Supplementary Text S1

The existence of steady states

The steady states of system (1)-(6) are given by equating the right-hand sides of system (1)-(6) to zero, and thus governed by the following equations:

\[
\frac{k_4}{1 + K_4 p} + k_{m1} R_{em} + k_{m2} R_{mc} = k_1 R_m R_e + k_2 R_m R_c + \delta_m R_m \quad (S1)
\]

\[
k_5 + k_{m1} R_{em} = k_1 R_m R_e + \delta_e R_e \quad (S2)
\]

\[
k_6 + k_{m2} R_{mc} = k_2 R_m R_c + \delta_c R_c \quad (S3)
\]

\[
k_1 R_m R_e = k_{m1} R_{em} + \delta_{em} R_{em} \quad (S4)
\]

\[
k_2 R_m R_c = k_{m2} R_{mc} + \delta_{mc} R_{mc} \quad (S5)
\]

\[
k_3 R_e = \delta_p P \quad (S6)
\]

With a direct computation, the above algebraic system gives the expression of the steady state in terms of \( R_m \) as follows:

\[
R_e = \frac{k_5 A_e}{\delta_e A_e + R_m}
\]

\[
R_c = \frac{k_6 A_c}{\delta_c A_c + R_m}
\]

\[
R_{em} = \frac{k_1 R_m R_e}{k_{m1} + \delta_e}
\]

\[
R_{mc} = \frac{k_2 R_m R_c}{k_{m2} + \delta_c}
\]

\[
P = \frac{M k_5 A_e}{R_m + D_e}
\]

where

\[
A_e = \frac{k_{m1} + \delta_{em}}{k_1 \delta_{em}}, \quad A_c = \frac{k_{m2} + \delta_{mc}}{k_2 \delta_{mc}}, \quad D_e = \delta_e A_e, \quad \text{and} \quad M = \frac{k_3}{\delta_p}
\]

Substituting these expressions into (S1) and rearranging the resulting equation, we obtain

\[
k_4 = h(R_m) \quad (S7)
\]

where
\[ h(x) = \left( \delta_m x + \frac{k_5 x}{x + \delta_e A_e} + \frac{k_6 x}{x + \delta_c A_c} \right) \frac{x + D_e + MA_e K_4 k_5}{x + D_e} \tag{S8} \]

Since \( h(0) = 0 \) and \( h(\infty) = \infty \), for any given \( k_4 > 0 \); there always exists \( R_m^* > 0 \) such that \( k_4 = h(R_m^*) \). This shows that for system (1)-(6), positive steady states always exist.

### The existence of multiple steady states

Next we give a condition for the existence of multiple steady states. Indeed, differentiating (S8) yields

\[ h'(x) = \frac{x + D_e + C}{x + D_e} \left( \delta_m + \frac{k_5 D_e}{(x + D_e)^2} + \frac{k_6 D_c}{(x + D_c)^2} \right) \tag{S9} \]

where \( C = MA_e K_4 k_5 \), \( D_e = \delta_e A_e \) and \( D_c = \delta_c A_c \). Hence, \( h'(x) \geq 0 \) if and only if

\[ \delta_m + \frac{k_5 D_e}{(x + D_e)^2} + \frac{k_6 D_c}{(x + D_c)^2} \geq \frac{Ch(x)}{(x + D_e + C)^2} \]

or, equivalently, by

\[ \frac{1}{C} \geq \frac{1}{x + D_e} \left( \frac{\delta_m D_e}{(x + D_e)^2} + \frac{k_5 (x^2 - D_e^2)}{(x + D_e)^2} \right) \tag{S10} \]

Hence, if \( k_5 + k_6 > \delta_m D_e \) and \( \frac{1}{C} < \max_{x \geq 0} l(x) \), then \( h' \) has two consecutive positive zeros, say \( 0 < x_1 < x_2 \). In this case, if \( k_4 \) lies between \( h(x_1) \) and \( h(x_2) \), then system (1)-(6) admits three positive steady states.

### Stability Analysis of system (1)-(6)

Finally, by evaluating the determinant of corresponding Jacobian matrix, we establish a sufficient condition on the instability for a given positive steady state of system (1)-(6). The Jacobian matrix \( J \) of system (1)-(6) evaluated at \( (R_m^*, R_e^*, R_c^*, R_{em}^*, R_{mc}^*, P^*) \) takes the form
\[
\begin{pmatrix}
-(k_1 R_e^* + k_2 R_c^* + \delta_m) & -k_1 R_m^* & -k_2 R_m^* & k_{m1} & k_{m2} & -k_4 K_4 \\
-k_1 R_e^* & -(k_1 R_m^* + \delta_e) & 0 & k_{m1} & 0 & 0 \\
-k_2 R_c^* & 0 & -(k_2 R_m^* + \delta_c) & 0 & k_{m2} & 0 \\
k_1 R_e^* & k_1 R_m^* & 0 & -(k_{m1} + \delta_{em}) & 0 & 0 \\
k_2 R_c^* & 0 & k_2 R_m^* & 0 & -(k_{m2} + \delta_{mc}) & 0 \\
0 & k_3 & 0 & 0 & 0 & -\delta_p
\end{pmatrix}
\]

With a direct computation, the determinant \(\det(J)\) of \(J\) takes

\[
\det(J) = \begin{vmatrix}
\delta_m & 0 & 0 & \delta_{em} & \delta_{mc} & k_4 K_4 \\
0 & \delta_e & 0 & \delta_{em} & 0 & 0 \\
0 & 0 & \delta_c & 0 & \delta_{mc} & 0 \\
-k_1 R_e^* & -k_1 R_m^* & 0 & k_{m1} + \delta_{em} & 0 & 0 \\
-k_2 R_c^* & 0 & -k_2 R_m^* & 0 & k_{m2} + \delta_{mc} & 0 \\
0 & -k_3 & 0 & 0 & 0 & \delta_p
\end{vmatrix} \frac{k_4 K_4}{(1 + K_4 P^*)^2}
\]

From Eqs.(S2)-(S5), we have \(k_5 = \delta_e R_e^* + \delta_{em} R_{em}^*\) and \(k_6 = \delta_c R_c^* + \delta_{mc} R_{mc}^*\). Together with relations (S4)-(S5), \(\det(J)\) is reduced to the form

\[
d \begin{vmatrix}
\delta_m & 0 & 0 & \delta_{em} R_{em}^* & \delta_{mc} R_{mc}^* & k_4 K_4 \\
0 & \delta_e R_e^* & 0 & \delta_{em} R_{em}^* & 0 & 0 \\
0 & 0 & \delta_c R_c^* & 0 & \delta_{mc} R_{mc}^* & 0 \\
1 & 1 & 0 & -1 & 0 & 0 \\
1 & 0 & 1 & 0 & -1 & 0 \\
0 & -k_3 R_c^* & 0 & 0 & 0 & \delta_p
\end{vmatrix} \frac{k_4 K_4}{(1 + K_4 P^*)^2}
\]

\[
d = \frac{k_1 k_2 R_m^*}{R_{em}^* R_{mc}^*} \begin{vmatrix}
\delta_m R_m^* & -\delta_e R_e^* & k_4 K_4 & k_3 R_c^* & 0 & 0 \\
\delta_{em} R_{em}^* & -\delta_e R_e^* & 0 & \delta_{em} R_{em}^* & 0 & 0 \\
\delta_{mc} R_{mc}^* & 0 & k_6 & 0 & \delta_{mc} R_{mc}^* & 0 \\
0 & 0 & 0 & -1 & 0 & 0 \\
0 & 0 & 0 & 0 & -1 & 0 \\
0 & 0 & 0 & 0 & 0 & \delta_p
\end{vmatrix} \frac{k_4 K_4}{(1 + K_4 P^*)^2}
\]

Recall that \(R_e^*, R_c^*, R_{em}^*, R_{mc}^*\) are expressed in terms of \(R_m^*\). Hence \(\det(J)\) can be reduced to the following form:
\[
\det(J) = \frac{\delta_p k_1 k_2 k_5 k_6 (R_m^*)^2}{R_{em} R_{mc}} \left( \delta_m + \frac{k_6 \delta_e A_c}{(R_m^* + \delta_e A_e)^2} + \frac{k_5 \delta_e A_e}{(R_m^* + \delta_e A_e)^2} - \frac{k_3 k_4 k_5 A_e}{\delta_p k_4} \right)
\]

Finally, using the relation \( k_4 = h(R_m^*) \) and (S9), we arrive at the identity

\[
\det(J) = \frac{\delta_p k_1 k_2 k_5 k_6 (R_m^*)^2}{R_{em} R_{mc}} \frac{R_m^* + D_e}{R_m^* + D_e + C} h'(R_m^*). 
\]

Hence, if \( h'(R_m^*) < 0 \) then the corresponding positive steady state is unstable. An immediate application of this result is that the steady states of the middle branch are always unstable.