A FINITE DIFFERENCE APPROXIMATION TO ERYTHROPOIESIS SUBJECT TO MALARIA INFECTION

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1 Introduction

In this paper we plan to investigate, by mathematical means, optimal treatment courses of intrahost malaria infections. We will first, however, take a look at current research supported models of both erythropoiesis and malaria infections, to try to better model the effect of malaria on red blood cell production.

2 Erythropoiesis Model

Erythropoiesis is the process by which new red blood cells are produced. Precursor erythrocytes reside in the bone marrow and consume hemoglobin. When they get to a certain age, they leave the bone marrow and join the mature erythrocyte population. The production of precursors is motivated by the hormone erythropoietin, which is secreted by the kidneys. Current biological research shows that erythropoiesis can be modeled with the following system of equations [1,2,3,4,5]:

$$\frac{\partial p(t,\mu)}{\partial t} + g(E(t))\frac{\partial p(t,\mu)}{\partial \mu} = \sigma(t,\mu,E(t))p(t,\mu) \qquad 0<\mu<\mu_F \qquad 0<t<T \qquad (1A)$$

$$\frac{\partial m(t,\nu)}{\partial t} + \frac{\partial m(t,\nu)}{\partial \nu} = -\gamma(t,\nu,M(t))m(t,\nu) \qquad 0<\nu<\nu_F \qquad 0<t<T \qquad (2A)$$

$$\frac{dE(t)}{dt} = f(t,M(t)) - a_E(P(t))E(t) \qquad 0<t<T \qquad (3)$$

$$g(E(t))p(t,0) = \phi(t)E(t) \qquad 0<t<T$$

$$m(t,0) = g(E(t))p(t,\mu_F) \qquad 0<t<T$$

$$p(0,\mu) = p^0(\mu) \qquad 0<\mu<\mu_F$$

$$m(0,\nu) = m^0(\nu) \qquad 0<\nu<\nu_F$$

$$E(0) = E^0$$

$p(t,\mu)$	density of precursor erythrocytes of age μ
$P(t)$	total precursor erythrocyte population
$m(t,\nu)$	density of mature erythrocytes of age ν
$M(t)$	total mature erythrocyte population
$E(t)$	erythropoietin hormone concentration level
$g(E(t))$	maturation rate of precursor cells
$\sigma(t,\mu,E(t))$	birth/death rate of precursor cells
$\gamma(t,\nu,M(t))$	death rate of mature erythrocytes
$f(t,M(t))$	erythropoietin response by kidneys
$a_E(P(t))$	erythropoietin decay rate
$\phi(t)$	proportionality function

3 Malaria Model

Malaria is a parasitic disease. When a person is bitten by a mosquito carrying a type of malaria, sporozoites are injected into the blood stream and accumulate in the liver, where they incubate for a period of about two weeks [8]. When they've matured to merozoites, they transfer back to the blood stream and begin infecting erythrocytes.

In [6], a model for malaria is given, but it assumes that red blood cell production is constant (Λ). The model is as follows:

$$\frac{dM(t)}{dt} = \Lambda - \gamma M(t) - k_s Y(t) M(t) \qquad 0 < t < T \tag{4}$$

$$\frac{dX(t)}{dt} = k_s Y(t) M(t) - (a_1 + s(t)) X(t) - a_c I(t) X(t) \qquad 0 < t < T \tag{5}$$

$$\frac{dY(t)}{dt} = r(t) s(t) X(t) - a_y Y(t) - k_s M(t) Y(t) - a_h I(t) Y(t) \qquad 0 < t < T \tag{6}$$

$$\frac{dI(t)}{dt} = \left[\lambda_y Y(t) + \lambda_x X(t)\right] I(t) - a_i I(t) \qquad 0 < t < T \tag{7}$$

$$M(0) = M^0 \quad X(0) = X^0 \quad Y(0) = Y^0 \quad I(0) = I^0$$

$M(t)$	total healthy erythrocyte population
$Y(t)$	total merozoite population
$X(t)$	total infected erythrocyte population
$I(t)$	total immune cell population
$s(t)$	bursting rate of infected erythrocytes
$r(t)$	number of merozoites released per burst cell
k_s	infection rate of mature erythrocytes by merozoites
a_1	natural death rate of infected erythrocytes
a_y	natural death rate of merozoites
a_i	natural death rate of immune cells
a_c	clearance rate of infected cells due to immune system
a_h	clearance rate of merozoites due to immune system
λ_y	proliferation of immune cells in response to the merozoite population
λ_x	proliferation of immune cells in response to the infected population

4 Combining the Two Models

In order to combine these two models, we will drop equation (4) altogether, since it assumes a constant red blood cell production, and replace it with a slightly modified version of the erythropoiesis model.

To account for the presence of malaria, which has been shown in [7] to affect precursor erythrocyte development indirectly, we will make the following adjustments to (1A) and (2A):

$$\frac{\partial p(t,\mu)}{\partial t} + g(E(t))\frac{\partial p(t,\mu)}{\partial \mu} = \left[\sigma(t,\mu,E(t)) - H(X(t))\right] p(t,\mu) \tag{1B}$$

$$\frac{\partial m(t,\nu)}{\partial t} + \frac{\partial m(t,\nu)}{\partial \nu} = -\left[\gamma(t,\nu,M(t)) + k_s Y(t)\right] m(t,\nu) \tag{2B}$$

The affect that malaria has on precursor development is related to a toxin, hemozoin, that the merozoites produce as they consume hemoglobin inside an erythrocyte. This toxin suppresses precursor development inside the bone marrow.

4.1 The New, Combined Model

$$\begin{aligned}
&\frac{\partial p(t,\mu)}{\partial t} + g(E(t))\frac{\partial p(t,\mu)}{\partial \mu} = \left[\sigma(t,\mu,E(t)) - H(X(t))\right] p(t,\mu) && 0<\mu<\mu_F \quad 0<t<T\\
&\frac{\partial m(t,\nu)}{\partial t} + \frac{\partial m(t,\nu)}{\partial \nu} = -\left[\gamma(t,\nu,M(t)) + k_s Y(t)\right] m(t,\nu) && 0<\nu<\nu_F \quad 0<t<T\\
&\frac{dE(t)}{dt} = f(t,M(t)) - a_E(P(t))E(t) && 0<t<T\\
&\frac{dX(t)}{dt} = k_s Y(t)M(t) - \left[a_1 + s(t)\right] X(t) - a_c I(t)X(t) && 0<t<T\\
&\frac{dY(t)}{dt} = r(t)s(t)X(t) - a_y Y(t) - k_s M(t)Y(t) - a_h I(t)Y(t) && 0<t<T\\
&\frac{dI(t)}{dt} = \left[\lambda_y Y(t) + \lambda_x X(t)\right] I(t) - a_i I(t) && 0<t<T\\
&g(E(t))p(t,0) = \phi(t)E(t) && 0<t<T\\
&m(t,0) = g(E(t))p(t,\mu_F) && 0<t<T\\
&p(0,\mu) = p^0(\mu) && 0<\mu<\mu_F\\
&m(0,\nu) = m^0(\nu) && 0<\nu<\nu_F\\
&E(0)=E^0 \quad M(0)=M^0 \quad X(0)=X^0 \quad Y(0)=Y^0 \quad I(0)=I^0
\end{aligned} \tag{8.1}$$

5 Setting Up The Finite Difference

First we will divide up the intervals $[0,\mu_F]$, $[0,\nu_F]$, and $[0,T]$ into n_1, n_2, and K subintervals respectively. If we do this, then we can define $\Delta\mu = \frac{\mu_F}{n_1}$, $\Delta\nu = \frac{\nu_F}{n_2}$, and $\Delta t = \frac{T}{K}$. This allows us to define age and time at specific steps by:

$$\mu_i = i\Delta\mu \text{ for } i = 0,1,2,\ldots,n_1$$
$$\nu_j = j\Delta\nu \text{ for } j = 0,1,2,\ldots,n_2$$
$$t_k = k\Delta t \text{ for } k = 0,1,2,\ldots,K$$

Which motivates the step notation: $p(t_k,\mu_i) = p_i^k$.

Next we will define our backwards difference operators for age and forward difference operator for time.

$$D^-_{\Delta\mu}(\alpha_i^k) = \frac{\alpha_i^k - \alpha_{i-1}^k}{\Delta\mu} \qquad D^-_{\Delta\nu}(\alpha_j^k) = \frac{\alpha_j^k - \alpha_{j-1}^k}{\Delta\nu} \qquad D^+_{\Delta t}(\alpha_i^k) = \frac{\alpha_i^{k+1} - \alpha_i^k}{\Delta t}$$

These should look fairly familiar, as they resemble the prototype difference quotient, which, in a limit, leads to actual derivatives.

6 Applying The Finite Difference to the Model

If we replace all of the derivative operators in (8.1) with the appropriate difference operator and adopt the step notation, we get:

$$\frac{p_i^{k+1}-p_i^k}{\Delta t}+g^k\frac{p_i^{k+1}-p_{i-1}^{k+1}}{\Delta\mu}=\left[\sigma_i^k-H^k\right]p_i^{k+1} \tag{8.2.1}$$

$$\frac{m_j^{k+1}-m_j^k}{\Delta t}+\frac{m_j^{k+1}-m_{j-1}^{k+1}}{\Delta\nu}=-\left[\gamma_j^k+k_sY^k\right]m_j^{k+1} \tag{8.2.2}$$

$$\frac{E^{k+1}-E^k}{\Delta t}=f^k-a_E^kE^{k+1} \tag{8.2.3}$$

$$\frac{X^{k+1}-X^k}{\Delta t}=k_sM^{k+1}Y^k-\left[s^k+a_1+a_cI^k\right]X^{k+1} \tag{8.2.4}$$

$$\frac{Y^{k+1}-Y^k}{\Delta t}=r^ks^kX^{k+1}-\left[k_sM^{k+1}+a_y+a_hI^k\right]Y^{k+1} \tag{8.2.5}$$

$$\frac{I^{k+1}-I^k}{\Delta t}=\left[\lambda_yY^{k+1}+\lambda_xX^{k+1}\right]I^k-a_iI^{k+1} \tag{8.2.6}$$

$$g^kp_0^{k+1}=\phi^kE^k \tag{8.2.7}$$

$$m_0^{k+1}=g^kp_{n_1}^{k+1} \tag{8.2.8}$$

Notice that terms on the right which are negative get $k+1$ time-steps while terms which are positive get k. We will see later that this allows us to get a strictly non-negative solution, which biologically makes sense.

6.1 Solving for the k+1 Step

Taking the first equation from the discretized system, (8.2.1), we will attempt to solve for the k+1 term.

$$\begin{aligned}\frac{p_i^{k+1}-p_i^k}{\Delta t}+g^k\frac{p_i^{k+1}-p_{i-1}^{k+1}}{\Delta\mu}-\left[\sigma_i^k-H^k\right]p_i^{k+1}&=0\\ \left(p_i^{k+1}-p_i^k\right)+g^k\frac{\Delta t}{\Delta\mu}\left(p_i^{k+1}-p_{i-1}^{k+1}\right)-\Delta t\left(\sigma_i^k-H^k\right)p_i^{k+1}&=0\\ -g^k\frac{\Delta t}{\Delta\mu}p_{i-1}^{k+1}+\left(1+g^k\frac{\Delta t}{\Delta\mu}-\Delta t\left(\sigma_i^k-H^k\right)\right)p_i^{k+1}&=p_i^k\end{aligned} \tag{9}$$

Notice that we have two different $k+1$ terms, one a age-step $i-1$ and one at age-step i. Equation (9), paired with the first boundary condition, (8.2.7), gives us the rules for building a matrix equation for this approximation.

To simplify this down a bit, we make the following definitions:
First is the variable vector. Eventually, we will be solving for this term:

$$\vec{p}^{k+1}=\left[p_0^{k+1},\,p_1^{k+1},\,\ldots,\,p_{n_1}^{k+1}\right]'$$

Next is the coefficient of the p_i^{k+1} term:

$$d_{1,i}^k=1+g^k\frac{\Delta t}{\Delta\mu}-\Delta t\left(\sigma_i^k-H^k\right),\quad i=1,2,...,n_1$$

Here is a vector representing the right hand side of equation (9). Notice that the first entry comes from the boundary condition:

$$\vec{b}_1^k = \left[\phi^k E^k,\, p_1^k,\, \ldots,\, p_{n_1}^k\right]'$$

And lastly is the characteristic matrix for the system, containing the coefficients of our variables:

$$A_1^k = \begin{pmatrix} g^k & 0 & 0 & \cdots & 0 & 0 \\ -g^k \frac{\Delta t}{\Delta \mu} & d_{1,1}^k & 0 & \cdots & 0 & 0 \\ 0 & -g^k \frac{\Delta t}{\Delta \mu} & d_{1,2}^k & \cdots & 0 & 0 \\ \cdots & \cdots & \cdots & \ddots & \cdots & \cdots \\ 0 & 0 & 0 & \cdots & -g^k \frac{\Delta t}{\Delta \mu} & d_{1,n_1}^k \end{pmatrix}$$

Using these definitions, equation (9) can be written as $A_1^k \vec{p}^{k+1} = \vec{b}_1^k$. Similar steps can be taken to get a matrix equation for (8.2.2).

6.2 The Complete Finite Difference Solution

With a little bit of algebra, the other equations (8.2.3,4,5,6) can be solved for the k+1 terms and we get the following system:

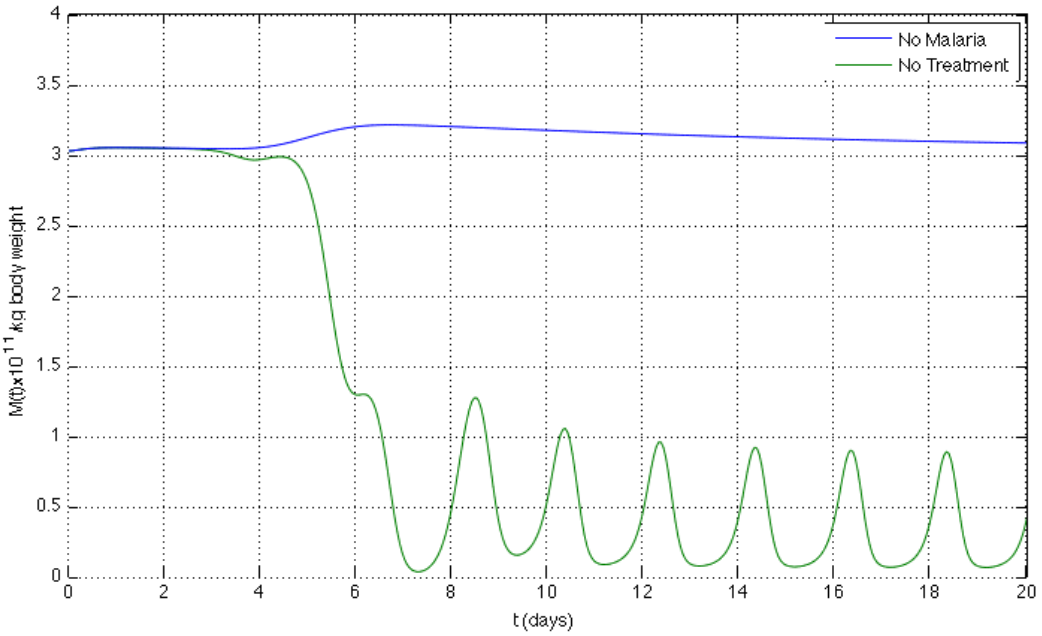
$$\begin{aligned} \vec{p}^{k+1} &= \bar{A}_1^k \vec{b}_1^k \\ \vec{m}^{k+1} &= \bar{A}_2^k \vec{b}_2^k \\ E^{k+1} &= \frac{E^k + \Delta t f^k}{1 + \Delta t a_E^k} \\ X^{k+1} &= \frac{X^k + \Delta t k_s M^{k+1} Y^k}{1 + \Delta t \left(a_1 + s^k + a_c I^k\right)} \\ Y^{k+1} &= \frac{Y^k + \Delta t r^k s^k X^{k+1}}{1 + \Delta t \left(k_s M^{k+1} + a_y + a_h I^k\right)} \\ I^{k+1} &= \frac{I^k \left(1 + \Delta t \left(\lambda_y Y^{k+1} + \lambda_x X^{k+1}\right)\right)}{1 + \Delta t a_i} \end{aligned}$$

Notice that since all the terms are naturally positive, and none are subtracted, so this system gives strictly non-negative solutions. The system is now ready to be programmed.

7 Generated Solutions

It's important to remember that since we're dealing with biologically processes, the quantitative difference between simulations doesn't mean very much; however, qualitatively, we should at least be able to determine which situations are more preferable and what kind of trends the treatments have.

The figure below shows graphs for when the person has no malaria (blue line) and untreated malaria (green line). The beginning of day 0 is when the merozoites leave the liver and start to roam the bloodstream. We will consider the no malaria case to be the benchmark for health when comparing other situations.



The no treatment case shows a staggering drop in healthy erythrocyte count between days 5 and 8, with a ∼100 fold drop. The periodic behavior seen in the no treatment case is due to the approximate 2 day infection period of the erythrocytes by merozoites (that is, a merozoite infects an erythrocyte, feeds and multiplies for two days, then the merozoites destroy the cell and move back into the bloodstream).

7.1 Treatment

First, we need to decide what we will treat. For what is presented here, we have decided on treating $r(t)$, the number of released merozoites from a burst infected erythrocyte, and $H(X(t))$, the precursor development suppression due to hemozoin toxin levels. Although there currently are methods for reducing r, the effect of hemozoin is currently not treatable, so we will also be attempting to determine if it's a worthwhile treatment course.

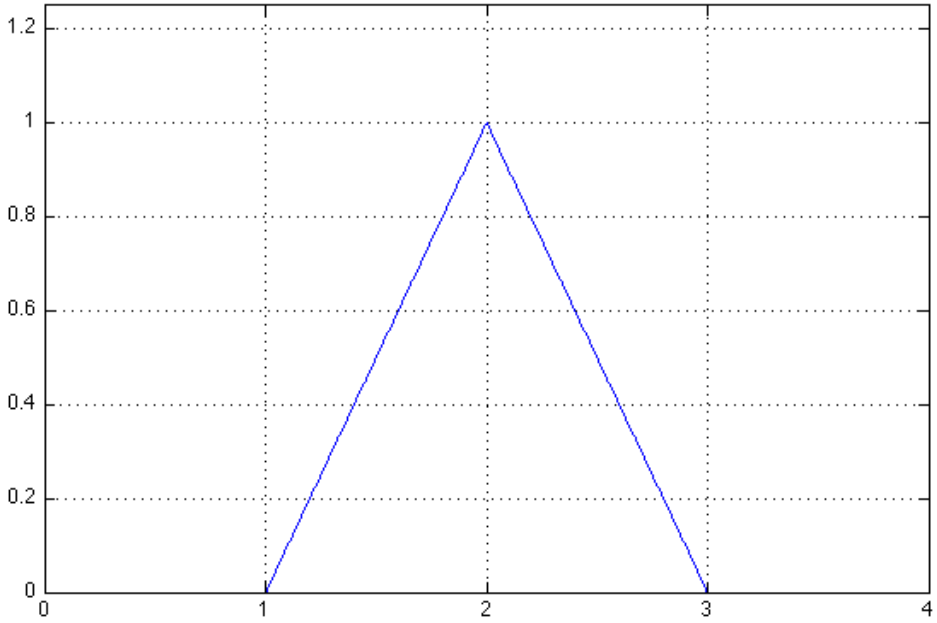
We also need a way to objectively determine which treatments are better. To that end we have designed a functional that quantifies a treatment, and we will attempt to find an $r(t)$ and $H(X(t))$ that minimizes it. The functional is as follows:

$$J(r(t), H(X(t))) = \frac{w_1}{T}\int_0^T |M(t) - \bar{M}_{\text{healthy}}|dt + \frac{w_2}{T}\int_0^T (X(t) + Y(t))dt$$

$$+\frac{w_3}{T}\int_0^T e^{-r(t)}dt + \frac{w_4}{T}\int_0^T \left(-\frac{H(X(t))}{2} + 1\right)dt$$

J computes the average deviation of the erythrocyte count from the healthy amount, the average population size of infected erythrocytes and merozoites, and the average health costs for treating the malaria infection. The expressions for the health costs, terms 3 and 4, were chosen based on the necessity for decreasing functions and range of values encountered under the no treatment case. The w_i terms are weights, which should sum to 1 and can be chosen based on the importance of each factor. Also, keep in mind that the health costs to which we refer are both medicinal expense and potential side effects from overdosing.

The method for choosing functions for $r(t)$ and $H(X(t))$ is to build piecewise linear functions for each of them, with a certain number of parameters. This is facilitated by defining a function, $\hat{\phi}(\vec{x}, i)$, that takes a vector of points on the x-axis, and builds a function that is 1 at x_i, 0 at the other x_j and connects the points with line segments. For example, let $x = [\ 0\ 1\ 2\ 3\ 4\ ]$ and let $i = 3$, then $\hat{\phi}(\vec{x}, i)$ returns the following function:



Using this to build $r(t)$ and $H(X(t))$, the functional J is then minimized by choosing appropriate parameters. For example, say we've decided that we will treat r on days 3, 6, 9, 12, 15, 18, and 20. We then build an interval vector:

$$\vec{x} = [\ 0\ 3\ 6\ 9\ 12\ 15\ 18\ 20\ ]$$

which defines the days on which treatment factors are changed. Then we choose an initial guess (representing a proportion of the no treatment value) for what we think a good treatment would be, say:

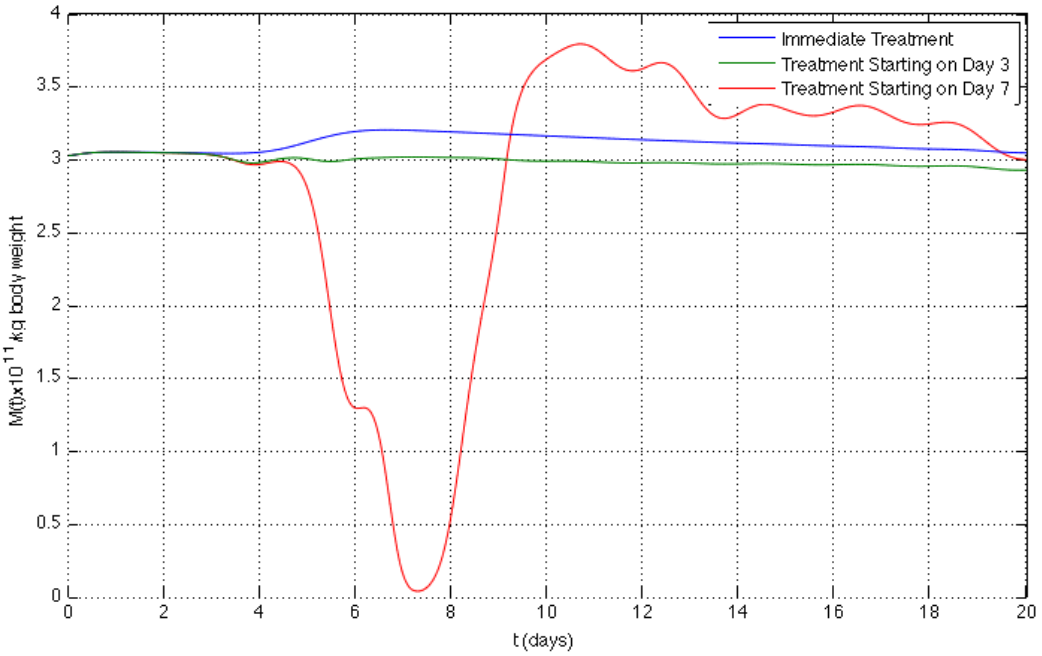
$$\vec{\alpha} = [\ 1.0\ 1.0\ 0.3\ 0.2\ 0.4\ 0.5\ 0.5\ 0.5\ ]$$

Notice that the first two are 1.0 because treatment doesn't start until day 3, and at the beginning of day 3, it's still the default value. So this treatment vector says, from day 3 to day 6, treat r so that on day 6, it is 30% of it's default value, then start treating so that by day 9 it's 20%, etc. The function $r(t)$ is then given, overall, by:

$$r(t) = \sum_{i=1}^{8} \alpha_i \hat{\phi}(\vec{x}, i)$$

We then feed the interval vector and initial guess (with constraints that the first two elements of the guess vector can't be modified) to a function that will minimize J based on the parameters (that is, it will adjust our guess until an optimal solution is found).

Below is a figure showing three optimal treatments starting on different days. The weights for these were $w_1 = w_2 = 0.35$ and $w_3 = w_4 = 0.15$, suggesting a strong lean toward stopping the infection, while not being overly concerned with, but not ignoring, the health costs.



The outlook is good for someone who is able to seek treatment immediately (though this case is a bit unrealistic) and someone seeking treatment by day 3. However, a person waiting until day 7 has to endure the large dip in healthy erythrocyte count.

The optimal treatment solution for immediate treatment was to treat both r and H down to about one fifth of their original values for the entire 20 day period. Treatment was more drastic for day 3, which was to reduce them to practically zero by day 6, ease off to about one tenth by day 8, and then hold around one sixth for the remainder of the 20 days. Treatment for day 7 was somewhat similar to the day 3 case, but with stronger treatments for the secondary and tertiary treatment intervals (about one twelfth to one tenth for the day 9 to day 13 and day 13 to day 20 respectively).

8 Conclusion

So we've seen that optimal treatments exist, however, we've also seen that waiting until day 7 may have catastrophic consequences. It would probably be realistic to assume that a person would seek treatment somewhere between day 3 and day 6. Further research goals are to collect data for more situations, especially for different starting days and different weight factors, and to refine the treatment vector to see if the optimal treatment course remains the same when increasing the opportunity to adjust the treatment.

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