Can multiple species of Malaria co-persist in a region? ——Dynamics of multiple malaria species

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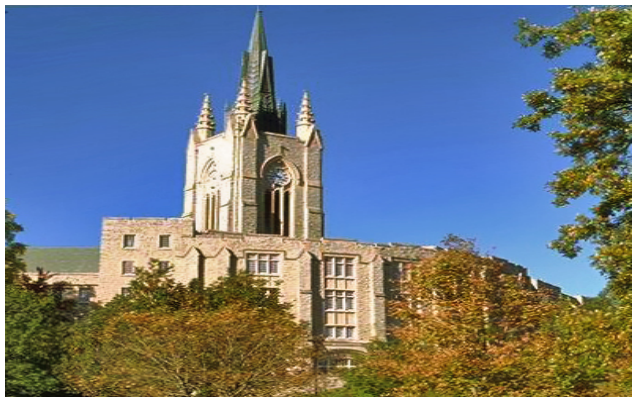

(Joint work with Yanyu Xiao)

Outline

Motivation

- Malaria remains a big problem and concern in many places in the world.
- There are more than 100 species of malaria parasites, currently endemic in differential regions. The major five are: *P. falciparum*, *P. vivax*, *P. ovale*, *P. malaria* and *P. knowles*.
- The world becomes highly connected (globaliztion), and travels between regions becomes more and more popular.
- More than one species have been reported in some places, e.g., Maitland and Willims (1997): no, one is supressing the other. McKenzie and Bossert (1997): yes, “claiming" that four have “established" in Madagascar and New Guinea.
- Natural question: would it possible for multiple malaria species to become endemic in a single region?

This work: seeking answer to this quesiton, using mathematical models.

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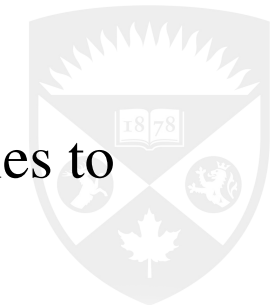

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A single strain model

Life cycle of malaria parasites inside human body

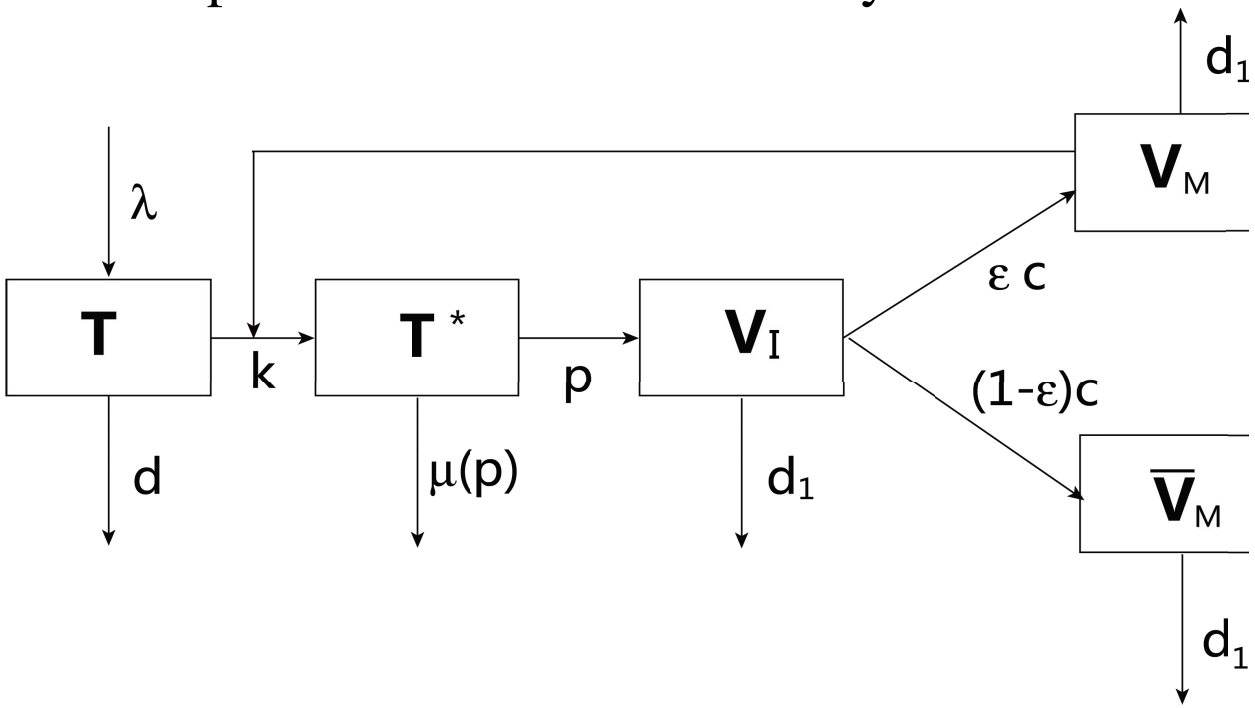


Figure: One-species case.

Translating the diagram into differential equations:

$$\begin{cases} \dot{T}(t) = \lambda - dT - kV_M T, \\ \dot{T}^*(t) = kV_M T - \mu(p)T^*, \\ \dot{V}_I(t) = pT^* - d_1 V_I - cV_I, \\ \dot{V}_M(t) = \epsilon_1 cV_I - d_1 V_M, \end{cases} \tag{1}$$

$$\dot{\bar{V}}_M(t) = (1-\epsilon_1)cV_I - d_1 \bar{V}_M.$$

Extending to two strains

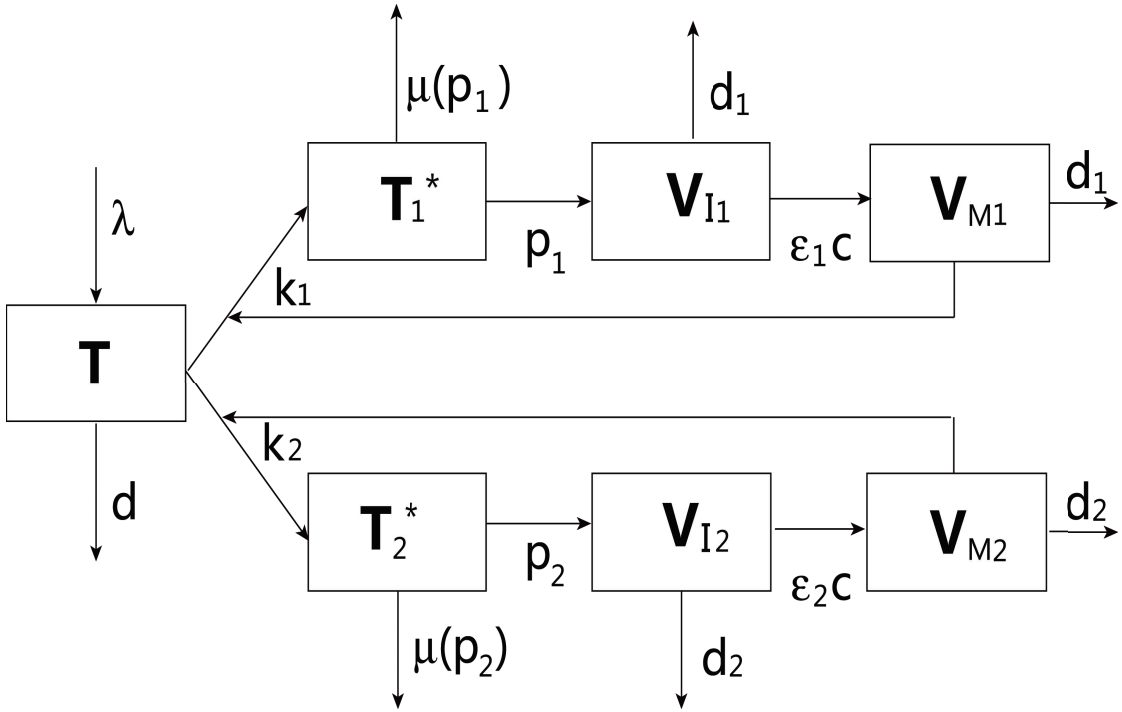


Figure: Two-species case.

Corresponding model system:

$$
\begin{cases}
\dot{T}(t) = \lambda - dT - k_1 V_{M1} T - k_2 V_{M2} T, \\
\dot{T}_1^*(t) = k_1 V_{M1} T - \mu(p_1) T_1^*, \\
\dot{T}_2^*(t) = k_2 V_{M2} T - \mu(p_2) T_2^*, \\
\dot{V}_{I1}(t) = p_1 T_1^* - d_1 V_{I1} - c_1 V_{I1}, \\
\dot{V}_{I2}(t) = p_2 T_2^* - d_2 V_{I2} - c_2 V_{I2}, \\
\dot{V}_{M1}(t) = \epsilon_1 c_1 V_{I1} - d_1 V_{M1}, \\
\dot{V}_{M2}(t) = \epsilon_2 c_2 V_{I2} - d_2 V_{M2}.
\end{cases} \tag{2}
$$

—A special case of the model studied in Iggidr et al (2006).

On (2):

The individual basic reproductive numbers:

$$\mathcal{R}_i = \frac{\lambda k_i \epsilon_i c_i p_i}{d d_i \mu(p_i)(d_i + c_i)}, \ i = 1, 2.$$

The overall basic reproduction number:

$$\mathcal{R}_0 = \max\{\mathcal{R}_1, \mathcal{R}_2\}$$

Theorem 2.1 (Iggidr et al (2006)) For (2), the following hold.

(i) If $\mathcal{R}_0 \leq 1$, then the infection free equilibrium (IFE) $E_0 = (\lambda/d, 0, 0, 0, 0, 0, 0,)$ is globally asymptotically stable in $\mathbb{R}^7_+$;

(ii) If $\mathcal{R}_0 > 1$, then E_0 becomes unstable. In this case, there are the following possibilities:

(ii)-1 If $\mathcal{R}_1 > 1$ and $\mathcal{R}_2 < 1$, then in addition to the IFE, there is the species 1 endemic equilibrium E_1, which is globally asymptotically stable in $\mathbb{R}^7_+ \setminus \{E_0\}$;

(ii)-2 If $\mathcal{R}_2 > 1$ and $\mathcal{R}_1 < 1$, then in addition to the IFE, there is the species 2 endemic equilibrium E_2, which is globally asymptotically stable in $\mathbb{R}^7_+ \setminus \{E_0\}$;

(ii)-3 If both $\mathcal{R}_1 > 1$ and $\mathcal{R}_2 > 1$, but $\mathcal{R}_1 > \mathcal{R}_2$, then in addition to the IFE, there are the species 1 endemic equilibrium E_1 and species 2 endemic equilibrium E_2; but E_2 is unstable and E_1 is globally asymptotically stable in $\mathbb{R}^7_+ \setminus \{E_0, E_2\}$;

(ii)-3 If both $\mathcal{R}_1 > 1$ and $\mathcal{R}_2 > 1$, but $\mathcal{R}_2 > \mathcal{R}_1$, then in addition to the IFE, there are the species 1 endemic equilibrium E_1 and species 2 endemic equilibrium E_2; but E_1 is unstable and E_2 is globally asymptotically stable in $\mathbb{R}^7_+ \setminus \{E_0, E_1\}$.

Conclusion at within host level:

- either both strains die out (when $\mathcal{R}_0 \leq 1$),
- or, competition exclusion generically holds (when $\mathcal{R}_0 > 1$), —"generic" in the sense of $\mathcal{R}_1 \neq \mathcal{R}_2$.

Suggesting ignoring the class of doublely infected individuals **in between host models.**

Between host level

A single species model of Ross-Macdonald type:

$$\begin{cases} S_H' = b_H N_H - d_H S_H - ac_1 \dfrac{S_H}{N_H} I_M + \beta R_H, \\ I_H' = ac_1 \dfrac{S_H}{N_H} I_M - d_H I_H - \gamma I_H, \\ R_H' = \gamma I_H - d_H R_H - \beta R_H, \\ S_M' = b_M N_M - d_M S_M - ac_2 S_M \dfrac{I_H}{N_H}, \\ I_M' = ac_2 S_M \dfrac{I_H}{N_H} - d_M I_M. \end{cases} \tag{3}$$

where, $N_H = S_H + I_H + R_H$ and $N_M = S_M + I_M$.

About the model parameters:

- b_H and b_M are the birth rates of humans and mosquitoes (for humans, 'birth' is in a general sense including other recruitments besides natural birth), and d_H and d_M are the death rates of humans and mosquitoes;
- a is the biting rate, c_1 is the probability that a bite by an infectious mosquito of a susceptible human being will cause infection, and c_2 is the probability that a bite by a susceptible mosquito of an infectious human being will cause infection;
- γ is the combined recover rate including the natural recovery and the recovery due to treatments;
- the temporary immunity of the recovered hosts follows a negative exponential distribution $e^{-\beta t}$, hence recovered hosts return to the susceptible class at rate β.

Some assumptions

It is known that malaria causes deaths to humans. Here, to make the model more mathematically tractable, we also assume that sufficient and effective treatments are available so that there will be no deaths caused by malaria.

We further assume that in the absence of the disease, recruitment and death for both human and mosquito populations are balanced so that the **total populations** of the host and the mosquito remain **constants**. This is achieved by assuming $b_H = d_H$ and $b_M = d_M$ in (3).

By rescaling to proportions, we only need to consider

$$\begin{cases} S_H' = d_H - d_H S_H - ac_1 m S_H I_M + \beta(1 - S_H - I_H), \\ I_H' = ac_1 m S_H I_M - d_H I_H - \gamma I_H, \\ I_M' = ac_2(1 - I_M) I_H - d_M I_M, \end{cases} \tag{4}$$

where $m = N_M/N_H$.

For this model, there is the disease free equilibrium: $E_0 = (1,\ 0,\ 0)$ and the basic reproduction number is

$$\mathcal{R}_0 = r(FV^{-1}) = \sqrt{\frac{a^2 c_1 c_2 m}{d_M(d_H + \gamma)}}. \tag{5}$$

Theorem 3.1 The disease free equilibrium E_0 is globally asymptotically stable if $\mathcal{R}_0 < 1$, and it is unstable when $\mathcal{R}_0 > 1$.

Proposition 3.1 Assume that $\mathcal{R}_0 > 1$. Then I_H and I_M are uniformly persistent in the sense that there exists an $\eta > 0$ such that for every solution of system (4) with $I_H(0) > 0$ and $I_M(0) > 0$,

$$\liminf_{t\to\infty} I_H(t) \geq \eta, \quad \liminf_{t\to\infty} I_M(t) \geq \eta.$$

When $\mathcal{R}_0 > 1$, there is a unique endemic equilibrium $E^* = (S_H^*, I_H^*, I_M^*)$ where

$$
\begin{aligned}
S_H^* &= \frac{N_H\left(d_H+\gamma\right)\left(d_M d_H + d_M\gamma + \beta d_M + d_H a e_{21} + \epsilon_1 a c_2\right)}{a c_2\left(a c_1 N_M d_H + a c_1 N_M \gamma + \beta N_H d_H + \beta N_H \gamma + {d_H}^2 N_H + d_H N_H \gamma + \beta a c_1 N_M\right)}, \\
I_H^* &= \frac{N_H d_M\left(d_H+\gamma_1\right)\left(d_H+\beta\right)\left(R_0-1\right)}{\left(a c_1 N_M d_H + a e_{11} N_M \gamma + \beta N_H d_H + \beta N_H \gamma + {d_H}^2 N_H + d_H N_H \gamma + \beta a c_1 N_M\right) c_2 a}, \\
I_M^* &= \frac{N_H d_M\left(d_H+\gamma_1\right)\left(d_H+\beta\right)\left(R_0-1\right)}{d_M d_H + d_M\gamma + \beta d_M + d_H a e_{21} + \beta a c_2}.
\end{aligned}
\tag{6}
$$

On stability of E^*

Let

$$\Gamma := \left\{x(t) = (S_H,\, I_H,\, I_M) \in \mathbb{R}^3_+ : S_H + I_H \leq 1, I_M \leq 1\right\}$$

and denote the interior of Γ by Γ_0.

Theorem 3.2 Assume that $R_0 > 1$. Then the unique endemic equilibrium E^* of system (4) is globally stable in Γ_0 provided that

$$d_H + d_M - \max\left(-\beta,\, \beta - \gamma\right) > 0. \tag{7}$$

Proof. Bendixon theorem based on **conpound matrix approach** developed by Li and Muldoney (1996).
Need to verify the **Bendixson criterion** $\bar{q} < 0$, which involves construction of related matrices, estimating **Lozinskii measure** of matrix—lengthy and extensive work (4 pages)

Remark 3.1 Relation (7) can be guaranteed by some more explicit condition. For example, each of the following is such a condition:

(C1) $\beta < \frac{r}{2}$;

(C2) $\frac{\gamma}{2} \leq \beta < d_H + d_M + \gamma$.

Extending to **two strain** case

$$
\begin{cases}
S'_H = d_H N_H - d_H S_H - ae_{11}\dfrac{S_H}{N_H} I_{M1} - ae_{12}\dfrac{S_H}{N_H} I_{M2} + \beta_1 R_{H1} + \beta_2 R_{H2}, \\
I'_{H1} = ae_{11}\dfrac{S_H}{N_H} I_{M1} - d_H I_{H1} - \gamma_1 I_{H1} + ae_1 \dfrac{R_{H2}}{N_H} I_{M1}, \\
R'_{H1} = \gamma_1 I_{H1} - ae_2 \dfrac{R_{H1}}{N_H} I_{M2} - d_H R_{H1} - \beta_1 R_{H1}, \\
I'_{H2} = ae_{12}\dfrac{S_H}{N_H} I_{M2} - d_H I_{H2} - \gamma_2 I_{H2} + ae_2 \dfrac{R_{H1}}{N_H} I_{M2}, \\
R'_{H2} = \gamma_2 I_{H2} - ae_1 \dfrac{R_{H2}}{N_H} I_{M1} - d_H R_{H2} - \beta_2 R_{H2}, \\
S'_M = d_M N_M - d_M S^*_M - ae_{21} S_M \dfrac{I_{H1}}{N_H} - ae_{22} S^*_M \dfrac{I_{H2}}{N_H}, \\
I'_{M1} = ae_{21} S_M \dfrac{I_{H1}}{N_H} - d_M I_{M1}, \\
I'_{M2} = ae_{22} S_M \dfrac{I_{H2}}{N_H} - d_M I_{M2}.
\end{cases}
\tag{8}
$$

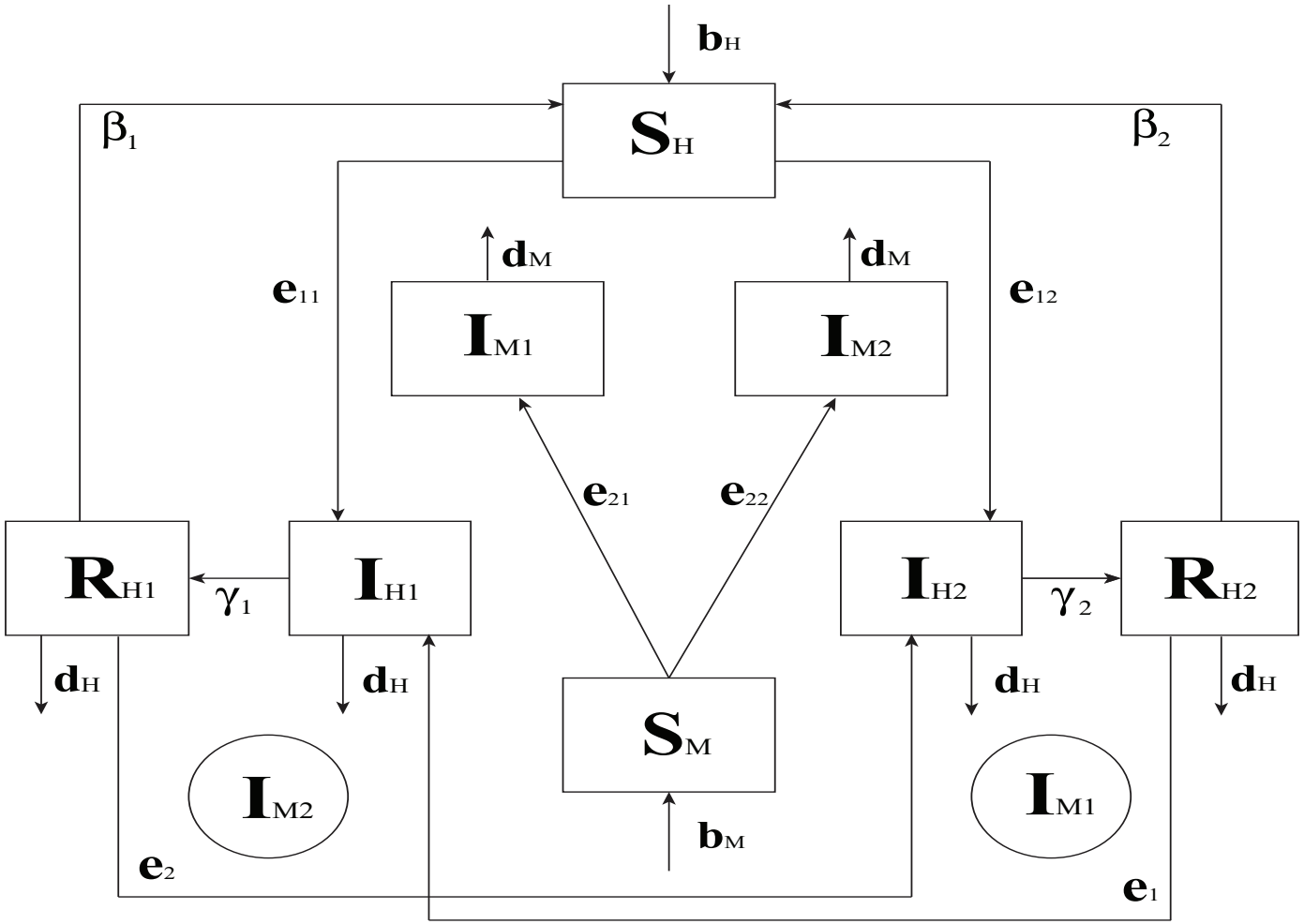


Figure: Two species case at population level

Rescaling

$$\frac{S_H}{N_H} \to S_H, \quad \frac{I_{Hi}}{N_H} \to I_{Hi}, \quad \frac{R_{Hi}}{N_H} \to R_{Hi}, \quad i = 1, 2,$$

and

$$\frac{S_M}{N_M} \to S_M, \quad \frac{I_{Mi}}{N_M} \to I_{Mi}, \quad i = 1, 2,$$

leads to

$$\begin{cases} S'_H = d_H - d_H S_H - ae_{11} m S_H I_{M1} - ae_{12} m S_H I_{M2} + \beta_1 R_{H1} + \beta_2 R_{H2}, \\ I'_{H1} = ae_{11} m S_H I_{M1} - d_H I_{H1} - \gamma_1 I_{H1} + ae_1 m R_{H2} I_{M1}, \\ R'_{H1} = \gamma_1 I_{H1} - ae_2 m R_{H1} I_{M2} - d_H R_{H1} - \beta_1 R_{H1}, \\ I'_{H2} = ae_{12} m S_H I_{M2} - d_H I_{H2} - \gamma_2 I_{H2} + ae_2 m R_{H1} I_{M2}, \\ R'_{H2} = \gamma_2 I_{H2} - ae_1 n R_{H2} I_{M1} - d_H R_{H2} - \beta_2 R_{H2}, \\ S'_M = d_M - d_M S_M - ae_{21} S_M I_{H1} - ae_{22} S_M I_{H2}, \\ I'_{M1} = ae_{21} S_M I_{H1} - d_M I_{M1}, \\ I'_{M2} = ae_{22} S_M I_{H2} - d_M I_{M2}, \end{cases} \tag{9}$$

where $m = N_M/N_H$. About e_{ij} and e_i ?

Both **competitive** and **cooperative** features are included in the model !

Only need to consider system (9) within the set

$$X = \left\{ \begin{array}{l} (S_H, I_{H1}, R_{H1}, I_{H2}, R_{H2}, S_M, I_{M1}, I_{M2}) \in \mathbb{R}^8 : \\ 0 \leq S_H, S_M I_{H1}, R_{H1}, I_{H2}, R_{H2}, I_{M1}, I_{M2} \leq 1, \\ S_H + I_{H1} + R_{H1} + I_{H2} + R_{H2} = 1,\ S_M + I_{M1} + I_{M1} = 1. \end{array} \right\},$$

which can be shown to be positively invariant.

Disease free equilibrium and basic reproduction number

The model (9) has a disease free equilibrium (DFE), given by $\bar{E}_0 = (1,0,0,0,0,1,0,0,)$.

In the absence of species j, the basic reproduction number for species i is

$$\bar{\mathcal{R}}_i = \sqrt{\frac{a^2 e_{1i} e_{2i} m}{d_M(d_H+\gamma_i)}},\ i = 1,2.$$

When $\bar{\mathcal{R}}_1 > 1$, there is a species 1 endemic equilibrium

$$\bar{E}_1^* = (S_{H1}^*, I_{H1}^*, R_{H1}^*, 0, 0, S_{M1}^*, I_{M1}^*, 0),$$

where S_{H1}^*, I_{H1}^*, S_M^* and I_{M1}^* are all positive constants and $R_{H1}^* = 1 - S_{H1}^* - I_{H1}^*$.

Simlarly, when $\bar{\mathcal{R}}_2 > 1$, there is a species 2 endemic equilibrium

$$\bar{E}_2^* = (S_{H2}^*, 0, 0, I_{H2}^*, R_{H2}^*, S_{M2}^*, 0, I_{M2}^*),$$

with $R_{H2}^* = 1 - S_{H2}^* - I_{H2}^*$.

In the linearization of model (9) at $\bar{E}_0$, the four equations for I'_{H1}, I'_{H2}, I'_{M1} and I'_{M2} are decoupled from the other four equations, forming the following sub-system:

$$\begin{cases} I'_{H1} = ae_{11}mI_{M1} - d_H I_{H1} - \gamma_1 I_{H1}, \\ I'_{M1} = ae_{21}I_{H1} - d_M I_{M1}, \\ I'_{H2} = ae_{12}mI_{M2} - d_H I_{H2} - \gamma_2 I_{H2}, \\ I'_{H1} = ae_{22}I_{H2} - d_M I_{M2}. \end{cases} \tag{10}$$

from which, we can obtain the following two matrices:

$$\bar{F} = \begin{pmatrix} 0 & ae_{11}m & 0 & 0 \\ ae_{21} & 0 & 0 & 0 \\ 0 & 0 & 0 & ae_{12}m \\ 0 & 0 & ae_{22} & 0 \end{pmatrix},$$

$$\bar{V} = \begin{pmatrix} (d_H + \gamma_1) & 0 & 0 & 0 \\ 0 & d_M & 0 & 0 \\ 0 & 0 & (d_H + \gamma_2) & 0 \\ 0 & 0 & & d_M \end{pmatrix}.$$

Thus, by the van den Driessche and Watmough (2002), the basic reproduction number is given by

$$\bar{\mathcal{R}}_0 = r(\bar{F}\bar{V}^{-1}) = \max\left\{\sqrt{\frac{a^2 e_{11} e_{21} m}{d_M(d_H+\gamma_1)}}, \sqrt{\frac{a^2 e_{12} e_{22} m}{d_M(d_H+\gamma_2)}}\right\} = \max\{\bar{\mathcal{R}}_1, \bar{\mathcal{R}}_2\} \tag{11}$$

and the following theorem.

Theorem 3.3 If $\bar{\mathcal{R}}_0 < 1$, then the disease free equilibrium is asymptotically stable. If $\bar{\mathcal{R}}_0 > 1$, it is unstable.

Global stability of *DFE* remains open.

Disease persistence

If $\bar{\mathcal{R}}_1 > 1$, then $\bar{E}_1^* = (S_{H1}^*, I_{H1}^*, R_{H1}^*, 0, 0, S_{M1}^*, I_{M1}^*, 0)$ exists. Define *the species 1 mediated basic reproduction number for species 2*:

$$\bar{\mathcal{R}}_{21} = \frac{a^2 e_{12} e_{22} m S_{H1}^* S_{M1}^* + a^2 e_{22} e_2 m S_{M1}^* R_{H1}^*}{d_M (d_H + \gamma_2)},$$

which measures the number of secondary infections by a species 2 individual, assuming that species 1 is settled at $\bar{E}_1^*$.

Symmetrically, if $\bar{\mathcal{R}}_2 > 1$, then $\bar{E}_2^* = (S_{H2}^*, 0, 0, I_{H2}^*, R_{H1}^*, S_{M2}^*, 0, I_{M2}^*)$ exists and we can define *the species 2 mediated basic reproduction number for species 1* by

$$\bar{\mathcal{R}}_{12} = \frac{a^2 e_{11} e_{21} m S_{H2}^* S_{M2}^* + a^2 e_{21} e_1 m S_{M2}^* R_{H2}^*}{d_M (d_H + \gamma_1)}.$$

Theorem 3.4 Assume that $\bar{\mathcal{R}}_0 > 1$.

(i) In the case $\bar{\mathcal{R}}_1 > 1$: if $\bar{\mathcal{R}}_{21} > 1$, then $\bar{E}_1^*$ is unstable; if $\bar{\mathcal{R}}_{21} < 1$, then $\bar{E}_1^*$ is asymptotically stable provided that

$$d_H + d_M - \max\left(-\beta_1,\ \beta_1 - \gamma_1\right) > 0. \tag{12}$$

(ii) In the case $\bar{\mathcal{R}}_2 > 1$: if $\bar{\mathcal{R}}_{12} > 1$, then $\bar{E}_2^*$ is unstable; if $\bar{\mathcal{R}}_{12} < 1$, then $\bar{E}_1^*$ is asymptotically stable provided that

$$d_H + d_M - \max\left(-\beta_2,\ \beta_2 - \gamma_2\right) > 0. \tag{13}$$

Proof: Similar to and making use of the proof of Theorem 3.2.

Theorem 3.5 Suppose $\bar{\mathcal{R}}_0 > 1$.

(i) If either (A1) $\bar{\mathcal{R}}_1 > 1$ and $\bar{\mathcal{R}}_2 < 1$; or (B1) $\bar{\mathcal{R}}_2 > 1$, $\bar{\mathcal{R}}_{12} > 1$ and condtion (13) holds, then I_{H1} and I_{M1} are uniformly persistent in the sense that there is a positive constant $\eta_1 > 0$ such that for every solution of system (9) with $I_{H1}(0) > 0$ and and $I_{M1}(0) > 0$, there hold

$$\liminf_{t\to\infty} I_{H1}(t) \geq \eta_1, \quad \liminf_{t\to\infty} I_{M1}(t) \geq \eta_1.$$

(ii) If either (A2) $\bar{\mathcal{R}}_2 > 1$ and $\bar{\mathcal{R}}_1 < 1$; or (B2) $\bar{\mathcal{R}}_1 > 1$, $\bar{\mathcal{R}}_{21} > 1$ and condition (12) holds, then I_{H2} and I_{M2} are uniformly persistent in the sense that there is a positive constant $\eta_2 > 0$ such that for every solution of system (9) with $I_{H2}(0) >$ and and $I_{M2}(0) > 0$, there hold

$$\liminf_{t\to\infty} I_{H2}(t) \geq \eta_2, \quad \liminf_{t\to\infty} I_{M2}(t) \geq \eta_2.$$

Proof. Persistence theory (e.g., Thieme (1993))

Theorem 3.6 Assume one of the following holds,

(i) $\bar{\mathcal{R}}_1 > 1,\ \bar{\mathcal{R}}_2 < 1,\ \bar{\mathcal{R}}_{21} > 1$ and condition (12) holds;

(ii) $\bar{\mathcal{R}}_2 > 1,\ \bar{\mathcal{R}}_1 < 1,\ \bar{\mathcal{R}}_{12} > 1$ and condition (13) holds; and

(iii) $\bar{\mathcal{R}}_1 > 1,\ \bar{\mathcal{R}}_2 > 1,\ \bar{\mathcal{R}}_{12} > 1,\ \bar{\mathcal{R}}_{21} > 1$ and conditions (12), (13) hold;

then both species are uniformly persistent in the sense that there is a positive constant $\bar{\eta}$, such that every solution $(S_H, I_{H1}, R_{H1}, I_{H2}, R_{H2}, S_M, I_{M1}, I_{M2})$ with initial condition in $\bar{X}_0$ satisfies,

$$\liminf_{t\to\infty} I_{Hi} \geq \eta, \quad \liminf_{t\to\infty} I_{Mi} \geq \eta, \quad i = 1, 2,$$

where $\bar{X}_0 = \{(S_H, I_{H1}, R_{H1}, I_{H2}, R_{H2}, S_M, I_{M1}, I_{M2}) | \, 0 < S_H,\ S_M \leq 1,\ 0 \leq R_{H1},\ R_{H2} < 1,\ 0 < I_{H1} < 1,\ 0 < I_{M1} < 1,\ 0 < I_{H2} < 1,\ 0 < I_{M2} < 1\}$.
Moreover, system ((9)) admits at least one positive equilibrium(co-existence equilibrium).

Proof. Unifor persistece part is by Theorem 3.5, existence of a positive equilibrium by Zhao (2005).

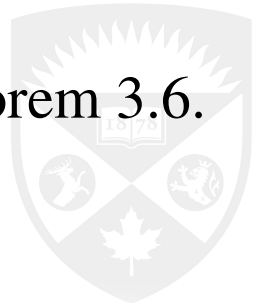
Stability of the positive equilibrium remains **open**.

Answer to the motivation question

Back to the question: **Can multiple species of Malaria co-persist in a region?**

Theorem 3.6 gives an answer: **Yes**, it is possible within certain range of parameters !

To prevent, effort should be made to avoid these conditions in Theorem 3.6.



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- NSERC, MITACS, PREA (Ontario)
- Thank You !

Acknowledgment

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