Math 636 - Mathematical Modeling

Age-Structured Models

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Outline

Introduction

Introduction

- ***Discrete models*** for total population at discrete times t_n:

$$P_{n+1} = f(t_n, P_n).$$

- ***Continuous models*** for total populations, using **ODEs**:

$$\frac{dP}{dt} = f(t, P).$$

- ***Leslie model*** divided population into discrete age classes:

$$P_{n+1} = LP_n.$$

- ***Continuous PDE model***, $p(t, a)$:
  - Allow the population to vary in both time t and age a.
  - Model described by a **PDE**.
  - Dynamics better describe population, but harder to follow from complexities of analysis.

Age-Structured Model

Age-Structured Model: Modeling with a ***hyperbolic PDE***.

- Mathematical modeling of ***populations*** often needs information about the ages of the individuals in the population.
- This modeling approach was developed primarily by McKendrick (1926) and Von Foerster (1959).
- **Key Elements in Model**
  - Let $n(t, a)$ denote the ***population*** at time t and age a.
  - The ***birth rate*** of individuals $b(a)$ depends on the age of the adult population.
  - Similarly, the ***death rate*** of individuals $\mu(a)$ depends on the age of the individuals.
  - Must specify the ***initial age distribution*** of the population, $f(a)$.

Age-Structured Population

Age-Structured Population: Consider a population, $n(t, a)$, dependent on time, t, and structured by age of individuals, a.

The dynamics in time must satisfy:

$$\frac{d}{dt}n(t,a) = \frac{\partial n}{\partial t} + \frac{da}{dt}\frac{\partial n}{\partial a},$$

by the ***chain rule***.

Most commonly, the age clocks along with time, so $\frac{da}{dt} = 1$, so it follows that

$$\frac{d}{dt}n(t,a) = \frac{\partial n}{\partial t} + \frac{\partial n}{\partial a}.$$

The ***births*** all occur at $a = 0$ (the boundary), so the dynamics of the population above is only deaths or

$$\frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} = -g(t, a, n).$$

Age-Structured Model

Age-Structured Model: The ***McKendrick-Von Foerster equation*** is:

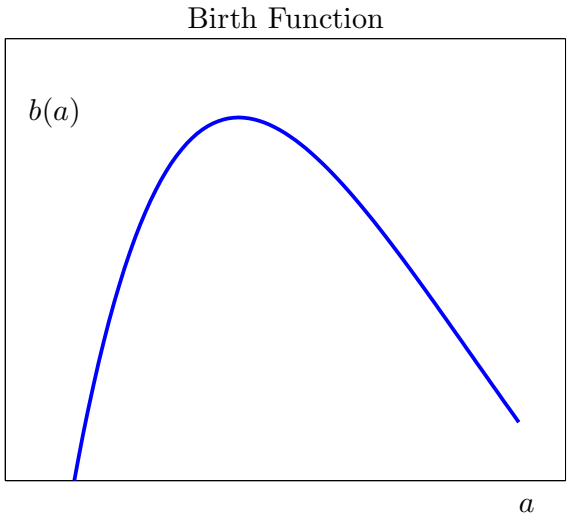
$$\frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} + \mu(a)n(t,a) = 0,$$

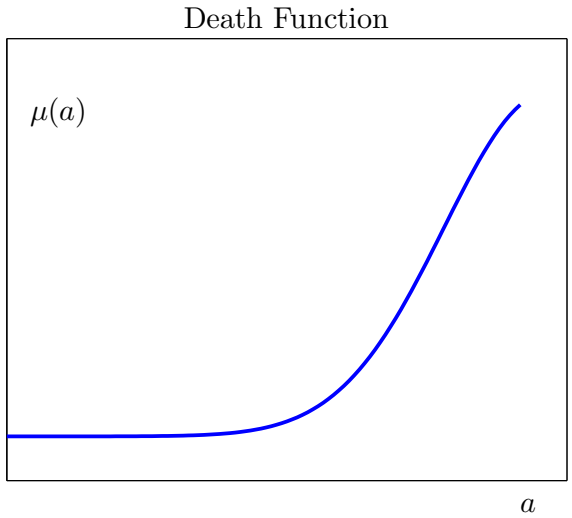
with the ***birth boundary condition*** (Malthusian):

$$n(t,0) = \int_0^\infty b(a)n(t,a)\,da,$$

and the ***initial condition***:

$$n(0,a) = f(a).$$





Age-Structured Model

Discussion for the ***Age-Structured Model***

$$\frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} = -\mu(a)n(t,a).$$

- The **PDE** shows that age advances with time.
- The right side shows that there is only a loss of population through death with death increasingly likely with age.
- The ***birth function***:
  - Young individuals are incapable of giving birth
  - The birth function increases to peak fertility.
  - Births are Malthusian - proportional to the population.
  - After peak fertility, reproductive ability decreases, and it could again decrease to zero.
- The initial population distribution could be anything
- However, in general the population distribution should decrease with increasing time.

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Age-Structured Model - Method of Characteristics

The ***Age-Structured Model***:

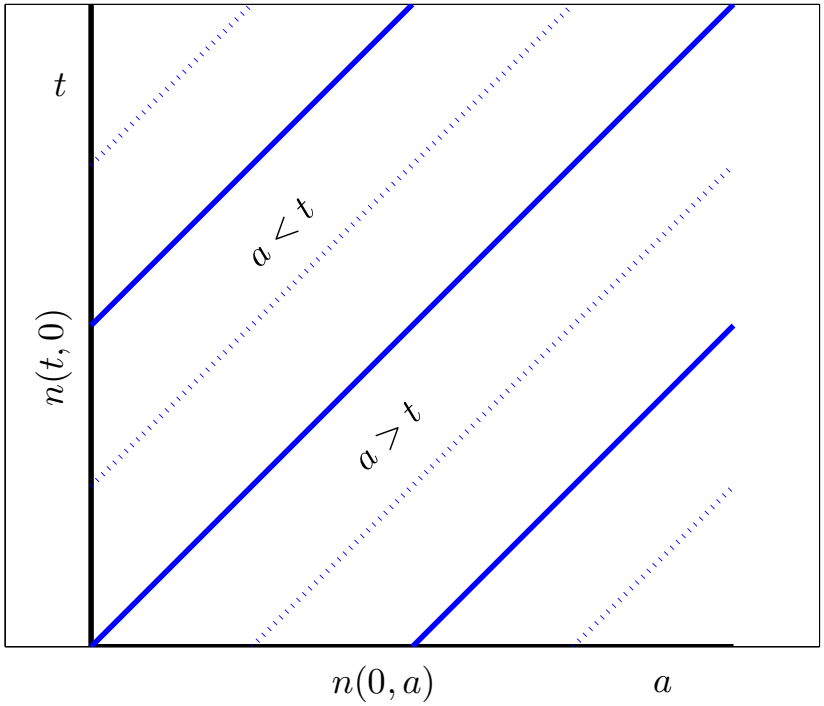
$$\frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} = -\mu(a)n(t,a).$$

can be written as an ***ODE***:

$$\frac{d}{dt}n(t,a) = -\mu(a)n(t,a),$$

along the ***characteristic***,

$$a(t) = t + c.$$



This has the solution:

$$N(t) = N_0\, e^{-\int_0^t \mu(s)\, ds},$$

which follows the population of a particular age cohort.

Age-Structured Model - Survival

We can define a ***survival function***

$$L(a) = e^{-\int_0^a \mu(s)\,ds},$$

which gives the fraction of individuals surviving from birth to age a.

The survival from a to b is given by

$$L(a,b) = e^{-\int_a^b \mu(s)\,ds}.$$

From the diagram above, we follow the characteristics to obtain the solution of the ***age-structured model***:

$$\begin{aligned} a < t: &\qquad n(t,a) = n(t-a,0)L(0,a), \\ a > t: &\qquad n(t,a) = n(0,a-t)L(a-t,a). \end{aligned}$$

Age-Structured Model

The ***age-structured model*** gives the dynamics of a particular age cohort following a characteristic.

The **long term behavior** depends significantly on the ***birth process*** on the boundary.

Since this is a type of ***Malthusian growth*** (with no limiting nonlinearities), we expect a type of ***exponential growth (or decline)*** with some rate r and having the form:

$$n(t,a) = Cn^*(a)e^{rt},$$

where $n^*(a)$ is the ***stable age distribution*** and C depends on the initial conditions.

For convenience, assume $n^*(0) = 1$, so that $n^*(a)$ is the fraction of age a individuals surviving to age a relative to age 0.

Age-Structure Model - Birth Function

The boundary condition of births is

$$n(t,0) = \int_0^\infty b(a)n(t-a,0)L(a)\,da.$$

Inserting the assumed ***stable form***, $n(t,a) = Cn^*(a)e^{rt}$, gives

$$\begin{aligned} Ce^{rt} &= \int_0^\infty b(a)Ce^{r(t-a)}L(a)\,da, \\ 1 &= \int_0^\infty e^{-ra}L(a)b(a)\,da. \end{aligned}$$

Whether r is positive or negative determines if the overall population grows or decays.

If $r > 0$, then the total population grows like Ce^{rt}

Age-Structure Model - R_0

Ecologists and epidemiologists define an important constant R_0, which is used to determine if a population (or disease) expands or contracts.

For this population, define

$$R_0 = \int_0^\infty L(a)b(a)\,da,$$

where R_0 represents the average number of (female) offspring from an individual (female) over her lifetime (integral of births times lifespan).

Note that if $R_0 < 1$, then $r < 0$ and if $R_0 > 1$, then $r > 0$. The latter condition indicates that each female during her lifetime must produce more than one female offspring for the population to grow.

Since $n(t,a) = n(t-a,0)L(a)$, the ***stable age distribution*** satisfies

$$\begin{aligned} Ce^{rt}n^*(a) &= Ce^{r(t-a)}n^*(0)L(a) = Ce^{r(t-a)}L(a), \\ n^*(a) &= e^{-ra}L(a). \end{aligned}$$

Age-Structured Model - Example

We can define the ***average generation time***, T, to satisfy:

$$e^{rT} = R_0,$$

so on average a mother replaces herself with R_0 offspring.

The value

$$T = \frac{1}{R_0} \int_0^\infty aL(a)b(a)\,da,$$

gives the ***average age of reproduction***.

Example: Let us examine the ***age-structured model***

$$\frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} + \mu(a)n(t,a) = 0,$$

with the ***birth boundary condition***:

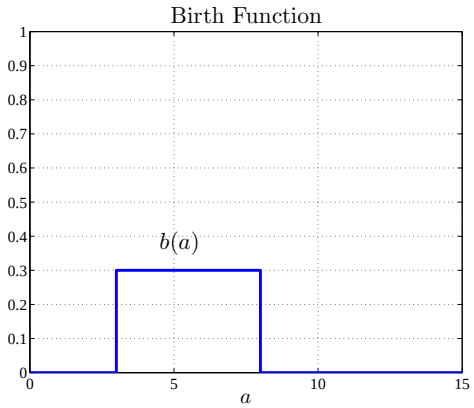
$$n(t,0) = \int_0^\infty b(a)n(t,a)\,da.$$

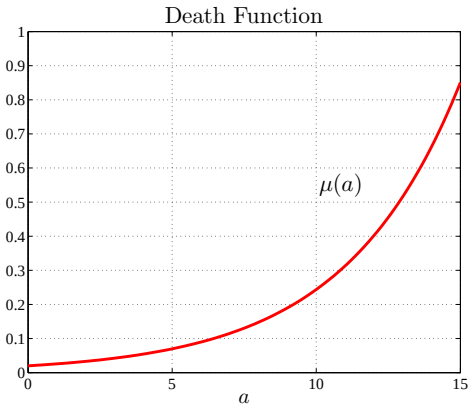
Age-Structured Model

In order to perform calculations (with the help of **Maple**), we take ***birth and death functions***

$$b(a) = \begin{cases} 0.3, & 3 < a < 8, \\ 0, & \text{otherwise}, \end{cases} \quad \text{and} \quad \mu(a) = 0.02\, e^{0.25a}.$$

The ***birth function*** assumes a constant fecundity of 0.3 between the ages of 3 and 8, while the ***death function*** assumes an ever increasing function with age.





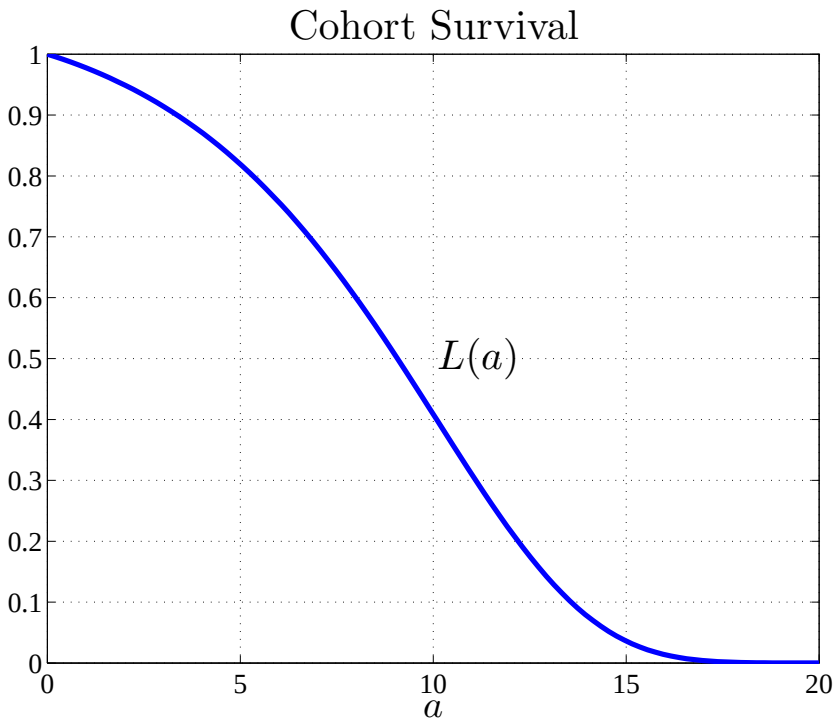
Note: These functions are very crude approximations to the forms displayed earlier.

Age-Structured Model

The ***age-structured model*** had a ***survival function***

$$L(a) = e^{-\int_0^a \mu(s)\,ds} = e^{-0.08(e^{0.25a}-1)},$$

which gives the fraction of individuals surviving from birth to age a.



Age-Structured Model

The ***basic reproduction number,*** R_0, was given by

$$R_0 = \int_0^\infty L(a)b(a)\,da = \int_3^8 0.3e^{-0.08(e^{0.25a}-1)}da = 1.1678,$$

which is the average number of (female) offspring from an individual (female) over her lifetime.

With the help of **Maple**, we can determine the average overall ***growth rate,*** r, for this example.

Maple solves the equation for r:

$$1 = \int_0^\infty e^{-ra}L(a)b(a)\,da = \int_3^8 0.3e^{-ra}e^{-0.08(e^{0.25a}-1)}da,$$

and obtains

$$r = 0.02925985.$$

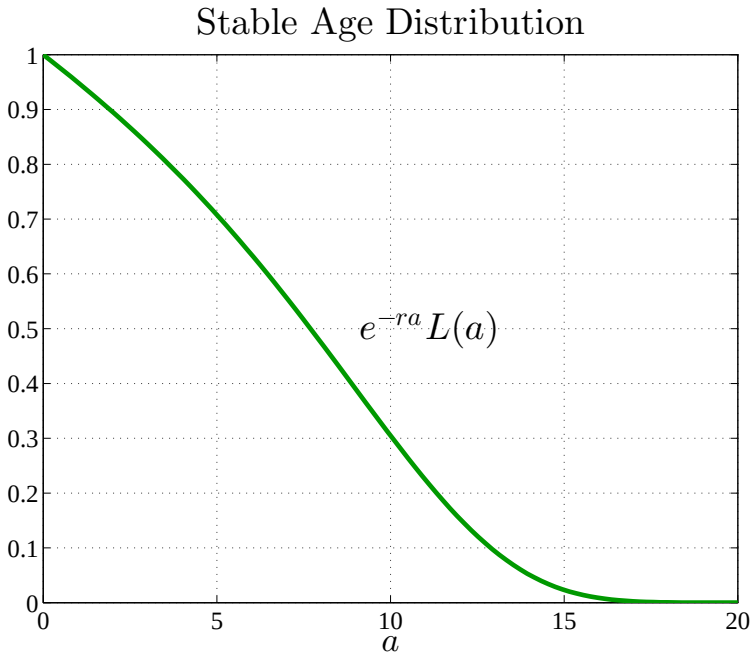
This shows the overall population is growing about 3% per unit time.

Age-Structured Model

The ***Malthusian growth*** would not be sustainable over long periods of time, so nonlinear terms for crowding and other factors would need to be included in the model, *e.g.*, ***logistic growth***.

With the overall population growth rate, we can obtain the ***steady-state age distribution*** of this population:

$$n^*(a) = e^{-ra}L(a) = e^{-0.02926a}e^{-0.08(e^{0.25a}-1)}.$$



Age-Structured Model

The ***average generation time***, T, satisfies:

$$e^{rT} = R_0 \qquad \text{or} \qquad e^{0.02926T} = 1.1678.$$

so on average a mother replaces herself with R_0 offspring in $T = 5.3024$ time units.

The value,

$$T = \frac{1}{R_0}\int_0^\infty aL(a)b(a)\,da = \frac{1}{1.1678}\int_3^8 0.3a\,e^{-0.08(e^{0.25a}-1)}da = 5.33205,$$

gives the ***average age of reproduction***.

In summary, the ***method of characteristics*** allows solutions for the ***age-structured model***, which can provide interesting information about the behavior of a population.

Needless to say, these models must be significantly expanded to manage more realistic populations, which in turn significantly complicates the mathematical analysis.

Introduction - Hematopoiesis

Hematopoiesis for **Erythrocytes** and **Platelets**

- All cells in bloodline begin as undifferentiated stem cells (**Multipotential Hematopoietic Stem Cells**)
- Different hormonal signals cause differentiation (**Common Myeloid Progenitor (CMP)**)
- Further signals for differentiation
  - Erythropoiesis – Proerythroblast
  - Thrombopoiesis – Megakaryoblast
- Proliferation via cell doubling
- Specialization
  - Erythropoiesis – Reticulocytes with hemoglobin
  - Thrombopoiesis – Endomitosis forming Megakaryocytes
- Maturation producing Erythrocytes and Platelets
- Cell number and volume monitored by body with **negative feedback** – Erythropoietin and Thrombopoietin

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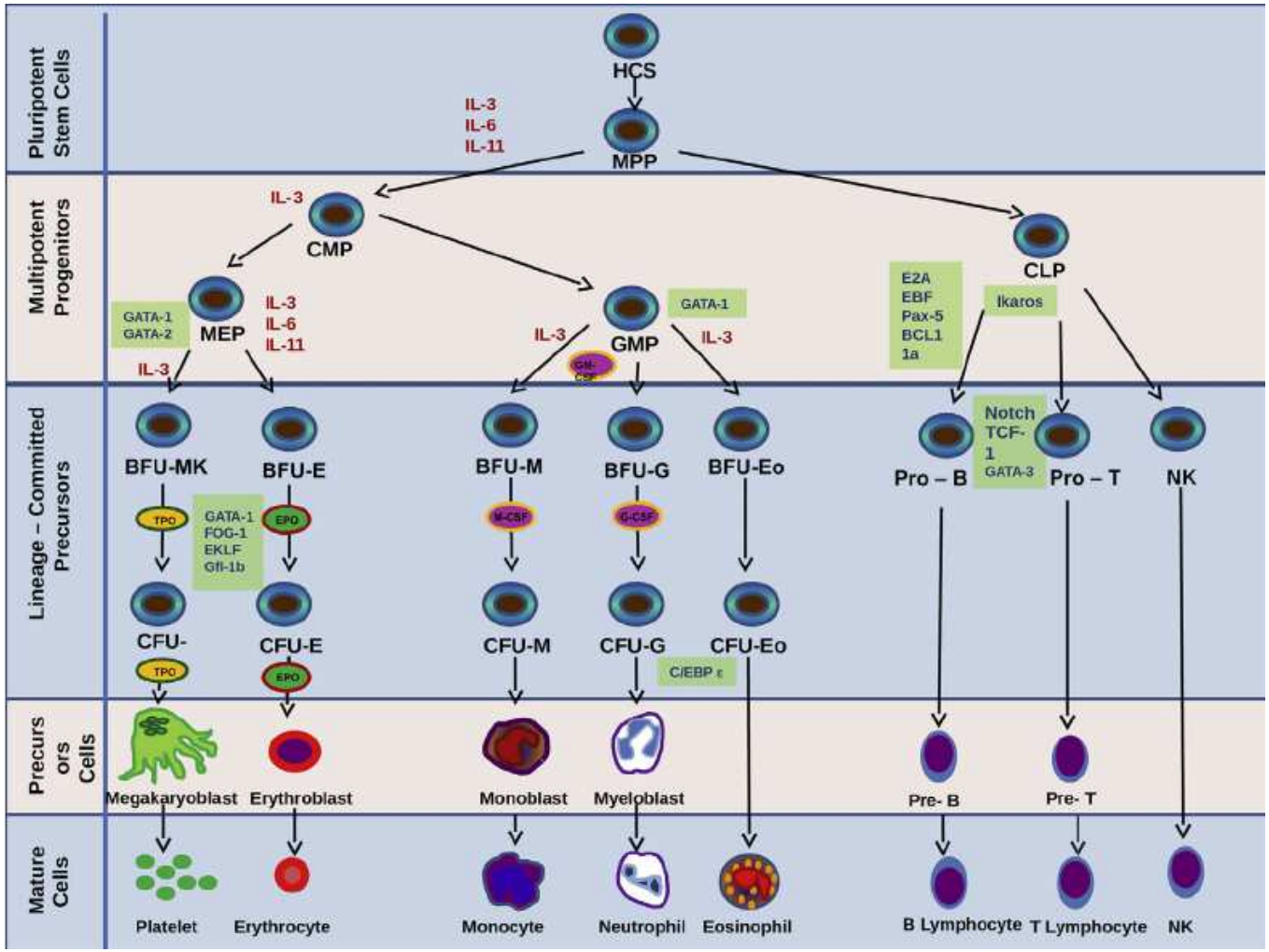
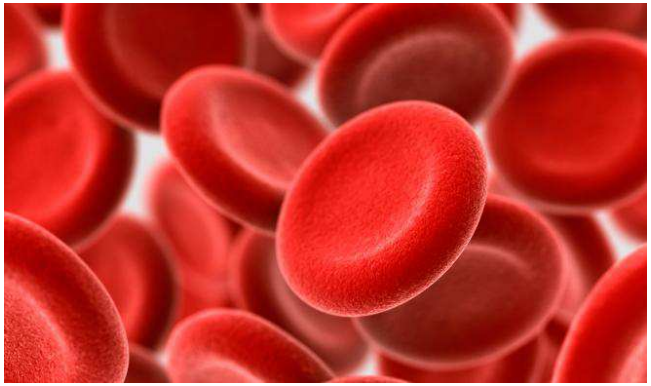
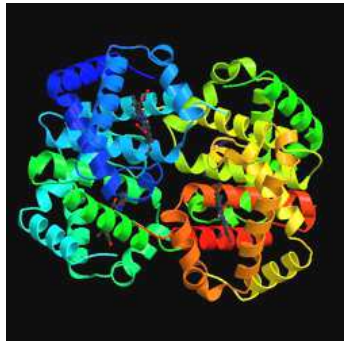
Diagram for Hematopoiesis



Erythropoiesis





Erythropoiesis is the process for producing ***Erythrocytes*** or ***Red Blood Cells (RBCs)***.

- **RBCs** are the most numerous cells that we produce in our bodies, accounting for almost 85% by numbers.
- Critical for carrying O_2 to our other cells, using the protein hemoglobin (Hb).
- By volume, **RBCs** are about 40% of blood ($\sim 3\%$ body wt).

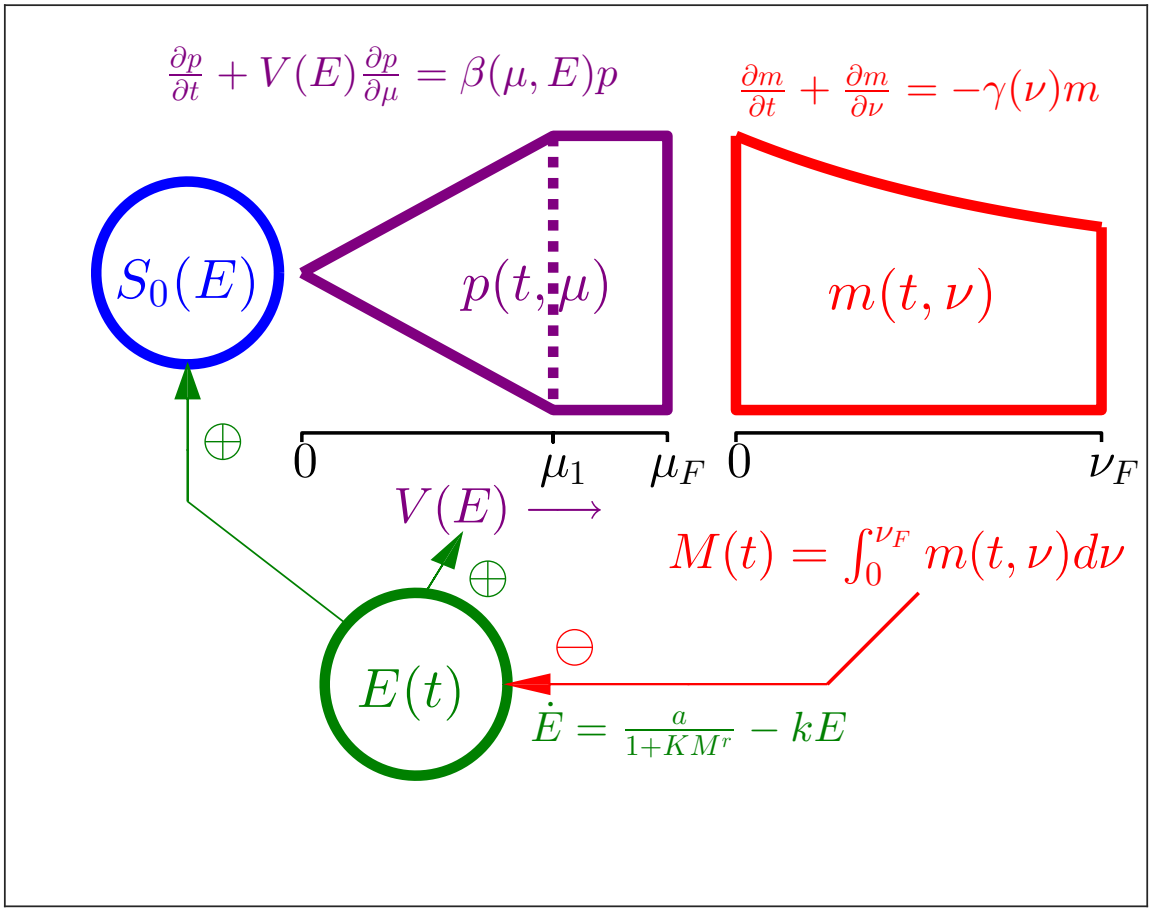
Erythropoiesis

Erythrocytes or Red Blood Cells

- **RBCs** begin from undifferentiated stem cells (multipotent progenitors), then based on ***erythropoietin (EPO)*** levels multiply and specialize.
- The body senses O_2 levels in the body and releases ***erythropoietin (EPO)*** inversely to the O_2 in the blood (negative feedback).
- Progenitor cells specialize though a series of cell divisions and intracellular changes (taking about 6 days), building ***hemoglobin (Hb)*** levels and becoming **RBCs**.
- **RBCs** circulate in the bloodstream for about 120 days, then are actively degraded.

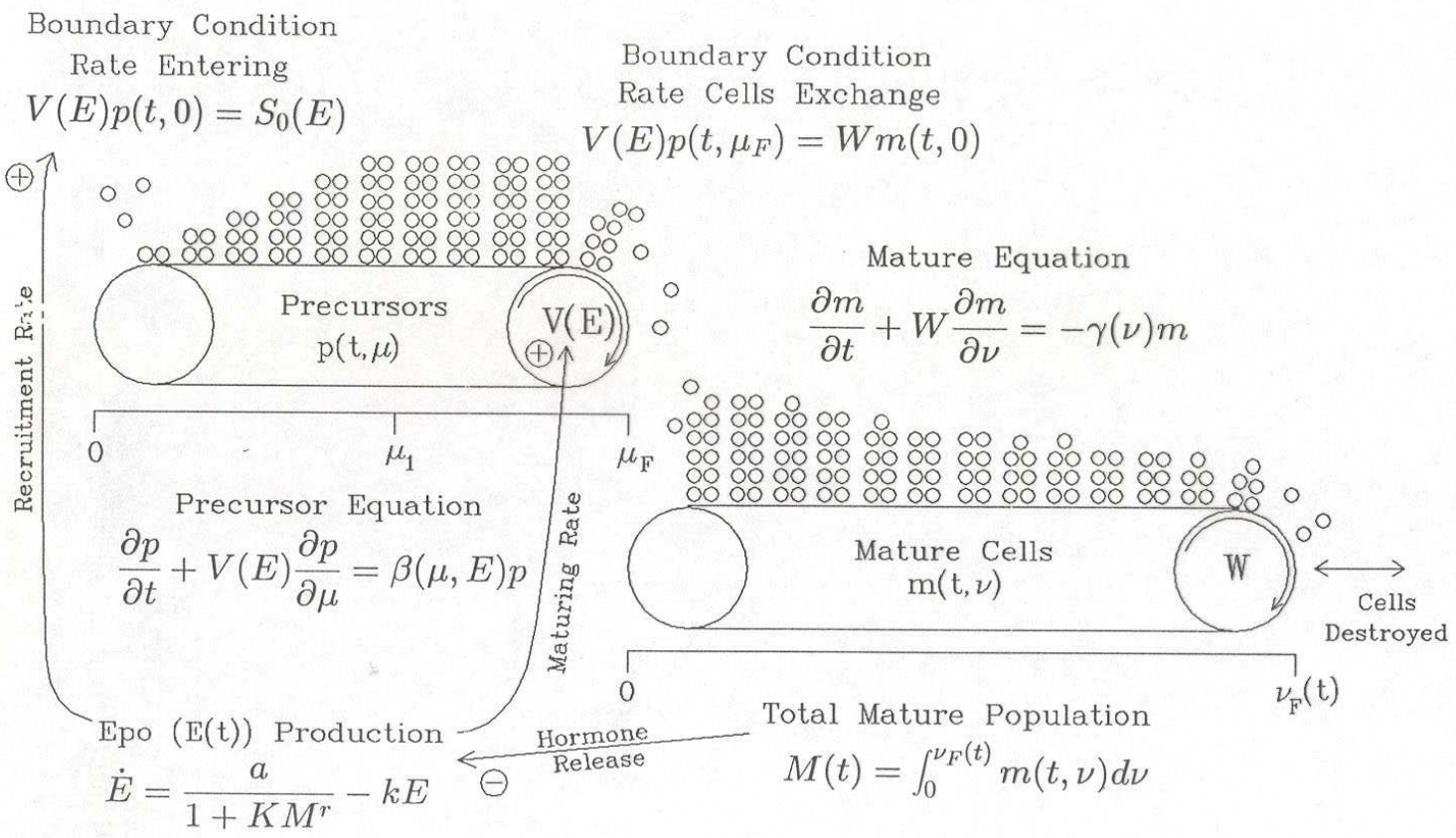
Model for Erythropoiesis

Age-Structured Model for Erythropoiesis



Model for Erythropoiesis

Age-Structured Model viewed as a conveyor system



Active Degradation of RBCs

Active Degradation of RBCs

- **RBCs** are lost from normal leakage (breaking capillaries), which is simply proportional to the circulating numbers
- **RBCs** age - Cell membrane breaks down (no nucleus to repair) from squeezing through capillaries
- Aged membrane is marked with antibodies
- **Macrophages** destroy least pliable cells based on the antibody markers
- Model assumes constant supply macrophages
  - Saturated consumption of **Erythrocytes**
    - Satiated predator eating a constant amount per unit time
  - Constant flux of **RBCs** being destroyed

Constant Flux Boundary Condition

Constant Flux Boundary Condition

- Let Q be rate of removal of erythrocytes
- **Erythrocytes** lost are $Q\Delta t$
- **Mean Value Theorem** - average number **RBCs**

$$m(\xi, \nu_F(\xi)) \qquad \text{for} \qquad \xi \in (t, t+\Delta t)$$

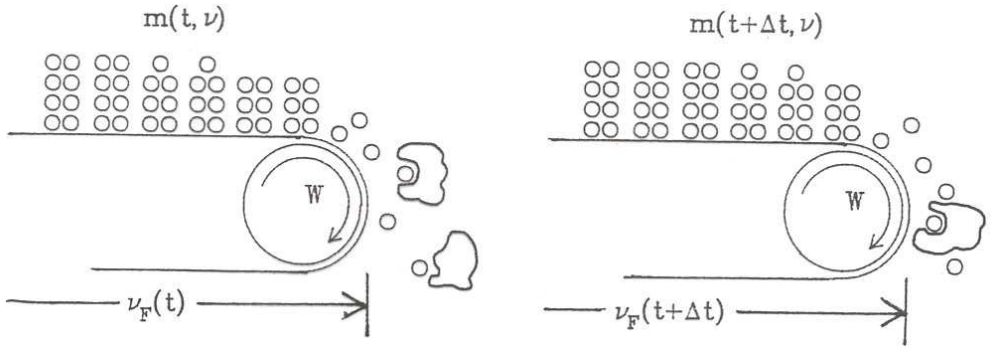
- Balance law

$$\begin{aligned} Q\Delta t &= W\Delta t\, m(\xi, \nu_F(\xi)) \\ &\quad -[\nu_F(t+\Delta t) - \nu_F(t)]m(\xi, \nu_F(\xi)) \end{aligned}$$

- As $\Delta t \to 0$,

$$Q = [W - \dot{\nu}_F(t)]m(t, \nu_F(t))$$

Constant Flux Boundary Condition



- If macrophages consume a constant amount of **RBCs** at the end of their, we obtain the ***natural BC***

$$Q = [W - \dot{\nu}_F(t)]m(t, \nu_F(t))$$

- This results in the lifespan of the **RBCs** either lengthening or shortening from the normal 120 days
- This implies that the lifespan of the **RBCs** depends on the ***state of the system***

Model Reduction

Model Reduction: Several simplifying assumptions are made:

- Assume that both velocities of aging go with time, t,
$$V(E) = W = 1.$$
- Assume the birth rate β satisfies:
$$\beta(\mu, E) = \begin{cases} \beta, & \mu < \mu_1, \\ 0, & \mu \geq \mu_1, \end{cases}$$
- Assume that γ is constant.

The model satisfies the ***age-structured partial differential equations***:

$$\begin{aligned} \frac{\partial p}{\partial t} + \frac{\partial p}{\partial \mu} &= \beta(\mu) p, \\ \frac{\partial m}{\partial t} + \frac{\partial m}{\partial \nu} &= -\gamma m. \end{aligned}$$

Model for Erythropoiesis

The boundary conditions for the ***age-structured PDEs*** are:

- Recruitment of the ***precursors*** based on **EPO** concentration circulating in the blood:
$$p(t,0) = S_0(E).$$
- Continuity of ***precursors*** maturing and entering the bloodstream as ***mature RBCs***:
$$p(t,\mu_F) = m(t,0).$$
- ***Active destruction*** of ***mature RBCs***:
$$(1-\dot{\nu}_F(t))m(t,\nu_F(t)) = Q.$$

The negative feedback by **EPO** satisfies the **ODE**:

$$\dot{E} = \frac{a}{1+KM^r} - kE,$$

where the total mature erythrocyte population is

$$M(t) = \int_0^{\nu_F(t)} m(t,\nu)d\nu.$$

Method of Characteristics

The ***precursor equation*** generally has maturing depending on **EPO,** $E(t)$, but we assume that $V(E) = 1$, so time and age are in lockstep.

If we define $P(s) = p(t(s), \mu(s))$, then

$$\frac{dP}{ds} = \frac{\partial p}{\partial t}\frac{dt}{ds} + \frac{\partial p}{\partial \mu}\frac{d\mu}{ds} = \beta(\mu(s))P(s).$$

The ***method of characteristics*** suggests we want

$$\frac{dt}{ds} = 1$$

or

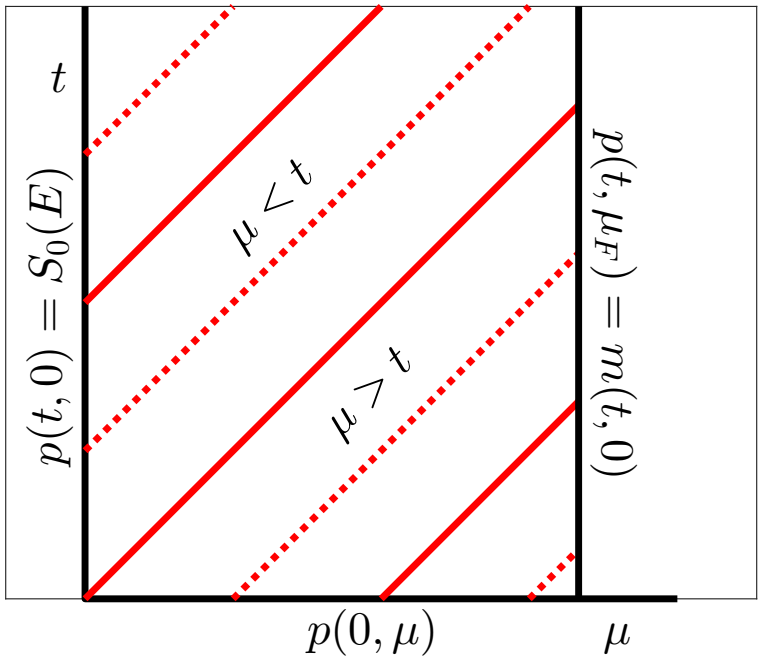
$$t(s) = s + t_0,$$

and

$$\frac{d\mu}{ds} = 1$$

or

$$\mu(s) = s + \mu_0.$$



Method of Characteristics

With the ***method of characteristics***, the ***precursor equation***,

$$\frac{dP}{ds} = \beta(\mu(s))P(s),$$

is a **birth only** population model.

The model assumes that the body uses ***apoptosis*** at the early recruitment stage (**CFU-E**) to decide how many ***precursor cells*** are allowed to mature.

The solution to the **ODE** above is

$$P(s) = p(t, \mu) = P(0)e^{\int_0^s \beta(\mu(r))dr},$$

which is valid for $0 < \mu < \mu_F$, focusing on the larger time solution.

Method of Characteristics

This aging process of the ***precursor cells*** is primarily a time of ***amplification*** in numbers before the final stages of simply add ***hemoglobin***.

The model shows how recruited cells amplify, then enter the ***mature compartment (bloodstream)*** to circulate and carry $\mathbf{O}_2$:

$$\begin{aligned} p(t,\mu_F) &= p(t_0,0)e^{\int_0^s \beta(\mu(r))dr} \\ &= p(t-\mu_F,0)e^{\beta\mu_1} = e^{\beta\mu_1}S_0(E(t-\mu_F)). \end{aligned}$$

From the ***method of characteristics*** on the ***mature RBCs***, a similar result gives:

$$m(t,\nu) = m(t-\nu,0)e^{-\gamma\nu}.$$

The continuity between the ***precursors*** and the ***mature RBCs*** gives:

$$m(t-\nu,0) = p(t-\nu,\mu_F) = e^{\beta\mu_1}S_0(E(t-\mu_F-\nu)).$$

Total RBCs

The O_2 carrying capacity of the body depends on the total number of **RBCs**, which is the integral over all $m(t,\nu)$ in ν:

$$\begin{aligned} M(t) &= \int_0^{\nu_F(t)} m(t-\nu,0)e^{-\gamma\nu}d\nu \\ &= \int_0^{\nu_F(t)} e^{\beta\mu_1}S_0(E(t-\mu_F-\nu))e^{-\gamma\nu}d\nu, \\ &= e^{-\gamma(t-\mu_F)}e^{\beta\mu_1}\int_{t-\mu_F-\nu_F(t)}^{t-\mu_F} S_0(E(w))e^{\gamma w}dw. \end{aligned}$$

We apply Leibnitz's rule for differentiating an integral:

$$\begin{aligned} \dot{M}(t) &= -\gamma e^{-\gamma(t-\mu_F)}e^{\beta\mu_1}\int_{t-\mu_F-\nu_F(t)}^{t-\mu_F} S_0(E(w))e^{\gamma w}dw, \\ &\quad +e^{\beta\mu_1}\left[S_0(E(t-\mu_F)) - S_0(E(t-\mu_F-\nu_F(t)))e^{-\gamma\nu_F(t)}(1-\dot{\nu}_F(t))\right] \\ &= -\gamma M(t) + e^{\beta\mu_1}S_0(E(t-\mu_F)) - Q, \end{aligned}$$

Model for Erythropoiesis with Delays

After reduction of PDEs, the state variables become ***total mature erythrocytes,*** M, **EPO,** E, and age of RBCs, ν_F.

$$\begin{aligned}
\frac{dM(t)}{dt} &= e^{\beta\mu_1} S_0(E(t-\mu_F)) - \gamma M(t) - Q \\
\frac{dE(t)}{dt} &= f(M(t)) - kE(t) \\
\frac{d\nu_F(t)}{dt} &= 1 - \frac{Qe^{-\beta\mu_1} e^{\gamma\nu_F(t)}}{S_0(E(t-\mu_F-\nu_F(t)))}
\end{aligned}$$

This is a state-dependent delay differential equation.

Model for Erythropoiesis with Delays

Properties of the Model: Integrating along the ***characteristics*** shows that the maturation process acts like a delay, changing the ***age-structured model*** into a ***delay differential equation***.

- The ***state-dependent delay model*** has a unique positive equilibrium.
- The delay μ_F accounts for maturing time.
- The ***state-dependent delay*** in equation for $\nu_F(t)$ comes from the varying age of mature cells.
- The $\nu_F(t)$ differential equation is uncoupled from the differential equations for M and E.
- ***Stability*** is determined by equations for M and E

DDE with One Delay

Consider the ***delay differential equation*** (DDE) with ***one delay***:

$$\dot{y}(t) = ay(t) + by(t-r)$$

If one tries the solution, $y(t) = ce^{\lambda t}$, then

$$c\lambda e^{\lambda t} = ace^{\lambda t} + bce^{\lambda(t-r)},$$

which gives the ***characteristic equation***

$$\lambda - a = be^{-\lambda r}$$

The ***boundary of stability*** is a subset of solutions to the ***characteristic equation*** with $\lambda = i\omega$ or

$$i\omega - a = be^{-i\omega r} = b\left(\cos(\omega r) - i\sin(\omega r)\right),$$

or for $\lambda = 0$, the ***real root crossing*** satisfies:

$$a = -b.$$

DDE with One Delay

From the ***characteristic equation*** with $\lambda = i\omega$, the real and imaginary parts give the parametric equations:

$$\begin{aligned} a(\omega) &= -b(\omega)\cos(\omega r), \\ \omega &= -b(\omega)\sin(\omega r). \end{aligned}$$

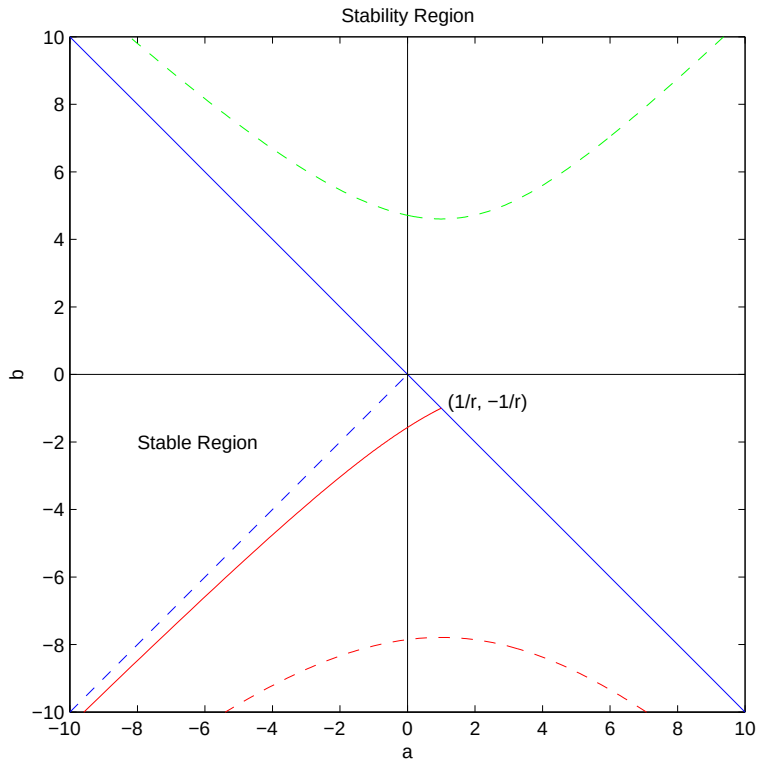
Solving these equations for $a(\omega)$ and $b(\omega)$ gives

$$\begin{aligned} a(\omega) &= \omega\cot(\omega r), \\ b(\omega) &= -\frac{\omega}{\sin(\omega r),} \end{aligned}$$

which are clearly singular at any $\frac{n\pi}{r}$, $n = 0, 1, ...$

This creates distinct curves $\omega \in \left(\frac{(n-1)\pi}{r}, \frac{n\pi}{r}\right)$ for $n = 1, 2, ...$

Stability Region - DDE with One Delay



- Real root crossing solid blue line ($\lambda = 0$ with $a = -b$).
- "Hopf bifurcation" crossing solid red line.
- Curves above create a **D-partitioning** of the complex plane into distinct regions with distinct integer number of ***eigenvalues*** with real positive parts.

Comments DDE with One Delay

The ***characteristic equation*** of a ***delay differential equation (DDE)*** is an ***exponential polynomial***, which can rarely be solved exactly.

Stability of the **DDE** is demonstrated by showing all roots (infinite) have negative real parts.

The analysis above finds the ***stability region*** for the **DDE**

$$\dot{y}(t) = ay(t) + by(t-r)$$

- Region with $a < 0$ and $|b| < |a|$ is stable independent of the delay
- As $r \to 0$, the DDE approaches the ODE with stability region $a + b < 0$
- Stability region comes to a point at $\left(\frac{1}{r}, -\frac{1}{r}\right)$
- Imaginary root crossings are distinct, non-intersecting curves, leaving this ***stability boundary*** generated by the parametric equations with $\omega \in \left(0, \frac{\pi}{r}\right)$.

Argument Principle

The **Argument Principle** from complex variables is one technique for locating the eigenvalues.

Theorem (Argument Principle)

*If $f(z)$ is a **meromorphic** function inside and on some closed contour C, with f having no zeros or poles on C, then the following formula holds:*

$$\oint_C \frac{f'(z)}{f(z)}\,dz = 2\pi i(N-P),$$

where N and P denote respectively the number of zeros and poles of $f(z)$ inside the contour C, with each zero and pole counted as many times as its multiplicity and order, respectively. This assumes that the contour C is simple and is oriented counter-clockwise.

Argument Principle: Stability Analysis

- Since the ***characteristic equation***, $f(\lambda)$, is an ***analytic function***, then the ***Argument Principle*** finds the **zeroes** of $f(\lambda)$.
- A ***geometric method*** of employing the ***Argument Principle*** is to consider a contour, C, (counterclockwise), then create a map $f(C)$ with the analytic function, $f(\lambda)$.
- The map $f(C)$ creates a curve in the complex plan, and the ***Argument Principle*** states that this map will encircle the origin N times (counterclockwise), where N is the number of **zeroes** inside C.
- ***Stability analysis*** for differential equations with the ***Argument Principle*** (sometimes called ***Nyquist criterion***) uses an appropriate contour in the right half of complex plane.
  - For **ODEs**, create semi-circle radius R with diameter on imaginary axis, then let $R \to \infty$.
  - For **DDEs**, often sufficient to take rectangle from $[-\frac{\pi}{r}, \frac{\pi}{r}]$ on imaginary axis and real part arbitrarily large.

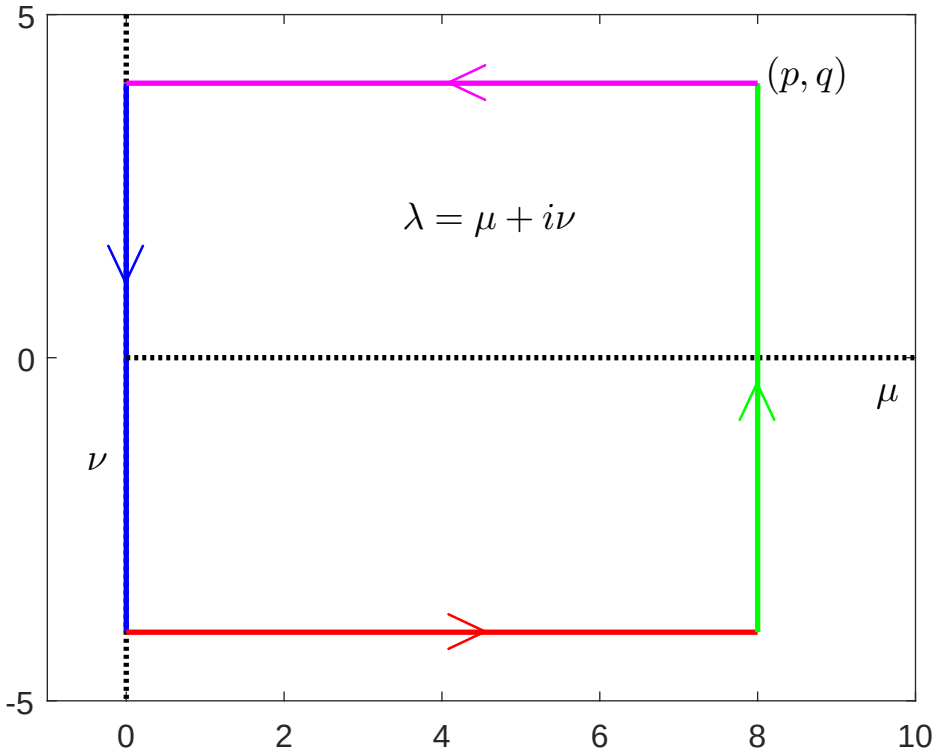
MatLab Application for ODEs

We want to show stability of ***examples from ODEs***

1. $\ddot{y} + \dot{y} - 6y = 0$
   - Characteristic equation: $\lambda^2 + \lambda - 6 = 0$
   - Shows 1 encirclements (Unstable)
2. $\ddot{y} - 2\dot{y} + 2y = 0$
   - Characteristic equation: $\lambda^2 - 2\lambda + 2 = 0$
   - Shows 2 encirclements (Unstable)
3. $\ddot{y} + 2\dot{y} + 2y = 0$
   - Characteristic equation: $\lambda^2 + 2\lambda + 2 = 0$
   - Shows no encirclements (Stable)

Contour

The graph below is the contour to which we apply our ***characteristic equations***.



Argument Principle for Polynomial

Consider the ***polynomial equation***

$$p(\lambda) = \lambda^2 + a\lambda + b.$$

```
1  function poly(a,b,p,q)
2  % Polynomial x^2 + ax + b
3  % p = x_max, q = y_max
4
5  h=p/100;
6  k=q/50;
7  x(1) = 0;
8  y(1) = q;
9  u1(1) = x(1)^2-y(1)^2+a*x(1)+b;
10 w1(1) = 2*x(1)*y(1)+a*y(1);
11 for i=2:101
12     x(i) = 0;
13     y(i) = y(i-1)-k;
14     u1(i) = x(i)^2-y(i)^2+a*x(i)+b;
```

Argument Principle for Polynomial

```
15      w1(i) = 2*x(i)*y(i)+a*y(i);
16  end
17  for i=102:201
18      x(i) = x(i-1)+h;
19      y(i) = -q;
20      u2(i-101) = x(i)^2-y(i)^2+a*x(i)+b;
21      w2(i-101) = 2*x(i)*y(i)+a*y(i);
22  end
23  for i=202:301
24      x(i) = p;
25      y(i) = y(i-1)+k;
26      u3(i-201) = x(i)^2-y(i)^2+a*x(i)+b;
27      w3(i-201) = 2*x(i)*y(i)+a*y(i);
28  end
```

Argument Principle for Polynomial

```
29  for i=302:401
30      x(i) = x(i-1)-h;
31      y(i) = q;
32      u4(i-301) = x(i)^2-y(i)^2+a*x(i)+b;
33      w4(i-301) = 2*x(i)*y(i)+a*y(i);
34  end
35  plot(u1,w1,'b-',u2,w2,'r-',u3,w3,'g-',u4,w4,'m-');grid
```

MatLab Application for DDEs

Eigenvalues for ***Examples from DDEs***

1. $\dot{y}(t) = -y(t) - 3y(t-1)$
   - Characteristic equation: $\lambda + 1 = -3e^{-\lambda}$
   - Shows 2 encirclements (Unstable)
2. $\dot{y}(t) = -y(t) - 3y(t-0.5)$
   - Characteristic equation: $\lambda + 1 = -3e^{-0.5\lambda}$
   - Shows no encirclements (Stable)
3. $\dot{y}(t) = -y(t) + 6y(t-1)$
   - Characteristic equation: $\lambda + 1 = 6e^{-\lambda}$
   - Shows 3 encirclements (Unstable)

Argument Principle for DDE

Consider the ***characteristic equation***

$$f(\lambda) = \lambda - a - b\,e^{-r\lambda}.$$

```
1  function delay_1abr(a,b,r,p,q)
2
3  % One-delay z - a - b*e^(-r*z)
4  % p = x_max, q = y_max
5
6  h=p/100;
7  k=q/50;
8  x(1) = 0;
9  y(1) = q;
10 u1(1) = x(1)-a-b*exp(-r*x(1))*cos(r*y(1));
11 w1(1) = y(1)+b*exp(-r*x(1))*sin(r*y(1));
12 for i=2:101
13     x(i) = 0;
14     y(i) = y(i-1)-k;
```

Argument Principle for DDE

```
15      u1(i) = x(i)-a-b*exp(-r*x(i))*cos(r*y(i));
16      w1(i) = y(i)+b*exp(-r*x(i))*sin(r*y(i));
17  end
18  for i=102:201
19      x(i) = x(i-1)+h;
20      y(i) = -q;
21      u2(i-101) = x(i)-a-b*exp(-r*x(i))*cos(r*y(i));
22      w2(i-101) = y(i)+b*exp(-r*x(i))*sin(r*y(i));
23  end
24  for i=202:301
25      x(i) = p;
26      y(i) = y(i-1)+k;
27      u3(i-201) = x(i)-a-b*exp(-r*x(i))*cos(r*y(i));
28      w3(i-201) = y(i)+b*exp(-r*x(i))*sin(r*y(i));
29  end
```

Argument Principle for DDE

```
30  for i=302:401
31      x(i) = x(i-1)-h;
32      y(i) = q;
33      u4(i-301) = x(i)-a-b*exp(-r*x(i))*cos(r*y(i));
34      w4(i-301) = y(i)+b*exp(-r*x(i))*sin(r*y(i));
35  end
36  plot(u1,w1,'b-',u2,w2,'r-',u3,w3,'g-',u4,w4,'m-');grid
```

Linear Analysis of the Model

Due to the ***negative control*** by **EPO**, it can be shown that this model has a ***unique equilibrium***:

$$(\bar{M}, \bar{E}, \bar{\nu}_F).$$

With the change of variables, $x_1(t) = M(t) - \bar{M}$, $x_2(t) = E(t) - \bar{E}$, and $x_3(t) = \nu_F(t) - \bar{\nu}_F$ and keeping only the ***linear terms***, we obtain the ***linear system***:

$$\begin{aligned}
\dot{x}_1(t) &= e^{\beta\mu_1} S_0'(\bar{E}) x_2(t - \mu_F) - \gamma x_1(t), \\
\dot{x}_2(t) &= f'(\bar{M}) x_1(t) - k x_2(t), \\
\dot{x}_3(t) &= \frac{1}{\bar{E}} x_2(t - \mu_F - \bar{\nu}_F) - \gamma x_3(t).
\end{aligned}$$

Linear Analysis of the Model

Let $X(t) = [x_1(t), x_2(t), x_3(t)]^T$, then the linear system can be written:

$$\dot{X}(t) = A_1 X(t) + A_2 X(t - \mu_F) + A_3 X(t - \mu_F - \bar{\nu}_F),$$

where

$$A_1 = \begin{pmatrix} -\gamma & 0 & 0 \\ f'(\bar{M}) & -k & 0 \\ 0 & 0 & -\gamma \end{pmatrix}, \quad A_2 = \begin{pmatrix} 0 & e^{\beta\mu_1} S_0'(\bar{E}) & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix},$$

and

$$A_3 = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & \frac{1}{\bar{E}} & 0 \end{pmatrix}.$$

We try solutions of the form $X(t) = \xi e^{\lambda t}$ giving:

$$\lambda I \xi e^{\lambda t} = \left[A_1 + A_2 e^{-\lambda \mu_F} + A_3 e^{-\lambda(\mu_F + \bar{\nu}_F)} \right] \xi e^{\lambda t}.$$

Characteristic Equation

Dividing by $e^{\lambda t}$ results in the ***eigenvalue equation***:

$$\left(A_1 + A_2 e^{-\lambda \mu_F} + A_3 e^{-\lambda(\mu_F + \bar{\nu}_F)} - \lambda I\right) \xi = 0.$$

So we must solve

$$\det \begin{vmatrix} -\gamma - \lambda & e^{\beta \mu_1} S_0'(\bar{E}) e^{-\lambda \mu_F} & 0 \\ f'(\bar{M}) & -k - \lambda & 0 \\ 0 & \frac{1}{\bar{E}} e^{-\lambda(\mu_F + \bar{\nu}_F)} & -\gamma - \lambda \end{vmatrix} = 0,$$

which gives the ***characteristic equation***

$$(\lambda + \gamma)\left[(\lambda + \gamma)(\lambda + k) + \bar{A} e^{-\lambda \mu_F}\right] = 0,$$

where $\bar{A} \equiv -e^{\beta \mu_1} S_0'(\bar{E}) f'(\bar{M}) > 0$.

Stability Analysis of Delay Model

Stability Analysis of the Delay Model

The ***characteristic equation*** is an ***exponential polynomial*** given by

$$(\lambda+\gamma)\Big((\lambda+\gamma)(\lambda+k)+\bar{A}e^{-\lambda\mu_F}\Big)=0,$$

which has one solution $\lambda=-\gamma$.

This shows the stability of the ν_F equation, which was the ***state-dependent*** portion of the ***delay model***.

Remains to analyze

$$(\lambda+\gamma)(\lambda+k)=-\bar{A}e^{-\lambda\mu_F}.$$

The boundary of the stability region occurs at a **Hopf bifurcation**, where the ***eigenvalues*** are $\lambda=i\omega$, purely imaginary.

Stability Analysis of Delay Model

Properties of the Exponential Polynomial (Characteristic Equation)

$$(\lambda+\gamma)(\lambda+k)+\bar{A}e^{-\lambda\mu_F}=0.$$

- The solution of the ***characteristic equation*** has infinitely many roots.
- ***Discrete delay model*** is infinite dimensional as the initial data must be a function of the history over the longest delay.
- The ***exponential polynomial*** has a leading pair of ***eigenvalues*** and many of trailing having negative real part (***Stable Manifold Theorem***).
- Analysis of the ***delay model*** is easier than the generalized ***age-structured model***.
- The models are **equivalent** under the assumption that $V(E)=W=1$.
- ***Stability*** changes to oscillatory when the leading pair of ***eigenvalues*** cross the imaginary axis, a ***Hopf bifurcation***.

Stability Analysis of Delay Model

Hopf Bifurcation Analysis

A ***Hopf bifurcation*** occurs when $\lambda = i\omega$ solves the ***characteristic equation***,

$$(i\omega + \gamma)(i\omega + k) = -\bar{A}e^{-i\omega\mu_F}.$$

From complex variables, we match the ***magnitudes***:

$$|(i\omega + \gamma)(i\omega + k)| = \bar{A},$$

where the left side is monotonically increasing in ω, and the ***arguments***

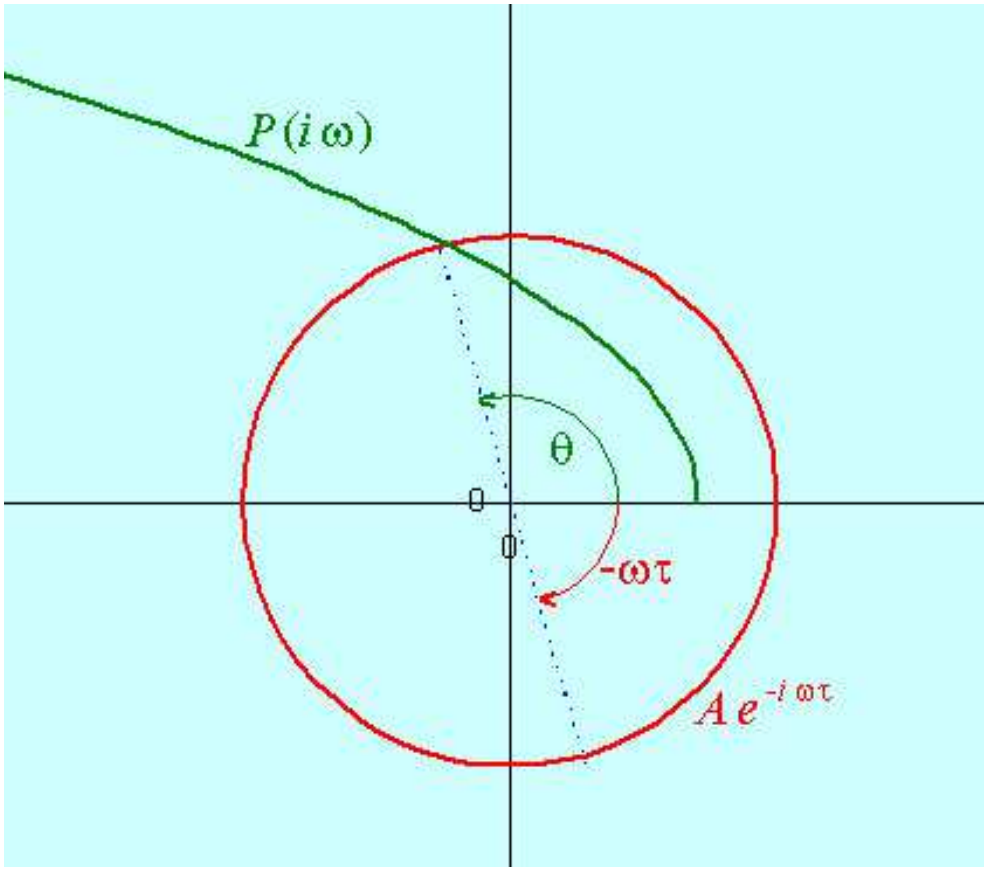
$$\Theta(\omega) \equiv \arctan\left(\frac{\omega}{\gamma}\right) + \arctan\left(\frac{\omega}{k}\right) = \pi - \omega\mu_F,$$

which has infinitely many solutions.

Solve for ω by varying parameters such as γ or μ_F.

Argument Principle

Hopf Bifurcation: One significant method for finding the roots of the ***characteristic equation*** at a Hopf bifurcation is the **Argument Principle** from complex variables.



Experiments and Model

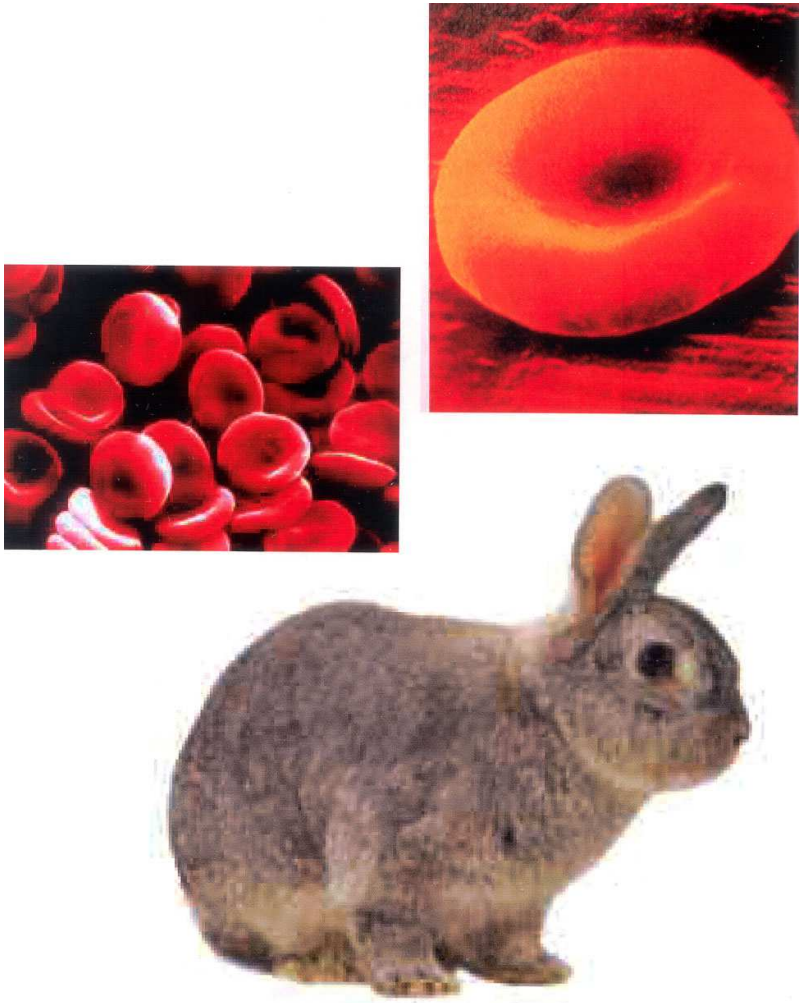
Experiment:

Give rabbits regular antibodies to **RBCs**.

This increases destruction rate γ.

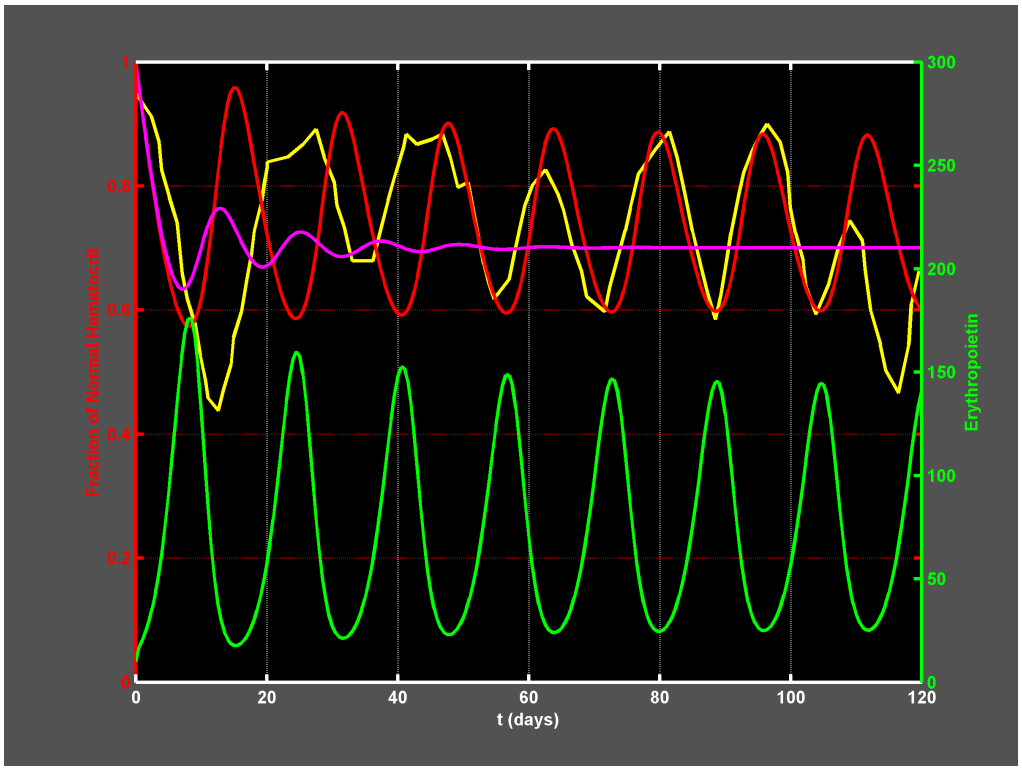
Observe ***oscillations*** in **RBCs**.

Model undergoes **Hopf bifurcation** with increasing γ.



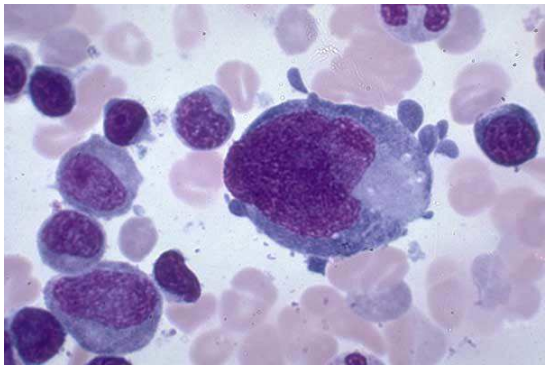
Model for Erythropoiesis

Model can reasonably match the rabbit data by fitting parameters that are reasonable.

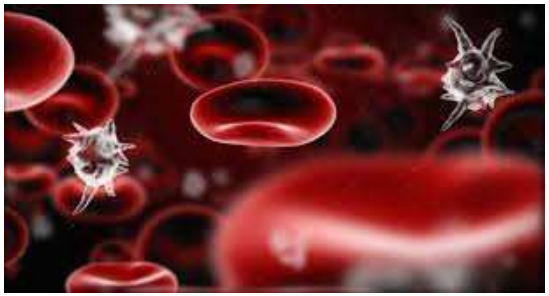


The **model** stabilizes with ***variable velocity,*** $V(E)$, but a more complicated model.

Thrombopoiesis



Megakaryocytes



Platelets

Thrombopoiesis is the process for producing ***Thrombocytes*** or ***Platelets***.

- **Platelets** are about 20% the size of **RBCs** and there are only about 10-20% by numbers compared to **RBCs**.
- They are critical for repairing damage to blood vessels by clumping together and creating clots.
- The half-life for platelets is significantly lower and results in a very high turnover.

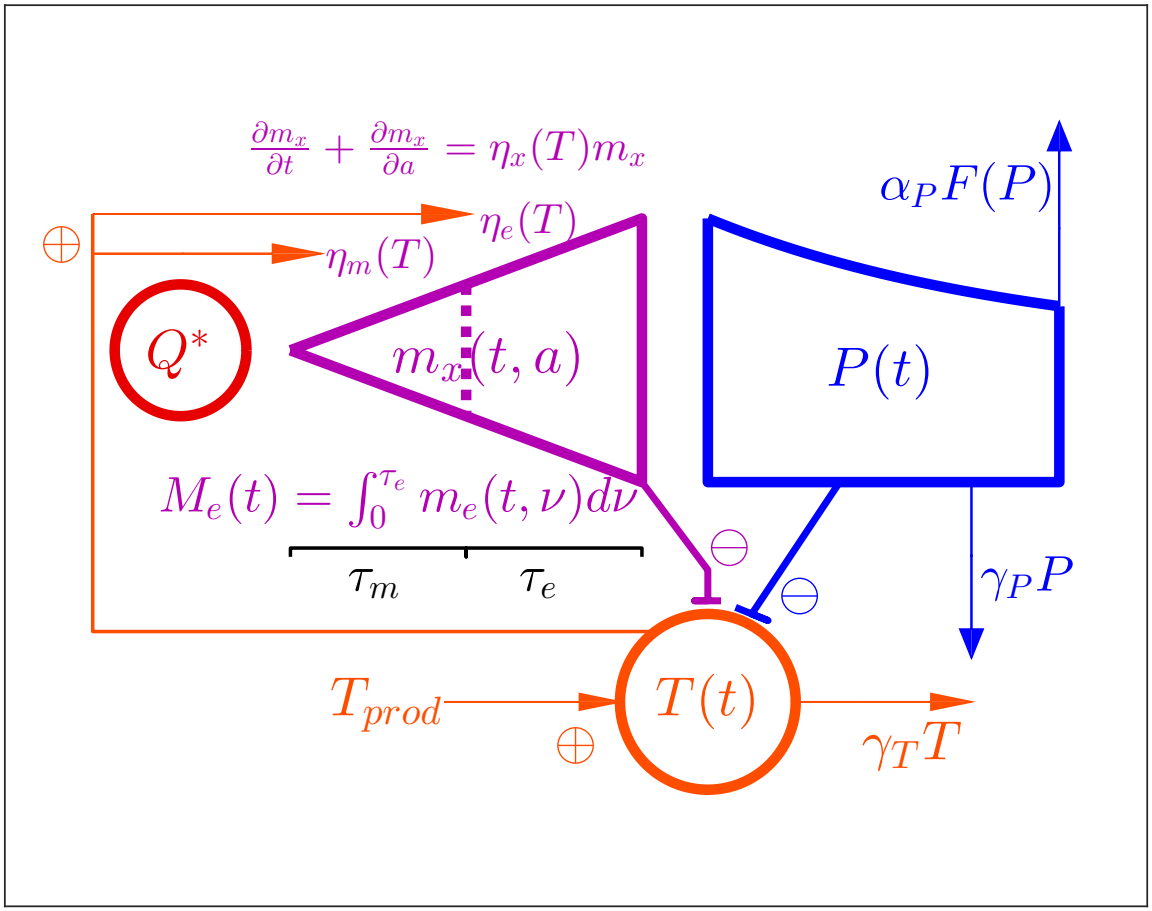
Thrombopoiesis

Thrombocytes or ***Platelets***

- ***Platelets*** begin from undifferentiated stem cells (multipotent progenitors), and based on ***thrombopoietin (TPO)*** levels multiply then stop dividing and undergo **endomitosis**, forming ***megakaryocytes*** (2-256 nuclei).
- ***Thrombopoietin (TPO)*** is produced constantly then absorbed by ***megakaryocytes*** and ***platelets*** (negative feedback).
- Maturation takes 10-14 days, then ***megakaryocytes*** protrude **filopodia** into blood vessels and platelets are released.
- **Platelets** circulate in the bloodstream for about 10 days, then are actively degraded.
- ***TPO*** circulates at significantly lower concentrations compared to ***EPO***.

Age-Structured Model for Thrombopoiesis

Age-Structured Model for Thrombopoiesis



Model for Thrombopoiesis

Model for Thrombopoiesis

$$\begin{aligned}\frac{dP}{dt} &= \frac{D_0}{\beta_P} m_e\left(t,\tau_e\right) - \gamma_P P - \alpha_P \frac{P^{n_P}}{b_P^{n_P} + P^{n_P}},\\ \frac{dT}{dt} &= T_{prod} - \gamma_T T - \alpha_T \left(M_e\left(t\right) + k_S \beta_P P\right) \frac{T^{n_T}}{k_T^{n_T} + T^{n_T}},\end{aligned}$$

where

$$m_e\left(t,a\right) = V_m \kappa_P Q^* \exp\left[\int_{t-a-\tau_m}^{t-a} \eta_m\left(T\left(s\right)\right) ds\right] \exp\left[\int_{t-a}^{t} \eta_e\left(T\left(s\right)\right) ds\right],$$

$$M_e\left(t\right) = \int_0^{\tau_e} m_e\left(t,a\right) da.$$

$$\eta_m\left(T\left(t\right)\right) = \eta_m^{min} + \left(\eta_m^{max} - \eta_m^{min}\right) \frac{T^{n_m}}{b_m^{n_m} + T^{n_m}},$$

$$\left(T\left(t\right)\right) \quad \min + \left(\max - \min\right) \quad \frac{T^{n_e}}{}$$

Notes on Model for Thrombopoiesis

Notes on Model for Thrombopoiesis

- The ***thrombopoiesis model*** is more complex with many more parameters than the ***erythropoiesis model***.
- The ***Functional differential equation*** form is substantially more complex, especially the **2 delays** of maturation (η_m and η_e).
- Age-structure reductions are very similar.
- The ***negative feedbacks*** differ significantly.
- Simulations show clear ***Hopf bifurcations***.
- ***Linear analysis*** is significantly more difficult.

Parameters for Model for Thrombopoiesis

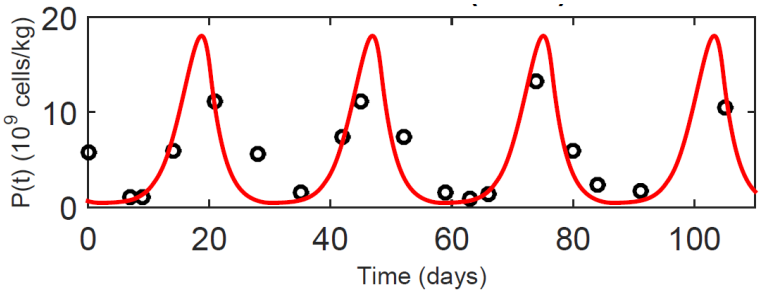
Parameters for Model for Thrombopoiesis

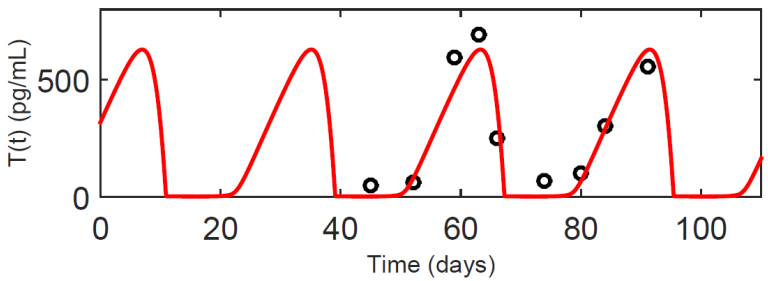
- Over 20 parameters in model.
- Extensive literature search
  - Identify some directly.
  - Fit many with existing experimental data.
  - Insufficient sensitivity analysis at this time.
- Found asymptotically stable equilibrium for normal subject.
- Could vary several parameters (**4**) to match diseased patients.

Cyclical Thrombocytopenia

Cyclical Thrombocytopenia

- Rare, but dangerous pathological state, with very high and low platelet counts oscillating with about a month period.
- Source of the disease is unknown, but suspect defective peripheral control – No good treatment to date.





Unique Equilibrium

From before, we have the **Thrombopoiesis Model**:

$$\begin{aligned}\frac{dP}{dt} &= \frac{D_0}{\beta_P} m_e(t,\tau_e) - \gamma_P P - \alpha_P \frac{P^{n_P}}{b_P^{n_P} + P^{n_P}},\\ \frac{dT}{dt} &= T_{prod} - \gamma_T T - \alpha_T \left(M_e(t) + k_S \beta_P P\right) \frac{T^{n_T}}{k_T^{n_T} + T^{n_T}},\end{aligned}$$

where the functions $m_e(t,\tau_e)$ and $M_e(t)$ are defined as before.

Theorem (Unique Equilibrium)

*The **Thrombopoiesis Model** has a unique positive equilibrium, (P^*, T^*).*

Proof: The proof of this result uses the monotonicity of the functions composing the right hand sides of this system of DEs. It is a highly nonlinear system, but the positive and negative feedbacks combine to give a unique equilibrium.

Linearization

Let $x(t) = P(t) - P^*$ and $y(t) = T(t) - T^*$ and ignore higher order terms, then the ***linearized system*** becomes:

$$\begin{aligned}
\frac{dx}{dt} &= A_2\left[\partial_T\eta_m(T^*)\int_{t-\tau_e-\tau_m}^{t-\tau_e} y(s)\,ds + \partial_T\eta_e(T^*)\int_{t-\tau_e}^{t} y(s)\,ds\right] \\
&\quad -\big(\gamma_P + \partial_P F(P^*)\big)x, \\
\frac{dy}{dt} &= -\alpha_T k_S\beta_P G(T^*)x - \big(\gamma_T + \alpha_T(A_1E_1 + k_S\beta_P P^*)\partial_T G(T^*)\big)y \\
&\quad - \alpha_T A_1 G(T^*)\left(\partial_T\eta_m(T^*)\int_0^{\tau_e} e^{\eta_e(T^*)a}\left(\int_{t-a-\tau_m}^{t-a} y(s)\,ds\right)da\right. \\
&\quad \left. + \partial_T\eta_e(T^*)\int_0^{\tau_e} e^{\eta_e(T^*)a}\left(\int_{t-a}^{t} y(s)\,ds\right)da\right),
\end{aligned}$$

where

$$A_2 = \frac{D_0 V_m \kappa_P Q^*}{\beta_P} e^{\eta_m(T^*)\tau_m + \eta_e(T^*)\tau_e}, \quad A_1 = V_m\kappa_P Q^* e^{\eta_m(T^*)\tau_m}, \quad E_1 = \frac{e^{\eta_e(T^*)\tau_e} - 1}{\eta_e(T^*)}.$$

Characteristic Equation

With solutions of the form $[x(t), y(t)]^T = [c_1, c_2]^T e^{\lambda t}$, the ***linear functional equation*** becomes:

$$\lambda \mathbf{I} \begin{pmatrix} c_1 \\ c_2 \end{pmatrix} = \begin{pmatrix} -L_1 & L_2(\lambda) \\ -L_3 & -L_4(\lambda) \end{pmatrix} \begin{pmatrix} c_1 \\ c_2 \end{pmatrix}.$$

The coefficients L_1, L_2, L_3, and L_4 are given by

$$L_1 = \gamma_P + \partial_P F(P^*),$$

$$L_2(\lambda) = \frac{A_2}{\lambda}\left[\partial_T \eta_m(T^*) e^{-\lambda \tau_e}\left(1 - e^{-\lambda \tau_m}\right) + \partial_T \eta_e(T^*)\left(1 - e^{-\lambda \tau_e}\right)\right],$$

$$L_3 = \alpha_T k_S \beta_P G(T^*),$$

$$L_4(\lambda) = C_1 + \frac{C_2}{\lambda}\left[\partial_T \eta_m(T^*)\left(1 - e^{-\lambda \tau_m}\right)\frac{\left(1 - e^{-(\lambda - \eta_e(T^*))\tau_e}\right)}{(\lambda - \eta_e(T^*))}\right.$$
$$\left. + \partial_T \eta_e(T^*)\left(\frac{e^{\eta_e(T^*)\tau_e} - 1}{\eta_e(T^*)} + \frac{e^{-(\lambda - \eta_e(T^*))\tau_e} - 1}{\lambda - \eta_e(T^*)}\right)\right],$$

Characteristic Equation

From the definitions above the ***Characteristic Equation*** becomes:

$$\det \begin{vmatrix} -L_1 - \lambda & L_2(\lambda) \\ L_3 & -L_4(\lambda) - \lambda \end{vmatrix} = (\lambda + L_1)(\lambda + L_4(\lambda)) - L_2(\lambda)L_3 = 0.$$

Eliminating the λ terms in the denominator leaves a complicated ***exponential polynomial*** of the form:

$$P_4(\lambda) + (\alpha_1\lambda + \alpha_0)e^{-\lambda\tau_m} + (\beta_1\lambda + \beta_0)e^{-\lambda\tau_e} + (\gamma_1\lambda + \gamma_0)e^{-\lambda(\tau_e+\tau_m)} = 0.$$

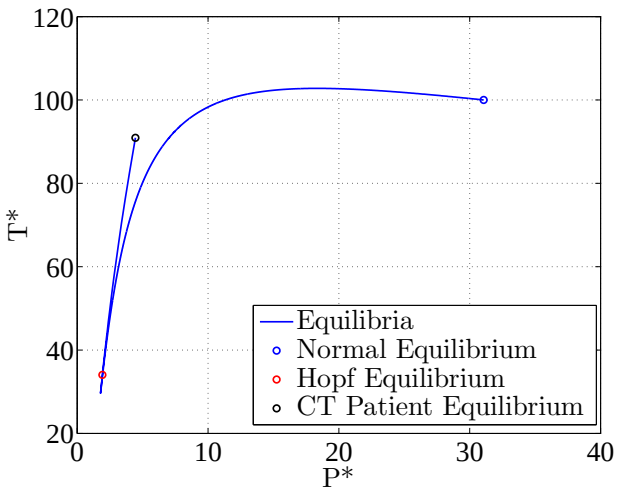
We have **failed** to obtain any analytic intuition on this ***exponential polynomial***, but it is readily solved numerically in **Maple** and **MatLab**.

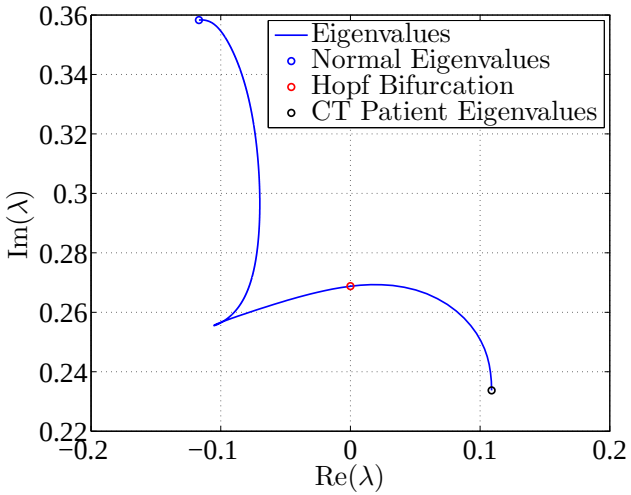
Numerical Hopf Bifurcation

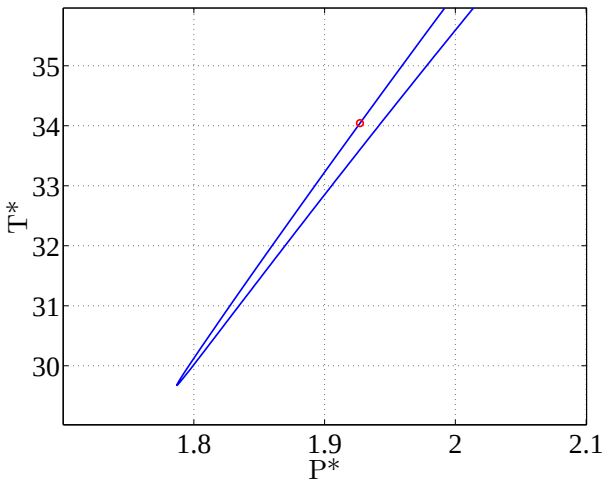
Numerical Hopf Bifurcation

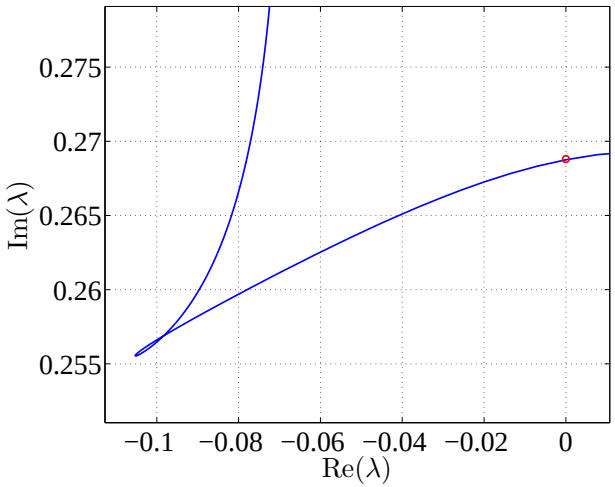
- As noted earlier, parameters were fit for a ***normal subject***.
  - Leading ***eigenvalues*** were $\lambda_1 \approx -0.059 \pm 0.053i$, which has the wrong frequency for observed diseased individuals.
  - The second set of ***eigenvalues*** were $\lambda_2 \approx -0.114 \pm 0.359i$.
  - λ_2 has appropriate frequency and connects numerically to all diseased patients studied.
- Created ***hyperline*** in parameter space connecting the **4** parameters varied between normal subject and each diseased patient.
- Following graphs show variations in the values of the ***equilibria*** and the ***eigenvalues*** as the **4** parameters vary continuously.

Numerical Hopf Bifurcation



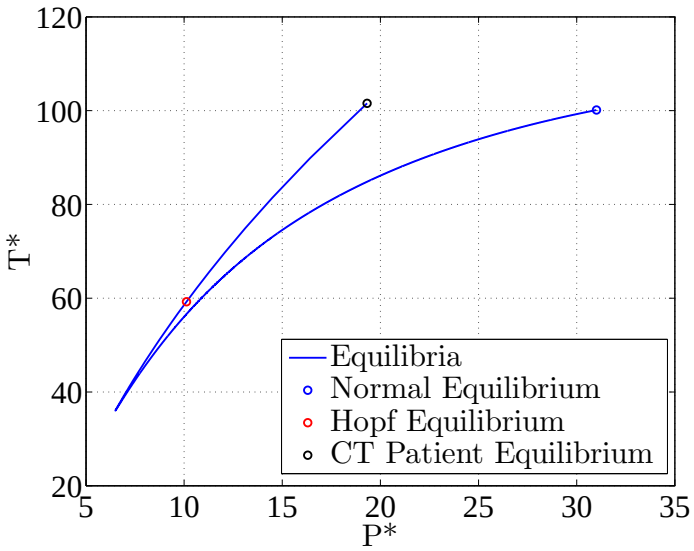


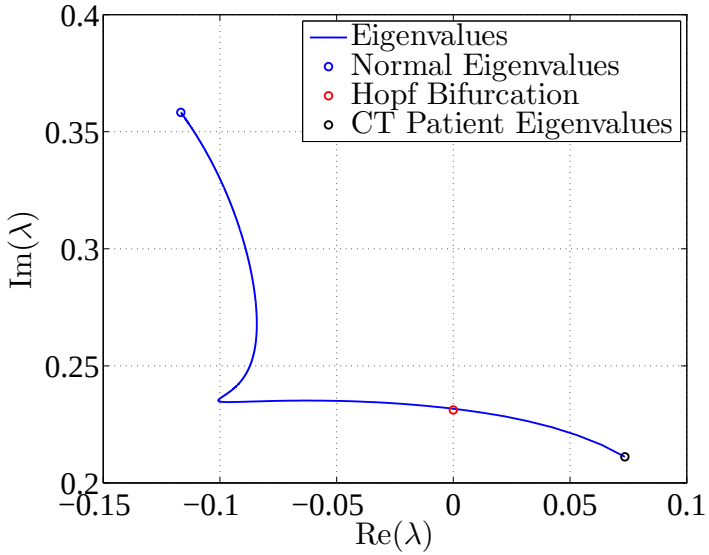




Numerical Hopf Bifurcation

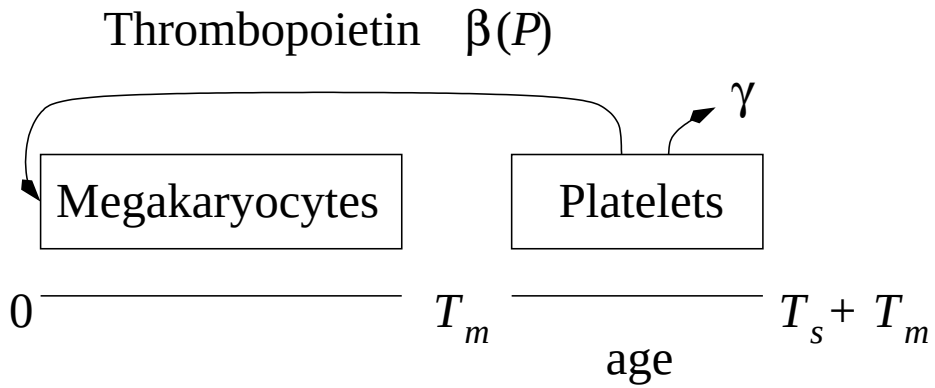
- As the **4** parameters vary linearly, the ***equilibria*** and the ***eigenvalues*** vary continuously.
- However, we observe a cusp-like change in a very small region of the hyperline (rapid transition).
- This needs more detailed exploration.





Bélair and Mackey Platelet Model

Two-delay Model for Platelets (Bélair and Mackey, 1987)



$$\frac{dP}{dt} = -\gamma P(t) - \gamma P(t) + \beta(P(t-T_m))\beta(P(t-T_m))\beta(P(t-T_m)) - \beta(P$$

Production of platelets $(\beta(P))$
Linear loss of platelets, (γP)
Discounted destruction of platelets $(\beta(P)e^{-\gamma T_s})$
Time delays for maturation (T_m) and life expectancy (T_s)

Modified Platelet Model

Modified Platelet Model

- Examine a modified form:

$$\frac{dP}{dt} = -\gamma P(t) + \frac{\beta_0 \theta^n P(t-R)}{\theta^n + P^n(t-R)} - f \cdot \frac{\beta_0 \theta^n P(t-1)}{\theta^n + P^n(t-1)}$$

- Scaled time to **normalize** the larger delay
- Chose parameters similar to Bélair and Mackey after scaling
- Introduced parameter f, which is different
- Wanted a scaling factor, instead of time delay varying discount

Modified Platelet Model

$$\frac{dP}{dt} = -\gamma P(t) + \frac{\beta_0 \theta P(t-R)}{\theta^n + P^n(t-R)} - f \cdot \frac{\beta_0 \theta P(t-1)}{\theta^n + P^n(t-1)}$$

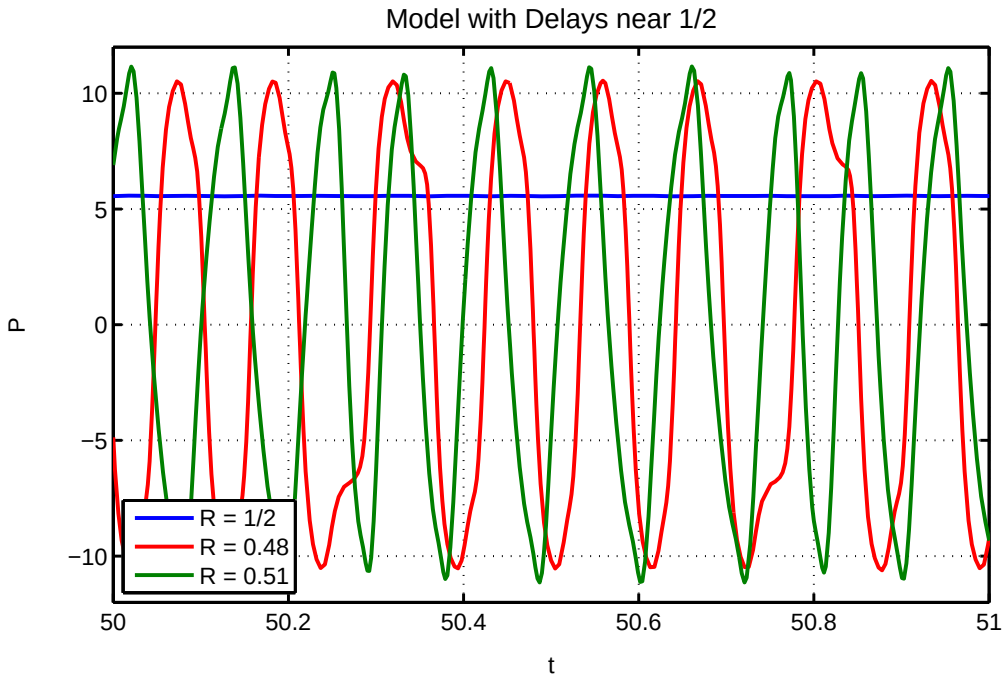


Figure shows stability at $R = \frac{1}{2}$, but irregular oscillations for delays nearby

Modified Platelet Model

$$\frac{dP}{dt} = -\gamma P(t) + \frac{\beta_0 \theta P(t-R)}{\theta^n + P^n(t-R)} - f \cdot \frac{\beta_0 \theta P(t-1)}{\theta^n + P^n(t-1)}$$

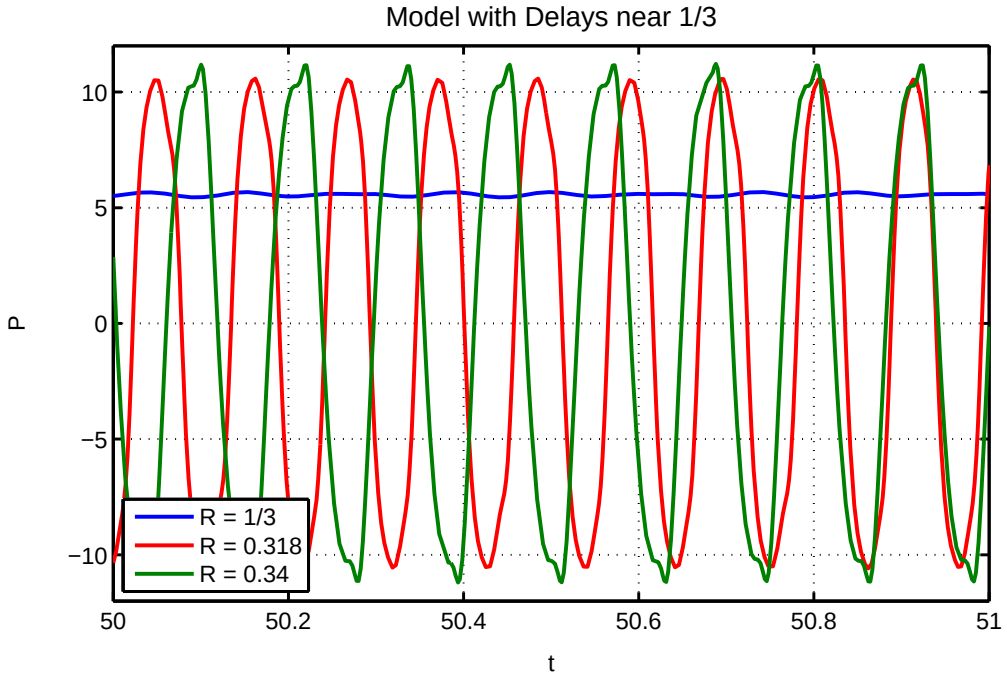


Figure shows stability at $R = \frac{1}{3}$, but irregular oscillations for delays nearby (Same parameters as $R = \frac{1}{2}$)

Two-Delay Differential Equation

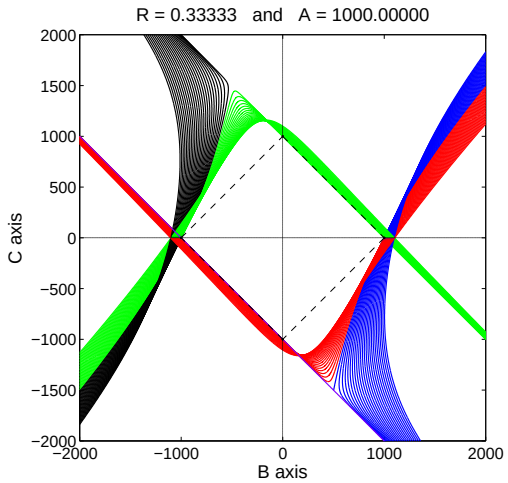
Two-Delay Differential Equation

$$\dot{y}(t) + A\,y(t) + B\,y(t-1) + C\,y(t-R) = 0$$

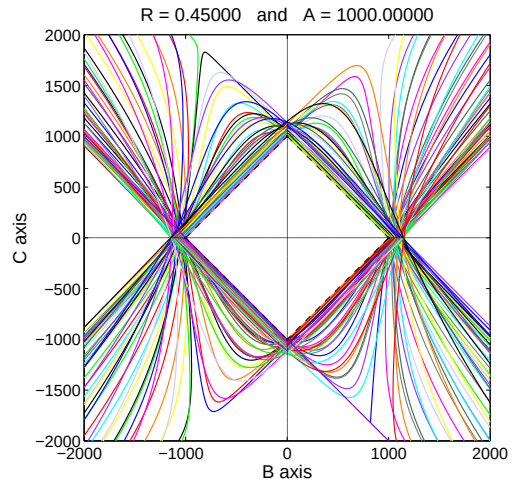
- Delay equations are important in modeling
- Two-delay problem
  - E. F. Infante noted an odd stability property observed in a two delay economic model, rational delays created a larger region of stability
  - Multiple delays are important for biological models
  - Developed special geometric techniques for analysis of delay equations
  - JM and T. C. Busken, Regions of stability for a linear differential equation with two rationally dependent delays, DCDS A, 35, 4955-4986 (2015)

Stability Regions for Different Delays

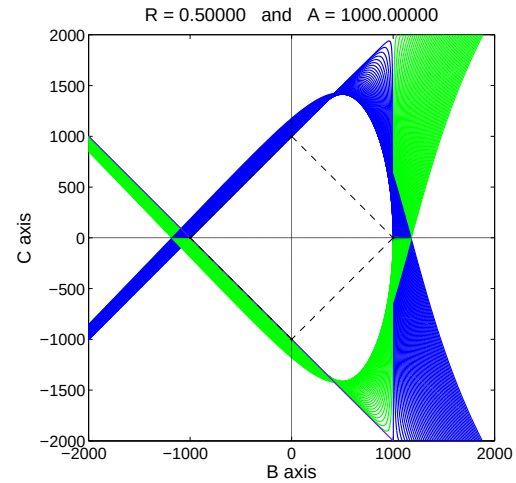
- Technique creates parametric families of curves from the image of the imaginary axis
- Similarity of limited family types prevent approach of Minimum Region of Stability (Black dashed lines)
- Below shows first 100 parametric curves for $A = 1000$



$R = \frac{1}{3}$



$R = 0.45$

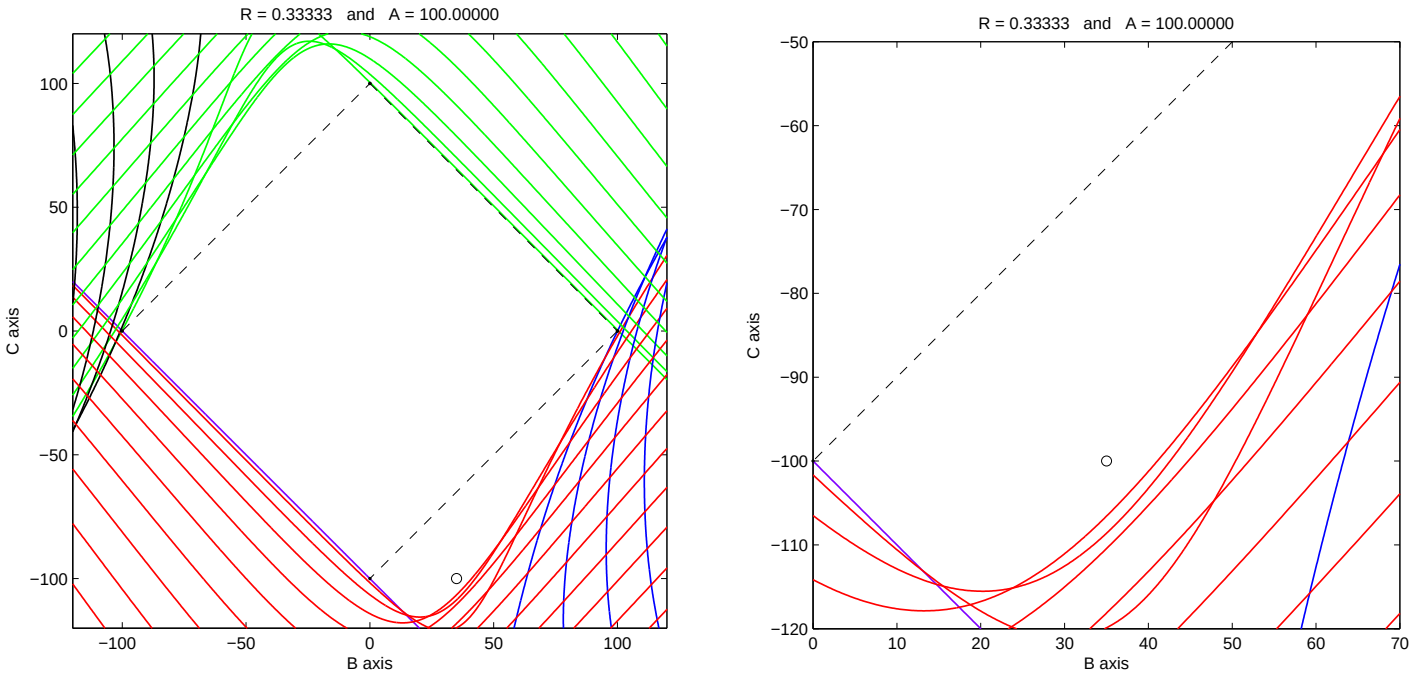


$R = \frac{1}{2}$

Modified Platelet Model

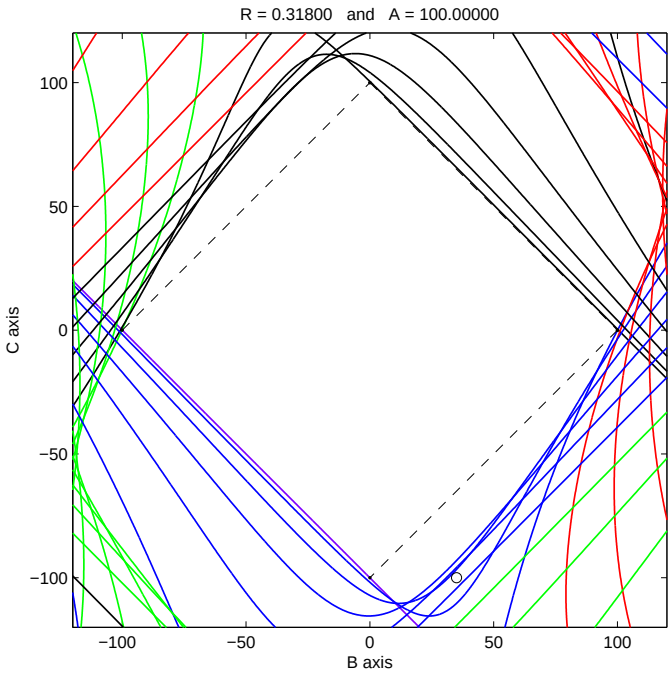
Returning to the ***modified platelet model***

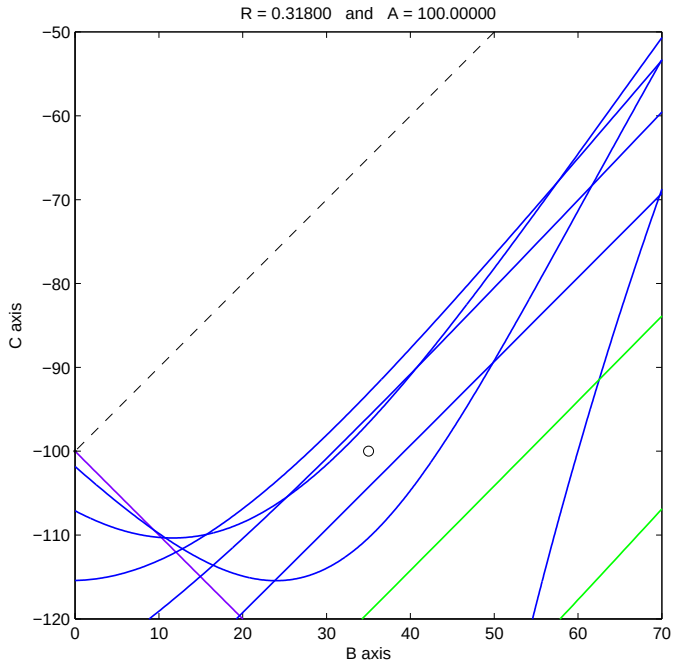
- The coefficients of the linearized model are approximately $(A, B, C) = (100, 35, -100)$ (black circle)
- Our D-partitioning curves for $R = \frac{1}{3}$ are below



Modified Platelet Model

- The coefficients of the linearized model are approximately $(A, B, C) = (100, 35, -100)$ (black circle)
- Our D-partitioning curves for $R = 0.318$ are below





Discussion/Conclusions

- Created *age-structured models for hematopoiesis*
- Can fit parameters to *experimental data*
- Reasonably fit normal and diseased patients
  - Provides some insight to *cyclical thrombocytopenia*
- Remains some sensitivity issues with parameters - start examining a simpler model
- Ultimately want model to give insights into treatments