| $$j\_{11}\left(P\_{2}\right)=β\_{s}\left(1-\left(\overbar{s}+\overbar{r}\right)\right)-β\_{s}\overbar{s}-m-μ\_{s}-\left(α\_{11}+α\_{12}+λ\_{1}α\_{11}α\_{12}\right)=-β\_{s}\overbar{s}$$ | (S18) |

and from the equation (S2b), we have:

|  |  |
| --- | --- |
| $j\_{22}(P\_{2})=β\_{r}\left(1-(\overbar{s}+\overbar{r})\right)-β\_{r}\overbar{r}-μ\_{r}-(α\_{21}+α\_{22}+λ\_{2}α\_{21} α\_{22})=-\frac{1}{\overbar{r}}(β\_{r}\overbar{r}+m\overbar{s})$. | (S19) |

Substituting equations (S18) and (S19) in equation (S16), *J(P2)* becomes:

|  |  |
| --- | --- |
| $J\left(P\_{2}\right)=\left[\begin{matrix}-β\_{s}\overbar{s}&-β\_{s}\overbar{s}&-(λ\_{1}α\_{11}α\_{12}+α\_{11})\overbar{s}&-(λ\_{1}α\_{11}α\_{12}+α\_{12})\overbar{s}\\-β\_{r}\overbar{r}+m&-\frac{1}{\overbar{r}}(β\_{r}\overbar{r}+m\overbar{s})&-(λ\_{2}α\_{21}α\_{22}+α\_{21})\overbar{r}&-(λ\_{2}α\_{21}α\_{22}+α\_{22})\overbar{r}\\0&0&-μ\_{1}&0\\0&0&0&-μ\_{2}\end{matrix}\right]$. | (S20) |

The eigenvalues of *J(P2)*$ $are:

|  |  |
| --- | --- |
| $$τ\_{1}=-μ\_{1}$$ | (S21a) |
| $$τ\_{2}=-μ\_{2}$$ | (S22b) |

and the eigenvalues of the matrix:

|  |  |
| --- | --- |
| $A=\left[\begin{matrix}-β\_{s}\overbar{s}&-β\_{s}\overbar{s}\\-β\_{r}\overbar{r}+m&-\frac{1}{\overbar{r}}(β\_{r}\overbar{r}^{2}+m\overbar{s})\end{matrix}\right]$. | (S23) |

Since

|  |  |
| --- | --- |
| $$Trace(A)=-β\_{s}\overbar{s}-\frac{1}{\overbar{r}}(β\_{r}\overbar{r}^{2}+m\overbar{s})<0$$ | (S24) |

and

|  |  |
| --- | --- |
| $Det(A)=\frac{1}{\overbar{r}}(β\_{s} β\_{r} \overbar{s} \overbar{r}^{2}+β\_{s}m \overbar{s}^{2})+β\_{s} β\_{r} \overbar{s} \overbar{r} - β\_{s} \overbar{s} m >0$. | (S25) |

The eigenvalues of *A* have a negative real part.

**Half maximal inhibitory concentration for resistant bacteria (*ICR 50*) as function of minimum inhibitory concentration for resistant bacteria (*MICr*)**

Supposed that a single antibiotic inhibits resistant bacteria, and sensitive bacteria do not spontaneously mutate to become resistant. By underestimating the logistic growth of resistant bacteria, the equation (4b) became:

|  |  |
| --- | --- |
| $$\frac{dR}{dt}=β\_{r}R-\frac{E\_{max}^{r}}{IC\_{50}^{R}}CR-μ\_{r}R$$ | (S26) |

Here *C* represents a concentration of antibiotics. At MIC (minimum inhibitory concentration) level *dR/dt* must equal to zero, so we can write the above equation as:

|  |  |
| --- | --- |
| $$0=β\_{r}R-\frac{E\_{max}^{r}}{IC\_{50}^{R}}CR-μ\_{r}R$$ | (S27) |

Dividing both side by *R* we obtain:

|  |  |
| --- | --- |
| $$0=β\_{r}-\frac{E\_{max}^{r}}{IC\_{50}^{R}}C-μ\_{r}$$ | (S28) |

Solving for *C*, we get:

|  |  |
| --- | --- |
| $$C=\frac{(β\_{r}-μ\_{r})IC\_{50}^{R}}{E\_{max}^{r}}=MIC$$ | (S29) |

Solving for *ICR 50* , we get:

|  |  |
| --- | --- |
| $$IC\_{50}^{R}=\frac{E\_{max}^{r}∙MIC}{(β\_{r}-μ\_{r})}$$ | (S30) |

**Role of synergistic interactions against wildtype bacteria and mutants on the deacceleration of antimicrobial resistance**

Our findings specifically emphasize that synergistic antibiotic interactions against wildtype bacteria do not play a pivotal role in retarding the growth rate of resistant mutants. Conversely, it is observed that when synergistic antibiotic interactions against mutants collaborate with antagonistic interactions against wildtype bacteria, there is a significant deceleration in the growth rate of resistant mutants.