

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:

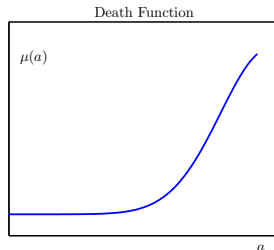
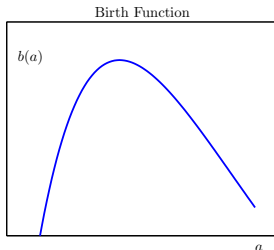
$$\frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} + \mu(a)n(t, a) = 0,$$

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.

Age-Structured Model - Method of Characteristics

The *Age-Structured Model*:

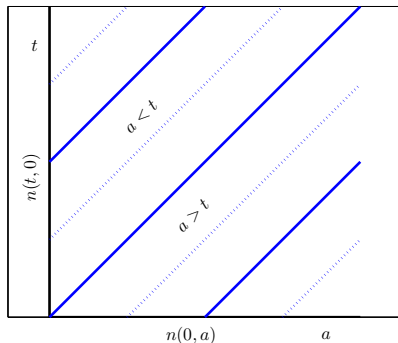
$$\frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} = -\mu(a)n(t, a).$$

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*:

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

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*:

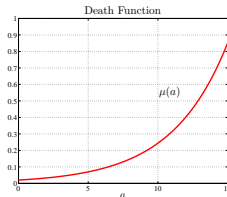
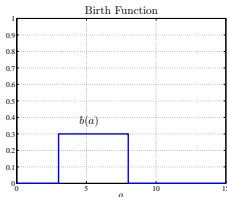
$$n(t, 0) = \int_0^\infty b(a)n(t, a) da.$$

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.



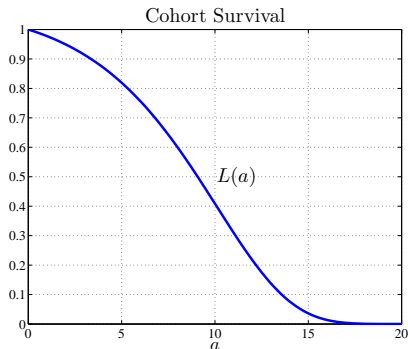
Note: These functions are very crude approximations to the forms displayed earlier.

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

$$r = 0.02925985.$$

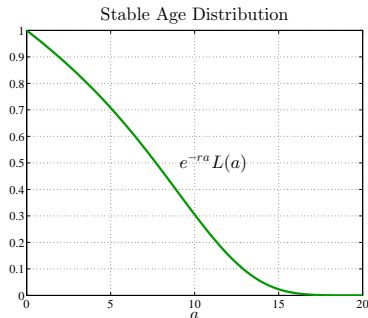
This shows the overall population is growing about 3% per unit time.

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:

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

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.

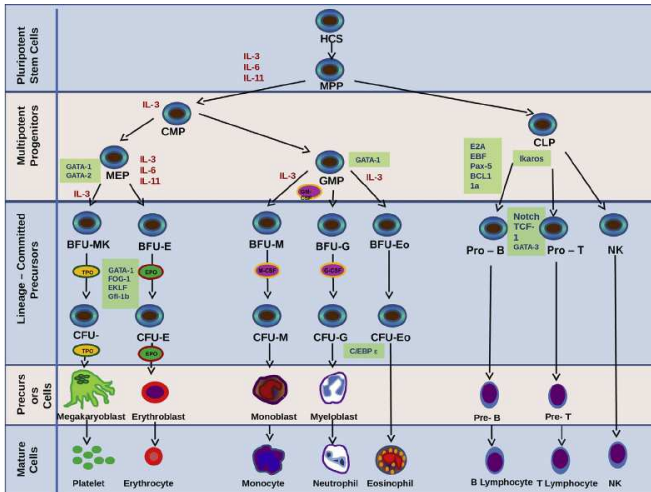
Needless to say, these models must be significantly expanded to manage more realistic populations, which in turn significantly complicates the mathematical analysis.

Introduction - Hematopoiesis

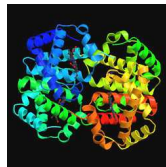
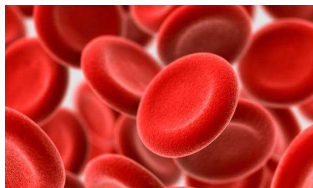
Hematopoiesis for Erythrocytes and Platelets

- 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

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).

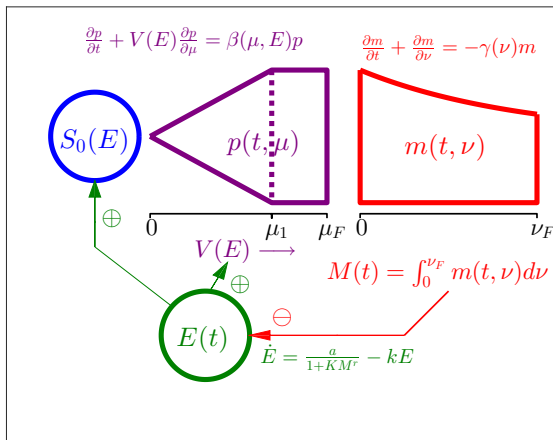
Erythropoiesis

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 through 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.

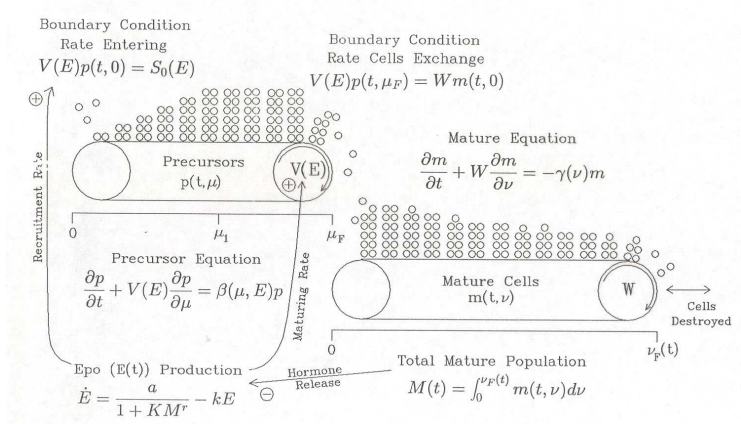
Model for Erythropoiesis

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**

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

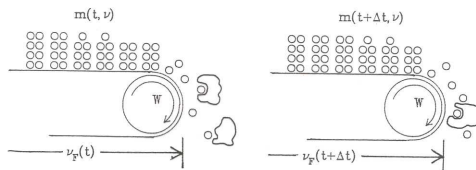
- Balance law

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

- As $\Delta t \rightarrow 0$,

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

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

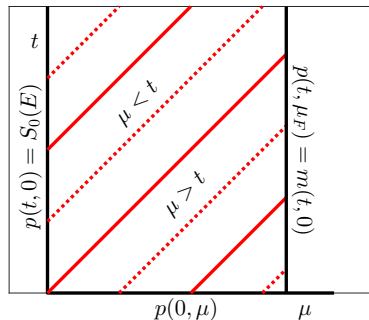
$$t(s) = s + t_0,$$

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 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

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

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:

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

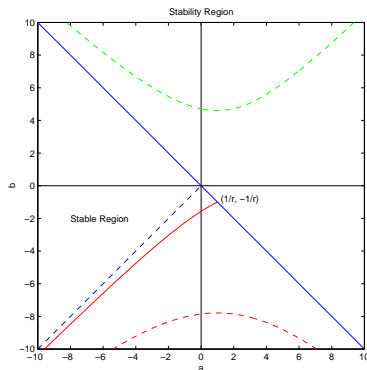
Solving these equations for $a(\omega)$ and $b(\omega)$ gives

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

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

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

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

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 $R \rightarrow \infty$.
 - 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*

❶ $\ddot{y} + \dot{y} - 6y = 0$

- Characteristic equation: $\lambda^2 + \lambda - 6 = 0$
- Shows 1 encirclements (Unstable)

❷ $\ddot{y} - 2\dot{y} + 2y = 0$

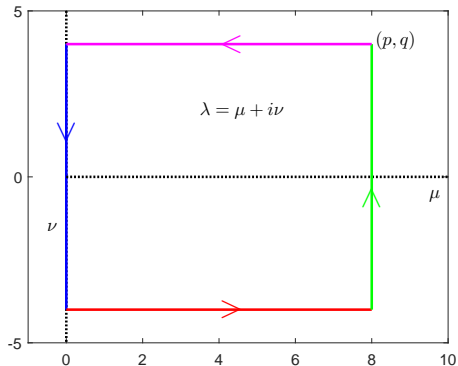
- Characteristic equation: $\lambda^2 - 2\lambda + 2 = 0$
- Shows 2 encirclements (Unstable)

❸ $\ddot{y} + 2\dot{y} + 2y = 0$

- 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*

❶ $\dot{y}(t) = -y(t) - 3y(t - 1)$

- Characteristic equation: $\lambda + 1 = -3e^{-\lambda}$
- Shows 2 encirclements (Unstable)

❷ $\dot{y}(t) = -y(t) - 3y(t - 0.5)$

- Characteristic equation: $\lambda + 1 = -3e^{-0.5\lambda}$
- Shows no encirclements (Stable)

❸ $\dot{y}(t) = -y(t) + 6y(t - 1)$

- 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_labr(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*:

$$\dot{x}_1(t) = e^{\beta\mu_1} S'_0(\bar{E})x_2(t - \mu_F) - \gamma x_1(t),$$

$$\dot{x}_2(t) = f'(\bar{M})x_1(t) - kx_2(t),$$

$$\dot{x}_3(t) = \frac{1}{\bar{E}}x_2(t - \mu_F - \bar{\nu}_F) - \gamma x_3(t).$$

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

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

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*

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

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

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

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*

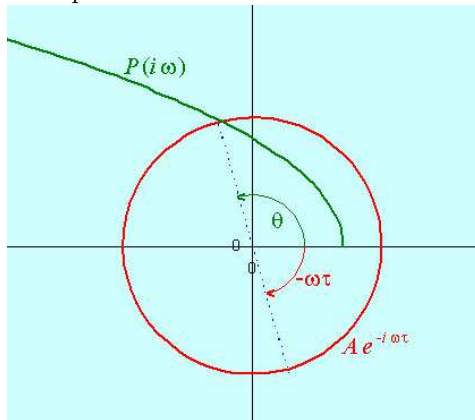
$$\Theta(\omega) \equiv \arctan\left(\frac{\omega}{\gamma}\right) + \arctan\left(\frac{\omega}{k}\right) = \pi - \omega\mu_F,$$

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

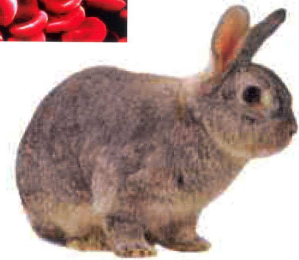
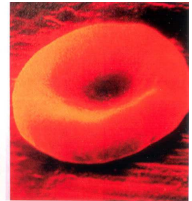
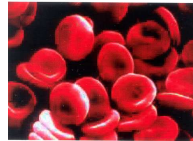
Experiment:

Give rabbits regular antibodies to **RBCs**.

This increases destruction rate γ .

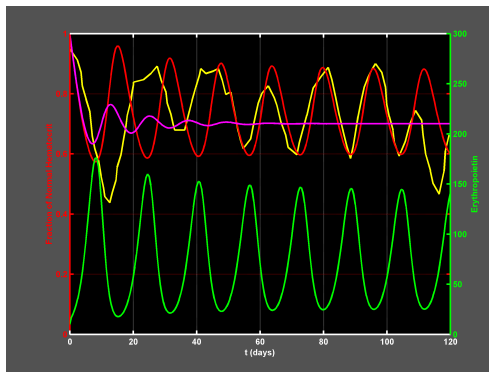
Observe *oscillations* in **RBCs**.

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



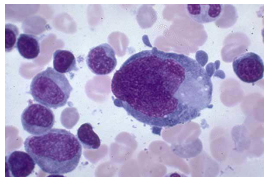
Model for Erythropoiesis

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.

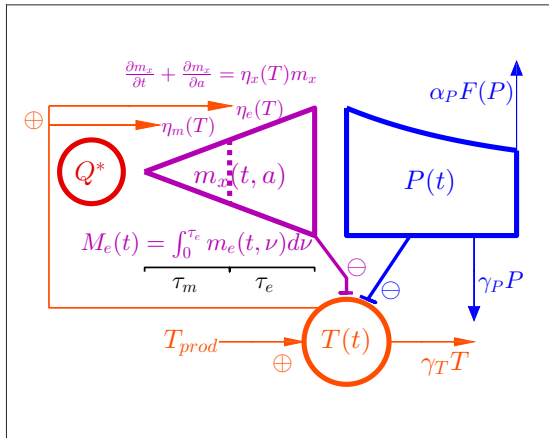
Thrombopoiesis

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

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

where

$$\begin{aligned}m_e(t, a) &= V_m \kappa_P Q^* \exp \left[\int_{t-a-\tau_m}^{t-a} \eta_m(T(s)) ds \right] \exp \left[\int_{t-a}^t \eta_e(T(s)) ds \right], \\ M_e(t) &= \int_0^{\tau_e} m_e(t, a) da.\end{aligned}$$

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

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

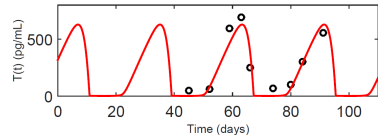
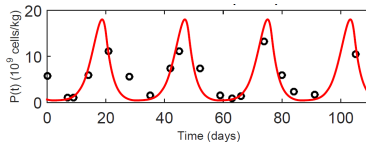
Parameters for Model for Thrombopoiesis

- 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**:

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

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:

$$\begin{aligned}\frac{dx}{dt} &= A_2 \left[\partial_T \eta_m(T^*) \int_{t-\tau_e-\tau_m}^{t-\tau_e} y(s) ds + \partial_T \eta_e(T^*) \int_{t-\tau_e}^t y(s) ds \right] \\ &\quad - (\gamma_P + \partial_P F(P^*)) x, \\ \frac{dy}{dt} &= -\alpha_T k_S \beta_P G(T^*) x - (\gamma_T + \alpha_T (A_1 E_1 + k_S \beta_P P^*) \partial_T G(T^*)) y \\ &\quad - \alpha_T A_1 G(T^*) \left(\partial_T \eta_m(T^*) \int_0^{\tau_e} e^{\eta_e(T^*)a} \left(\int_{t-a-\tau_m}^{t-a} y(s) ds \right) da \right. \\ &\quad \left. + \partial_T \eta_e(T^*) \int_0^{\tau_e} e^{\eta_e(T^*)a} \left(\int_{t-a}^t y(s) ds \right) da \right),\end{aligned}$$

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

1

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

$$\begin{aligned} L_1 &= \gamma_P + \partial_P F(P^*), \\ L_2(\lambda) &= \frac{A_2}{\lambda} \left[\partial_T \eta_m(T^*) e^{-\lambda \tau_e} (1 - e^{-\lambda \tau_m}) + \partial_T \eta_e(T^*) (1 - e^{-\lambda \tau_e}) \right], \\ L_3 &= \alpha_T k_S \beta_P G(T^*), \\ L_4(\lambda) &= C_1 + \frac{C_2}{\lambda} \left[\partial_T \eta_m(T^*) (1 - e^{-\lambda \tau_m}) \frac{(1 - e^{-(\lambda - \eta_e(T^*)) \tau_e})}{(\lambda - \eta_e(T^*))} \right. \\ &\quad \left. + \partial_T \eta_e(T^*) \left(\frac{e^{\eta_e(T^*) \tau_e} - 1}{\eta_e(T^*)} + \frac{e^{-(\lambda - \eta_e(T^*)) \tau_e} - 1}{\lambda - \eta_e(T^*)} \right) \right], \end{aligned}$$

Characteristic Equation

2

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

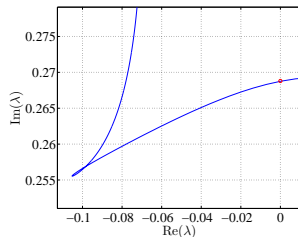
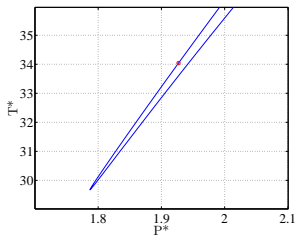
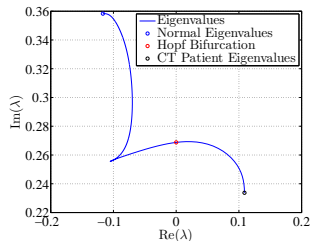
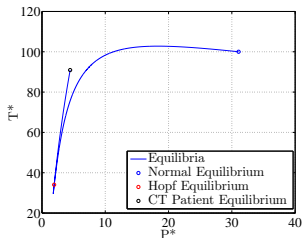
1

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.

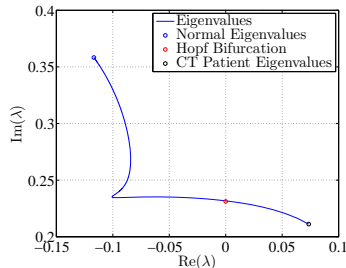
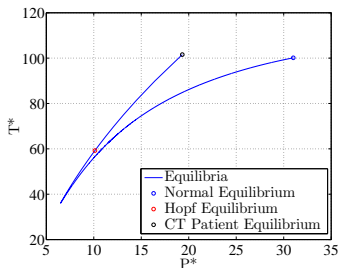
Numerical Hopf Bifurcation

2



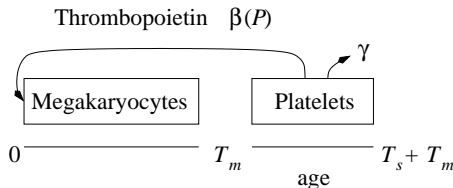
Numerical Hopf Bifurcation

- 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)



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

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

1

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

2

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

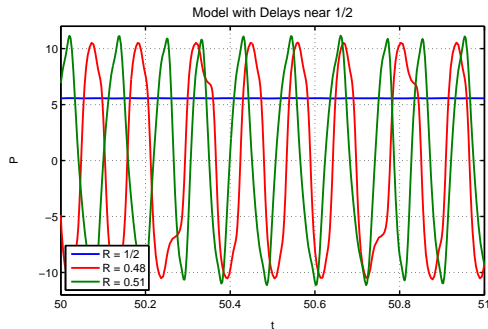


Figure shows stability at $R = \frac{1}{2}$, but irregular oscillations for delays nearby

Modified Platelet Model

3

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

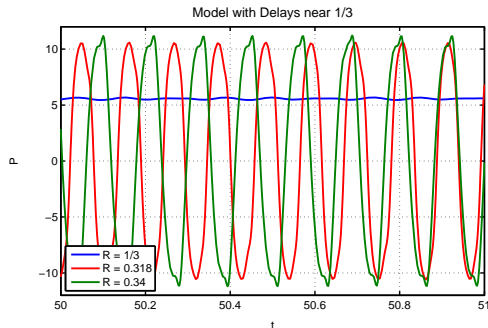


Figure shows stability at $R = \frac{1}{3}$, but irregular oscillations for delays nearby (Same parameters as $R = \frac{1}{2}$)

Two-Delay Differential Equation

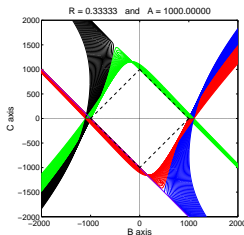
Two-Delay Differential Equation

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

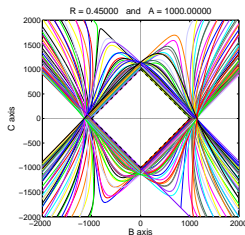
- Delay equations are important in modeling
- Two-delay problem
 - E. F. Infante noted an odd stability property observed in a two delay economic model, rational delays created a larger region of stability
 - Multiple delays are important for biological models
 - Developed special geometric techniques 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

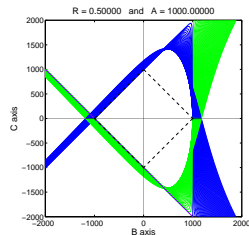
- Technique creates parametric families of curves from the image of the imaginary axis
- Similarity of limited family types prevent approach of Minimum Region of Stability (Black dashed lines)
- Below shows first 100 parametric curves for $A = 1000$



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



$$R = 0.45$$



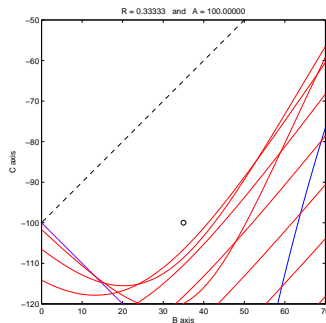
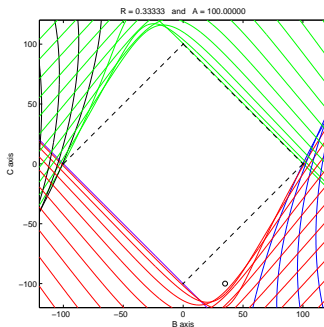
$$R = \frac{1}{2}$$

Modified Platelet Model

1

Returning to the *modified platelet model*

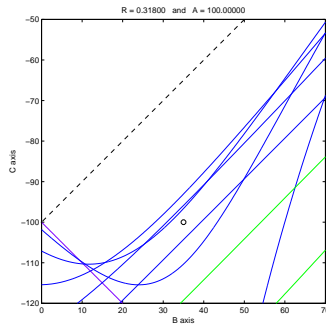
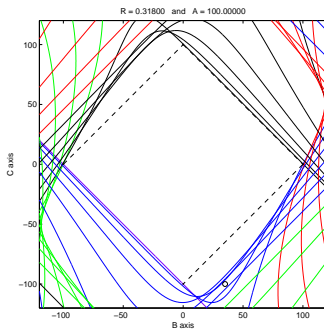
- The coefficients of the linearized model are approximately $(A, B, C) = (100, 35, -100)$ (black circle)
- Our D-partitioning curves for $R = \frac{1}{3}$ are below



Modified Platelet Model

2

- 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