A multi-patch malaria model with demographic structure

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Outline

- §1 Brief Introduction to Malaria
- §2 Model Formulation
- §3 The Disease Free Equilibrium and The Basic Reproduction Number
- §4 The Effect of Human Movement
- §5 Future work

§1 Brief Introduction to Malaria

- Malaria is a parasitic vector-borne disease caused by the Plasmodium.
- It is transmitted to humans via the bites of infected female mosquitoes of the genus Anopheles.

Symptoms of Malaria

- People with malaria often experience fever, chills, and flu-like illness.
- If not treated promptly and effectively, they may develop severe complications and die.

Facts on Malaria

- 3.3 billion people live in areas at risk of malaria transmission in 109 countries and territories.
- WHO estimates that in 2008 there were 247 million malaria cases and nearly one million deaths – mostly among children in Africa.
- Malaria is the 2nd leading cause of death from infectious diseases in Africa, after HIV/AIDS.

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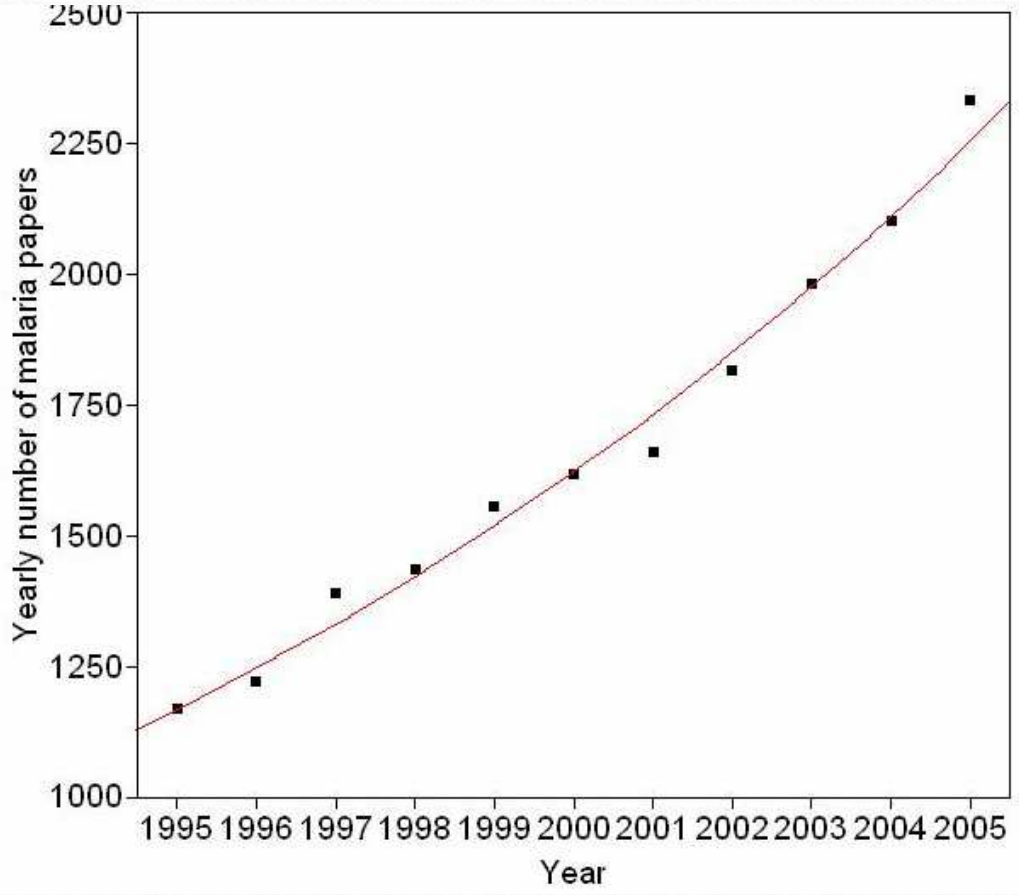
§2 Model Formulation

The mathematical modeling of malaria transmission has a long history and the literature is vast.

- Ross, 1911;
- Macdonald, 1952, 1956, 1957;
- Dietz, 1974;
- Nedelman, 1985;
- Koella, 1991;

- Gupta et al, 1994;
- Feng et al, 2004;
- Ngwa, 2004, 2006;
- Chitnis et al, 2006, 2008;
- Ruan et al, 2008;
- Auger et al, 2008;
- Cosner et al, 2009.
- Lou and Zhao, 2010
- And so on…

Growth of the yearly number of malaria publications
Doubling time: 10 years and 7 months



Motivation

- Malaria varies greatly in different locations in the level of intensity, in the vectors that transmit it and in the species causing the disease.
- It can be easily transmitted from one region to other regions due to extensive travel and migration.
- On average, 1500 cases of malaria are reported every year in the United States, even though malaria has been eradicated in this country since the early 1950's.

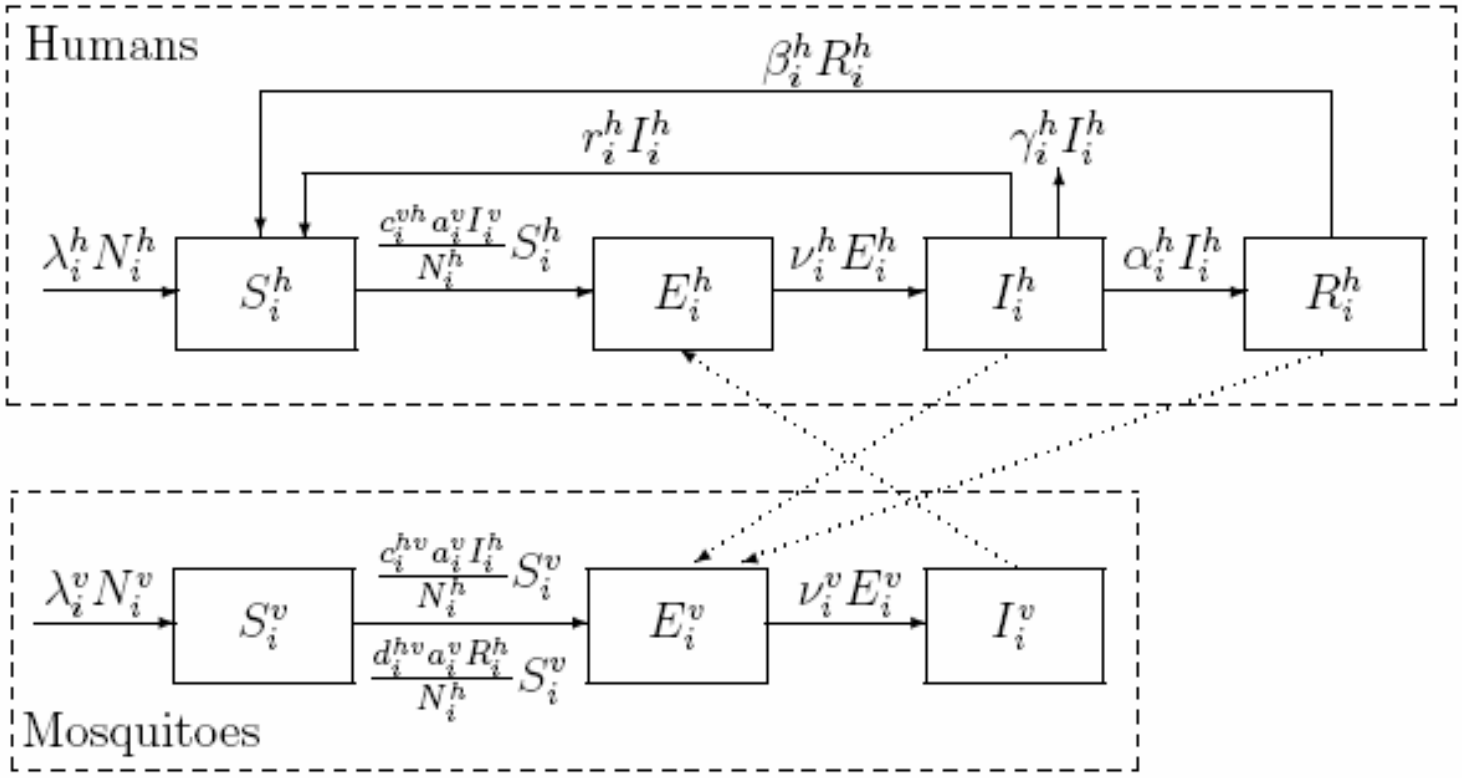
Multi-patch malaria model

- In 2000, Ngwa and Shu proposed an ODE compartmental model for the transmission of malaria involving **variable human and mosquito populations**.
- A threshold parameter $\mathfrak{R}_0$ is established and the disease can persist if and only if $\mathfrak{R}_0 > 1$. The disease-free equilibrium always exists and is globally stable when $\mathfrak{R}_0$ is below 1.
- We generalize Ngwa and Shu's model to n-patch to describe the dynamics of disease spread among patches due to population dispersal.

Epidemiological Classes

- Let $S_i^h(t), E_i^h(t), I_i^h(t)$ and $R_i^h(t)$ denote respectively the number of susceptible, exposed, infectious and recovered humans in patch i at time t.
- The total human population in patch i at time t is $N_i^h(t) = S_i^h(t) + E_i^h(t) + I_i^h(t) + R_i^h(t)$.
- Let $S_i^v(t), E_i^v(t)$ and $I_i^v(t)$ denote respectively the number of susceptible, exposed and infectious mosquitoes in patch i at time t.
- The total mosquito population in patch i at time t is $N_i^v(t) = S_i^v(t) + E_i^v(t) + I_i^v(t)$.

Flow diagram of the mosquito-borne model in patch i



Model Equations

$$\frac{dS_i^h}{dt} = \lambda_i^h N_i^h + \beta_i^h R_i^h + r_i^h I_i^h - \frac{c_i^{vh} a_i^v I_i^v}{N_i^h} S_i^h - f_i^h(N_i^h) S_i^h + \sum_{j=1}^{n} \varphi_{ij}^S S_j^h$$

$$\frac{dE_i^h}{dt} = \frac{c_i^{vh} a_i^v I_i^v}{N_i^h} S_i^h - [\nu_i^h + f_i^h(N_i^h)] E_i^h + \sum_{j=1}^{n} \varphi_{ij}^E E_j^h$$

$$\frac{dI_i^h}{dt} = \nu_i^h E_i^h - [r_i^h + \alpha_i^h + \gamma_i^h + f_i^h(N_i^h)] I_i^h + \sum_{j=1}^{n} \varphi_{ij}^I I_j^h$$

$$\frac{dR_i^h}{dt} = \alpha_i^h I_i^h - [\beta_i^h + f_i^h(N_i^h)] R_i^h + \sum_{j=1}^{n} \varphi_{ij}^R R_j^h \quad \square 2.1$$

$$\frac{dS_i^v}{dt} = \lambda_i^v N_i^v - \frac{c_i^{hv} a_i^v I_i^h}{N_i^h} S_i^v - \frac{d_i^{hv} a_i^v R_i^h}{N_i^h} S_i^v - f_i^v(N_i^v) S_i^v + \sum_{j=1}^{n} \psi_{ij}^S S_j^v$$

$$\frac{dE_i^v}{dt} = \frac{c_i^{hv} a_i^v I_i^h}{N_i^h} S_i^v + \frac{d_i^{hv} a_i^v R_i^h}{N_i^h} S_i^v - [\nu_i^v + f_i^v(N_i^v)] E_i^v + \sum_{j=1}^{n} \psi_{ij}^E E_j^v$$

$$\frac{dI_i^v}{dt} = \nu_i^v E_i^v - f_i^v(N_i^v) I_i^v + \sum_{j=1}^{n} \psi_{ij}^I I_j^v$$

Parameters

$f_i^h(N_i^h) = \mu_i^h + \rho_i^h N_i^h$ is the density-dependent death rate for humans;
$f_i^v(N_i^v) = \mu_i^v + \rho_i^v N_i^v$ is the density-dependent death rate for mosquitoes;
λ_i^h is the birth rate of humans;
λ_i^v is the birth rate of mosquitoes;
a_i^v is the number of bites given to humans by each mosquito per unit time;
c_i^{vh} is the probability that a bite by an infectious mosquito on a susceptible human will transfer the infection to the human;
c_i^{hv} is the probability that a bite by a susceptible mosquito on an infectious human will transfer the infection to the mosquito;
d_i^{hv} is the probability that a bite by a susceptible mosquito on a recovered human will transfer the infection to the mosquito;
ν_i^h is the progression rate of humans from the exposed state to the infectious state;
ν_i^v is the progression rate of mosquitoes from the exposed state to the infectious state;
r_i^h is the recovery rate for humans from the infectious state to the susceptible state;
α_i^h is the recovery rate for humans from the infectious state to the recovered state;
γ_i^h is the disease-induced death rate for humans;
β_i^h is the rate of loss of immunity for humans;

Continued

$\varphi_{ij}^K \geq 0$ for $K = S, E, I, R$ is the immigration rate from patch j to patch i for $i \neq j$ of susceptible, exposed, infectious, and recovered humans, respectively;

$\psi_{ij}^L \geq 0$ for $L = S, E, I$ is the immigration rate from patch j to patch i for $i \neq j$ of susceptible, exposed, and infectious mosquitoes, respectively;

$\varphi_{ii}^K \leq 0$ for $K = S, E, I, R$ is the emigration rate of susceptible, exposed, infectious, and recovered humans in patch i, respectively;

$\psi_{ii}^L \leq 0$ for $L = S, E, I$, is the emigration rate of susceptible, exposed, and infectious mosquitoes in patch i, respectively.

Assumption on Parameters

- Assume that individuals do not change their disease state during travel. Thus, we have

$$\sum_{j=1}^{n} \varphi_{ji}^{K} = 0, K = S, E, I, R, \text{ and } \sum_{j=1}^{n} \psi_{ji}^{L} = 0, L = S, E, I, 1 \le i \le n.$$

- The travel rates matrices (φ_{ij}^{K}) for $K = S, E, I, R$ and (ψ_{ij}^{L}) for $L = S, E, I$ are assumed irreducible.
- Let $s(((\lambda_i^h - \mu_i^h)\delta_{\mathrm{ij}} + \varphi_{ij}^{\mathrm{S}})_{\mathrm{n\times n}}) > 0$ and $s(((\lambda_i^v - \mu_i^v)\delta_{\mathrm{ij}} + \psi_{ij}^{\mathrm{S}})_{\mathrm{n\times n}}) > 0$
- Unless otherwise indicated, it is assumed that all parameters are strictly positive with the exception of the travel rates matrices.

Well-Posedness

Let $N_i^h(t) = \sum_{i=1}^{n} N_i^h(t)$ and $N_i^v(t) = \sum_{i=1}^{n} N_i^v(t)$. Then the following theorem demonstrates that the model (2.1) is epidemiologically well-posed.

Theorem 2.1. Consider model (2.1) with non-negative initial conditions satisfying $N_i^h(0) > 0$ and $N_i^v(0) > 0$ for $i = 1, \cdots, n$. Then the system has a unique solution and all variables remain non-negative for all time $t \geq 0$. Moreover, the total human population $N^h(t)$ and the total mosquito population $N^v(t)$ both are bounded.

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The Disease Free Equilibrium (DFE)

- There is a DFE if and only if the subsystems

$$\frac{dS_i^h}{dt} = \lambda_i^h S_i^h - f_i^h(S_i^h)S_i^h + \sum_{j=1}^{n} \varphi_{ij}^S S_j^h, 1 \le i \le n \quad \square 3.1$$

and

$$\frac{dS_i^v}{dt} = \lambda_i^v S_i^v - f_i^v(S_i^v)S_i^v + \sum_{j=1}^{n} \psi_{ij}^S S_j^v, 1 \le i \le n, \quad \square 3.2$$

have positive equilibria, denoted by

$$S^{h*} = (S_1^{h*}, S_2^{h*}, \ldots, S_n^{h*}) \text{ and } S^{v*} = (S_1^{v*}, S_2^{v*}, \ldots, S_n^{v*}),$$

respectively.

Existence and Uniqueness of DFE

Lemma 3.1. *For system* (3.1), *there is a unique nonzero equilibrium* S^{h*}. $S^{h*} \in Int\mathbb{R}^n_+$ *and it is globally asymptotically stable with respect to* $\mathbb{R}^n_+ \backslash \{0\}$. *Moreover, if* $\lambda^h_i > \mu^h_i$ *for* $1 \leq i \leq n$, *we have*

$$P^h \equiv \min\{\frac{K^h_1}{L^h_1}, \ldots, \frac{K^h_{n-1}}{L^h_{n-1}}, K^h_n\} \cdot L^h \leq S^{h*} \leq Q^h \equiv \max\{\frac{K^h_1}{L^h_1}, \ldots, \frac{K^h_{n-1}}{L^h_{n-1}}, K^h_n\} \cdot L^h$$

where $K^h_i = \frac{\lambda^h_i - \mu^h_i}{\rho^h_i}$ *for* $1 \leq i \leq n$, *and* $L^h = (L^h_1, \ldots, L^h_{n-1}, 1)$ *is the unique solution to*

$$\sum_{j=1}^{n} \varphi^S_{ij} S^h_j = 0, S^h_n = 1.$$

with $L^h_i > 0$ *for* $1 \leq i \leq n-1$. *Similar result holds for system* (3.2).

The Basic Reproduction Number

To derive the basic reproduction number $\mathfrak{R}_0$ for (2.1), we order the infected variables by species, then by patch, i.e.,

$$E_1^h, E_2^h, \ldots, E_n^h, E_1^v, E_2^v, \ldots, E_n^v, I_1^h, I_2^h, \ldots, I_n^h, I_1^v, I_2^v, \ldots, I_n^v, R_1^h, R_2^h, \ldots, R_n^h$$

and make use of the methods from van den Driessche and Watmough to obtain

$$F = \begin{pmatrix} 0 & 0 & 0 & A_{64} & 0 \\ 0 & 0 & A_{73} & 0 & A_{75} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix} \text{ and } V = \begin{pmatrix} A_{11} & & & & \\ 0 & A_{22} & & & \\ -A_{31} & 0 & A_{33} & & \\ 0 & -A_{42} & 0 & A_{44} & \\ 0 & 0 & -A_{53} & 0 & A_{55} \end{pmatrix}$$

Let δ_{ij} be the Kronecker delta (i.e., 1 when $i = j$ and 0 otherwise). Then

$$A_{11} = (\delta_{ij}(\nu_i^h + f_i^h(S_i^{h*})) - \varphi_{ij}^E)_{n\times n},$$

$$A_{22} = (\delta_{ij}(\nu_i^v + f_i^v(S_i^{v*})) - \psi_{ij}^E)_{n\times n},$$

$$A_{31} = (\delta_{ij}\nu_i^h)_{n\times n} = diag\{\nu_1^h, \nu_2^h, \ldots, \nu_n^h\},$$

$$A_{33} = (\delta_{ij}(r_i^h + \alpha_i^h + \gamma_i^h + f_i^h(S_i^{h*})) - \varphi_{ij}^I)_{n\times n},$$

$$A_{42} = (\delta_{ij}\nu_i^v)_{n\times n} = diag\{\nu_1^v, \nu_2^v, \ldots, \nu_n^v\},$$

$$A_{44} = (\delta_{ij} f_i^v(S_i^{v*}) - \psi_{ij}^I)_{n\times n},$$

$$A_{53} = (\delta_{ij}\alpha_i^h)_{n\times n} = diag\{\alpha_1^h, \alpha_2^h, \ldots, \alpha_n^h\},$$

$$A_{55} = (\delta_{ij}(\beta_i^h + f_i^h(S_i^{h*})) - \varphi_{ij}^R)_{n\times n},$$

$$A_{64} = (\delta_{ij}c_i^{vh}a_i^v)_{n\times n} = diag\{c_1^{vh}a_1^v, c_2^{vh}a_2^v, \ldots, c_n^{vh}a_n^v\},$$

$$A_{73} = (\delta_{ij}c_i^{hv}a_i^v S_i^{v*} / S_i^{h*})_{n\times n},$$

$$A_{73} = (\delta_{ij}d_i^{hv}a_i^v S_i^{v*} / S_i^{h*})_{n\times n}.$$

The inverse of V exists and equals

$$V^{-1} = \begin{pmatrix} A_{11}^{-1} & & & & \\ 0 & A_{22}^{-1} & & & \\ A_{33}^{-1}A_{31}A_{11}^{-1} & 0 & A_{33}^{-1} & & \\ 0 & A_{44}^{-1}A_{42}A_{22}^{-1} & 0 & A_{44}^{-1} & \\ A_{55}^{-1}A_{53}A_{33}^{-1}A_{31}A_{11}^{-1} & 0 & A_{55}^{-1}A_{53}A_{33}^{-1} & 0 & A_{55}^{-1} \end{pmatrix}.$$

Thus, the next generation matrix is

$$FV^{-1} = \begin{pmatrix} 0 & M^{vh} & 0 & A_{64}A_{44}^{-1} & 0 \\ M^{hv} & 0 & (A_{73} + A_{75}A_{55}^{-1}A_{53})A_{33}^{-1} & 0 & A_{75}A_{55}^{-1} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

where $M^{vh} = A_{64}A_{44}^{-1}A_{42}A_{22}^{-1}$ and $M^{hv} = (A_{73} + A_{75}A_{55}^{-1}A_{53})A_{33}^{-1}A_{31}A_{11}^{-1}$.

Calculating $\Re_0$

We find $\Re_0^2 = \rho(W)$ where ρ denotes the spectral radius and

$$W = M^{vh} M^{hv} = A_{64} A_{44}^{-1} A_{42} A_{22}^{-1} (A_{73} + A_{75} A_{55}^{-1} A_{53}) A_{33}^{-1} A_{31} A_{11}^{-1}$$

Theorem 3.1. The disease free equilibrium of (2.1) is locally asymptotically stable if $\Re_0 < 1$ and unstable if $\Re_0 > 1$.

Estimation of $\mathfrak{R}_0$

Theorem 3.2. $\max\limits_{1\le i\le n}(\tilde{\mathcal{R}}_0^{(i)})^2 \le \mathcal{R}_0^2 \le \max\limits_{1\le i\le n}(\hat{\mathcal{R}}_{01}^{(i)})^2 + \max\limits_{1\le i\le n}(\hat{\mathcal{R}}_{02}^{(i)})^2$, *where*

$$
\begin{aligned}
(\tilde{\mathcal{R}}_0^{(i)})^2 =& c_i^{vh}a_i^v(\mu_i^v+\rho_i^v S_i^{v*}-\psi_{ii}^I)^{-1}\nu_i^v(\nu_i^v+\mu_i^v+\rho_i^v S_i^{v*}-\psi_{ii}^E)^{-1}\cdot\\
&[\frac{c_i^{hv}a_i^v S_i^{v*}}{S_i^{h*}}+\frac{d_i^{hv}a_i^v S_i^{v*}}{S_i^{h*}}(\beta_i^h+\mu_i^h+\rho_i^h S_i^{h*}-\varphi_{ii}^R)^{-1}\alpha_i^h]\cdot\\
&(r_i^h+\alpha_i^h+\gamma_i^h+\mu_i^h+\rho_i^h S_i^{h*}-\varphi_{ii}^I)^{-1}\nu_i^h(\nu_i^h+\mu_i^h+\rho_i^h S_i^{h*}-\varphi_{ii}^E)^{-1},
\end{aligned}
$$

and

$$
\begin{aligned}
(\hat{\mathcal{R}}_{01}^{(i)})^2 =& c_i^{vh}a_i^v(\mu_i^v+\rho_i^v S_i^{v*})^{-1}\nu_i^v(\nu_i^v+\mu_i^v+\rho_i^v S_i^{v*})^{-1}\frac{c_i^{hv}a_i^v S_i^{v*}}{S_i^{h*}}\cdot\\
&(r_i^h+\alpha_i^h+\gamma_i^h+\mu_i^h+\rho_i^h S_i^{h*})^{-1}\nu_i^h(\nu_i^h+\mu_i^h+\rho_i^h S_i^{h*})^{-1},\\
(\hat{\mathcal{R}}_{02}^{(i)})^2 =& c_i^{vh}a_i^v(\mu_i^v+\rho_i^v S_i^{v*})^{-1}\nu_i^v(\nu_i^v+\mu_i^v+\rho_i^v S_i^{v*})^{-1}\frac{d_i^{hv}a_i^v S_i^{v*}}{S_i^{h*}}(\beta_i^h+\mu_i^h+\rho_i^h S_i^{h*})^{-1}\cdot\\
&\alpha_i^h(r_i^h+\alpha_i^h+\gamma_i^h+\mu_i^h+\rho_i^h S_i^{h*})^{-1}\nu_i^h(\nu_i^h+\mu_i^h+\rho_i^h S_i^{h*})^{-1}.
\end{aligned}
$$

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§4 The Effect of Human Movement

- **Question**: does $\Re_0$ depend on travel rate in a monotone way? How?
- We study the dependence of $\Re_0$ on **infected human movement** for the two-patch case.
- Recall that $\Re_0^2 = \rho(W)$ where ρ denotes the spectral radius and

$$W = M^{vh} M^{hv} = A_{64} A_{44}^{-1} A_{42} A_{22}^{-1} (A_{73} + A_{75} A_{55}^{-1} A_{53}) A_{33}^{-1} A_{31} A_{11}^{-1}$$

- Note that $A_{ii}^{-1}, i = 1, \cdots, 5$ is a positive matrix with positive determinant, so is W.

Dependence on residence and disease status

- First, we consider the case when the human travel rate from one patch to the other depends on both residence and disease status.

Proposition 4.1. Let $A = \begin{pmatrix} e & f \\ g & h \end{pmatrix} \begin{pmatrix} a_1 + k_1 & -k_2 \\ -k_1 & a_2 + k_2 \end{pmatrix}^{-1}$, where all involving parameters are positive and $eh > fg$. Then $\rho(A)$ is decreasing in k_1 if $(e+g)/a_1 > (f+h)/a_2$ and increasing otherwise.

Remark 4.1. It is still true if $e, h, a_1, a_2 > 0$, $f, g, k_1, k_2 \geq 0$, $eh > fg$ and $hk_2 + f(a_2 + k_2) > 0$ (this is equivalent to $k_2 > 0$ or $f > 0$ which implies that there is also non-susceptible human migration from patch 2 to patch 1). Epidemiologically, this means that the disease becomes less prevalent if more infected people migrate from high transmission area to low transmission area.

- The following result assumes that the travel rates depend on disease status but symmetric between patches (i.e., the travel rates matrices are symmetric).

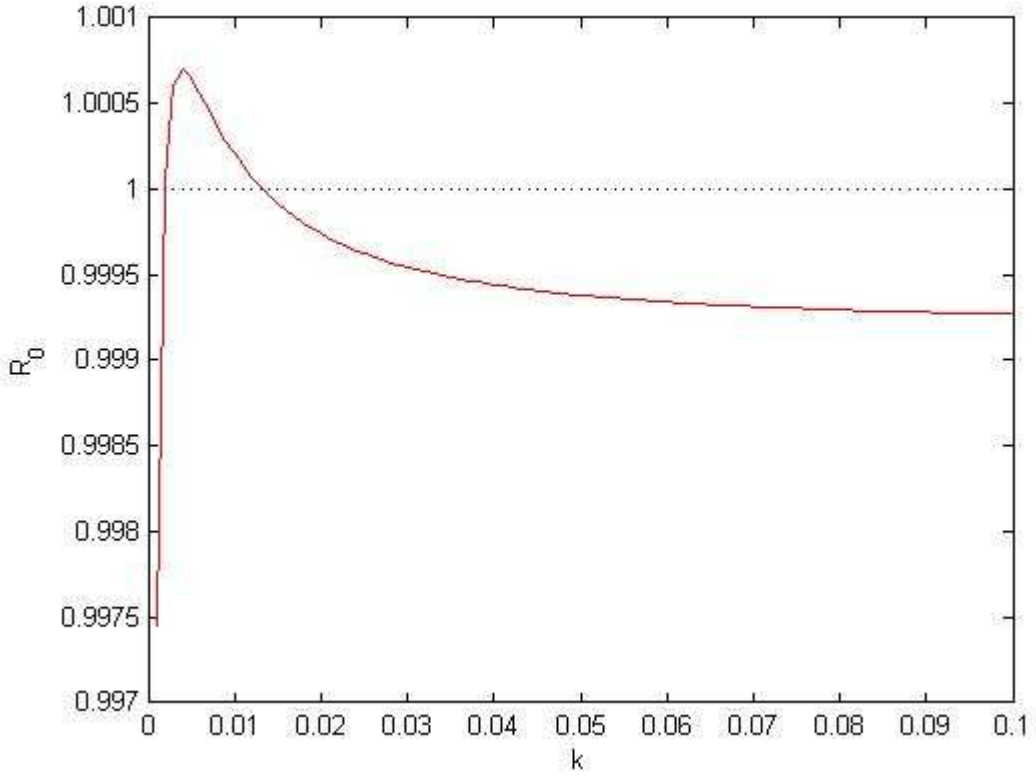
Proposition 4.2. Let $A = \begin{pmatrix} e & f \\ g & h \end{pmatrix} \begin{pmatrix} a_1 + k & -k \\ -k & a_2 + k \end{pmatrix}^{-1}$, where all involving parameters are positive and $eh > fg$. Then $\rho(A)$ is decreasing in k if $(e+g)/a_1 > (f+h)/a_2$ and $(e+f)/a_1 > (g+h)/a_2$, or, $(e+g)/a_1 < (f+h)/a_2$ and $(e+f)/a_1 < (g+h)/a_2$; and increasing otherwise.

- It is still true if $e, h, a_1, a_2 > 0, f, g, k \geq 0$ and $eh > fg$

Epidemiologically, this means that the trend of prevalence depends on a double-side effect, but mainly relies on itself. In particular, when $f = g = 0$, then it is always non-increasing in k.

- The above two propositions do not work for the movement of recovered human R_i^h which is more complicated.
- When the travel rate is independent of location and disease state, the dependence of $\mathcal{R}_0$ on the travel rate becomes very complicated and non-monotone phenomena may occur.

Independent of location and residence



$$\Re_0^{(1)} = 0.9602$$

$$\nu_1^h = 0.1, \mu_1^h = 8.8*10\text{^}(-6), \rho_1^h = 2.0*10\text{^}(-7),$$

$$\nu_1^v = 0.083, \mu_1^v = 0.033, \rho_1^v = 4.0*10\text{^}(-5),$$

$$r_1^h = 3.6*10\text{^}(-3), \alpha_1^h = 0.0035, \gamma_1^h = 1.8*10\text{^}(-5),$$

$$\beta_1^h = 2.7*10\text{^}(-3), c_1^{vh} = 0.119, a_1^v = 0.14,$$

$$c_1^{hv} = 0.08, d_1^{hv} = 0.008, \lambda_1^h = 5.5*10\text{^}(-5), \lambda_1^v = 0.13$$

$$\Re_0^{(2)} = 0.9492$$

$$\nu_2^h = 0.1, \mu_2^h = 8.8*10\text{^}(-6), \rho_2^h = 2.0*10\text{^}(-7),$$

$$\nu_2^v = 0.083, \mu_2^v = 0.033, \rho_2^v = 4.0*10\text{^}(-5),$$

$$r_2^h = 3.6*10\text{^}(-3), \alpha_2^h = 0.0035, \gamma_2^h = 1.8*10\text{^}(-5),$$

$$\beta_2^h = 2.7*10\text{^}(-3), c_2^{vh} = 0.0119, a_2^v = 0.14,$$

$$c_2^{hv} = 0.50, d_2^{hv} = 0.30, \lambda_2^h = 5.5*10\text{^}(-5), \lambda_2^v = 0.13$$

$$\psi_{12}^S = \psi_{21}^S = \psi_{12}^E = \psi_{21}^E = \psi_{12}^I = \psi_{21}^I = 0.002$$

$$\varphi_{12}^S = \varphi_{21}^S = 0.1, \varphi_{12}^E = \varphi_{21}^E = \varphi_{12}^I = \varphi_{21}^I = \varphi_{12}^R = \varphi_{21}^R = k$$

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§5 Future work

1. Existence and stability of endemic equilibria.
2. Bifurcation analysis with respect to $\mathcal{R}_0$.
3. Sensitivity analysis with real data.
4. The dependence of $\mathcal{R}_0$ on travel rates.

Thank you!