Multiscale Modeling of Malaria Dynamics

Micah Manary, Priya Nayal and Daniel Ortiz
BENG221 Mathematical Methods in Bioengineering

November 28, 2014

1 Introduction

Malaria infections are a major cause of morality worldwide, resulting in over 1 million deaths each year, especially in children under five years of age [3, 7, 8, 10]. In addition, some 300 million non-lethal cases produce an extremely heavy burden on the populations of tropical regions, resulting in an economic loss estimated in the billions of dollars, and a health burden totaling some billions of days in cumulative hospital treatment [6, 9, 11]. Figure 1 illustrates the mortality burden exhibited by malaria infections in 2010.1 As such, malaria is a primary target for researchers in both tropical medicine and global health. However, the biology of Plasmodium presents unique challenge to researchers, and new methods are required if these challenges are to be overcome.

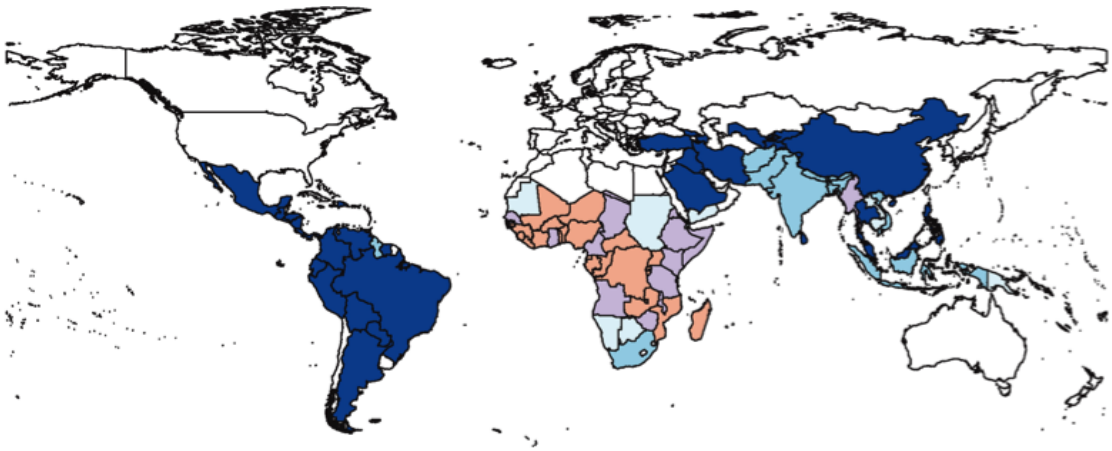

Figure 1: The distribution of the global malaria burden expressed in cumulative probability of death; white indicates no transmission, dark blue up to 0-0.1% probability of death, light blue 0.1-1 %, grey up 1-5%, purple 5-10%, orange 10-20 %, and red>20%.

Malaria infections in humans are primarily caused by single-celled eukaryotic parasites of the genus Plasmodium. While Plasmodium is known to infect reptiles, birds and mammals, only five species are able to cause human infections. Plasmodium falciparum is responsible for the majority of cases in sub-Saharan Africa, and the majority of deaths worldwide. Plasmodium vivax is more prevalent in the tropical regions of South America and Southeast Asia, but has not been implicated in as many deaths. Plasmodium malariae is found throughout the tropical regions of the world, but the absolute transmission of the species is very low. Plasmodium ovale is found primarily in West Africa and in Oceania, and also results in a very small number of cases. In addition to these four species, Plasmodium knowlesi is a zoonotic disease that has also been reported to cause some cases of human malaria.

The Plasmodium life cycle can be divided into three major stages: the vector stage, which takes place in the midgut and salivary glands of the female Anopheles mosquito, the liver stage, which takes place in the hepatocytes of the secondary host, in this case, humans, and the erythrocytic stage, occurring in the red blood cells of the secondary cost. The vector stage includes the sexual development of the parasite, while asexual reproduction occurs in both the hepatic and erythrocytic stages. Figure 2 illustrates the Plasmodium life cycle in all three of these stages. Clinical malaria is identified in the erythrocytic stage, where patients become febrile and fatigued due to the anemia caused by a loss of infected red blood cells. While only one round of meiosis occurs in the vector stage, and only one set of mitotic events in the hepatic stage, the erythrocytic stage is cyclical in nature, and the majority of parasites undergo a set of mitotic events many times, until they are removed by the host immune system or an antimalarial treatment, or a case fatality results. Consequently, immense genetic diversity is created in the hundreds of mitoses that occur during this critical stage of infection.

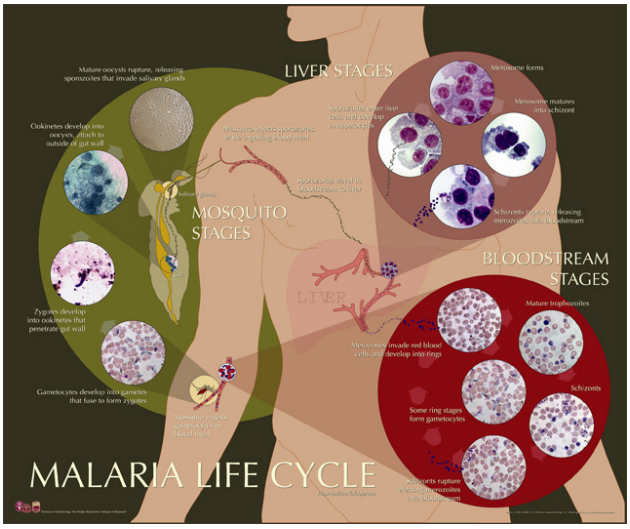

Figure 2: Diagram of the malaria life cycle, including the hepatic, erythrocytic, and vector stages taken from: http://www.afrims.org/images/immuno-image1.jpg

In this work, we proposed the use of mathematical tools for the modeling of three distinctive stages in the dynamics of malaria spread. First, we propose the invasion of the malaria parasites as a 3D random walk phenomenon. Second, we model the number of infected red blood cells vs healthy at a given time. And third, we model the spread of malaria over a population of humans and mosquitoes using predator prey models.

2 The models

2.1 Parasite Invasion of The Liver

Malaria parasites invade the liver from specific cells called kupffer cells. When the parasites reaches this cells it attaches and starts crawling into the liver tissue killing several cells on its way. Several studies have reported the dynamics of this movement. Investigations have been performed in different scenarios such as in vitro, in vivo in dermic tissue and in vivo in liver tissue. All of this studies have reported the parasites movement to be of a random walk nature. Figure 3 shows a summary of these findings.

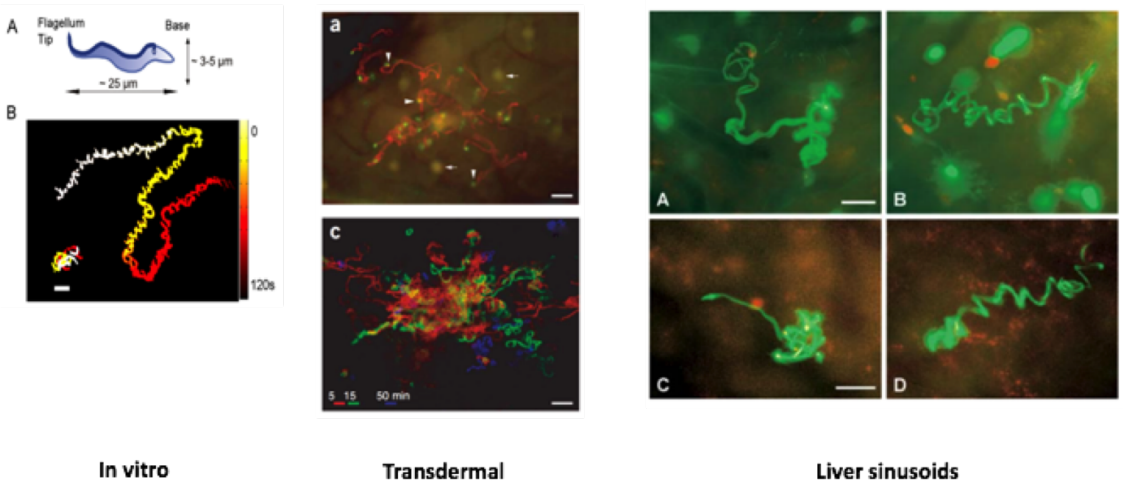

Figure 3: Findings showing the random walk nature of the parasite movement in different scenarios. Left panel: A. Schematic representation of a typical parasite B. Trajectories of a parasite in an invert setting over time Taken from [5]. Middle panel: A and C show the trajectories of a malaria parasite in the dermal tissue of a mouse taken from [1]. Right panel: A-D trajectories of different Malaria parasites in liver sinusoids. Taken from [2]

Given the challenge that is acquiring experimental data of the parasite movement into the liver in 3D (most of the data comes from 2D preparations) we decided to use some of the information that has been reported for the 2D case to build a 3D random walk model of the parasite invasion. The model was built using the following assumptions:

- The parasites are already attached to a kupffer cell and will start migration towards the liver parenchyma. They will not have backwards movement to the blood vessel.
- The parasite has the same probability to move in any direction
- The blood vessel is situated over the x axis
- Each step of the parasite is equal to 1/10 of its own size
- Each step takes 2s

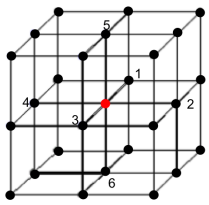

Figure 4: Schematic of the discretization used to determine the movement of the parasite. At a given time point the parasite is in the red spot. According to our assumptions the parasite will not move to 6

The 3D random walk is formulated as:

$$P(t + \Delta t) = P(t) + step$$

Where step is defined by the probability of the parasite to move in a specific direction.

$$step = f(P(x, y, z))$$

$$Step = \begin{bmatrix} x(t) + \Delta x & y & z \\ x(t) - \Delta x & y & z \\ x & y(t) + \Delta y & z \\ x & y(t) - \Delta y & z \\ x & y & z(t) + \Delta z \end{bmatrix}$$

Using this model can obtain different spatial distribution of a given number of parasites over time:

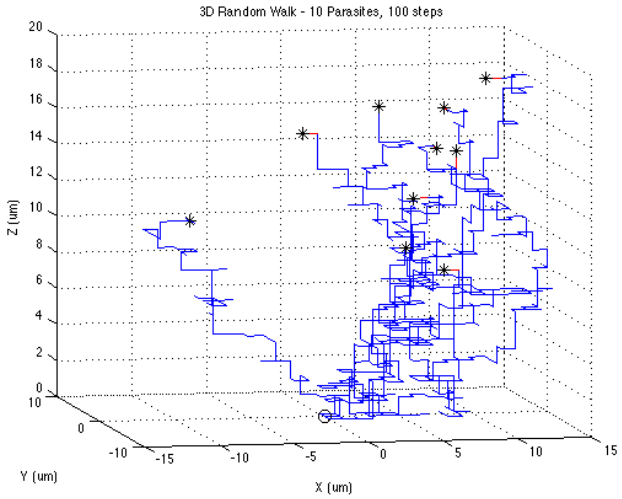

Figure 5: Spatial distribution of 10 parasites invading a cupful cell after 100 steps(i.e 200 s)

Moreover, we can analyze the distance covered by the parasites as a function of time:

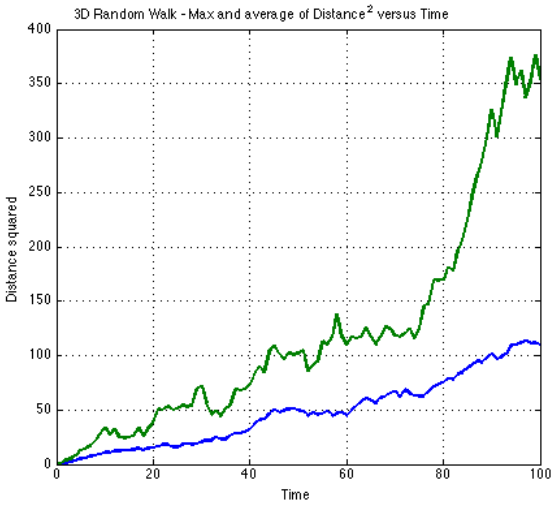

Figure 6: Distance covered vs Time for a group of parasites invading a kuppffer cell. The green line shows the maximum distance covered and the blue line the average distance.

As can be seen the mean distance covered has a trend of growing with the squared root of time as in a standard diffusion problem. For this specific problem we consider a 3D random walk to be more realistic that a continuos diffusion approximation given (i) the fact that the parasites ara actively moving and (ii) the relationship between parasite size and pore size on the liver matrix.

This type of model could help to identify the spacific location where the parasites accumulate in the liver in order to design better drugs.

2.2 Blood Stage: Effect of Immune Response

The parasite Plasmodium spends part of its life-cycle inside human red blood cells. The anemia that results is a major cause of mortality and morbidity in patients, especially children and pregnant women, living in malarial endemic areas. [12] A model that weighs the factors that effect red blood cell count during a Plasmodium infection could be useful to see how varying those factors changes the severity of anemia.

The model looks at the quantity of uninfected cells since those are the ones that function normally in the circulation. Erythropoiesis, the creation of new blood cells in the bone marrow, increases the pool of healthy while infection is the dominant force that decreases the pool. The number of uninfected cells that are decreased by the immune system is small compared to the other factors, so that was neglected in this model. The pool of uninfected cells is mainly decreased by periodic bursting due to infection. The number of parasites available to infect depends on their proliferation as well as the removal of infected cells by the immune system. Thus a robust immune system should reduce the depletion of the pool of healthy cells. A Schematic representation of the model is shown in Figure 7.

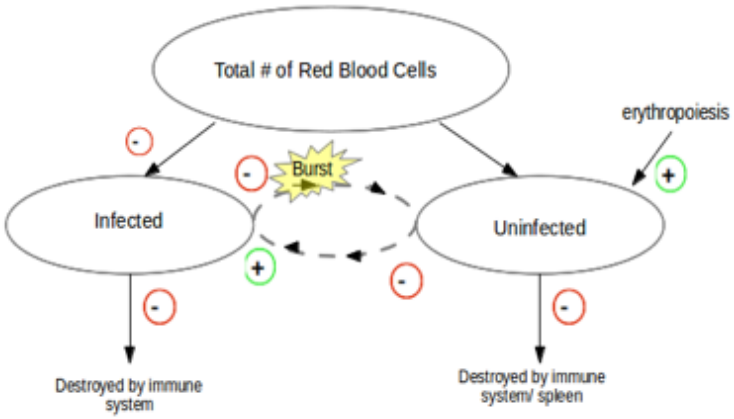

Figure 7: Schematic of the proposed model

According to Haydon et al. [4] the number of infected cells can be modeled as:

$$\frac{dP}{dt} = rP - \beta P I_{mm}$$

Imm is a function that represents the activation of the immune system. In this case, we assume a very conservative linear activation:

$$I_{mm} = kt$$

The function is the:

$$\frac{dP}{dt} = rP - \beta Pkt$$

Where,

- P is the number of infected cells.
- r is the rate of parasite proliferation inside the cell, which was picked to be 8/day following the paper. Then rP is the total number of parasites released from the infected cells at a given burst. There is no time dependence here because we assume that the burst happens over a course of a few minutes, so this number is roughly constant over a period of one day which is the time between bursts.
- β is the strength of interaction between the immune system and infected cells; the higher ? is the more effectively the immune system kills infected cells.
- k is the rate at which the immune system ramps up. So βPkt is then the number of infected cells that are killed by the immune system over a given period of time.

This can be solved with straightforward integration to give:

$$P = P_0 e^{rt - \beta k t^2}$$

During the burst, the number of healthy cells are infected at a rate:

$$\frac{dB}{dw} = -\alpha MB$$

Where, M is the number of parasites per burst, which can be give by: $M = rP$ Then the rate at which healthy cells are infected during each cell burst is:

$$\frac{dB}{dw} = -\alpha rPB$$

Where P is the number of infected cells solved for above.

We can split the parameters into:

Pro-parasite

- P number of infected cells
- r (rate of parasite proliferation)
- M (number of parasites)
- α (how well parasites are able to infect RBCs). α goes between 0 and 1, where $\alpha = 0$ means no parasites enter healthy cells, and $\alpha = 1$ means all the parasites enter healthy cells.

Anti-parasite

- B (number of healthy cells),
- β (Strength of interaction between immune system and infected cells),
- k (rate at which immune system ramps up)

The balance of these parameters will determine the strength of the infection, as seen in the plots below. The x-axis is the time in days; the y-axis is the rate at which healthy cells are infected (Healthy cells per microliter per day). The size of the peak is determined by the number of parasites, while the amount of time it takes to peak is determined by how quickly they are eliminated by the immune system.

At baseline:

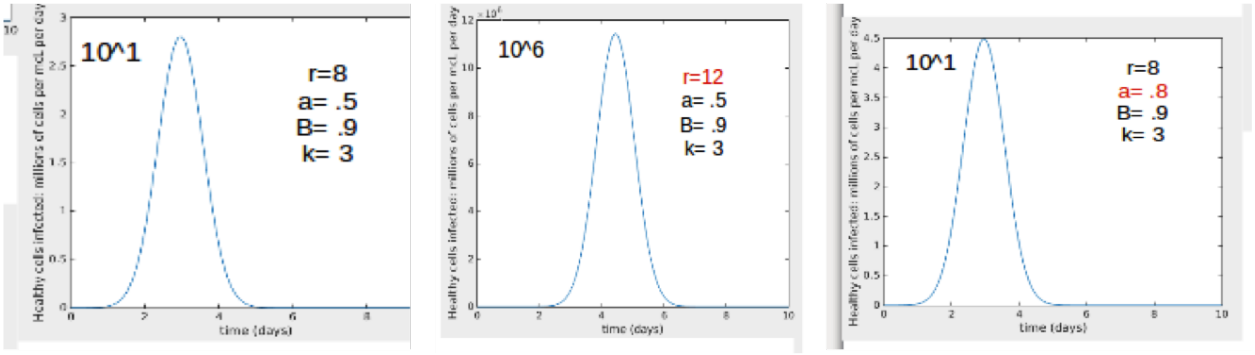

Figure 8: At Baseline

Increasing the rate of proliferation, r, causes both a shift in the timing of the peak as well as a great increase in the maximum, reflecting the inability of the immune system to keep up. Increasing the ability of the parasites to infect new cells caused a slight increase in the maximum and did not shift the timing of the peak.

Increase the anti-parasite parameters:

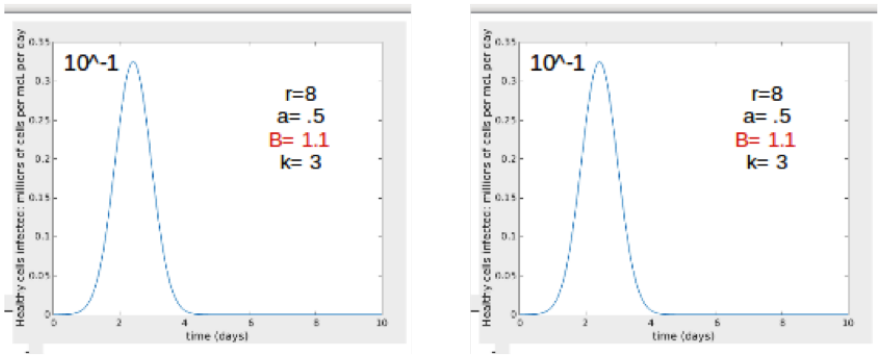

Figure 9: After increasing anti-parasite parameters

Increasing the ability of the immune system to kill infected cells β results in a decreased peak. Increasing the rate of increase of the immune system leads to both a much smaller peak, as well as decreasing the time it takes to peak. This reflects the robust nature of the immune response.

We would like to use a circuit to model the dynamics of red blood cells in a patient with malaria. One advantage of this model is that it is easy to conceptualize and can be made better relatively easily by introducing more time dependencies to the resistances and the voltage source, without changing the basic framework.

The number of electrons on the capacitor will stand for the number of healthy red blood cells in the circulation. We will model the charge of the capacitor over time. Then the charging of the capacitor is erythropoiesis, and the short discharge is infection of healthy RBCs, taking them out of the pool (eg reducing the charge of the capacitor).

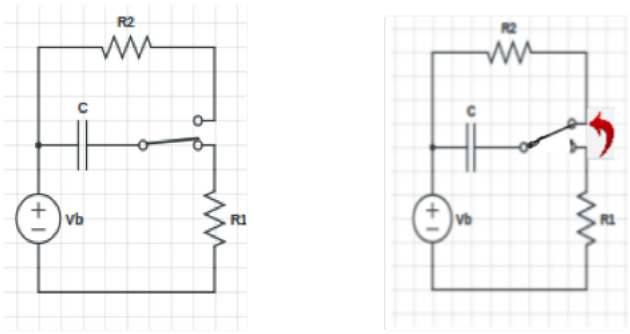

Figure 10: Circuit model for A. Erythropoiesis (circuit in the config for one day) and B.Infection (circuit in this config for 3 mins)

Since the time of bursting is so small, and since during that time, the infection of cells is by far the dominant process, it is acceptable to model the system as switching between two states, instead of having erythropoiesis ON all the time.

Erythropoiesis (charging):

$$V_b = Q/C + IR_1$$
$$0 = \frac{dQ/dt}{C} + dI/dtR_1$$
$$-\frac{I}{RC} = dI/dt$$
$$I = I_0 e^{-\frac{t}{RC}}$$
$$I_0 = \frac{V_b}{R_1} e^{-\frac{t}{RC}} since Q = 0 at t = 0$$
$$I = \frac{V_b}{R_1} e^{-\frac{t}{RC}}$$

Plug into top equation to get:

$$Q = V_b C(1 - e^{-\frac{t}{RC}})$$

Infection/ discharging:

$$-\frac{Q}{C} = IR_2$$
$$-\frac{I}{R_2 C} = \frac{dI}{dt}$$

Similar to the charging case Plug into top to get Q:

$$Q = CV_b e^{\frac{t}{R_2 C}}$$

These are both first-order ODEs that can be solved with straightforward integration.

- Q is the charge on the capacitor; it is the number of healthy red blood cells.

- VC is the number of healthy red blood cells that are normally in the body.
- Normal blood count is 5 million cells/uL
- The voltage of the battery represents the ?potential? of the bone marrow to produce more RBCS.
- 1/R1C is the rate of erythropoiesis.
- At 500 billion cells per day, assuming total blood volume of 5.5L, this is .09 million cells/(uL*day)
- 1/R2C is the rate of infection, which we found previously to be $P = P_0 e^{rt - \beta k t^2}$

Using these model we can obtain Infection and clearing in a normal patient, normal virulence parasite:

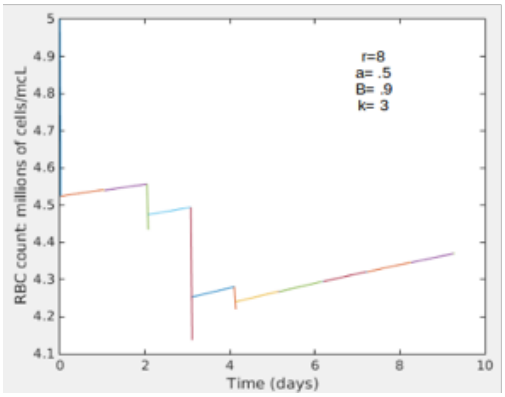

Figure 11: Infection clearing on normal patient over time

The initial burst is followed by subsequent bursts that deplete the pool of healthy red blood cells, but the immune system catches up around day 3-4. After that the number of cells infected decreases until the immune system has eliminated the parasites. Then erythropoiesis continues until the initial value is reached. In this plot, erythropoiesis looks linear, but if one were to run the erythropoiesis for 1 month it would asymptotically approach the initial value.

Infection in a patient with sickle cell trait:

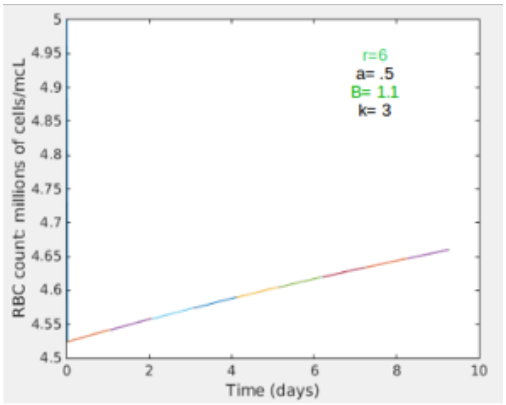

Figure 12: Infection in a patient with sickle cell trait over time

People with sickle cell trait are resistant to Plasmodium infections because the sickled cells both make it hard for the parasite to infect and also hamper the organisms reproduction inside the cell. The parameter

were changed to reflect this and we see that after the initial infection, the infection is at a low enough level that it can be cleared immediately, even if the immune system has not ramped up.

Infection in a patient with weakened immunity, with a slightly more virulent strain:

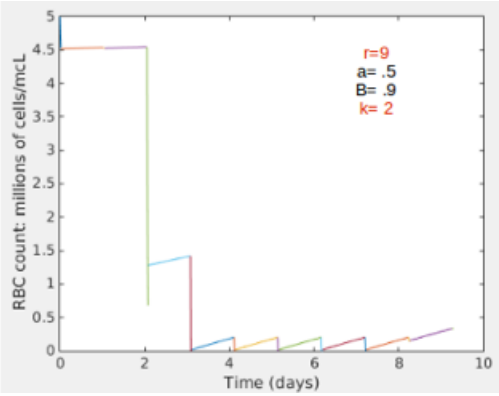

Figure 13: Infection in a patient with weakened immunity over time

In patients who have weakened immune systems from HIV or malnutrition, the parasite can proliferate unchecked causing a massive decline in healthy red blood cells. The severe anemia can lead to death in this case.

Improvements to the model:

- Include a time dependence to the voltage source, as erythropoiesis ramps up during infection, and when there is anemia.
- When the immune system rams up, it also increases the healthy cells it removes. In some cases this can be substantial. We can also introduce a time dependence into 1/R1C, the rate of accumulation of normal RBCs to reflect this.

2.3 Epidemiology of Malaria

We would like to model the epidemiology of malaria as a system of coupled differential equations, one describing the infected human population and the other describing the infected mosquito population. Available to us are the following variables:

Variable	Description	Estimates
$H(t)$	proportion of infected humans	(n/a)
$M(t)$	proportion of infected mosquitoes	(n/a)
a	human biting rate (bites/mosquito/day)	$0.01 - 0.5$
b	bite success rate (proportion bites)	$0.2 - 0.5$
c	mosquito bite infection rate	0.5
m	ratio of female mosquitoes to humans	$0.5 - 40$
r	human recovery rate (chance of recovery/person/day)	$0.005 - 0.05$
u_1	human mortality rate (chance/person/day)	0.017
u_2	mosquito mortality rate (chance/mosquito/day)	$0.05 - 0.5$
h	proportional treatment rate (rate/infected person)	$0.1 - 0.5$

We will model the rate of change of the infected human and mosquito proportions relative to their populations, as below:

$$\frac{dH(t)}{dt} = abmM(t)\left[1 - H(t)\right] - \left(r + u_1 + hH(t)\right)H(t) \tag{1}$$

$$\frac{dM(t)}{dt} = acH(t)\left[1 - M(t)\right] - u_2 M(t) \tag{2}$$

$$\frac{dM(t)}{dt} = acH(t)\left[1 - M(t)\right] f(t) - u_2 M(t) \tag{3}$$

These equations are not explicitly solvable without some simplifying assumptions, though they are easily numerically solvable. To simplify, we will assume that the proportion of infected humans and mosquitoes is small:

$$1 - H(t) \approx 1 - M(t) \approx 1, hH(t) \approx 0$$

This reduces our equations to:

$$\frac{dH(t)}{dt} = abmM(t) - \left(r + u_1\right)H(t) \tag{4}$$

$$\frac{dM(t)}{dt} = acH(t) - u_2 M(t) \tag{5}$$

For convenience sake, let:

$$a' = abm, b' = r + u_1, c' = ac, d' = u_2$$
$$c_1 = \sqrt{4a'c' + (b' - d')^2}, c_2 = -b' - d'$$

Solving the equations explicitly, we get:

$$H(t) = \left[\left(\frac{k_1}{2c_1}\left(b' - d'\right) + \frac{c'k_2}{c_1}\right)\left(e^{c_1} - e^{-c_1}\right) + c_1\left(e^{c_1} + e^{-c_1}\right)\right]e^{\frac{1}{2}tc_2} \tag{6}$$

$$M(t) = \left[\left(\frac{k_2}{2c_1}\left(d' - b'\right) + \frac{a'k_1}{c_1}\right)\left(e^{c_1} - e^{-c_1}\right) + c_1\left(e^{c_1} + e^{-c_1}\right)\right]e^{\frac{1}{2}tc_2} \tag{7}$$

Using this model we can get the following results:

Without seasonal term:

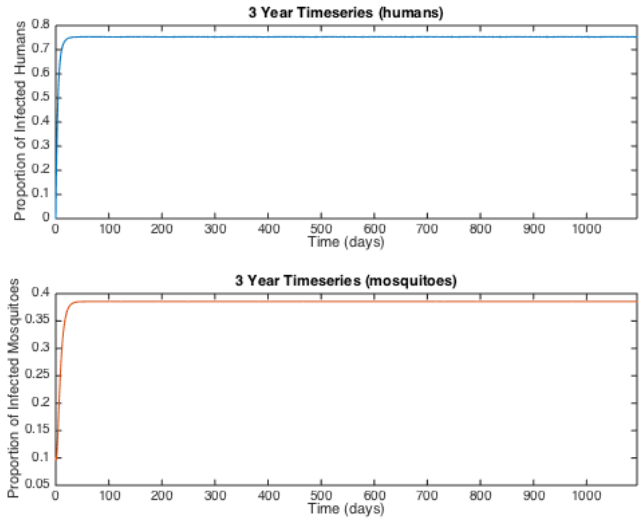

Figure 14: 3 Year population of infected humans and mosquitoes

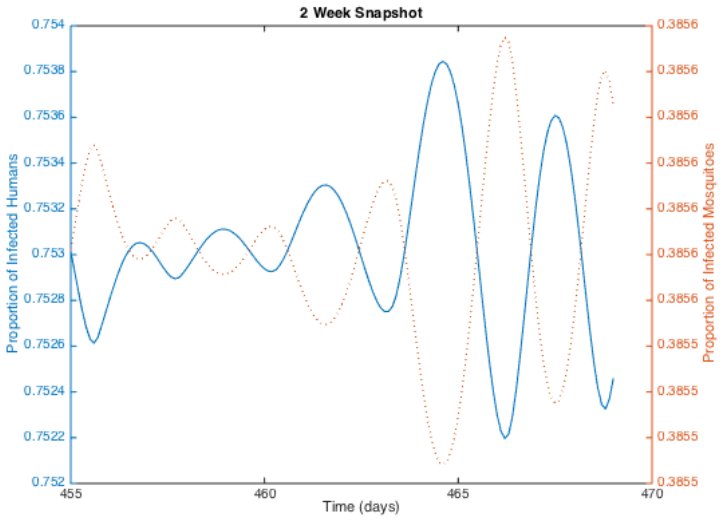

Figure 15: 2 week snapshot of infected humans and mosquitoes

Including seasonal term:

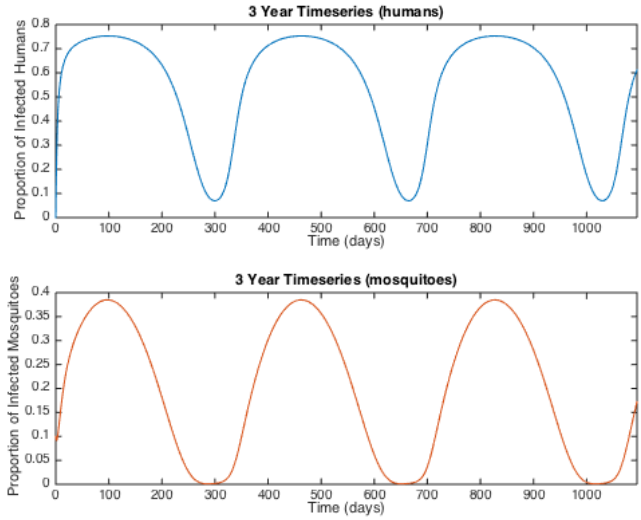

Figure 16: 3 Year population of infected humans and mosquitoes with seasonal term

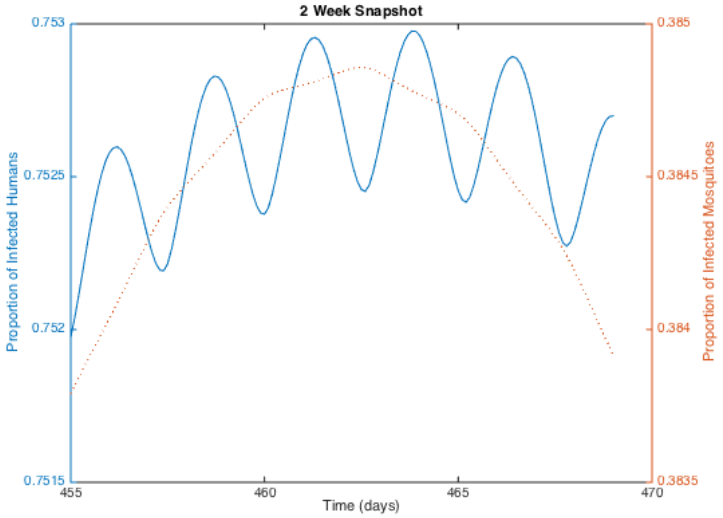

Figure 17: 2 week snapshot of infected humans and mosquitoes with seasonal term

Matlab code
Random Walk

```
%Adapted from : http://people.sc.fsu.edu/~jburkardt/m_src/
%random_walk_3d_simulation/random_walk_3d_simulation.html
step_num=100;
  walk_num = 0;

  hold on
  plot3 ( 0.0, 0.0, 0.0, 'ko', 'MarkerSize', 10 )
  grid on
```

```
Parasites=10;
for i=1:Parasites

  walk_num = walk_num + 1;


  x = zeros(step_num+1,1);
  y = zeros(step_num+1,1);
  z = zeros(step_num+1,1);

  x(:,1)=x(:,1)+(i-1);



 for step = 2 : step_num + 1

    destination = [ x(step-1) + 1.0, y(step-1),       z(step-1); ...
                    x(step-1) - 1.0, y(step-1),       z(step-1); ...
                    x(step-1),       y(step-1) + 1.0, z(step-1); ...
                    x(step-1),       y(step-1) - 1.0, z(step-1); ...
                    x(step-1),       y(step-1),       z(step-1) + 1.0; ...
                    x(step-1),       y(step-1),       z(step-1)];


    k = ceil ( 6.0 * rand ( 1, 1 ) );


    x(step) = destination(k,1);
    y(step) = destination(k,2);
    z(step) = destination(k,3);

    plot3 ( [ x(step-1), x(step) ], [ y(step-1), y(step) ], [ z(step-1), z(step) ], ...
      'r-', 'LineWidth', 1 );

  end

  plot3 ( x(step_num+1), y(step_num+1), z(step_num+1), 'r*', 'MarkerSize', 10 )

  title_string = sprintf ( '3D Random Walk - %d Parasites, %d steps', walk_num, step_num );
  title ( title_string );
  xlabel ( 'X (um)' )
  ylabel ( 'Y (um)' );
  zlabel ( 'Z (um)' );

  for step = 2 : step_num
    plot3 ( [ x(step-1), x(step) ], [ y(step-1), y(step) ], [ z(step-1), z(step) ], ...
      'b-', 'LineWidth', 1 );
  end
  plot3 ( x(step_num+1), y(step_num+1), z(step_num+1), 'k*', 'MarkerSize', 10 )

end

hold off
```

Blood stage

```
VbC = 5;
R1C = .00375;
t = 0:.01:10;
a = .6;
r = 9;
B = .9;
k = 2;
g = 1:.1:1000;
Q = VbC * (1-exp(-R1C*g));
```

```
R2Co = 5;
P = R2Co*exp(r*t - 0.5*B*k*t.^2)/10^6;
R2C = a*r*P;
Qd = VbC*exp(-R2Co*t);
plot(t(1:3),Qd(1:3))
hold on

g = 1:.1:1000;
Q = VbC * (1-exp(-R1C*g));
Qn = Qd(3)-Q;
Qabs = abs(Qn);
[min pos] = min(Qabs);
plot(t(106:206),Q(pos:pos+100))

%plot(t(5:105),Q(5:105));
%xlim([0,50])
%hold on

for i = 0:1:9
    Qn = Qd(3)-Q;
    Qabs = abs(Qn);
    [min pos] = min(Qabs);
    j = 3+i*103;
    plot(t(j:j+100),Q(pos:pos+100))

    init = Q(pos+100);
    Qd = init*exp(-R2C(j+100)*t);
    plot(t(j+100:j+103),Qd(1:4))
    hold on
    clear pos
    clear min
end
```

Epidemiological

```
colors = get(gca,'ColorOrder');
[t,y]=ode45(@episystem,0:0.1:1095,[0;.1]);
subplot(2,1,1)
plot(t,1.*y(:,1),'Color',colors(1,:))
title('3 Year Timeseries (humans)')
ylabel('Proportion of Infected Humans')
xlabel('Time (days)')
xlim([0 1095])
subplot(2,1,2)
plot(t,y(:,2),'Color',colors(2,:))
title('3 Year Timeseries (mosquitoes)')
ylabel('Proportion of Infected Mosquitoes')
xlabel('Time (days)')
xlim([0 1095])
figure
flatstart = 455;
flatend = 469;
flatrange = (flatstart*10+1):(flatend*10+1);
[hAx,hLine1,hLine2] = plotyy(t(flatrange),y(flatrange,1),t(flatrange),y(flatrange,2));
title('2 Week Snapshot')
xlabel('Time (days)')
hLine1.LineStyle = '-';
hLine2.LineStyle = ':';
ylabel(hAx(1),'Proportion of Infected Humans')
ylabel(hAx(2),'Proportion of Infected Mosquitoes')
```

```
a = 0.2; %man biting rate, bites per mosquito per day [0.01-0.5]
b = 0.5; %proportion of bites that produce human infection [0.2-0.5]
c = 0.5; %mosquito infection bite rate, porpotion in which one mosquito becomes infected [0.5]
m = 20; %ratio of female mosquitoes to humans [0.5-40]
```

```
r = 0.01; %human recovery rate, chance per day [0.005-0.05]
u1 = 0.017; %per capita human mortality rate, per year [0.017]
u2 = 0.12; %per capita mosquito mortality rate, per day [0.05-0.5]

a1 = a*b*m;
b1 = r+u1;
c1 = a*c;
d1 = u2;
C1 = (4*a1*c1+(b1-d1)^2)^.5;
C2 = -b1-d1;

tmesh = 0:0.1:100;
Hmesh = .1*((1/(2*C1)*(b1-d1)+(c1/C1))*(exp(C1)-exp(-C1))+C1*(exp(C1)+exp(-C1)))*exp(.5*C2*tmesh);
Mmesh = .1*((1/(2*C1)*(d1-b1)+(a1/C1))*(exp(C1)-exp(-C1))+C1*(exp(C1)+exp(-C1)))*exp(.5*C2*tmesh);

plot(tmesh,Hmesh,tmesh,Mmesh)



colors = get(gca,'ColorOrder');
[t,y]=ode45(@episystem_seasonal,0:0.1:1095,[0;.1]);
subplot(2,1,1)
plot(t,1.*y(:,1),'Color',colors(1,:))
title('3 Year Timeseries (humans)')
ylabel('Proportion of Infected Humans')
xlabel('Time (days)')
xlim([0 1095])
subplot(2,1,2)
plot(t,y(:,2),'Color',colors(2,:))
title('3 Year Timeseries (mosquitoes)')
ylabel('Proportion of Infected Mosquitoes')
xlabel('Time (days)')
xlim([0 1095])
figure
flatstart = 455;
flatend = 469;
flatrange = (flatstart*10+1):(flatend*10+1);
[hAx,hLine1,hLine2] = plotyy(t(flatrange),y(flatrange,1),t(flatrange),y(flatrange,2));
title('2 Week Snapshot')
xlabel('Time (days)')
hLine1.LineStyle = '-';
hLine2.LineStyle = ':';
ylabel(hAx(1),'Proportion of Infected Humans')
ylabel(hAx(2),'Proportion of Infected Mosquitoes')



function yprime = episystem_seasonal(t,y)
H = y(1); %propotion of infected humans
M = y(2); %proportion of infected moquitoes
a = 0.2; %man biting rate, bites per mosquito per day [0.01-0.5]
b = 0.5; %proportion of bites that produce human infection [0.2-0.5]
c = 0.5; %mosquito infection bite rate, porpotion in which one mosquito becomes infected [0.5]
m = 20; %ratio of female mosquitoes to humans [0.5-40]
r = 0.01; %human recovery rate, chance per day [0.005-0.05]
u1 = 0.017; %per capita human mortality rate, per year [0.017]
u2 = 0.12; %per capita mosquito mortality rate, per day [0.05-0.5]
h = 0.3; %treatment rate proportional to number of infected indivudals [0.1-0.5]
yprime = ...
    [(a*b*m*M)*(1-H)-(r+u1+h*H)*H;...
    (a*c*H)*(1-M)*(0.5)*(1+sin(2*pi*t/365))-u2*M];



function yprime = episystem(t,y)
H = y(1); %propotion of infected humans
M = y(2); %proportion of infected moquitoes
a = 0.2; %man biting rate, bites per mosquito per day [0.01-0.5]
b = 0.5; %proportion of bites that produce human infection [0.2-0.5]
```

```
c = 0.5; %mosquito infection bite rate, porpotion in which one mosquito becomes infected [0.5]
m = 20; %ratio of female mosquitoes to humans [0.5-40]
r = 0.01; %human recovery rate, chance per day [0.005-0.05]
u1 = 0.017; %per capita human mortality rate, per year [0.017]
u2 = 0.12; %per capita mosquito mortality rate, per day [0.05-0.5]
h = 0.3; %treatment rate proportional to number of infected indivudals [0.1-0.5]
yprime = ...
    [(a*b*m*M)*(1-H)-(r+u1+h*H)*H;...
    (a*c*H)*(1-M)-u2*M];
```

References

[1] Rogerio Amino, Sabine Thiberge, Béatrice Martin, Susanna Celli, Spencer Shorte, Friedrich Frischknecht, and Robert Ménard. Quantitative imaging of plasmodium transmission from mosquito to mammal. *Nature medicine*, 12(2):220–224, 2006.

[2] Ute Frevert, Sabine Engelmann, Sergine Zougbédé, Jörg Stange, Bruce Ng, Kai Matuschewski, Leonard Liebes, and Herman Yee. Intravital observation of plasmodium berghei sporozoite infection of the liver. *PLoS biology*, 3(6):e192, 2005.

[3] Daniel E Goldberg, Robert F Siliciano, and William R Jacobs Jr. Outwitting evolution: fighting drug-resistant tb, malaria, and hiv. *Cell*, 148(6):1271–1283, 2012.

[4] Daniel T Haydon, Louise Matthews, Rebecca Timms, and Nick Colegrave. Topndash; down or bottom–up regulation of intra–host blood–stage malaria: do malaria parasites most resemble the dynamics of prey or predator? *Proceedings of the Royal Society of London. Series B: Biological Sciences*, 270(1512):289–298, 2003.

[5] Janina Kristin Hellmann, Sylvia Münter, Mikhail Kudryashev, Simon Schulz, Kirsten Heiss, Ann-Kristin Müller, Kai Matuschewski, Joachim P Spatz, Ulrich S Schwarz, and Friedrich Frischknecht. Environmental constraints guide migration of malaria parasites during transmission. *PLoS pathogens*, 7(6):e1002080, 2011.

[6] Richard J Maude, Yoel Lubell, Duong Socheat, Shunmay Yeung, Sompob Saralamba, Wirichada Pongtavornpinyo, Ben S Cooper, Arjen M Dondorp, Nicholas J White, and Lisa J White. The role of mathematical modelling in guiding the science and economics of malaria elimination. *International health*, 2(4):239–246, 2010.

[7] Christopher JL Murray, Lisa C Rosenfeld, Stephen S Lim, Kathryn G Andrews, Kyle J Foreman, Diana Haring, Nancy Fullman, Mohsen Naghavi, Rafael Lozano, and Alan D Lopez. Global malaria mortality between 1980 and 2010: a systematic analysis. *The Lancet*, 379(9814):413–431, 2012.

[8] Ines Petersen, Richard Eastman, and Michael Lanzer. Drug-resistant malaria: molecular mechanisms and implications for public health. *FEBS letters*, 585(11):1551–1562, 2011.

[9] Francesco Ricci. Social implications of malaria and their relationships with poverty. *Mediterranean journal of hematology and infectious diseases*, 4(1), 2012.

[10] Juliana M Sa, Jason L Chong, and Thomas E Wellems. Malaria drug resistance: new observations and developments. *Essays in biochemistry*, 51:137–160, 2011.

[11] Renu Tuteja. Malaria- an overview. *FEBS Journal*, 274(18):4670–4679, 2007.

[12] DJ Weatherall, S Abdalla, and MJ Pippard. The anaemia of plasmodium falciparum malaria. In *Malaria and the Red Cell, Ciba Foundation Symposium*, volume 94, pages 74–88, 2009.