

Analytical Models of Malaria Transmission and Approximations of MACRO

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1 Introduction

The purpose of this document is to review the analytical expressions and some key results of the Ross-Macdonald family of models for malaria transmission. These results will be key to properly calibrating the MACRO-PfSI version of MASH that will be used to simulate vaccine interventions on Bioko Island. Additionally, the results for the analytical model will be compared to the algorithm used to simulate malaria transmission in MACRO-PfSI. A mean-field approximation of MACRO-PfSI is discussed, and compared with the Ross-Macdonald model's results.

2 Generalized Ross-Macdonald Model

The Ross-Macdonald model may be stated as follows:

$$\begin{aligned} \frac{dX}{dt} &= \underbrace{h(H-X)}_{\text{Humans become sick}} - \underbrace{rX}_{\text{Human Recovery}} \\ \frac{dZ}{dt} &= \underbrace{a\kappa(M-Z)}_{\text{Mosquitoes become infectious}} - \underbrace{gZ}_{\text{Death of Infected Mosquitoes}} \end{aligned} \tag{1}$$

The variables are defined:

- $X \equiv$ Total number of infected humans
- $H \equiv$ Total number of humans
- $Z \equiv$ Total number of infectious mosquitoes
- $M \equiv$ Total number of mosquitoes
- $h \equiv$ "Happenings" - the rate at which non-infected humans become sick by interacting with infectious mosquitoes
- $\kappa = \frac{cX}{H} =$ the rate at which non-infected mosquitoes become infected by interacting with infectious humans, where c is the fraction of bites on infectious humans that lead to the transmission of the parasite to the biting mosquito. (Note that the units of κ are a rate, even though the expression on the right has no units - need to be careful of this when checking the consistency of the solutions.)
- $r \equiv$ The rate at which humans shed recover or shed infection.
- $g \equiv$ The rate at which mosquitoes die

The rate of "happenings" that drives the transmission of infection to humans may be defined in a number of different ways, depending on one's choice of notation. For now, we will use $h \equiv mabZ/M = mabz$ where

- $m \equiv M/H$ = The density of mosquitoes per human
- $a \equiv$ Number of bites on humans, per mosquito, per day
- $b \equiv$ "Efficiency" - fraction of bites on humans by infectious mosquitoes that results in the transmission of the parasite to the humans

The units of h are the number of bites per human per day. Essentially, h is the rate at which the interactions between non-infected humans and infectious mosquitoes converts non-infected humans to infected humans.

The Entomological Inoculation Rate (EIR) is another way of measuring the rate of exposure to mosquito bites that humans experience.

$$EIR \equiv a \frac{Z}{H} = \frac{M}{H} a \frac{Z}{M} = maz \quad (2)$$

So, in this version of the model, $h = bEIR$ where EIR is defined as the number of bites per human per day

2.1 Assumptions

A number of important assumptions have gone into the above model:

- All mosquitoes are assumed to be identical.
- All humans are assumed to be identical - that is, all humans are equally likely to become exposed to mosquito bites
- The ratio of mosquitoes per human m is assumed to be constant over time
- The mosquitoes and humans are assumed to mix completely
- The rates r and g at which humans recover and mosquitoes die are assumed to be constant, meaning an exponential rate of recovery/death.
- There is no latency period between becoming infected and becoming infectious.

(Many of these may be relaxed in more complicated versions of this model.)

2.2 Solutions

The steady-state solution to Eq. 1 may be found by setting the left hand sides of each to zero and solving. Using $PR = x \equiv X/H$:

$$\begin{aligned} 0 &= mbEIR(1 - PR) - rPR \\ x^* &= PR = \frac{EIR}{EIR + r/b} \end{aligned} \quad (3)$$

Similarly, using $z \equiv Z/M$:

$$\begin{aligned} 0 &= a\kappa(1 - z) - gz \\ z^* &= \frac{a\kappa}{a\kappa + g} \\ EIR &= maz^* = m \frac{a^2 \kappa}{a\kappa + g} = mg \frac{S^2 \kappa}{S\kappa + 1} \end{aligned} \quad (4)$$

$S \equiv a/g$ is known as the "stability index," and represents the average number of bites by a mosquito over its average lifetime ($1/g$). Note that the units of κ are a rate, such that $S\kappa$ has no units.

We can also re-write κ in terms of $PR = x^*$, such that we can relate the Parasite Rate to the Entomological Inoculation Rate. This intermediate step is important for properly calibrating the

model, if PR and EIR are already known.

$$\begin{aligned} PR &= \frac{EIR}{EIR + r/b} \\ EIR &= \frac{ma^2cPR}{acPR + g} \end{aligned} \tag{5}$$

Note that each of these equations is separate from the other, such that we can tweak certain details in one equation without it affecting the more general solution.

Solving the above two equations, we obtain one trivial solution with zero infection ($(PR, EIR) = (0, 0)$) and one nontrivial solution:

$$\begin{aligned} PR &= \frac{ma^2bc - gr}{ma^2bc + acr} \\ EIR &= \frac{ma^2bc - gr}{abc + bg} \end{aligned} \tag{6}$$

This solution (combined with linear systems analysis of the fixed points) suggests that there is a condition above which there is a nonzero amount of transmission in the steady state.

$$R_0 \equiv \frac{ma^2bc}{gr} > 1$$

This condition is readily identified as R_0 , the number of secondary cases arising from the infection of a single host in a completely naive population. As long as each case results in at least one additional secondary case, the disease will continue to spread and remain endemic. This quantity, while canonical in mathematical infectious disease modeling, is not exactly useful when it comes to thinking about populations where malaria is endemic.

We can rewrite Eq. in terms of R_0 :

$$\begin{aligned} PR &= \frac{R_0 - 1}{R_0 + \frac{ac}{g}} \\ z^* &= \frac{EIR}{ma} = \frac{R_0 - 1}{R_0} \frac{a/c}{1 + a/c} \end{aligned} \tag{7}$$

3 Extensions to the Ross-Macdonald Model

3.1 Latent period

Field measurements of the sporozoite rate z^* , the fraction of mosquitoes who are infectious, seem to suggest that z^* is very low - only a few percent at most. The above model allows for solutions where, as PR becomes large, EIR and z^* also become large, which is not reflected in the field data. To compensate for this, the model may be adjusted by adding an incubation period during which mosquitoes carry the parasite but are not yet able to transmit sporozoites to humans. We assume that it takes n days for the parasite to incubate in the mosquito, such that only after n days does the mosquito become infectious.

Given that g is the exponential rate at which mosquitoes die out, we expect that only a fraction e^{-gn} of mosquitoes survive the incubation period. Using this, we can define a new compartment in our model Y that tracks the number of mosquitoes who are infected but not infectious, during the incubation period. We also introduce the notation $\hat{x} = x(t - n)$ to mean the fraction of humans infected at n prior to the current time t .

$$\begin{aligned}
\frac{dx}{dt} &= \underbrace{h(1-x)}_{\text{Humans become sick}} - \underbrace{rx}_{\text{Human Recovery}} \\
\frac{dy}{dt} &= \underbrace{a\kappa(1-y-z)}_{\text{Mosquitoes become infected}} - \underbrace{a\hat{\kappa}(1-\hat{y}-\hat{z})e^{-gn}}_{\text{Mosquitoes survive to become infectious}} - \underbrace{gy}_{\text{Death of Infectious Mosquitoes}} \\
\frac{dz}{dt} &= \underbrace{a\hat{\kappa}(1-\hat{y}-\hat{z})e^{-gn}}_{\text{Mosquitoes survive to become infectious}} - \underbrace{gz}_{\text{Death of Infectious Mosquitoes}}
\end{aligned} \tag{8}$$

Note that the equation describing the infection in humans is largely unchanged.

The key to solving these equations is realizing that in the steady state $(\hat{x}, \hat{y}, \hat{z}) = (x, y, z)$. Using $\kappa = cx = cPR$ and $h = bEIR = mabz$, Eq. 8 becomes:

$$\begin{aligned}
0 &= bEIR(1-PR) - rPR \\
0 &= acPR(1-y-z)(1-e^{-gn}) - gy \\
0 &= acPR(1-y-z)e^{-gn} - gz
\end{aligned} \tag{9}$$

Solving Eq. 9 for y and z ,

$$\begin{aligned}
y^* &= \frac{e^{-gn}}{1-e^{-gn}}z^* \\
z^* &= \frac{acPR}{acPR+g}e^{-gn}
\end{aligned} \tag{10}$$

And so, the two equations for Parasite Rate and Entomological Inoculation Rate become:

$$\begin{aligned}
PR &= \frac{EIR}{EIR+r/b} \quad \text{as before} \\
EIR &= \frac{ma^2cPR}{acPR+g}e^{-gn} \quad \text{modified by } e^{-gn}
\end{aligned} \tag{11}$$

Solving:

$$\begin{aligned}
PR &= \frac{ma^2bce^{-gn}-gr}{ma^2bce^{-gn}+acr} \\
EIR &= \frac{ma^2bce^{-gn}-gr}{abc+bg}
\end{aligned} \tag{12}$$

And R_0 now becomes:

$$R_0 = \frac{ma^2bc}{gr}e^{-gn}$$

Rewriting Eq. 22 in terms of the new R_0 and compare to Eq. 7, we find that the PR is unchanged but the sporozoite rate has been modified by a factor of e^{-gn} . Now, one can tune the parameters of the model such that PR and EIR match field measurements, using the additional factor of e^{-gn} to keep the sporozoite rate low.

$$\begin{aligned}
PR &= \frac{R_0-1}{R_0+\frac{ac}{g}} \\
z^* &= \frac{EIR}{ma} = \frac{R_0-1}{R_0} \frac{ac/g}{1+ac/g} e^{-gn}
\end{aligned} \tag{13}$$

3.2 Care-Seeking Behavior

After being bitten by a mosquito and becoming symptomatic, humans may seek care that helps them immediately shed the infection. We model this by saying that a certain fraction of humans ρ become protected instead of infected following a mosquito bite. With probability ρ , humans are moved to the protected class P , where they shed the infection and cannot receive new infections. Humans lose the protected status at rate η . The first equation in Eq. 8 becomes two equations:

$$\begin{aligned} \frac{dx}{dt} &= \underbrace{(1 - \rho)h(1 - x - p)}_{\text{Humans become sick}} - \underbrace{rx}_{\text{Human Recovery}} \\ \frac{dp}{dt} &= \underbrace{\rho h(1 - x - p)}_{\text{Humans become protected}} - \underbrace{\eta p}_{\text{Lose protection}} \end{aligned} \quad (14)$$

Note that we assume that humans immediately seek care after becoming infectious, meaning that there is no asymptomatic period during which they may transmit the parasite to mosquitoes who bite them before seeking care. (One way to account for this would be to separately track infected, infectious, and symptomatic humans similar to the way the sporozoite incubation period is tracked.)

Solving Eq. 14, we obtain:

$$PR = \frac{EIR}{(1 + \frac{\rho}{\eta} \frac{r}{1-\rho})EIR + \frac{r}{(1-\rho)b}} \quad (15)$$

The equation for EIR in terms of PR is unchanged. So, we can solve for PR and EIR as before:

$$\begin{aligned} PR &= \frac{ma^2bce^{-gn} - gr/(1 - \rho)}{(1 + \frac{\rho}{\eta} \frac{r}{1-\rho})ma^2bce^{-gn} + acr/(1 - \rho)} \\ EIR &= \frac{ma^2bce^{-gn} - gr/(1 - \rho)}{(1 + \frac{\rho}{\eta} \frac{r}{1-\rho})bg + abc} \end{aligned} \quad (16)$$

We recover Eq. 22 in the $\rho \rightarrow 0$ limit, when nobody receives protection from infection.

4 Variable Mosquito Emergence Rate

5 MACRO-PfSI

We use the MACRO-PfSI modules to simulate the Ross-Macdonald equations. There are some important differences between MACRO-PfSI and the analytical model described above:

- Discrete time - While the humans' statuses are updated in real time, the mosquitoes' statuses are updated in discrete time - the updates occur once daily. Effectively, because the interactions between humans and mosquitoes (EIR and κ) are calculated and updated in discrete time, everything may be thought of as occurring in real time.
- Survival fractions - In the continuous time analytical model, the rate at which mosquitoes died was g , such that e^{-gn} mosquitoes survived the n -day incubation period. In the discrete time model, a fraction p mosquitoes survive in each time step - this is slightly different from the rate g - such that p^n mosquitoes survive the incubation period.
- Emergence - the analytical model defined the density of mosquitoes per human as constant. The simulation instead stochastically simulates the number of mosquitoes that emerge during each time period by drawing from a Poisson distribution with mean λ .

- Number of bites - for each human, the simulation calculates the number of bites by mosquitoes during each time step by drawing from a Poisson distribution with mean `bw*EIR`, where `bw` is the biting weight for that human. Note that the Poisson distribution may be replaced by another distribution - the Negative Binomial distribution is one candidate that more closely matches measurements of heterogeneous biting patterns made in the field.

We define the following state variables:

- `M` = total number of mosquitoes
- `Z` = total number of infectious mosquitoes
- `ZZ` = a vector that keeps track of the infected mosquitoes as they incubate
- `Y` = total number of infected mosquitoes, who are incubating the parasite
- `Y0` = number of mosquitoes infected at the current time step
- `H` = total number of humans
- `X` = number of infected humans
- `kappa` = rate of mosquito infections per time step
- `EIR` = number of bites on humans by mosquitoes per time step

Additionally, these are some parameters that are used in the algorithm

- `lambda` = mosquito emergence rate - the mean number of adult mosquitoes that are added to the population at each time step
- `p` = mosquito survival rate - the fraction of mosquitoes that survive from one time step to the next
- `EIP` = entomological incubation period - the mean number of days it takes for infected mosquitoes to become infectious
- `a` = rate of bites by mosquitoes per time step, as above
- `b` = efficiency - fraction of infectious mosquito bites that result in new infections, as above
- `c` = efficiency - fraction of mosquito bites on infectious humans that result in newly infected mosquitoes
- `ttClearPf` = `DurationPf` = duration of infection

MACRO-PfSI simulates the dynamics of malaria transmission using a function called `simMacro` (defined in `MACRO-Tile-Simulation.R`). Following the initial setup, `simMacro` works by simulating the transmission of malaria between humans and parasites over each day. To compare the workings of `simMacro` with the analytical model described in the previous sections, we will make a number of simplifying assumptions:

- Identical humans - We will assume that all humans may be treated identically. The biting weight of each human is set to 1, so that on average no human is more likely to be bitten than any other.
- Compartmental model - Rather than tracking the infection status of each human separately, it is simpler to combine all humans with the same status into the same compartment. This allows us to track over time the total numbers of susceptible, infected, and protected humans in the simulation and compare those quantities to the results from the analytical model.
- Large population sizes - Strictly speaking, the number of infected humans `X` must always be an integer in the simulation, but with large enough population sizes we can assume that the *fraction* of infected humans `X/N` is roughly continuous. For this reason, we will allow all state variables (`M`, `Y`, `Z`, `X`) to be continuous rather than discrete.
- Constant `EIP` - In the most general version of this model, `EIP` might vary across different mosquitoes, or it might vary depending on the time of year. Below, we assume that `EIP = 11` at all times and for all mosquitoes

- Single isolated population - MACRO-PfSI can simulate multiple separate populations (“patches”) and can also simulate traffic of humans and mosquitoes as they move from one patch to another. In this case, we will assume a single patch containing a population of humans and a population of mosquitoes that does not otherwise interact with its surroundings.
- “Mean field” dynamics - There are several stochastic processes included in the basic version of `simMacro`. As a first order approximation, we will assume that these stochastic processes may be replaced by their mean values at each time step.
 - Mosquito Emergence - `lambda` is the mean number of adult mosquitoes added to the population at each time step, stochastically generated by drawing from a Poisson distribution with mean `lambda`. To first order, we replace this process by adding `lambda` new mosquitoes at each time step.
 - Biting Events - At each time step, `EIR` is calculated for each human separately. In `simMacro`, each human’s `EIR` = `bWeight*a*Z/bWeightTotal`. Then, the number of bites for each human is calculated by drawing from a Poisson distribution with mean equal to that human’s `EIR`. Each of those bites successfully transmits the parasite with probability `b`. Because each human’s biting weight is equal (`bWeight = 1`), we replace the process of stochastically drawing the number of bites for each humans with the mean number of bites distributed evenly across the full population of humans. Using `bWeightTotal = H*bWeight`, the `EIR` (and mean number of bites) for the full population becomes `EIR = a*Z/H`. Note that this is the same as how $EIR = maZ/M = aZ/H$ was defined in the analytical model above.
 - Time until Recovery - When humans are infected, `simMacro` creates an event called `add2Q_endPfSI` which clears the infection at a time `ttClearPf` in the future. Rather than say that each infected human recovers after exactly `ttClearPf` time steps, we assume that infected humans recover at a constant rate `r` that is analogous to the recovery rate r in the analytical equations above. For the purposes of comparing the simulation against our mean field approximation, $r = 1/ttClearPf$

Note that EIR in the simulation is defined

With these assumptions, we re-write a single time step from `simMacro` in pseudocode as follows:

```

1: {New mosquitoes emerge - MACRO-Patch-Simulation}
2: M ← M + lambda
3: {Ross-Macdonald Population Dynamics - MOSQUITO-MosquitoRM-Simulation}
4: M ← p*M {Mosquito survival}
5: Y ← p*Y
6: Y0 = a*kappa*(M - Y) {Newly infected mosquitoes}
7: Y ← Y + Y0
8: Z ← p*Z {Infectious mosquitoes }
9: Z ← Z + ZZ[0]
10: ZZ[0:EIP-1] = ZZ[1:] {Track the maturation of the sporozoites}
11: ZZ[EIP] = (p^EIP)*Y0
12: {Infectious Humans - Mean field description of the queueing process described in PATHOGEN-PfSI-Methods}
13: X ← X - r*X + b*EIR*(H - X)
14: {Update kappa for each human - MACRO-Human-Kappa}
15: kappa ← c*X/H {Sums over all infectious humans to find kappa for each patch}
16: {Update EIR - MACRO-Human-Kappa}
17: EIR ← a*Z/H

```

We now summarize the pseudocode description of `simMacro` using a simple recurrence relation,

expressing a discrete-time version of the Ross-Macdonald model:

$$\begin{aligned}
M_{t+1} &= p(M_t + \lambda) \\
Y_0 &= acX(p(M_t + \lambda) - pY_t)/H \\
Y_{t+1} &= pY_t + Y_0 \\
ZZ_{t+1}^{(1)} &= pZ_t + ZZ_t^{(1)} \\
ZZ_{t+1}^{(i)} &= ZZ_t^{(i+1)} \\
ZZ_{t+1}^{(EIP)} &= p^{EIP}Y_0 \\
X_{t+1} &= X_t - rX_t + baZ(H - X)/H
\end{aligned} \tag{17}$$

We now solve for the fixed point of Eq. 17 by setting all state variables constant across time. First, the steady-state mosquito population:

$$M^* = \frac{p}{1-p}\lambda$$

Then, using the fact that all elements of the vector ZZ^* are equal in the steady state, we obtain three equations:

$$\begin{aligned}
Y^* &= pY^* + ac\frac{X^*}{H}(M^* - pY^*) \\
Z^* &= pZ^* + ac\frac{X^*}{H}(M^* - pY^*)p^{EIP} \\
X^* &= X^* - rX^* + baZ^*\left(1 - \frac{X^*}{H}\right)
\end{aligned} \tag{18}$$

Simplifying:

$$\begin{aligned}
Y^* &= \frac{ac}{1-p}\frac{X^*}{H}(M^* - pY^*) \\
Z^* &= p^{EIP}Y^* \\
X^* &= \frac{ba}{r}Z^*\left(1 - \frac{X^*}{H}\right)
\end{aligned} \tag{19}$$

Rewriting these in terms of $PR = X/H$ and $EIR = aZ/H$:

$$\begin{aligned}
EIR &= \frac{ac}{1-p}PR\left(\frac{M^*}{H}ap^{EIP} - pEIR\right) \\
PR &= \frac{b}{r}EIR(1 - PR)
\end{aligned} \tag{20}$$

Rearranging, we find equations similar to Eq. 11 above:

$$\begin{aligned}
EIR &= \frac{M^*}{H}ap^{EIP}\frac{acPR}{(1-p) + pacPR} \\
PR &= \frac{EIR}{EIR + r/b}
\end{aligned} \tag{21}$$

Solving:

$$\begin{aligned}
PR &= \frac{ma^2bcp^{EIP} - r(1-p)}{ma^2bcp^{EIP} + pacr} \\
EIR &= \frac{ma^2bcp^{EIP} - r(1-p)}{pabc + b(1-p)}
\end{aligned} \tag{22}$$

Note that we come very close to recovering Eq. 11 if we let $p^{EIP} \leftarrow e^{-gn}$ and $1-p \leftarrow g$. There is an additional factor of p that appears in the denominator of the expression for PR that is not

present in the analytic model - this factor results from the way that Y_0 is calculated at each time step (line 7 from the `simMacro` algorithm). Note also that removing the extra factors of p in the denominator result in very small numerical changes, such that it might not be possible to tell the difference between Eq 2.2 and Eq. 22.

For the discrete time simulation model, we find the following expression for R_0 .

$$R_0 = \frac{ma^2bc}{r(1-p)} p^{EIP} = \frac{p}{1-p} \frac{\lambda}{H} \frac{a^2bc}{r(1-p)} p^{EIP}$$

The key environmental parameter that determines R_0 is the emergence rate λ , which gives us a condition for when an isolated patch can sustain endemic malaria.

5.1 Comparison

To verify that Eq 22 accurately reflects how MACRO-PfSI behaves, we use the simulation to generate an ensemble of trajectories and compare the mean behavior of that ensemble the derived mean field values of PR and EIR over time. We simulate 10 trajectories with the following parameter values:

- $H = 500$ - Human population size
- $\lambda = 50$ - Mean emerging mosquitoes per time step
- $r = 1/200$ - 1/Days spent infected, where the time to clear infection is fixed at 200 days for all Humans
- $(a, b, c) = (.27, .55, .15)$
- $p = 0.9$ - Mosquito survival rate
- $EIP = 11$ - Incubation period

With this set of input parameters, Eq. 22 predicts $PR = 0.64$ and $EIR = 0.016$. We plot the mean of the ensemble of simulations over time, along with two additional curves that indicate a margin of one standard deviation across the ensemble of simulations, and find that there is excellent agreement between the mean field approximation of MACRO-PfSI and the simulation results.

5.2 Adding Protection

To add care-seeking behavior and protection to the MACRO-PfSI model, we introduce the parameter `rho` which defines the probability of a human seeking and receiving treatment and chemoprophylaxis. Strictly speaking, in MACRO-PfSI humans seek care after they become symptomatic (develop a fever), so we choose simulation parameters such that all humans (set `FeverPf` = 1) immediately become symptomatic (set `mnFeverPf` = 0) and a fraction `TreatPf` = `rho` of them immediately receive treatment (set `mnTreatPf` = 0). Humans who receive treatment, instead of becoming infected are instead assigned to the protected status `P`. While a human is protected, they shed all infections and cannot acquire new ones. This protection lasts `mnChemoprophylaxisPf` = 30 days, which we incorporate into the mean field model by setting the average rate of loss of protection $\eta = 1/30$.

The only required change to the `simMacro` algorithm is to adjust the number of humans who become infected, and to keep track of the number of protected humans:

- 1: {Infectious Humans - Mean field description of the queueing process described in PATHOGEN-PfSI-Methods}
- 2: $X \leftarrow X - r*X + (1-\rho)*b*EIR*(H - X - P)$
- 3: $P \leftarrow P - \eta*P + \rho*b*EIR*(H - X - P)$

Solving for $PR = X^*/H$ during the steady state:

$$PR = \frac{EIR}{\left(1 + \frac{\rho}{\eta} \frac{r}{1-\rho}\right) EIR + \frac{r}{(1-\rho)b}}$$

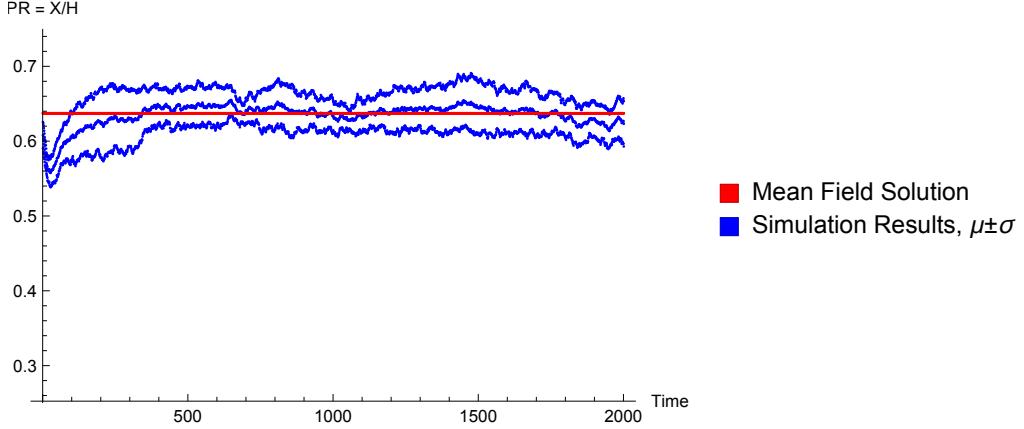


Figure 1: Parasite Rate Comparison

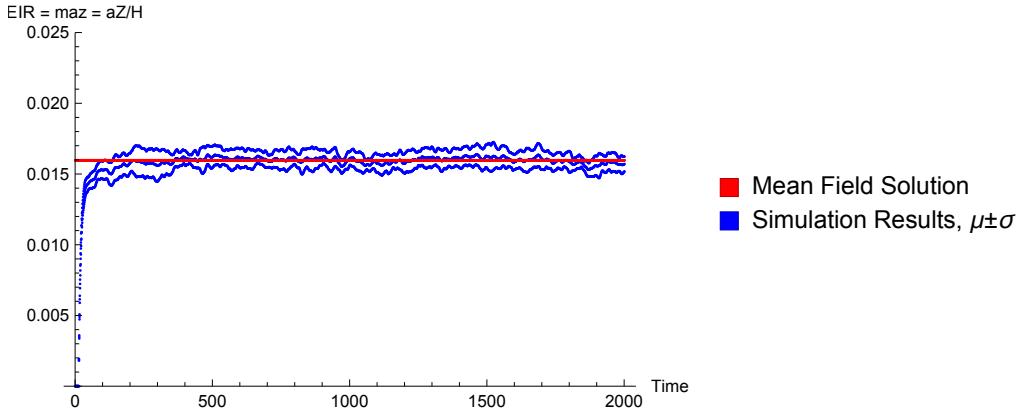


Figure 2: EIR Comparison

Repeating the analysis from above, we can obtain expressions for PR and EIR that now also depend on ρ and η :

$$\begin{aligned} PR &= \frac{ma^2bc^{EIP} - (1-p)r/(1-\rho)}{(1 + \frac{\rho}{\eta} \frac{r}{1-\rho})ma^2bc^{EIP} + pacr/(1-\rho)} \\ EIR &= \frac{ma^2bc^{EIP} - (1-p)r/(1-\rho)}{(1 + \frac{\rho}{\eta} \frac{r}{1-\rho})b(1-p) + pabc} \end{aligned} \quad (23)$$

We compare these expressions to simulation results by simulating 10 trajectories with the following parameter values:

- $H = 500$ - Human population size
- $\lambda = 50$ - Mean emerging mosquitoes per time step
- $r = 1/200$ - 1/Days spent infected, where the time to clear infection is fixed at 200 days for all Humans
- $(a, b, c) = (.27, .55, .15)$
- $p = 0.9$ - Mosquito survival rate
- $EIP = 11$ - Incubation period
- $\rho = 0.3$ - Probability of seeking care
- $\eta = 1/30$ - Average time spent protected

With this set of input parameters, Eq. 23 predicts $PR = 0.48$ and $EIR = 0.0125$. Note that the inclusion of protection against the parasite suppresses both the fraction of infected humans

and the rate of exposure. We plot the mean of the ensemble of simulations over time, along with two additional curves that indicate a margin of one standard deviation across the ensemble of simulations, and again find that there is excellent agreement between the mean field approximation of MACRO-PfSI and the simulation results.

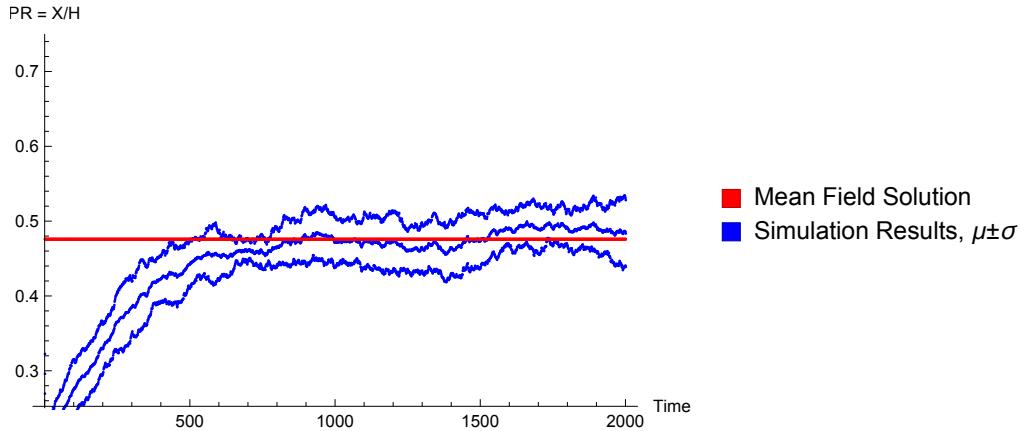


Figure 3: **Parasite Rate Comparison**, chemoprophylaxis included

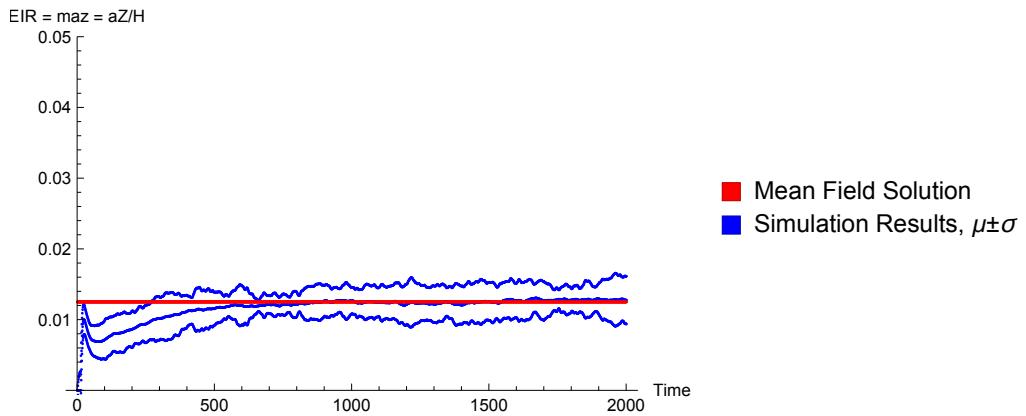


Figure 4: **EIR Comparison**, chemoprophylaxis included

6 Model Calibration

When it comes to using MACRO-PfSI so as to represent malaria transmission in a way that reflects reality, we need to correctly calibrate our model to match empirical data. Most of the parameters included in MACRO-PfSI can be measured, but one key parameter that is very difficult to estimate is the emergence rate λ . After all, the model that adult mosquitoes suddenly “emerge” at a constant rate oversimplifies the realities of how mosquitoes reproduce and under what circumstances the mosquito population remains stable. However, given measurements of PR (or EIR), it is possible to use the analytical results described above to calibrate λ . Assuming that measurements of PR represent a steady state prevalence level, we can re-arrange the expression for PR as a function of other parameters (Eq. 23) to solve for the mosquito emergence rate:

$$m = \frac{p}{1-p} \frac{\lambda}{H} = \frac{pacrPR + (1-p)r}{a^2 bcp^{EIP} \left((1-\rho) - (1-\rho + \frac{r\rho}{\eta}) PR \right)} \quad (24)$$

This equation only holds for the assumptions stated above. In particular, we must be able to assume that there is a nontrivial steady state solution to the mean field version of the model for this calibration trick to work. Altering the details of how the stochastic parts of MACRO-PfSI operate would necessitate relying on the simulation to calibrate λ . Measuring PR vs. λ in a series

of simulations allows us to calibrate λ to match the empirically-measured PR in cases when PR is known but the details of the mosquito ecology are not.

Another problem that arises when it comes to model calibration is deriving the relationship between PR and EIR . In the most general case, the rate at which events occur h , may be adjusted so that it is no longer a simple linear function of EIR . In this case, in order to derive the relationship between PR and EIR we re-arrange the first equation in 8, setting the left-hand side to 0 and letting $h = f(EIR, b)$.

$$\begin{aligned} 0 &= h = f(EIR, b)(1 - x) - rx \\ \frac{rx}{1 - x} &= h = f(EIR, b) \end{aligned} \quad (25)$$

And so, given a series of simulations where EIR and PR both vary, it is possible to empirically determine a mapping from EIR onto PR by plotting $\frac{rPR}{1-PR}$ vs. EIR . In the simplest case, with $h = bEIR$ and homogeneous biting weights, the plotted relationship should be a straight line with slope b .

Using $EIR = maz$ and Eq. 9 for z^* , we can further re-arrange Eq. 25 to obtain an expression that relates PR to the Vectorial Capacity:

$$\begin{aligned} \frac{rPR}{1-PR} &= bmaz = bma \frac{a\kappa}{a\kappa + g} e^{-gn} \\ \frac{rPR}{1-PR} &= \left(\frac{ma^2}{g} e^{-gn} \right) \frac{a\kappa}{1 + \frac{a\kappa}{g}} \\ \frac{rPR}{1-PR} &= VC \frac{acPR}{1 + \frac{acPR}{g}} \end{aligned} \quad (26)$$

In the last line, we have used $\kappa = cPR$, again the simplest relationship for the rate at which the parasite is transferred to mosquitoes. For the purposes of model calibration, the Vectorial Capacity VC contains m , which in turn contains the rate of mosquito emergence λ .

7 Migration

The simplest way to incorporate the movements of people between different otherwise isolated areas is to define a movement matrix P . The rows of P are normalized to 1 ($\sum_j p_{ij} = 1$), such that p_{ij} represents the proportion of **time at risk** spent by individuals from site i experienced in site j . To put this another way, because individuals from site i spend time at home (in site i) as well as abroad (in other sites $j \neq i$), the average individual from site i is exposed to the mosquitoes from site j a proportion of the time equal to p_{ij} . As such, the Ross-Macdonald equation for humans is extended as follows:

$$\frac{dx_i}{dt} = \sum_j p_{ij} h_j (1 - x_i) - rx_i \quad (27)$$

Note that the term $\sum_j p_{ij} h_j$ represents a linear combination of biting events that affect a human from i at all other sites.

Similarly, all mosquitoes at site i have a chance of becoming infected when they bite an infected visitor who comes from site j . The expression for κ needs to be altered to reflect how mosquitoes may be exposed to infected humans from multiple locations:

$$\frac{dz_i}{dt} = a_i c_i \kappa_i (e^{-g_i n_i} - z_i) - gz_i \quad (28)$$

With this in mind, the Ross-Macdonald equation for infectious mosquitoes is extended as follows:

$$\kappa_i = \frac{\text{Infected Locals and Visitors to } i}{\text{Total Locals and Visitors to } i} = \frac{\sum_j p_{ij} X_j H_j}{\sum_j p_{ij} H_j} \quad (29)$$

At equilibrium, we set the left hand side of Eq. 29 to 0 and solve for z_i in terms of κ_i and other parameters:

$$z_i^* = \frac{a_i c_i \kappa_i}{g_i + a_i c_i \kappa_i} e^{-g_i n_i} \quad (30)$$

Using the simplest expression for the rate of biting events, $h_j = b_j EIR_j = m_j a_j b_j z_j$, we obtain an expression that relates $PR = x$ to the vector of Vectorial Capacities for each of the sites included in the model:

$$\begin{aligned} 0 &= \sum_j p_{ij} h_j (1 - x_i) - rx_i \\ \frac{rx_i}{1 - x_i} &= \sum_j p_{ij} h_j = \sum_j p_{ij} m_j a_j b_j z_j \\ \frac{rx_i}{1 - x_i} &= \sum_j p_{ij} \left(\frac{m_j a_j^2}{g_j} e^{-g_j n_j} \right) \frac{b_j c_j \kappa_j}{1 + \frac{a_j c_j \kappa_j}{g_j}} \\ \frac{rx_i}{1 - x_i} &= \sum_j p_{ij} V C_j \frac{b_j c_j \kappa_j}{1 + \frac{a_j c_j \kappa_j}{g_j}} \end{aligned} \quad (31)$$

Changing notation, Eq. 31 can be expressed as a matrix multiplication. Let $g(X)$ be a vector whose i th component is $\frac{rx_i}{1 - x_i}$. Let C be a vector whose i th component is VC_i . Let $d(\kappa)$ be a diagonal matrix where the i th element on the diagonal is $\frac{b_j c_j \kappa_j}{1 + \frac{a_j c_j \kappa_j}{g_j}}$.

$$\begin{aligned} g(X) &= P d(\kappa) C \\ C &= (P d(\kappa))^{-1} g(X) \end{aligned} \quad (32)$$

And so, by inverting this matrix equation, we can solve for the vector C in terms of the travel matrix P , the vector of $X = PR$ at each site, and all of the other fixed parameters. In this way, we can use the travel matrix P to calibrate a model that includes migration between patches. Note that if $P = \mathbb{1}$ we recover the same expression as in Eq. 26 for a set of isolated patches.

7.1 Simplified example

To illustrate how this might work in practice, let us assume a landscape has only two patches, and that the connections between them are weak. The probability of a person in patch 1 traveling to patch 2 is ϵ_1 and the probability of a person in patch 2 traveling to patch 1 is ϵ_2 , where $0 < \epsilon_1 \ll 1$ and $0 < \epsilon_2 \ll 1$. Remembering that the rows of the travel matrix P need to be normalized to 1, P can be expressed in terms of the identity matrix plus a small correction:

$$\begin{aligned} P &= \begin{pmatrix} 1 - \epsilon_1 & \epsilon_1 \\ \epsilon_2 & 1 - \epsilon_2 \end{pmatrix} = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} - \begin{pmatrix} \epsilon_1 & -\epsilon_1 \\ -\epsilon_2 & \epsilon_2 \end{pmatrix} \\ P &= \mathbb{1} - \epsilon \end{aligned} \quad (33)$$

Writing the matrix P in terms of the identity plus a correction term makes it straightforward to write out a simplified version of Eq. 32. We can approximate the inverse of P using the Neumann

series expansion to write out an expression for C in terms of the migration-free case (Eq. 26) and a small correction term:

$$\begin{aligned} C &= d(\kappa)^{-1} P^{-1} g(X) = d(\kappa)^{-1} (\mathbb{1} - \epsilon) g(X) \\ C &= d(\kappa)^{-1} g(X) + d(\kappa)^{-1} (\epsilon + \epsilon^2 + \dots) \end{aligned} \quad (34)$$

This helps us more explicitly see how the matrix ϵ affects the solution for C , and how that solution differs from the case where all patches are isolated and $P = \mathbb{1}$. Depending on how large the elements of the matrix ϵ are, this correction may be significant or insignificant.

8 Heterogeneous Biting Weights

9 Vaccinations

With a vaccine, we hope to suppress transmission of malaria by reducing the efficiency with which people receive new infections. If the vaccine is 100% effective, then this is equivalent to shrinking the population of susceptible humans. If the vaccine is only partially effective, we can again use a variation on the Ross-Macdonald model to explore how the fraction of people with malaria changes.

We will partition our population into two groups - vaccinated and control - and assume that the size of each group remains constant over time. In practice, vaccines wear off over time, but for now we will assume that the vaccine remains effective indefinitely. The fraction of people who are vaccinated is v , and the fraction of the people who remain unvaccinated is $1 - v$. The total number of vaccinated people with malaria is X_v and the total number of unvaccinated people with malaria is X_c , such that the total parasite rate for the population is $PR = \frac{X_v + X_c}{H}$. Among the vaccinated people the parasite rate is $\frac{PR_v}{v} = \frac{X_v}{vH}$, and likewise among the unvaccinated people the parasite rate is $\frac{PR_c}{1-v} = \frac{X_c}{(1-v)H}$. We will also model the vaccine's efficacy by saying that the vaccine decreases the efficiency with which people acquire new infections: $b \rightarrow b_v < b$.

Using this notation, the Ross-Macdonald equations become (analogous to Eq. 11):

$$\begin{aligned} PR_v &= \frac{vb_v EIR}{b_v EIR + r} \\ PR_c &= \frac{(1-v)b EIR}{b EIR + r} \\ EIR &= \frac{ma^2 c (PR_v + PR_c)}{ac(PR_v + PR_c) + g} e^{-gn} \end{aligned} \quad (35)$$

Solving for (PR_v, PR_c) yields some very complicated equations that aren't particularly enlightening to look at, but they have behavior that matches our intuition in certain limits.

- If the vaccine is completely ineffective ($b_v \rightarrow b$) then we find that $PR_v + PR_c$ is equal to PR in the familiar solution from before (Eq. 22).
- If the vaccine is completely effective ($b_v \rightarrow 0$) then we find that $PR_v = 0$, as expected. In the unvaccinated group, $PR_c = \frac{(1-v)ma^2 bce^{-gn} - gr}{ma^2 bce^{-gn} + acr}$, which is the same as if we treated the vaccinated group as being completely removed from the population.
- If everyone is vaccinated ($v \rightarrow 1$) then we find that $PR_c = 0$ and $PR_v = \frac{ma^2 b_v ce^{-gn} - gr}{ma^2 b_v ce^{-gn} + acr}$, meaning that we have changed $b \rightarrow b_v$ for the full population.

Generally speaking, in order to have a large effect size (reduction in $PR = PR_v + PR_c$) we need to have both a very effective vaccine $b_v \rightarrow 0$ and high coverage $v \rightarrow 1$.

By partitioning the population into two compartments, vaccinated and unvaccinated, where the transmission dynamics are different in each compartment, allows us to then explore different effect sizes. If PR is the parasite rate in a population with no intervention through vaccination, then the direct effect size, as expressed as a relative rate, is $\frac{PR_v}{v} / \frac{PR_c}{1-v}$. The indirect effect size is $\frac{PR_c}{1-v} / PR$. The total effect size is $\frac{PR_v}{v} / PR$.