Measuring Malaria in Complex Transmission Systems

A Time-at-Risk-Based Approach

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1 Background

1.1 Ross-Macdonald Equations

The Ross-Macdonald equations describe malaria transmission through both human and mosquito populations. They take the following form:

$$\frac{dX}{dt} = abe^{-gn}\frac{Y}{H}(H - X) - rX \tag{1}$$

$$\frac{dY}{dt} = ac\frac{X}{H}(V - Y) - gY \tag{2}$$

Equation 1 describes the dynamics of infected humans, while Equation 2 describes the dynamics of infected mosquitoes. The variables of interest are X and Y, which represent the number of infected humans and mosquitoes, respectively. The rest of the parameters are intrinsic to the system under study:

Parameter	*Meaning*
b	Proportion of bites by infectious mosquitoes that cause an infection
r	Rate that humans recover from an infection
c	Proportion of mosquitoes infected after biting infectious human
n	Time for sporogonic cycle
a	Human blood feeding rate
g	Per capita death rate of mosquitoes
V	Vector population
H	Human population

Note that, in Equation 1, an assumption is made about the equilibrium number of infectious mosquitoes Z:

$$Z = e^{-gn}Y$$

1.2 Forest Malaria

A unique malaria transmission landscape is present in the case of forest malaria, which is a problem in countries such as those that make up the Greater Mekong Subregion: Cambodia, Laos, Vietnam, Thailand, Myanmar, and China. In these areas, people live in villages that surround a forest and frequently travel into the forest for various activities, where they contract malaria and proceed to carry it back to the village. This landscape is especially unique because it involves multiple transmission levels, one for each village and one for the forest; therefore, interventions that aim to eliminate malaria transmission must account for their effect on all of the transmission levels in the system.

1.3 Time-at-Risk

When considering multiple villages and/or forests, a key parameter to consider is travel between these areas. For this analysis, we assume that each human lives in a village and spends some proportion of their time in forests and/or other villages. These proportions are represented by $\mathbf{\Psi}$, the Time-at-Risk (TaR) matrix. The TaR matrix is square and takes the following form:

$$\mathbf{\Psi} = \begin{bmatrix} p_{11} & p_{12} & \cdots & p_{1n} \\ p_{21} & p_{22} & \cdots & p_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ p_{n1} & p_{n2} & \cdots & p_{nn} \end{bmatrix}$$

where n is the total number of locations (villages and forests) and p_{ij} is the proportion of time that a person from location i spends in location j. Note that the proportions in each row must sum to one:

$$\sum_{j=1}^{n} p_{ij} = 1 \quad \text{for } i \in [1, n]$$

2 Objective

The goal of this analysis is to determine how reproductive numbers affect malaria transmission in complex systems with multiple interconnected locations. This unique transmission environment presents challenges to successful interventions, which must take into account these specific features. For instance, deploying insecticide-treated bednets (ITNs) in all the villages may reduce their transmission levels below the endemic level; however, if the transmission in the forest remains high enough, forest-goers may still bring enough malaria back to the villages to sustain transmission there.

3 Simplification of Ross-Macdonald Equations

3.1 Equilibrium Assumptions

By assuming equilibrium populations of mosquitoes and humans, it is possible to reduce the system to one equation describing the number of infected humans.

Start by assuming equilibrium mosquito population:

$$\frac{dY}{dt} = 0 = ac\frac{X}{H}(V - Y) - gY$$

Then solve for Y:

$$Y = \frac{acVX}{Hg + acX}$$

Next, plug the equilibrium Y value into the equation for human population at equilibrium:

$$\frac{dX}{dt} = 0 = abe^{-gn} \cdot \frac{1}{H} \cdot \frac{acVX}{Hg + acX}(H - X) - rX \tag{3}$$

3.2 Simplified Parameters

Since most of the parameters in the Ross-Macdonald equations do not vary with time, it can be useful to combine them into one parameter. This reduces the dimensions of the equations, and

can be accomplished by rearranging Equation 3.

First, group together constant parameters, divide everything by r, and multiply the first term by $\frac{1}{g}/\frac{1}{g}$:

$$0 = \frac{Va^2bce^{-gn}}{Hgr} \cdot \frac{X}{H + \frac{a}{g}cX}(H - X) - X \tag{4}$$

3.2.1 Stability Index

The first simplified parameter is the *stability index*, which is defined as

$$S = \frac{a}{g}$$

The stability index can be interpreted as the number of human bites per mosquito over its lifetime.

3.2.2 Reproductive Rate

The next parameter is the reproductive rate:

$$R_0 = \frac{Va^2bce^{-gn}}{Hgr}$$

The reproductive rate makes sense intuitively. In the malaria transmission cycle, mosquito biting occurs twice, hence the a^2 factor. Transmission is helped by large numbers of mosquitoes per human host (large V/H) and by large b and c. Transmission is hindered by high mosquito death rates (large g) by fast disease recovery (large r). Finally, quick sporogonic cycles (low n) produce mosquitoes more quickly, supporting transmission.

Introducing the stability index and the reproductive rate simplifies Equation 4:

$$0 = R_0 \frac{X}{H + ScX}(H - X) - X \tag{5}$$

3.2.3 R_0 as a Threshold

The R_0 value in a system describes the average number of new cases that each case of malaria will cause. For example, in a system with an R_0 value of 3, each case of malaria would cause, on average, 3 more cases to occur.

The use of R_0 introduces a convenient threshold for malaria endemicity:

$$R_0 \begin{cases} < 1 & \text{transmission dies out over time} \\ > 1 & \text{sustained endemic transmission} \end{cases}$$

This threshold can be used when planning malaria interventions; a successful intervention will reduce the R_0 value below 1 and eliminate malaria. R_0 can also be used when comparing interventions against one another. An intervention with a lower R_0 value, assuming both values are below 1, will lead to elimination faster than interventions with higher R_0 values.

4 Matrix Math

4.1 Converting Ross-Macdonald Variables to Matrices

Recall Equations 1 and 2:

$$\frac{dX}{dt} = abe^{-gn}\frac{Y}{H}(H - X) - rX$$

$$\frac{dY}{dt} = ac\frac{X}{H}(V - Y) - gY$$

In a system with multiple locations, each location must have both of these equations describing the infection of humans and mosquitoes. In order to consolidate notation, it is convenient to describe the system using matrices: each variable is represented by a matrix containing the value of that variable for each location in the system. The variables are now represented in the following way, where n is the total number of locations in the system:

$$\mathbf{X} = \begin{bmatrix} X_1 \\ X_2 \\ \vdots \\ X_n \end{bmatrix} \qquad \mathbf{Y} = \begin{bmatrix} Y_1 \\ Y_2 \\ \vdots \\ Y_n \end{bmatrix} \qquad \mathbf{H} = \begin{bmatrix} H_1 \\ H_2 \\ \vdots \\ H_n \end{bmatrix} \qquad \mathbf{V} = \begin{bmatrix} V_1 \\ V_2 \\ \vdots \\ V_n \end{bmatrix}$$

4.2 Matrix Notation

The use of matrices invokes the need for specific notation:

Matrix Product:

If $\mathbf{A}$ is an $n \times m$ matrix and $\mathbf{B}$ is an $m \times p$ matrix,

$$\mathbf{A} = \begin{bmatrix} a_{11} & a_{12} & \dots & a_{1m} \\ a_{21} & a_{22} & \dots & a_{2m} \\ \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & \dots & a_{nm} \end{bmatrix} \qquad \mathbf{B} = \begin{bmatrix} b_{11} & b_{12} & \dots & b_{1p} \\ b_{21} & b_{22} & \dots & b_{2p} \\ \vdots & \vdots & \ddots & \vdots \\ b_{m1} & b_{m2} & \dots & b_{mp} \end{bmatrix}$$

the matrix product $\mathbf{C} = \mathbf{AB}$ is defined to be the $n \times p$ matrix

$$\mathbf{C} = \begin{bmatrix} c_{11} & c_{12} & \dots & c_{1p} \\ c_{21} & c_{22} & \dots & c_{2p} \\ \vdots & \vdots & \ddots & \vdots \\ c_{n1} & c_{n2} & \dots & c_{np} \end{bmatrix}$$

such that

$$c_{ij} = a_{i1}b_{1j} + \cdots + a_{im}b_{mj} = \sum_{k=1}^{m} a_{ik}b_{kj}$$

Hadamard Product (Elementwise Multiplication):

For two matrices, $\mathbf{A}$, $\mathbf{B}$, of the same dimension, $m \times n$, the Hadamard product, $\mathbf{A} \circ \mathbf{B}$, is a matrix, of the same dimension as the operands, with elements given by

$$(\mathbf{A} \circ \mathbf{B})_{i,j} = (\mathbf{A})_{i,j} (\mathbf{B})_{i,j}$$

Scalar Multiplication:

The scalar multiplication of a matrix $\mathbf{A}$ with a scalar λ gives another matrix $\lambda\mathbf{A}$ of the same size as $\mathbf{A}$. The entries of $\lambda\mathbf{A}$ are defined by

$$\lambda (\mathbf{A})_{ij} = (\lambda\mathbf{A})_{ij}$$

Transposition:

Transposing a matrix reflects it over its main diagonal, such that

$$\left[\mathbf{A}^{\mathbf{T}}\right]_{ij} = [\mathbf{A}]_{ji}$$

If $\mathbf{A}$ is an $m \times n$ matrix, then $\mathbf{A}^{\mathbf{T}}$ is an $n \times m$ matrix.

5 Ross-Macdonald Equations in Matrix Form

5.1 Scaling by Time-at-Risk

The Time-at-Risk (TaR) matrix, $\mathbf{\Psi}$, from Section 1.3 can be used to scale the human populations (both infected and total populations). This is done by matrix multiplying the transpose of the TaR matrix by the respective population matrix:

$$\mathbf{X}_{\Psi} = \mathbf{\Psi}^{\mathbf{T}}\mathbf{X} \qquad\qquad \mathbf{H}_{\Psi} = \mathbf{\Psi}^{\mathbf{T}}\mathbf{H}$$

The act of scaling by $\mathbf{\Psi}$ accounts for the fact that different populations of humans spend different amounts of time in different places.

5.2 Mosquito Populations

Start with the Ross-Macdonald equation for mosquito populations (Equation 2), modified to use matrices:

$$\frac{d\mathbf{Y}}{dt} = ac\frac{\mathbf{X}_\Psi}{\mathbf{H}_\Psi} \circ (\mathbf{V} - \mathbf{Y}) - g\mathbf{Y}$$

At equilibrium, $\frac{d\mathbf{Y}}{dt} = 0$

$$0 = ac\frac{\mathbf{X}_\Psi}{\mathbf{H}_\Psi} \circ \mathbf{V} - \left(ac\frac{\mathbf{X}_\Psi}{\mathbf{H}_\Psi} + g\right) \circ \mathbf{Y}$$

Solve for $\mathbf{Y}$:

$$\mathbf{Y} = \frac{ac\frac{\mathbf{X}_\Psi}{\mathbf{H}_\Psi} \circ \mathbf{V}}{ac\frac{\mathbf{X}_\Psi}{\mathbf{H}_\Psi} + g} = \frac{ac\mathbf{X}_\Psi \circ \mathbf{V}}{ac\mathbf{X}_\Psi + \mathbf{H}_\Psi g} \tag{6}$$

5.3 Human Populations

Start with the Ross-Macdonald equation for human populations (Equation 1), modified to use matrices:

$$\frac{d\mathbf{X}}{dt} = abe^{-gn}\left(\mathbf{\Psi}\frac{\mathbf{Y}}{\mathbf{H}_\Psi}\right) \circ (\mathbf{H} - \mathbf{X}) - r\mathbf{X}$$

At equilibrium, $\frac{d\mathbf{X}}{dt} = 0$. By inserting Equation 6, we obtain the following:

$$0 = abe^{-gn}\left(\mathbf{\Psi}\frac{1}{\mathbf{H}_\Psi} \circ \frac{ac\mathbf{X}_\Psi \circ \mathbf{V}}{ac\mathbf{X}_\Psi + \mathbf{H}_\Psi g}\right) \circ (\mathbf{H} - \mathbf{X}) - r\mathbf{X}$$

Divide through by r and multiply the first term by g/g:

$$0 = \left(\mathbf{\Psi}\left(\frac{\mathbf{V}a^2bce^{-gn}}{\mathbf{H}_\Psi gr} \circ \frac{g\mathbf{X}_\Psi}{ac\mathbf{X}_\Psi + \mathbf{H}_\Psi g}\right)\right) \circ (\mathbf{H} - \mathbf{X}) - \mathbf{X}$$

Now insert a term for the matrix of R_0 values:

$$0 = \left(\mathbf{\Psi}\left(\mathbf{R}_\Psi \circ \frac{\mathbf{X}_\Psi}{cS\mathbf{X}_\Psi + \mathbf{H}_\Psi}\right)\right) \circ (\mathbf{H} - \mathbf{X}) - \mathbf{X} \tag{7}$$

Note that Equation 7 is similar to Equation 5, except adapted for time-at-risk-scaling and matrices of variables.

It is now possible to introduce a term for prevalence:

$$\boldsymbol{\Theta}_{\Psi} = \frac{\mathbf{X}_{\Psi}}{\mathbf{H}_{\Psi}}$$

$$0 = \left(\boldsymbol{\Psi} \left(\mathbf{R}_{\Psi} \circ \frac{\boldsymbol{\Theta}_{\Psi}}{cS\boldsymbol{\Theta}_{\Psi} + 1} \right) \right) \circ (\mathbf{H} - \mathbf{X}) - \mathbf{X} \tag{8}$$

6 Simple Example: One Village, One Forest

6.1 Establish Parameters & Variables

$$\mathbf{X} = \begin{bmatrix} X_V \\ X_F \end{bmatrix} \qquad \mathbf{H} = \begin{bmatrix} H_V \\ H_F \end{bmatrix} \qquad \mathbf{R}_{\Psi} = \begin{bmatrix} R_{\Psi,V} \\ R_{\Psi,F} \end{bmatrix}$$

$$\boldsymbol{\Psi} = \begin{array}{c} \\ \text{V} \\ \text{F} \end{array} \begin{array}{c} \begin{array}{cc} \text{V} & \text{F} \end{array} \\ \begin{pmatrix} 1 & 0 \\ 1-p & p \end{pmatrix} \end{array}$$

$$\mathbf{X}_{\Psi} = \boldsymbol{\Psi}^{\mathbf{T}}\mathbf{X} = \begin{bmatrix} 1 & 1-p \\ 0 & p \end{bmatrix} \begin{bmatrix} X_V \\ X_F \end{bmatrix} = \begin{bmatrix} X_V + (1-p)X_F \\ pX_F \end{bmatrix}$$

$$\mathbf{H}_{\Psi} = \boldsymbol{\Psi}^{\mathbf{T}}\mathbf{H} = \begin{bmatrix} 1 & 1-p \\ 0 & p \end{bmatrix} \begin{bmatrix} H_V \\ H_F \end{bmatrix} = \begin{bmatrix} H_V + (1-p)H_F \\ pH_F \end{bmatrix}$$

$$\boldsymbol{\Theta}_{\Psi} = \frac{\mathbf{X}_{\Psi}}{\mathbf{H}_{\Psi}} = \begin{bmatrix} \Theta_{\Psi,V} \\ \Theta_{\Psi,F} \end{bmatrix} = \begin{bmatrix} \dfrac{X_V + (1-p)X_F}{H_V + (1-p)H_F} \\ \dfrac{X_F}{H_F} \end{bmatrix}$$

6.2 Simplify Equations

Our governing equation:

$$0 = \left(\mathbf{\Psi}\left(\mathbf{R}_\Psi \circ \frac{\mathbf{\Theta}_\Psi}{cS\mathbf{\Theta}_\Psi + 1}\right)\right) \circ (\mathbf{H} - \mathbf{X}) - \mathbf{X}$$

First, expand this term:

$$\frac{\mathbf{\Theta}_\Psi}{cS\mathbf{\Theta}_\Psi + 1} = \frac{\begin{bmatrix}\Theta_{\Psi,V}\\ \Theta_{\Psi,F}\end{bmatrix}}{\begin{bmatrix}cS\Theta_{\Psi,V} + 1\\ cS\Theta_{\Psi,F} + 1\end{bmatrix}} = \begin{bmatrix}\dfrac{\Theta_{\Psi,V}}{cS\Theta_{\Psi,V} + 1}\\ \dfrac{\Theta_{\Psi,F}}{cS\Theta_{\Psi,F} + 1}\end{bmatrix}$$

Now include that in this bigger term:

$$\begin{aligned}\left(\mathbf{\Psi}\left(\mathbf{R}_\Psi \circ \frac{\mathbf{\Theta}_\Psi}{cS\mathbf{\Theta}_\Psi + 1}\right)\right) &= \mathbf{\Psi}\begin{bmatrix}R_{\Psi,V}\\ R_{\Psi,F}\end{bmatrix} \circ \begin{bmatrix}\dfrac{\Theta_{\Psi,V}}{cS\Theta_{\Psi,V} + 1}\\ \dfrac{\Theta_{\Psi,F}}{cS\Theta_{\Psi,F} + 1}\end{bmatrix}\\ &= \begin{bmatrix}1 & 0\\ 1-p & p\end{bmatrix}\begin{bmatrix}R_{\Psi,V} \cdot \dfrac{\Theta_{\Psi,V}}{cS\Theta_{\Psi,V} + 1}\\ R_{\Psi,F} \cdot \dfrac{\Theta_{\Psi,F}}{cS\Theta_{\Psi,F} + 1}\end{bmatrix}\\ &= \begin{bmatrix}R_{\Psi,V} \cdot \dfrac{\Theta_{\Psi,V}}{cS\Theta_{\Psi,V} + 1}\\ R_{\Psi,F} \cdot (1-p) \cdot \dfrac{\Theta_{\Psi,F}}{cS\Theta_{\Psi,F} + 1} + R_{\Psi,F} \cdot p \cdot \dfrac{\Theta_{\Psi,F}}{cS\Theta_{\Psi,F} + 1}\end{bmatrix}\end{aligned}$$

Tie it all together:

$$0 = \left(\mathbf{\Psi}\left(\mathbf{R}_\Psi \circ \frac{\mathbf{\Theta}_\Psi}{cS\mathbf{\Theta}_\Psi + 1}\right)\right) \circ (\mathbf{H} - \mathbf{X}) - \mathbf{X}$$

$$0 = \begin{bmatrix}R_{\Psi,V} \cdot \dfrac{\Theta_{\Psi,V}}{cS\Theta_{\Psi,V} + 1}\\ R_{\Psi,F} \cdot (1-p) \cdot \dfrac{\Theta_{\Psi,F}}{cS\Theta_{\Psi,F} + 1} + R_{\Psi,F} \cdot p \cdot \dfrac{\Theta_{\Psi,F}}{cS\Theta_{\Psi,F} + 1}\end{bmatrix} \circ \begin{bmatrix}H_V - X_V\\ H_F - X_F\end{bmatrix} - \begin{bmatrix}X_V\\ X_F\end{bmatrix}$$

$$0 = \begin{bmatrix} R_{\Psi,V} \cdot \dfrac{\Theta_{\Psi,V}}{cS\Theta_{\Psi,V}+1} \cdot (H_V - X_V) - X_V \\ \left(R_{\Psi,F} \cdot (1-p) \cdot \dfrac{\Theta_{\Psi,F}}{cS\Theta_{\Psi,F}+1} + R_{\Psi,F} \cdot p \cdot \dfrac{\Theta_{\Psi,F}}{cS\Theta_{\Psi,F}+1} \right) \cdot (H_F - X_F) - X_F \end{bmatrix}$$