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:

|  |  |
| --- | --- |
|  | (S1a) |
|  | (S1b) |
|  | (S1c) |
| . | (S1d) |

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

|  |  |
| --- | --- |
|  | (S2a) |
| . | (S2b) |

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

|  |  |
| --- | --- |
|  | (S3) |

where *m=q1+q2.*

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

|  |  |
| --- | --- |
|  | (S4) |

which implies or:

|  |  |
| --- | --- |
|  | (S5) |

where

|  |  |
| --- | --- |
| . | (S6) |

Therefore, we obtain the equilibrium solutions

|  |  |
| --- | --- |
|  | (S7a) |
| . | (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:

|  |  |
| --- | --- |
|  | (S8) |

where

|  |  |
| --- | --- |
| . | (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 to be positive is:

|  |  |
| --- | --- |
| . | (S10) |

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

|  |  |
| --- | --- |
| . | (S11) |

Replacing 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:

|  |  |
| --- | --- |
| . | (S12) |

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

|  |  |
| --- | --- |
|  | (S13a) |
|  | (S13b) |
|  | (S13c) |
| . | (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:

|  |
| --- |
|  |

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

|  |
| --- |
| . |

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:

|  |
| --- |
|  |

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

|  |
| --- |
| . |

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:

|  |  |
| --- | --- |
| . | (S14) |

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

|  |  |
| --- | --- |
|  | (S15a) |
|  | (S15b) |
|  | (S15c) |
| . | (S15d) |

We see that *ω1* < 0 if and only if *Rr* > *Rs* and that *ω2* < 0 if and only if *Rr* >1. Since , , , and 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:

|  |
| --- |
|  |

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

|  |
| --- |
| . |

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:

|  |  |
| --- | --- |
|  | (S16) |

where

|  |  |
| --- | --- |
|  | (S17a) |
| . | (S17b) |

From (S3), it follows:

|  |  |
| --- | --- |
|  | (S18) |

and from the equation (S2b), we have:

|  |  |
| --- | --- |
| . | (S19) |

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

|  |  |
| --- | --- |
| . | (S20) |

The eigenvalues of *J(P2)*are:

|  |  |
| --- | --- |
|  | (S21a) |
|  | (S22b) |

and the eigenvalues of the matrix:

|  |  |
| --- | --- |
| . | (S23) |

Since

|  |  |
| --- | --- |
|  | (S24) |

and

|  |  |
| --- | --- |
| . | (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:

|  |  |
| --- | --- |
|  | (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:

|  |  |
| --- | --- |
|  | (S27) |

Dividing both side by *R* we obtain:

|  |  |
| --- | --- |
|  | (S28) |

Solving for *C*, we get:

|  |  |
| --- | --- |
|  | (S29) |

Solving for *ICR 50* , we get:

|  |  |
| --- | --- |
|  | (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.