Malaria

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Abstract

Abstract In this paper we model parasite development in infected blood cells via an age structured population equation coupled to a boundary condition which yields the number of newly infected cells at time t of age zero in terms of the number of cells which burst at time t and release daughter parasites into the blood stream which quickly invade uninfected red blood cells. Sharp conditions for the existence of nontrivial equilibrium distributions are established as are conditions for the stability of the trivial and non-trivial equilibrium distributions. When these conditions are violated, steady state oscillatory solutions are established and these are examined.

1 Introduction

Most mathematical models of malaria take the form of an age-structured population equation

$$\frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} = -D(a,t)n, \ \ 0 \le a < \infty \text{ and } 0 < t, \tag{1.1}$$

where $n(a,t)$ represents the concentration of infected blood cells at time t which are a units old. The death rate, $D(\cdot,\cdot)$, is typically assumed to be of the form

$$D(a,t) = d_0(a) + \sum_{i=1}^{p} \lambda_i(n(\cdot,t))d_i(a) \tag{1.2}$$

where the functions $a \to d_i(a)$, $0 \le i \le p$, are non-negative on $a \ge 0$ and the mappings $N \to \lambda_i(N)$, $1 \le i \le p$, are assumed to be continuous linear functionals on bounded continuous functions on $[0, \infty)$ which map non-negative functions into R^+. Typical such functionals are $\int_{T_1}^{T_2} N(a)da$. If we note that infected red blood cells tend to burst when they are approximately 48 hours old and recognize that each burst cell releases daughter parasites that quickly invade healthy red blood cells to renew the malaria cycle, we find we are provided with a mechanism to connect $n(0,t)$ to the tail of the distribution $n(\cdot,t)$ for a near 48 and a much needed boundary condition. The specific details of the boundary condition are not particularly important. We work with

$$n(0,t) = R(t)N_{[T_3,T_4]}(t) \tag{1.3}$$

where

$$N_{[T_3,T_4]}(t) = \int_{T_3}^{T_4} n(a,t)da \tag{1.4}$$

and $T_4/2 < T_3 \leq 48 \leq T_4$. Following Rouzine and McKenzie [1] we assume that

$$R(t) = R_0 \exp(-\mu N_{[T_3,T_4]}(t)), \quad 0 < R_0 \text{ and } 0 < \mu. \tag{1.5}$$

An equally satisfactory and a somewhat more tractable theory would result if we instead insisted that

$$n(0,t) = R_0 \exp(-\mu n(48,t)) n(48,t). \tag{1.6}$$

Our goal is a comprehensive analysis of solutions of (1.1) satisfying the initial conditions

$$n(a,0) = n_0(a) \geq 0 \quad , \quad 0 \leq a \tag{1.7}$$

and the boundary conditions (1.3)-(1.5) or (1.6). In particular we would like to know (i) when solutions converge to the trivial equilibrium, $n(a,t) \equiv 0$, (ii) when there exists a secondary equilibrium solution and when this solution is stable and (iii) when do solutions oscillate indefinitely and fail to converge to an equilibrium. Though these are essentially mathematical issues some of our estimates could, conceivably, give some indications for an effective drug treatment strategy to kill off the disease.

Before proceeding with the program outlined above we would like to say a few words about the connection between the continuous model used here and the compartmental models studied by many other authors; for details see [2] - [4]. For simplicity we let $\Delta a = \frac{48}{K}$, K an integer, be the length of a compartment and we assume that

$$T_3 = K_3 \Delta a \quad \text{and} \quad T_4 = K_4 \Delta a \tag{1.8}$$

where $K_3 \leq K \leq K_4$ are integers. For any $1 \leq j \leq K_4$ we let

$$N_j(t) = \frac{1}{\Delta a} \int_{(j-1)\Delta a}^{j\Delta a} n(a,t)da \tag{1.9}$$

represent the cell average of the density $n(\cdot, t)$ over the interval $((j-1)\Delta a, j\Delta a)$ and we assume that each of the functions $d_i(\cdot),\ 0 \le i \le p$, in (1.2) are constant in $((j-1\Delta a, j\Delta a)$; i.e. that

$$d_i(a) = d_{i,j} \quad , \quad (j-1)\Delta a < a < j\Delta a \tag{1.10}$$

and

$$D(a,t) = D_j(t) \stackrel{def}{=} d_{0,j} + \sum_{i=1}^{p} \lambda_i(N_{(\cdot)}(t)) d_{i,j} \quad , \quad (j-1)\Delta a < a < j\Delta a. \tag{1.11}$$

To obtain the compartmental model for the cell averages one integrates (1.1) from $(j-1)\Delta a$ to $j\Delta a$ and notes that since information propagates from left to right (the characteristics of (1.1) are the curves satisfying $\frac{da}{dt} = 1$) a consistent approximation to the flux $n(j\Delta a, t)$ is $N_j(t)$. The resulting compartmental equations are

$$\frac{dN_j}{dt} = \frac{1}{\Delta a}(N_{j-1} - N_j) - D_j(t) N_j \quad , \quad 1 \le j \le K_4. \tag{1.12}$$

For $N_0(t)$ we use the discrete version of the boundary condition (1.3) - (1.5), namely the equation

$$N_0(t) = R_0 N_{[K_3,K_4]}(t) \exp\left(-\mu N_{[K_3,K_4]}(t)\right) \tag{1.13}$$

where

$$N_{[K_3,K_4]}(t) = \Delta a \sum_{j=K_3+1}^{K_4-1} N_j(t). \tag{1.14}$$

2 Equilibrium Solutions and Their Stability

We start by looking for equilibrium or time independent solutions of (1.1). These satisfy

$$\frac{dn_{eq}}{da} = D(a) n_{eq} \quad , \quad 0 \le a \tag{2.1}$$

where now

$$D(a) = d_0(a) + \sum_{i=1}^{p} \lambda_i(n_{eq}(\cdot)) d_i(a) \tag{2.2}$$

and again $a \to d_i(a),\ 0 \le i \le p$, are non-negative on $0 \le a$ and the mappings $n_{eq}(\cdot) \to \lambda_i\ (n_{eq}(\cdot)),\ 1 \le i \le p$, are continuous linear functionals on bounded continuous functions on $[0, \infty)$ which map non-negative functions into R^+.

Solutions to (2.1) satisfying (1.3) - (1.5) are

$$n_{eq}(a) = n_{eq}(0)\ \exp\left(-\int_0^a D(r)dr\right) \tag{2.3}$$

where

$$n_{eq}(0) = R_0 A\ \exp(-\mu A) \tag{2.4}$$

and

$$A = \int_{T_3}^{T_4} n_{eq}(a)da \geq 0. \tag{2.5}$$

Combining (2.3) - (2.5) we arrive at the following equation for A:

$$A = R_0 A\ \exp(-\mu A) \int_{T_3}^{T_4} \exp\left(-\int_0^a d_0(r)dr\right) \exp\left(-\int_0^a \sum_{j=1}^{p} \mu_j d_j(r)dr\right) da \tag{2.6}$$

where $\mu_j \stackrel{def}{=} \lambda_j(n_{eq}(\cdot)),\ 1 \leq j \leq p$. These satisfy

$$\mu_i = R_0 A\ \exp(-\mu A)\lambda_i \left(\exp\left(-\int_0^{\cdot} \left(d_0(r) + \sum_{j=1}^{p} \mu_j d_j(r)\right) dr\right)\right),\quad 1 \leq i \leq p. \tag{2.7}$$

One solution of (2.6) and (2.7) is $A = \mu_1 = \ldots = \mu_p = 0$ which of course yields $n_{eq}(a) \equiv 0$ and any other solution must satisfy

$$1 = R_0\ \exp(-\mu A) \int_{T_3}^{T_4} \exp\left(-\int_0^a d_0(r)dr\right) \exp\left(-\int_0^a \sum_{j=1}^{p} \mu_j d_j(r)dr\right) da \tag{2.8}$$

and $(2.7)_i$, $1 \leq i \leq p$.

For illustrative purposes we shall restrict our attention to the case when only one linear functional is present in $D(\cdot)$, that is where

$$D(a) = d_0 + \lambda_1(n_{eq}(\cdot))d_1(a)\quad ,\quad 0 \leq a. \tag{2.9}$$

Then (2.7) and (2.8) reduce the system

$$1 = R_0 \exp(-\mu A) \int_{T_3}^{T_4} \exp\left(-\int_0^a d_0(r)dr\right) \exp\left(-\mu_1 \int_0^a d_1(r)dr\right) da \tag{2.10}$$

and

$$\mu_1 = R_0 A \exp(-\mu A)\lambda_1 \left(\exp\left(-\int_0^{\cdot} \left(d_0(r) + \mu_1 d_1(r)\right) dr\right)\right). \tag{2.11}$$

Our interest is when there exist solutions to (2.10) and (2.11) with $A > 0$ and $\mu_1 > 0$. We first note that the function defined by the right hand side of (2.10) satisfies the bound

$$R_0\exp(-\mu A)\int_{T_3}^{T_4}\exp\left(-\int_0^a d_0(r)dr\right)\exp\left(-\mu_1\int_0^a d_1(r)dr\right)da \le R_0\int_{T_3}^{T_4}\exp\left(-\int_0^a d_0(r)dr\right)da \tag{2.12}$$

on $A \ge 0$ and $\mu_1 \ge 0$ and thus if

$$R_0\int_{T_3}^{T_4}\exp\left(-\int_0^a d_0(r)dr\right)da < 1, \tag{2.13}$$

then (2.10) and (2.11) have no solutions satisfying $A > 0$ and $\mu_1 > 0$. Later, we shall show that if (2.13) holds, then the trivial equilibrium $n_{eq}(a) \equiv 0,\ 0 \le a$, is exponentially asymptotically stable on compact intervals $0 \le a \le \overline{a}$.

If, on the other hand, the inequality

$$1 < R_0\int_{T_3}^{T_4}\exp\left(-\int_0^a d_0(r)dr\right)da \tag{2.14}$$

holds, then (2.10) and (2.11) have a solution satisfying $A > 0$ and $\mu_1 > 0$. To establish this assertion we first note that for any $0 < \mu_1$ such that

$$1 < R_0\int_{T_3}^{T_1}\exp\left(-\int_0^a d_0(r)dr\right)\exp\left(-\mu_1\int_0^a d_1(r)dr\right)da \tag{2.15}$$

equation (2.10) has a unique solution

$$A(\mu_1) = \frac{1}{\mu}ln\left(R_0\int_{T_3}^{T_4}\exp\left(-\int_0^a d_0(r)dr\right)\exp\left(-\mu_1\int_0^a d_1(r)dr\right)da\right) > 0 \tag{2.16}$$

satisfying

$$\frac{dA}{d\mu_1} = -\frac{\displaystyle\int_{T_3}^{T_4}\exp\left(-\int_0^a d_0(r)dr\right)\exp\left(-\mu_1\int_0^a d_1(r)dr\right)\int_0^a d_1(r)drda}{\displaystyle\mu\int_{T_3}^{T_4}\exp\left(-\int_0^a d_0(r)dr\right)\exp\left(-\mu_1\int_0^a d_1(r)dr\right)da} < 0. \tag{2.17}$$

In the sequel, we let $\overline{\mu}_1 > 0$ be the unique solution of

$$R_0\int_{T_3}^{T_4}\exp\left(-\int_0^a d_0(r)dr\right)\exp\left(-\overline{\mu_1}\int_0^a d_1(r)dr\right)da = 1 \tag{2.18}$$

and note that $\lim_{\mu_1\to\overline{\mu_1}} A(\mu_1) = 0$. To complete our proof we must show that the equation

$$\mu_1 - R_0 A(\mu_1)\exp\left(-\mu A(\mu_1)\right)\lambda_1\left(\exp\left(-\int_0^a (d_0(r)+\mu_1 d_1(r))\,dr\right)\right) = 0 \tag{2.19}$$

has a solution. We note that the function defined by the left-hand side of (2.19) is negative at $\mu_1 = 0$, positive at $\overline{\mu_1}$, and continuous in the parameter μ_1. Thus, the intermediate value theorem guarantees that the equation has a zero for some $\mu_1 \in (0, \overline{\mu_1})$ and that $A(\mu_1) > 0$.

We now turn out attention to the stability of the various equilibria. For definiteness we again limit our attention to the situation where

$$D(a,t) = d_0(a) + \lambda_1(n(\cdot,t))d_1(a) \quad , \quad 0 \le a. \tag{2.20}$$

We start with a representation of the solution to (1.1) satisfying

$$n(a,0) = n_0(a) \quad , \quad 0 \le a \tag{2.21}$$

and the boundary condition (1.3) - (1.5). In the region $t \le a$ the solution is given by

$$n(a,t) = n_0(a-t)\exp\left(-\int_0^t (d_0(a-t+r) + \lambda_1(n(\cdot,r))d_1(a-t+r))\,dr\right) \tag{2.22}$$

while in the region $a < t$

$$n(a,t) = R_0 N_{[T_3,T_4]}(t-a)\exp\left(-\mu N_{[T_3,T_4]}(t-a)\right)\exp\left(-\int_0^a (d_0(r) + \lambda_1\left(n(\cdot, t-a+r)\right)d_1(r))\,dr\right) \tag{2.23}$$

and again

$$N_{[T_3,T_4]}(t) \stackrel{def}{=} \int_{T_3}^{T_4} n(a,t)da. \tag{2.24}$$

If $T_4 \le t,\ N_{[T_3,T_4]}(\cdot)$ satisfies

$$N_{[T_3,T_4]}(t) = R_0 \int_{T_3}^{T_4} N_{[T_3,T_4]}(t-a)\exp\left(-\mu N_{[T_3,T_4]}(t-a)\right)\exp\left(-\int_0^a (d_0(r) + \lambda_1\left(n(\cdot,t-a+r)\right)d_1(r))\,dr\right)da. \tag{2.25}$$

The formulas (2.22) and (2.23) may also be used to obtain a functional equation for $\mu_1(t) \stackrel{def}{=} \lambda_1(n(\cdot,t)) \ge 0$.

The observation that $n \to R_0 n\ \exp(-\mu n)$ is non-negative and bounded from above by $R_0\ \exp(-1)/\mu$ on $[0,\infty)$, the hypothesis that the linear functional $\lambda_1(\cdot)$ maps non-negative functions into R^+, and the representation (2.22) and (2.23) guarantee that

$$0 \leq n(a,t) \leq M \stackrel{def}{=} \max \left[\sup_{0 \leq a} n_0(a),\ R_0 \exp\,(-1)/\mu \right]. \tag{2.26}$$

Moreover, on $T_4 \leq t,\ N_{[T_3,T_4]}(t)$ satisfies

$$0 \leq N_{[T_3,T_4]}(t) \leq R_0 \int_{T_3}^{T_4} \exp\left(- \int_0^a d_0(r)dr \right) \sup_{T_3 \leq a \leq T_4} N_{[T_3,T_4]}(t-a) \tag{2.27}$$

and this last inequality, along with (2.26) and $T_4/2 \leq T_3$, guarantees that if

$$\Lambda \stackrel{def}{=} R_0 \int_{T_3}^{T_4} \exp\left(- \int_0^a d_0(r)dr \right) < 1, \tag{2.28}$$

then

$$0 \leq \eta_{(k)} \stackrel{def}{=} \sup_{kT_4 \leq t \leq (k+1)T_4} N_{[T_3,T_4]}(t) \tag{2.29}$$

satisfies

$$0 \leq \eta_{(k)} \leq \Lambda^k \eta_{(0)}. \tag{2.30}$$

The latter inequality guarantees that on any compact interval $0 \leq a \leq \overline{a},\ n(\cdot,t)$ tends to zero at an exponential rate. With a little more work it is not difficult to show that if $1 < \Lambda$, then the solution $0 \equiv n(a,t)$ is linearly unstable. Recall, when $1 < \Lambda$ we are guaranteed the existence of an alternate non-trivial equilibria.

We now turn to the linear stability of the non-trivial equilibrium when $\Lambda > 1$. The simplest situation is when

$$D(a,t) \equiv d_0(a),\ 0 \leq a. \tag{2.31}$$

In that case we look for solutions of (1.1) of the form

$$n(a,t) = n_{eq}(a) + \delta u(a,t),\ 0 < \delta << 1 \tag{2.32}$$

and find the approximating linearized equations for $u(\cdot,\cdot)$ are

$$\frac{\partial u}{\partial t} + \frac{\partial u}{\partial a} = -d_0(a)u,\ 0 \leq a < \infty \text{ and } 0 < t \tag{2.33}$$

$$u(a,0) = u_0(a),\ 0 \leq a \tag{2.34}$$

and

$$u(0,t) = R_0 \exp(-\mu A)(1 - \mu A) u_{[T_3,T_4]}(t) \tag{2.35}$$

where

$$1 = R_0 \exp(-\mu A) \int_{T_3}^{T_4} \exp\left(-\int_0^a d_0(r)dr\right) da, \tag{2.36}$$

$$u_{[T_3,T_4]}(t) = \int_{T_3}^{T_4} u(a,t)da, \tag{2.37}$$

and

$$T_4/2 \leq T_3 < T_4. \tag{2.38}$$

The system (2.35) - (2.37) may be integrated along characteristics and for times $T_4 \leq t$ we obtain the following integral equation for $u_{[T_3,T_4]}(\cdot)$

$$u_{[T_3,T_4]}(t) = R_0 \exp(-\mu A)(1-\mu A) \int_{T_3}^{T_4} \exp\left(-\int_0^a d_0(r)dr\right) u_{[T_3,T_4]}(t-a)da. \tag{2.39}$$

On the interval $0 \leq t \leq T_3$, $u_{[T_3,T_4]}(\cdot)$ is completely determined by the initial conditions while for $T_3 < t < T_4$, $u_{[T_3,T_4]}(\cdot)$ satisfies an equation similar to (2.39). We note that (2.36), (2.39), and the integral mean value theorem imply that for $T_4 \leq t$

$$u_{[T_3,T_4]}(t) = (1-\mu A) u_{[T_3,T_4]}(t - a_1(t)) \tag{2.40}$$

for some $T_3 \leq a_1(t) \leq T_4$. The last identity implies that for $kT_4 \leq t < (k+1)T_4$ we can write

$$u_{[T_3,T_4]}(t) = (1-\mu A)^{p(k)} u_{[T_3,T_4]}\left(t - \sum_{j=1}^{p(k)} a_j(t)\right) \tag{2.41}$$

where $a_I(t)$ is such that

$$u_{[T_3,T_4]}\left(t - \sum_{j=1}^{I-1} a_j(t)\right) = (1-\mu A) u_{[T_3,T_4]}\left(t - \sum_{j=1}^{I} a_j(t)\right) \tag{2.42}$$

and

$$T_3 \leq a_I(t) \leq T_4. \tag{2.43}$$

The index $p(k) \geq k$ is the smallest integer so that

$$0 \leq t - \sum_{j=1}^{p(k)} a_j(t) \leq T_4. \tag{2.44}$$

The identity (2.41) implies that if

$$0 < A < \frac{2}{\mu} \tag{2.45}$$

the solutions are linearly exponentially stable while if

$$\frac{2}{\mu} < A \tag{2.46}$$

they are linearly exponentially unstable. The stability analysis when $D(a,t)$ is given by (2.20) is considerably more complicated. One scenario with conditions similar to (2.45) and (2.46) is when the function $d_1(\cdot)$ satisfies

$$d_1(a) = \begin{cases} 0, & a \notin [T_1, T_2] \\ > 0, & a \in (T_1, T_2) \end{cases}, \tag{2.47}$$

when the linear functional $\lambda_1(\cdot)$ is determined by the restriction of the function $a \to n(a)$ to the interval $[T_5, T_6]$, and finally when $0 \le T_5 < T_6 < T_1 < T_2 < T_3 < T_4$. There one obtains the estimate that

$$|\lambda_1(u(\cdot,t))| \le (1+\mu_1)|1-\mu A| \sup_{T_5 \le a \le T_6} \left| u_{[T_3,T_4]}(t-a) \right| \tag{2.48}$$

and this estimate is sufficient to guarantee that if

$$(1+\mu_1)|1-\mu A| < 1, \tag{2.49}$$

then $t \to u_{[T_3,T_4]}(t)$ converges at an exponential rate. We conjecture that if (2.49) is strictly violated, then the solutions to (2.33) - (2.37) is linearly exponentially unstable but we have not succeeded in showing this. One other case that yields similar results is when $\lambda_1(u(\cdot,t)) = u_{[T_3,T_4]}(t)$.

One of the reasons we gave something less than an exhaustive analysis of (1.1) when $D(\cdot,\cdot)$ was given by (1.2) was the realization that if $d_0(\cdot)$ and R_0 do not satisfy (2.28) there was nothing that the additional terms, $\sum_{j=1}^{p} \lambda_j(n(\cdot,t))d_j(a)$, in $D(\cdot,\cdot)$ could do to turn the situation around and make $n(a,t) \equiv 0$ exponentially asymptotically stable. This observation would suggest that any effective drug therapy to treat malaria would have to focus on making $0 < R_0$ smaller or $a \to d_0(a), 0 \le a$, larger; the nonlinear terms in the system simply are not going to save the day.

3 Computational Experiments and Conclusions

In this section we present some computational experiments with the system (1.1) - (1.5). Throughout time is measured in hours and we choose

$$\Delta a = \Delta t = 1 \text{ minute } = 1/60 \text{ hours}.$$

We work on the computational grid

$$a_k = k\Delta a,\ 0 \le k \text{ and } t_n = n\Delta t,\ 0 \le n. \tag{3.1}$$

and we let n_k^n denote the approximate values of $n(a_k, t_n)$, i.e.

$$n_k^n \,\hat{=}\, n(a_k, t_n). \tag{3.2}$$

For definiteness we choose

$$T_3 = 46 \text{ hours and } T_4 = 50 \text{ hours}. \tag{3.3}$$

This choice yields

$$K_3 = 2760 \text{ and } K_4 = 3000. \tag{3.4}$$

To integrate the system we use a characteristic Euler method to obtain

$$n_k^{n+1} = \exp\left(-\Delta a\left(d_{0,k-1} + \sum_{j=1}^{p} \mu_j^n d_{j,k-1}\right)\right) n_{k-1}^n,\ 1 \le k \le K_4 \tag{3.5}$$

where

$$d_{i,k} = d_i(a_k),\ 0 \le k \text{ and } 0 \le i \le p. \tag{3.6}$$

We further let

$$N_{[K_3,K_4]}^{n+1} = \Delta a \sum_{k=K_3}^{K_4-1} n_k^{n+1} \tag{3.7}$$

and

$$n_0^{n+1} = R_0 N_{[K_1,K_4]}^{n+1} \exp\left(-\mu N_{[K_3,K_4]}^{n+1}\right). \tag{3.8}$$

The numbers μ_j^{n+1} are computed by applying the linear functionals $\lambda_j(\cdot)$ to the piecewise linear interpolates

$$\tilde{n}^{n+1}(a) = n_k^{n+1} + \frac{(a-a_k)}{\Delta a}\left(n_{k+1}^{n+1} - n_k^{n+1}\right),\ a_k \le a \le a_{k+1} \text{ and } 0 \le k \le K_4. \tag{3.9}$$

We are of course assuming that the linear functionals are determined by function values on the interval $0 \le a \le T_4$. The algorithm presented in (3.5) - (3.8) satisfies estimates analogous to those of the continuous system (1.1) - (1.5). Specifically, if we let

$$M \overset{def}{=} \max\left(\max_{0\le k\le K_4} n_k^0,\ R_0 \frac{\exp(-1)}{\mu}\right) \tag{3.10}$$

and

$$\lambda_{j,1} = \lambda_j(1);\ 1 \leq j \leq p, \tag{3.11}$$

then

$$0 \leq n_k^n \leq M,\ 0 \leq k \leq K_4 \text{ and } 0 \leq n \tag{3.12}$$

$$0 \leq \mu_j^n \leq M\lambda_{j,1},\ 1 \leq j \leq p \tag{3.13}$$

$$0 \leq N^n_{[K_3,K_4]} \leq M(T_4 - T_3). \tag{3.14}$$

When $\Delta a R_0 \sum_{k=K_3}^{K_4-1} \exp\left(-\Delta a \sum_{m=0}^{k-1} d_{0,m}\right) > 1$ the discrete equations (1.1) - (1.5) have non-trivial equilibria analogous to those constructed in section 2.

All of our computations were run with

$$d_0(a) = \begin{cases} .025 & , \quad 0 \leq a < T_2 \\ 0 & . \quad T_2 \leq a < T_3 \\ .5 & , \quad T_3 \leq a < T_4 \end{cases} \tag{3.15}$$

and, as stated previously, $T_3 = 46$ and $T_4 = 50$. We allowed T_2 to vary over the range 8 to 24. We employed two linear functionals

$$\lambda_1 = C_1 N_{[T_3,T_4]}(t) \text{ and } \lambda_2 = C_2 N_{[0,T_2]}(t) \tag{3.16}$$

where $C_1 > 0$ and $C_2 > 0$ were varied. Finally

$$d_1(a) = \begin{cases} 1 & , \quad 0 \leq a < T_2 \\ 0 & , \quad T_2 \leq a < T_3 \\ 1 & , \quad T_3 \leq a < T_4 \end{cases} \tag{3.17}$$

and

$$d_2(a) = \begin{cases} 1 & , \quad 0 \leq a < T_2 \\ 0 & , \quad T_2 \leq a < T_4 \end{cases} \tag{3.18}$$

and throughout $\mu = 1$.

The first set of simulations were run with $T_2 = 12$. With our choice of $d_0(\cdot)$ the trivial equilibrium, $n_{eq}(a) \equiv 0$, is stable so long as

$$0 \leq R_0 < \frac{\exp(.3)}{1 - \exp(-2)} = .7806\ldots \tag{3.19}$$

and the non-constant equilibrium is stable for

$$.7806\ldots < R_0 < 5.7677\ldots \tag{3.20}$$

Figure 1 shows four distinct equilibrium density profiles, $a \to n_{eq}(a)$. All were run with $R_0 = 3$ and $T_2 = 12$. The black profile was run with $(C_1, C_2) = (0, 0)$, the blue with $(C_1, C_2) = (0.01, 0)$, the green with $(C_1, C_2) = (0, 1)$, and finally the red curve with $(C_1, C_2) = (0.01, 1)$.

Figures 2 - 8 show the type of oscillations which may be expected when the non-constant equilibrium becomes unstable. All Figures were run with the death rate $d_0(\cdot)$ given by (3.15) and $R_0 = 20$, a situation well into the unstable region. All simulations were run with a random seed for the initial data $a \to n(a, 0)$ until such a time that steady state oscillations had been established. The top frame in each Figure gives a snapshot of $a \to n(a, t)$ (red curve) and one of $a \to D(a, t)$ (black curve - see (1.2)). The second frame in each Figure shows time histories of $t \to N_{[0,T_2]}(t)$ (blue curve), $t \to n(0, t)$ (black curve) and $t \to N_{[T_3,T_4]}(t)$ (magenta curve) over a window of 200 hours. The third frame shows histories of $t \to N_{[0,T_4]}(t)$ (black curve) and $t \to R(t) = R_0 \exp\left(-N_{[T_3,T_4]}(t)\right)$ (red curve) over a window of the same width.

For a given set of parameters C_1 and C_2, the striking features to us is how the number of characteristic pulses in $a \to n(a, t)$ depends on the width, T_2, of the death rate $d_0(\cdot)$. This parameter also has a strong effect on the period of the averaged quantities $N_{[0,T_4]}(\cdot)$, $N_{[0,T_2]}(\cdot)$, and $N_{[T_3,T_4]}(\cdot)$ and on their characteristic shapes.

Most researchers working on malaria and in particular those studying plasmodium falciparum describe the disease in infected blood cells in terms of the parasite development within the cell. During the first 12 or so hours after parasitic invasion of the cell the parasites are in the "young ring" stage while during the next 12 or so hours the parasites are in the "old ring" or "young trophozoites" stage of development. Infected blood cells with "parasites" in these two stages of development circulate freely. During the last 24 or so hours of parasite development - typically referred to as "old trophozoites" and "schizonts" and "segmenters" - the infected cells leave the circulating blood and bind to the endothelium in the microvasculature. Cells in this latter stage of development have a negligible natural death rate. It is only when the cells reach the end of their developmental cycle - in our case between 46 and 50 hours - that their natural death rate increases because the infected blood cells burst and release daughter parasites which invade new uninfected red blood cells.

Our model has attempted to capture this developmental cycle by having significant cell death rates occur only during the period $0 \le a < T_2$ and $T_3 \le a < T_4$ and by our choice of the parameters T_2, T_3 and T_4. Having said all this, we find that only the death rate $a \to d_0(a)$ determines whether the uninfected state, $n(a, t) \equiv 0$, is exponentially asymptotically stable and moreover, the particular details of this function are relatively unimportant. All that really seems to matter is the size of the parameter $R_0 \int_{T_3}^{T_4} \exp\left(-\int_0^a d_0(r)dr\right) da$; if it is small enough the disease dies off and if it is too large the disease either establishes itself in an alternative steady state or a stable oscillatory state. The details of the oscillatory state are far more sensitive to the details of the overall death rate, $D(a, t)$ (see (1.2)). Clearly, an effective therapeutic treatment for this disease requires a drug which will reduce the parameter $R_0 \int_{T_3}^{T_4} \exp\left(-\int_0^a d_0(r)dr\right) da$.

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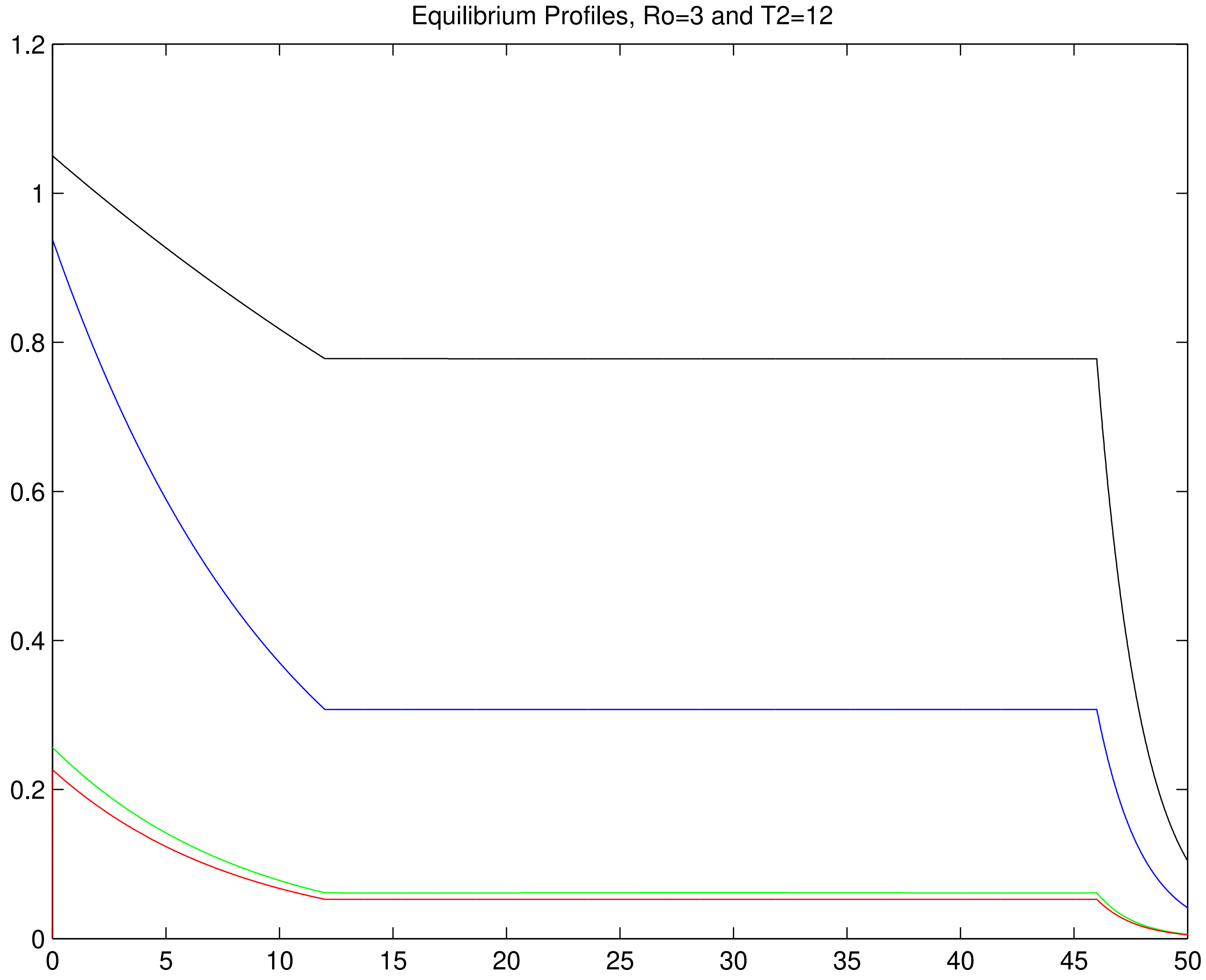
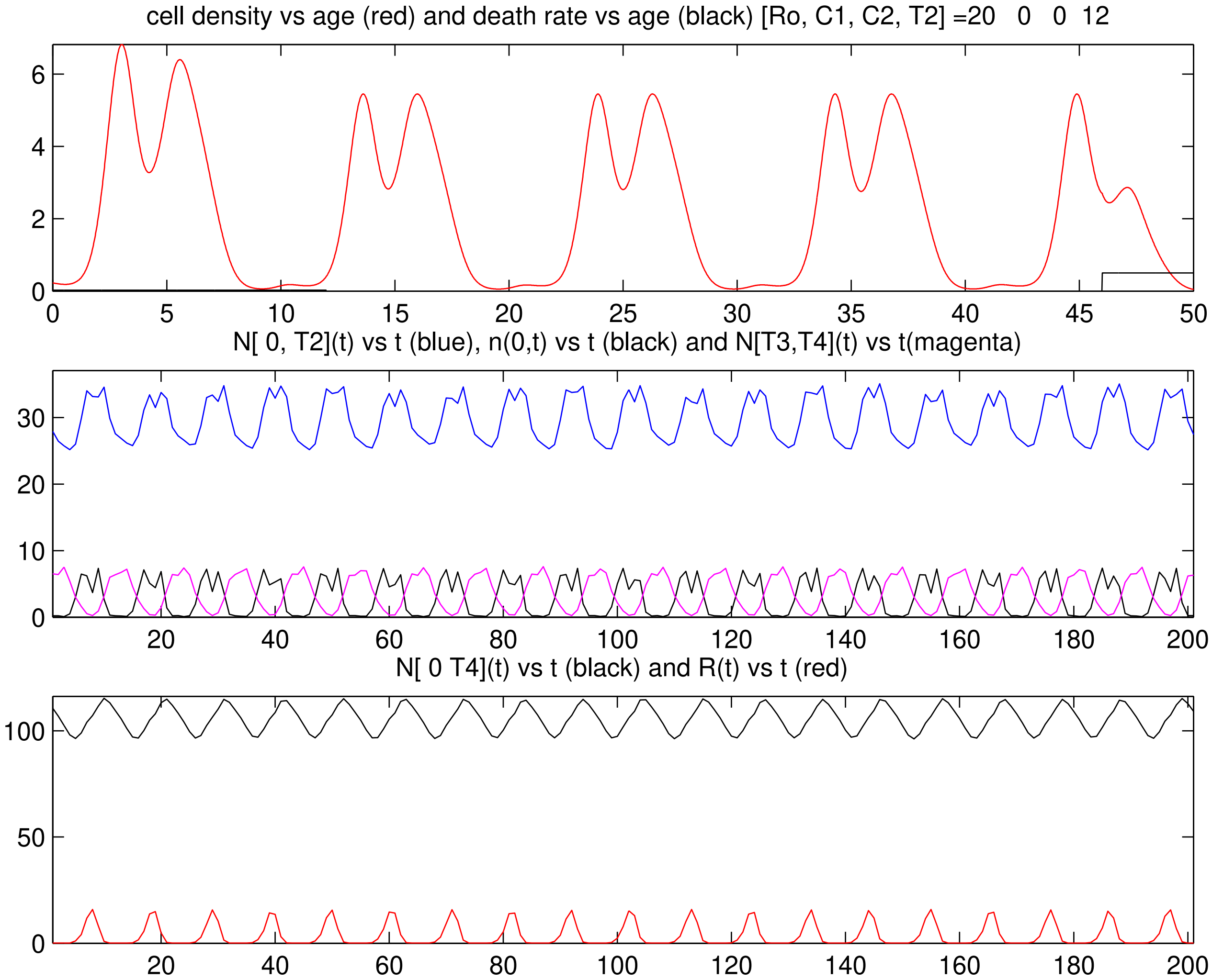


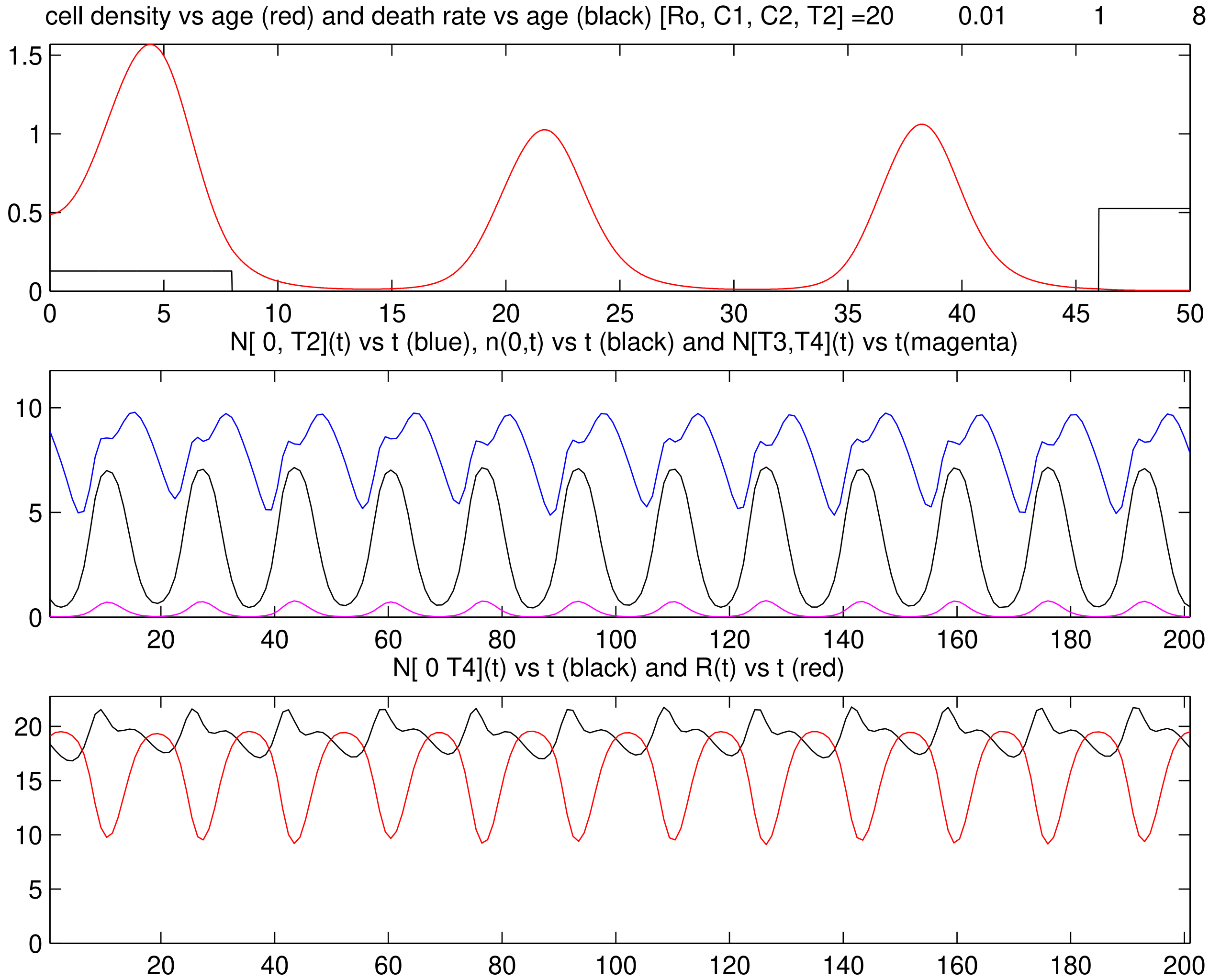
Equilibrium Profiles, Ro=3 and T2=12
1.2
1
0.8
0.6
0.4
0.2
0
0
5
10
15
20
25
30
35
40
45
50

Figure 1



cell density vs age (red) and death rate vs age (black) [Ro, C1, C2, T2] =20 0 0 12
N[0, T2](t) vs t (blue), n(0,t) vs t (black) and N[T3,T4](t) vs t(magenta)
N[0 T4](t) vs t (black) and R(t) vs t (red)

Figure 2



cell density vs age (red) and death rate vs age (black) [Ro, C1, C2, T2] =20 0.01 1 8
1.5
1
0.5
0
0 5 10 15 20 25 30 35 40 45 50
N[0, T2](t) vs t (blue), n(0,t) vs t (black) and N[T3,T4](t) vs t(magenta)
10
5
0
20 40 60 80 100 120 140 160 180 200
N[0 T4](t) vs t (black) and R(t) vs t (red)
20
15
10
5
0
20 40 60 80 100 120 140 160 180 200

Figure 3

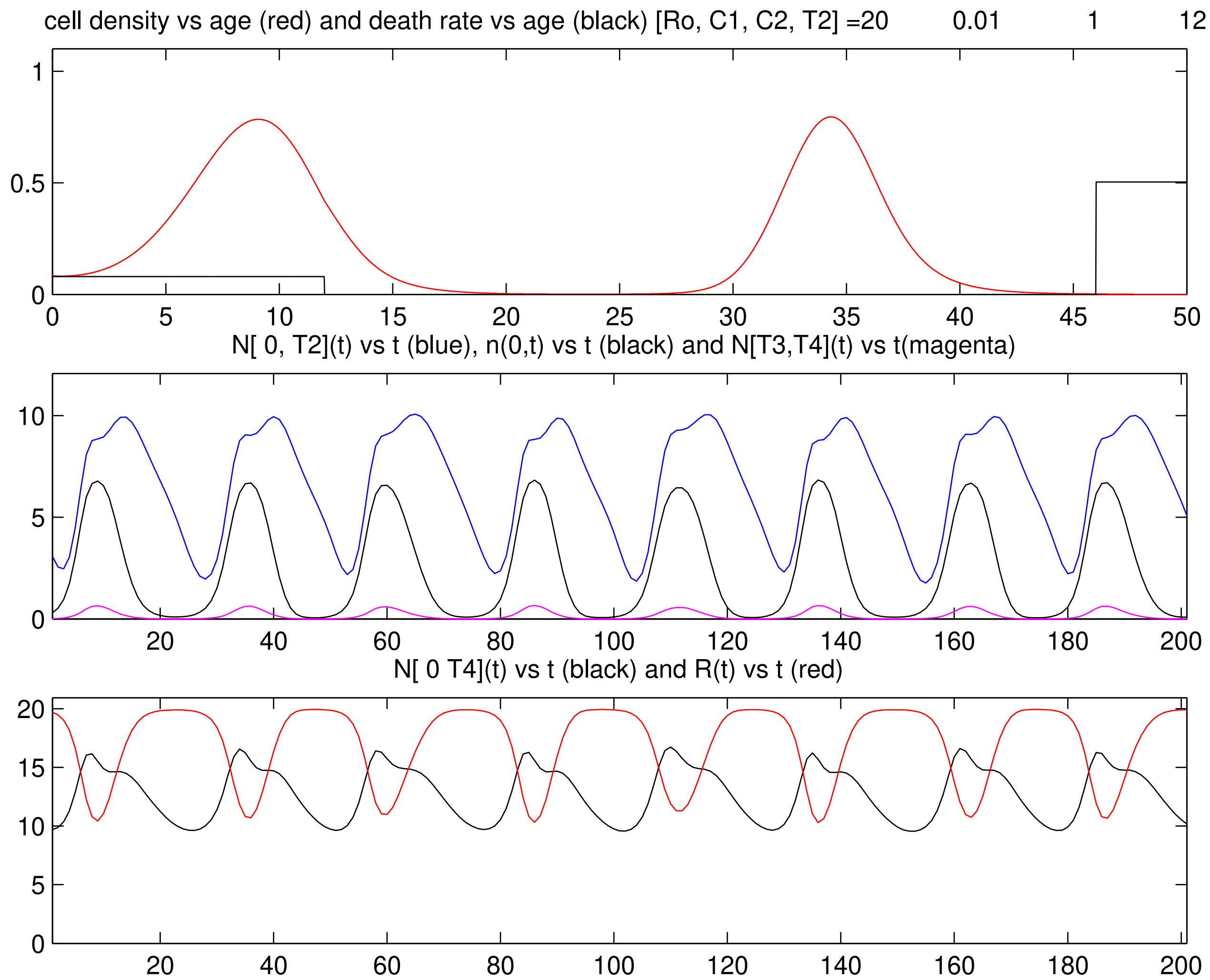

cell density vs age (red) and death rate vs age (black) [Ro, C1, C2, T2] =20 0.01 1 12
N[0, T2](t) vs t (blue), n(0,t) vs t (black) and N[T3,T4](t) vs t(magenta)
N[0 T4](t) vs t (black) and R(t) vs t (red)

Figure 4

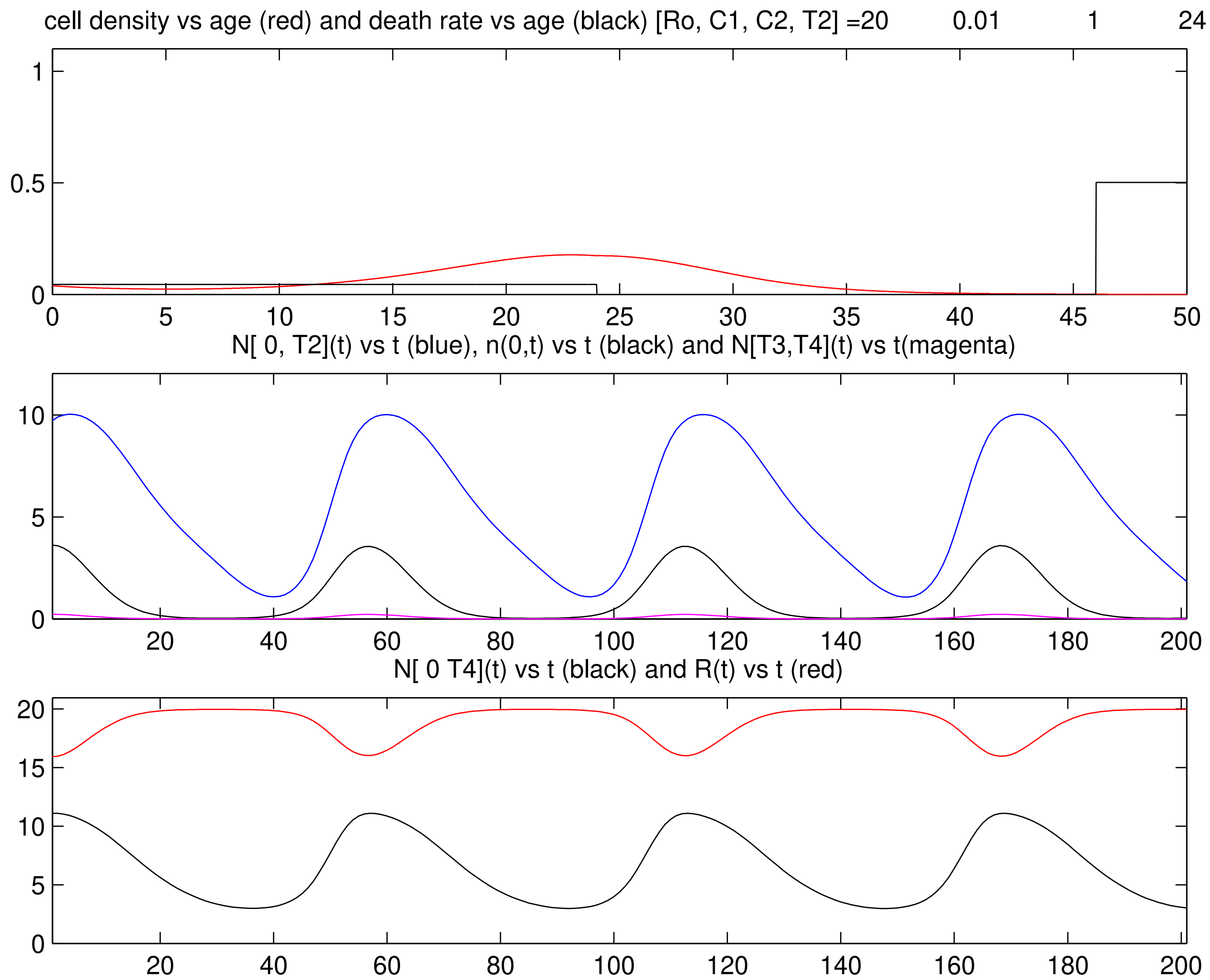

cell density vs age (red) and death rate vs age (black) [Ro, C1, C2, T2] =20 0.01 1 24
N[0, T2](t) vs t (blue), n(0,t) vs t (black) and N[T3,T4](t) vs t(magenta)
N[0 T4](t) vs t (black) and R(t) vs t (red)

Figure 5

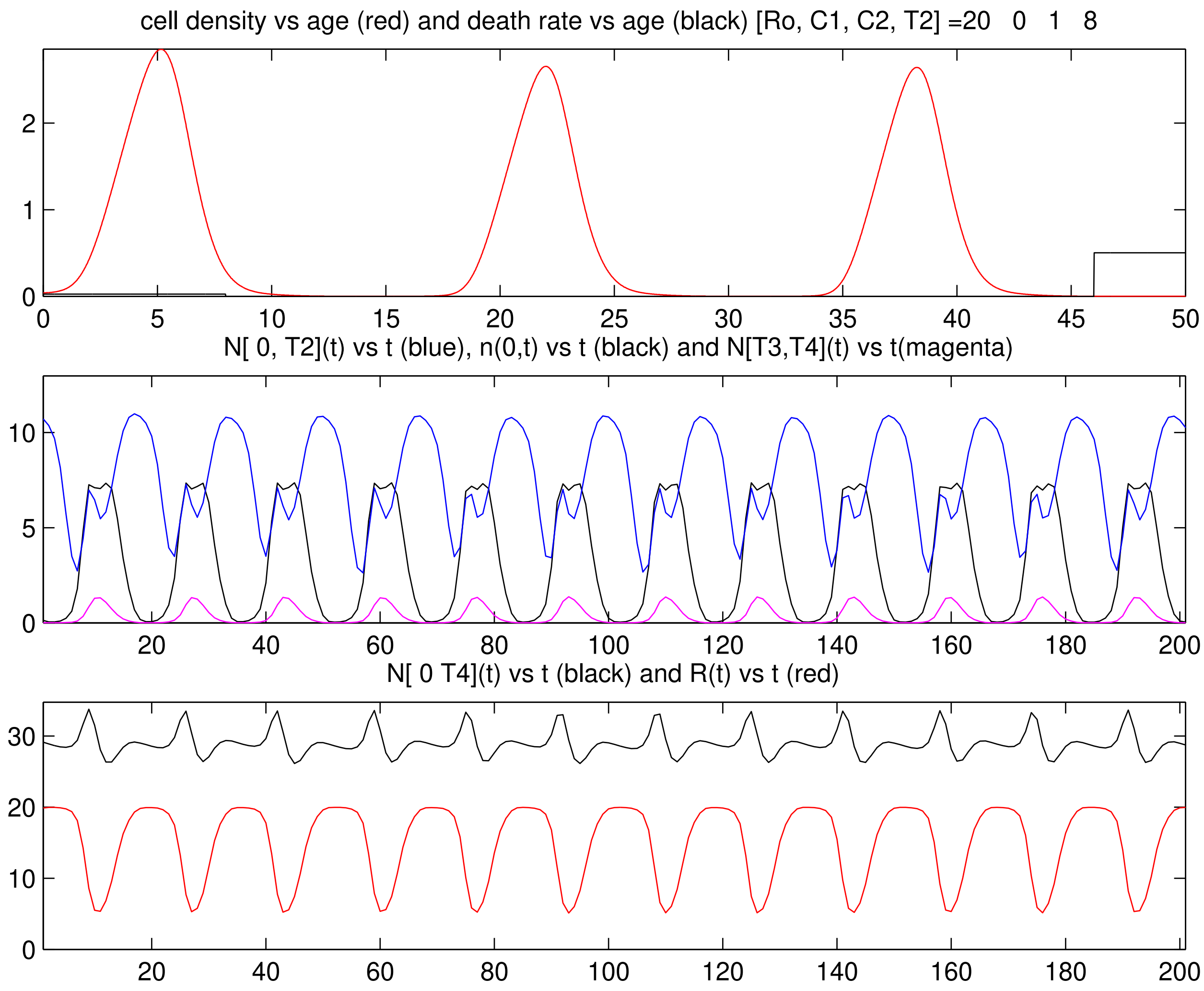

cell density vs age (red) and death rate vs age (black) [Ro, C1, C2, T2] =20 0 1 8
0
1
2
0
5
10
15
20
25
30
35
40
45
50
N[0, T2](t) vs t (blue), n(0,t) vs t (black) and N[T3,T4](t) vs t(magenta)
0
5
10
20
40
60
80
100
120
140
160
180
200
N[0 T4](t) vs t (black) and R(t) vs t (red)
0
10
20
30
20
40
60
80
100
120
140
160
180
200

Figure 6

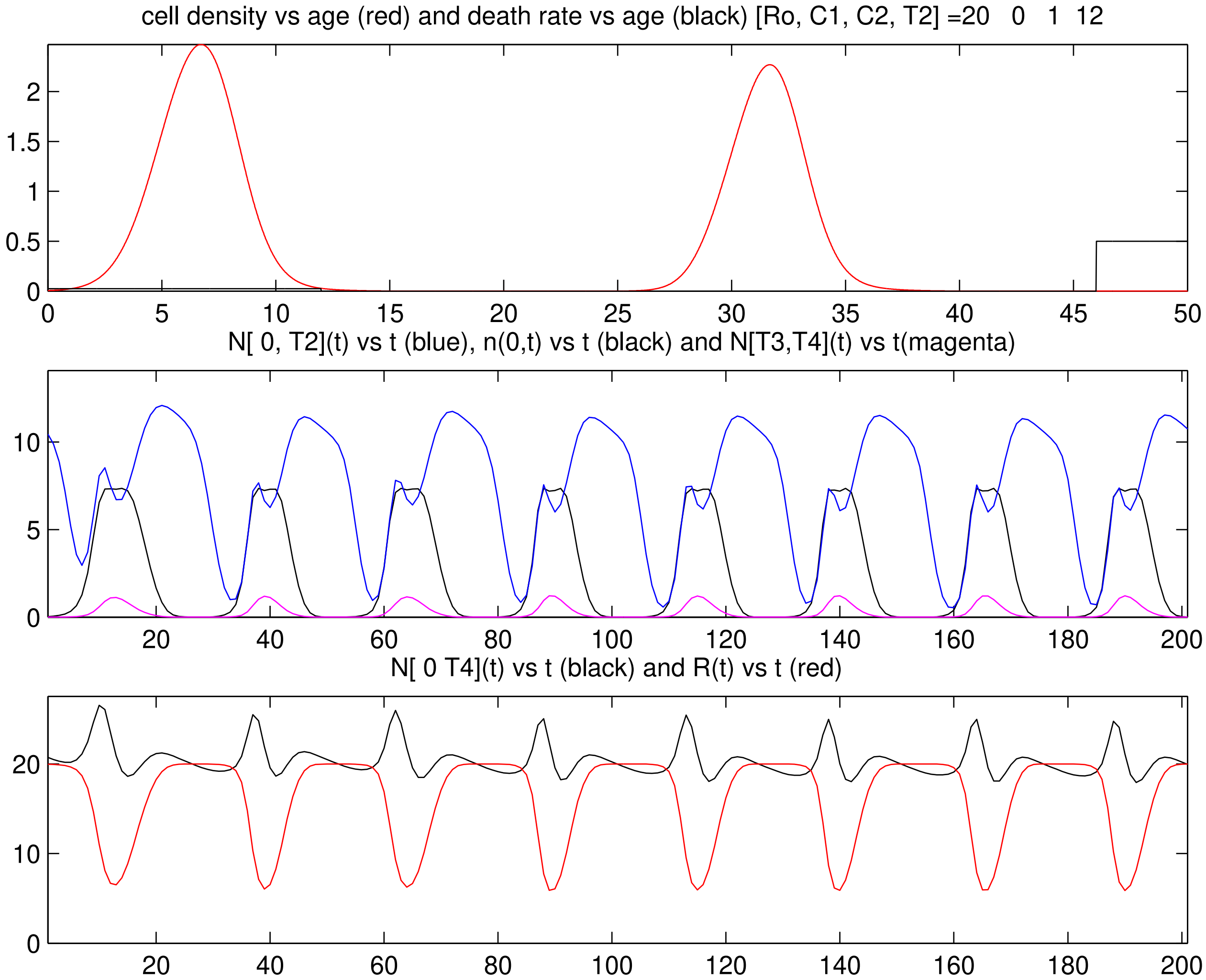

cell density vs age (red) and death rate vs age (black) [Ro, C1, C2, T2] =20 0 1 12
N[0, T2](t) vs t (blue), n(0,t) vs t (black) and N[T3,T4](t) vs t(magenta)
N[0 T4](t) vs t (black) and R(t) vs t (red)

Figure 7

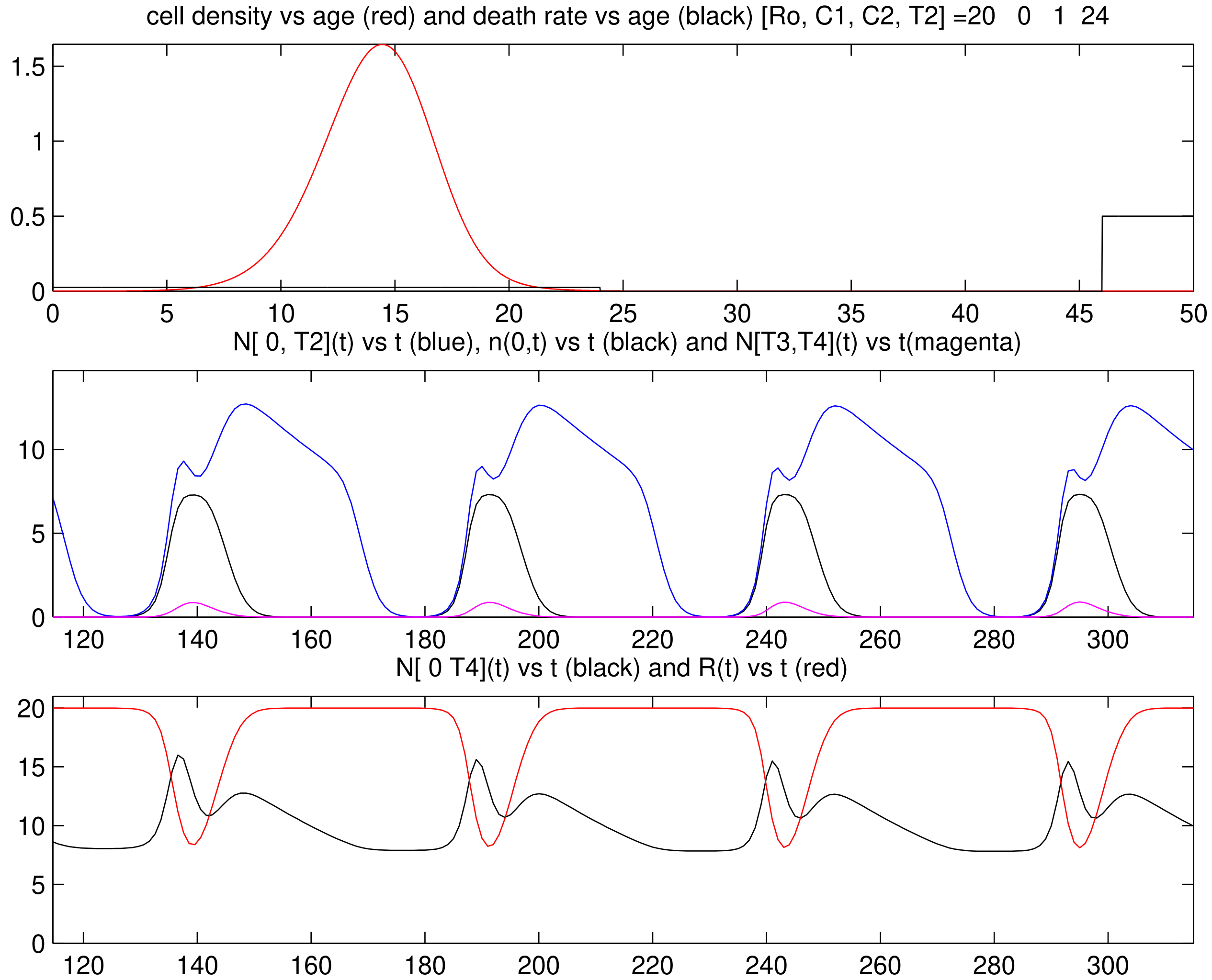

cell density vs age (red) and death rate vs age (black) [Ro, C1, C2, T2] =20 0 1 24
N[0, T2](t) vs t (blue), n(0,t) vs t (black) and N[T3,T4](t) vs t(magenta)
N[0 T4](t) vs t (black) and R(t) vs t (red)

Figure 8