

Math 531 - Partial Differential Equations

Method of Characteristics for PDEs

Joseph M. Mahaffy,
(jmahaffy@mail.sdsu.edu)

Department of Mathematics and Statistics
Dynamical Systems Group
Computational Sciences Research Center
San Diego State University
San Diego, CA 92182-7720

<http://jmahaffy.sdsu.edu>

Spring 2020



Introduction - Wave Equation

The one-dimensional **Wave Equation** satisfies:

$$\frac{\partial^2 u}{\partial t^2} = c^2 \frac{\partial^2 u}{\partial x^2},$$

with **ICs**

$$u(x, 0) = f(x) \quad \text{and} \quad u_t(x, 0) = g(x).$$

We saw that when $u(0, t) = 0 = u(L, t)$ (fixed ends), the Fourier series solution was

$$u(x, t) = \sum_{n=1}^{\infty} \sin\left(\frac{n\pi x}{L}\right) \left[a_n \cos\left(\frac{n\pi ct}{L}\right) + b_n \sin\left(\frac{n\pi ct}{L}\right) \right].$$

This can be shown to be the sum of forward and backward moving waves:

$$u(x, t) = \frac{f(x-ct) + f(x+ct)}{2} + \frac{1}{2c} \int_{x-ct}^{x+ct} g(s) ds,$$

where $f(x)$ and $g(x)$ are odd periodic extensions of the **ICs**.



Outline

- 1 Introduction - Wave Equation
 - Characteristics - Wave Equation
 - Example
 - D'Alembert's Solution
- 2 Age-Structured Model
 - Method of Characteristics
 - Birth Boundary Condition
 - Example
- 3 Model for Erythropoiesis
 - Model for Erythropoiesis
 - Method of Characteristics
 - Model for Erythropoiesis with Delays

Introduction - Wave Equation

We also demonstrated with **Fourier transforms** through the use of **Euler's formula** that the **Wave equation** on an infinite domain starting at rest satisfies:

$$u(x, t) = \frac{1}{2} [f(x-ct) + f(x+ct)],$$

which again leads to waves traveling to the right and left with speed c .

The **method of characteristics** is introduced to solve the one-dimensional **Wave equation** in greater generality.

By moving along a "**characteristic**" with speed c , the **PDE** is reduced to an **ODE** and gives the solution

$$u(x, t) = F(x-ct) + G(x+ct).$$



Characteristics - Wave Equation

The one-dimensional **Wave Equation** is given by:

$$\frac{\partial^2 u}{\partial t^2} - c^2 \frac{\partial^2 u}{\partial x^2} = 0,$$

which can be written in "**factored**" form:

$$\left(\frac{\partial}{\partial t} + c \frac{\partial}{\partial x} \right) \left(\frac{\partial u}{\partial t} - c \frac{\partial u}{\partial x} \right) = 0$$

or

$$\left(\frac{\partial}{\partial t} - c \frac{\partial}{\partial x} \right) \left(\frac{\partial u}{\partial t} + c \frac{\partial u}{\partial x} \right) = 0.$$

Let $w = \frac{\partial u}{\partial t} - c \frac{\partial u}{\partial x}$ and $v = \frac{\partial u}{\partial t} + c \frac{\partial u}{\partial x}$, then the **1st order wave equations** are given by:

$$\frac{\partial w}{\partial t} + c \frac{\partial w}{\partial x} = 0 \quad \text{and} \quad \frac{\partial v}{\partial t} - c \frac{\partial v}{\partial x} = 0.$$



Characteristics - Wave Equation

Consider the **1st order wave equation**:

$$\frac{\partial w}{\partial t} + c \frac{\partial w}{\partial x} = 0.$$

We examine the behavior of this equation from the perspective of a moving observer, $x(t)$, so

$$\frac{d}{dt} w(x(t), t) = \frac{\partial w}{\partial t} + \frac{dx}{dt} \frac{\partial w}{\partial x}.$$

If $\frac{dx}{dt} = c$, then the observer sees

$$\frac{dw}{dt} = 0,$$

so the solution $w(x(t), t)$ **is constant**.

Thus, the observer sees no change in the solution if the observer is moving with constant speed c , so

$$x(t) = ct + x_0.$$



Characteristics - Wave Equation

Along the **characteristic** $x(t)$, $w(x, t)$ is constant.

w propagates as a wave with wave speed c .

General Solution:

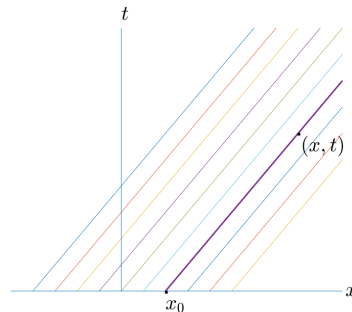
If $w(x, t)$ is given at $t = 0$

$$\begin{aligned} w(x, 0) &= P(x), \\ w(x, t) &= w(x_0, 0) = P(x_0), \end{aligned}$$

but $x_0 = x - ct$, so

$$w(x, t) = P(x - ct).$$

This is a wave traveling to the right with **speed** c and maintaining its shape.



Characteristics - Wave Equation

The observer moves along the **red line** with constant **speed** c .

The observer sees no change in the shape of the wave as time progresses.

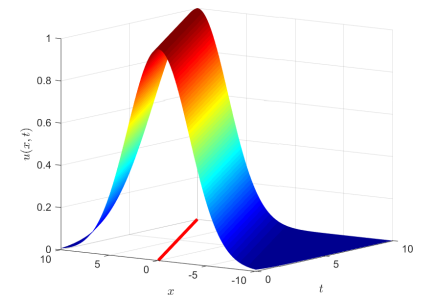
The solution is

$$w(x, t) = P(x - ct).$$

The full **wave equation**

$$u_{tt} = c^2 u_{xx}$$

starts with an initial shape, then half moves to the right with speed c and half moves to the left with speed c .



Characteristics - Example

Example: Consider the *first order PDE* given by:

$$\frac{\partial w}{\partial t} + 2t \frac{\partial w}{\partial x} = \cos(t)w,$$

with the initial condition

$$w(x, 0) = P(x) = e^{-0.05x^2}.$$

From the *method of characteristics*, we can reduce the **PDE** to an **ODE** provided

$$\frac{dx}{dt} = 2t, \quad \text{or} \quad x(t) = t^2 + x_0.$$

The **ODE** is

$$\frac{dw}{dt} = \cos(t)w,$$

which has a solution along the *characteristic*, $x(t) = t^2 + x_0$,

$$w(x(t), t) = ke^{\sin(t)}.$$



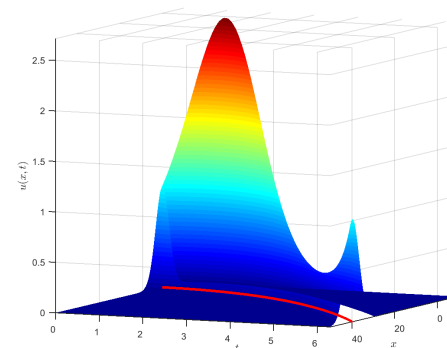
Characteristics - Example

From the initial condition, $w(x_0, 0) = k = P(x_0) = e^{-0.05x_0^2}$.

However, $P(x_0) = P(x - t^2)$, so it follows that the solution satisfies:

$$w(x, t) = P(x_0)e^{\sin(t)} = P(x - t^2)e^{\sin(t)} = e^{-0.05(x-t^2)^2} e^{\sin(t)},$$

which is shown below.



D'Alembert's Solution - Wave Equation

The solutions above suggest that the natural variables are not t and x , but a change moving along the *characteristics* would be better.

Let $\xi = x + ct$ and $\eta = x - ct$, which gives

$$x = \frac{\xi + \eta}{2} \quad \text{and} \quad t = \frac{\xi - \eta}{2c}.$$

By the chain rule, we have

$$\frac{\partial}{\partial \xi} = \frac{\partial}{\partial x} \frac{\partial x}{\partial \xi} + \frac{\partial}{\partial t} \frac{\partial t}{\partial \xi} = \frac{1}{2c} \left(\frac{\partial}{\partial t} + c \frac{\partial}{\partial x} \right)$$

and

$$\frac{\partial}{\partial \eta} = \frac{\partial}{\partial x} \frac{\partial x}{\partial \eta} + \frac{\partial}{\partial t} \frac{\partial t}{\partial \eta} = -\frac{1}{2c} \left(\frac{\partial}{\partial t} - c \frac{\partial}{\partial x} \right).$$

From the partials above, we have

$$-4c^2 \frac{\partial^2 u}{\partial \xi \partial \eta} = \left(\frac{\partial}{\partial t} + c \frac{\partial}{\partial x} \right) \left(\frac{\partial}{\partial t} - c \frac{\partial}{\partial x} \right) u = \frac{\partial^2 u}{\partial t^2} - c^2 \frac{\partial^2 u}{\partial x^2} = 0.$$



D'Alembert's Solution - Wave Equation

It follows that

$$\frac{\partial^2 u}{\partial \xi \partial \eta}(\xi, \eta) = 0.$$

Integrating with respect to ξ implies that

$$\frac{\partial u}{\partial \eta}(\xi, \eta) = \bar{\phi}(\eta),$$

which can be integrated with respect to η to give

$$u(\xi, \eta) = \int \bar{\phi}(\eta) d\eta + \psi(\xi) = \phi(\eta) + \psi(\xi).$$

This is *D'Alembert's solution* for the wave equation.

Changing back the variables gives the form we have seen before

$$u(x, t) = F(x - ct) + G(x + ct).$$



D'Alembert's Solution - Wave Equation

Recall the **ICs** were

$$u(x, 0) = f(x) \quad \text{and} \quad u_t(x, 0) = g(x),$$

so our solution $u(x, t) = F(x - ct) + G(x + ct)$ satisfies:

$$u(x, 0) = F(x) + G(x) = f(x)$$

and

$$u_t(x, 0) = -cF'(x) + cG'(x) = g(x).$$

This latter condition can be integrated to give

$$-cF(x) + cG(x) = \int_0^x g(s) ds + A.$$



D'Alembert's Solution - Wave Equation

Solving the system of equations above gives:

$$F(x) = \frac{1}{2}f(x) - \frac{1}{2c} \left(\int_0^x g(s) ds + A \right)$$

and

$$G(x) = \frac{1}{2}f(x) + \frac{1}{2c} \left(\int_0^x g(s) ds + A \right).$$

It follows that

$$u(x, t) = \frac{1}{2}[f(x - ct) + f(x + ct)] + \frac{1}{2c} \int_{x-ct}^{x+ct} g(s) ds.$$

This gives the complete **D'Alembert's solution** for the wave equation for $x \in (-\infty, \infty)$.



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 Model

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

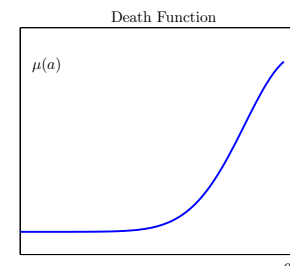
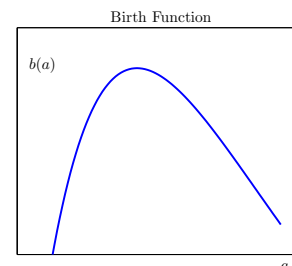
$$\frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} + \mu(a)n(t, a) = 0,$$

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.

SDSU

Age-Structured Model - Method of Characteristics

The *Age-Structured Model*:

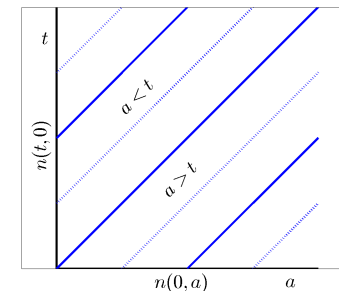
$$\frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} = -\mu(a)n(t, a).$$

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.

SDSU

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*:

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

SDSU

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.

SDSU

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*:

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

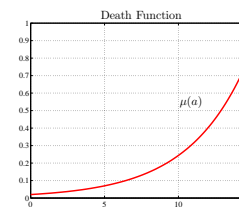
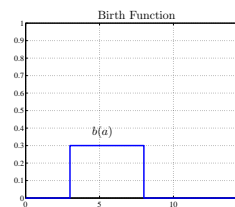


Age-Structured Model

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.

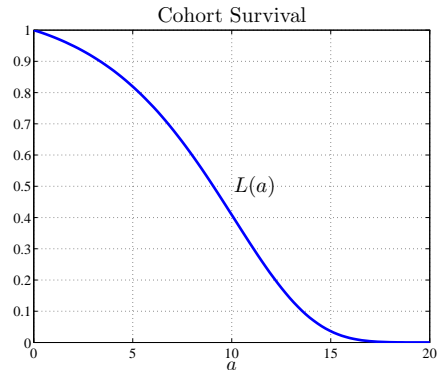


Age-Structured Model

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 .



SDSU

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

$$r = 0.02925985.$$

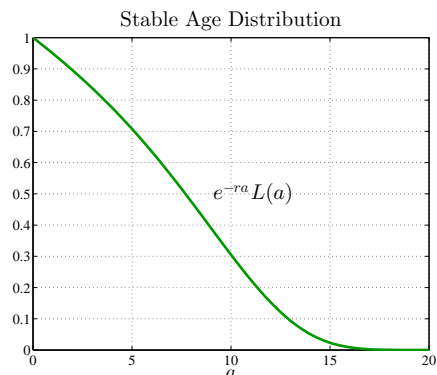
This shows the overall population is growing about 3% per unit time. **SDSU**

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:

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



SDSU

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,

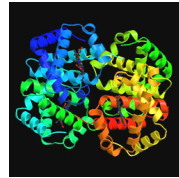
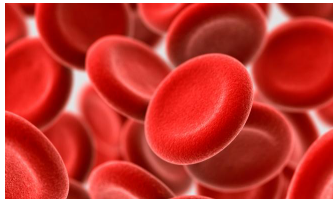
$$T = \frac{1}{R_0} \int_0^\infty aL(a)b(a) da = \frac{1}{1.1678} \int_3^8 0.3a e^{-0.08(e^{0.25a}-1)} da = 5.33205,$$

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. **SDSU**

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.
- By volume, **RBCs** are about 40% of blood.



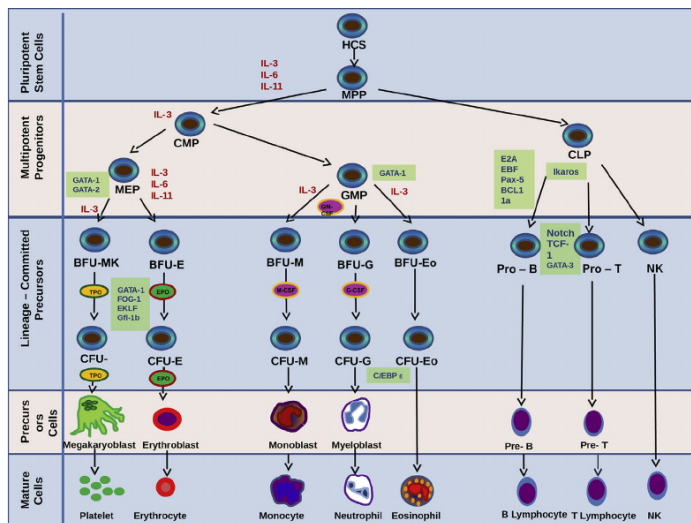
Erythropoiesis

Erythrocytes or red blood cells

- **RBCs** are one of the most actively produced cells in our bodies.
- **RBCs** begin from a group of undifferentiated stem cells (multipotent progenitors).
- The body senses O_2 levels in the body and releases *erythropoietin (EPO)* inversely to the O_2 in the blood.
- **EPO** stimulates commitment of stem cells to become **RBCs** and proliferate.
- Progenitor cells specialize through a series of cell divisions and intracellular changes (taking about 6 days).
- Erythropoietic cells shrink, even losing their nucleus, to become reticulocytes then **RBCs**, which serve as vessels for hemoglobin.
- **RBCs** circulate in the bloodstream for about 120 days, then are actively degraded.



Diagram for Erythropoiesis



Model for Erythropoiesis

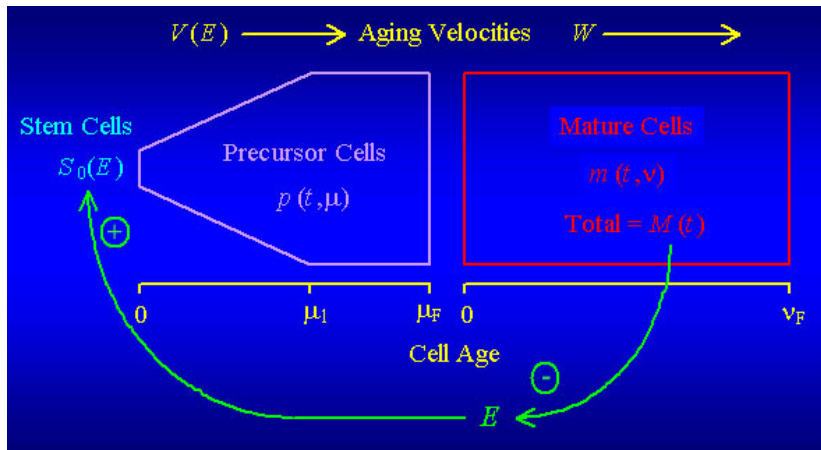
Important Elements in Model for Erythropoiesis

- BFU-E and CFU-E differentiate and proliferate in response to **EPO**
- Maturation requires about 6 days
 - **EPO** accelerates maturation
 - Lack of **EPO** causes apoptosis
- Cell divisions every 8 hours for about 4 days
- Reticulocytes do not divide - increase hemoglobin
- Erythrocytes lose nucleus - live 120 days
- Macrophages actively degrade **RBCs**
- **EPO** released near kidneys with half-life of 6 hours



Model for Erythropoiesis

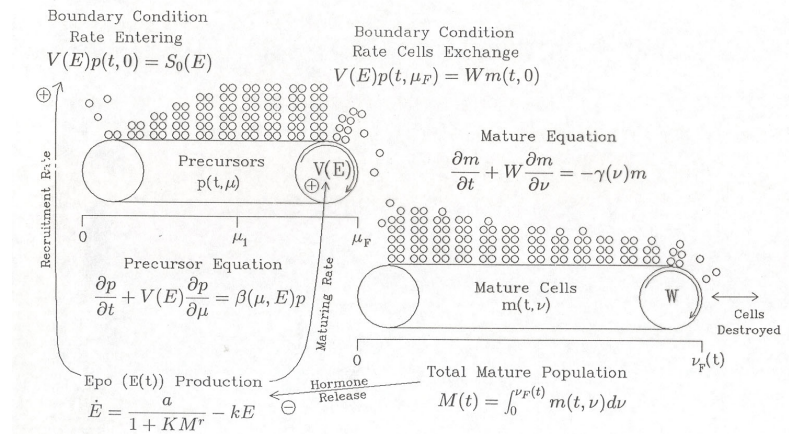
Age-Structured Model for Erythropoiesis



SDSU

Model for Erythropoiesis

Age-Structured Model viewed as a conveyor system



SDSU

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

SDSU

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

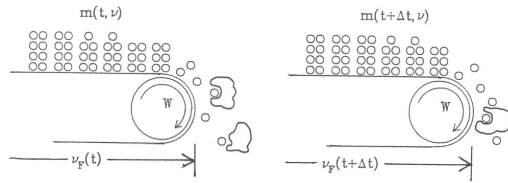
$$Q\Delta t = W\Delta t m(\xi, \nu_F(\xi)) - [\nu_F(t + \Delta t) - \nu_F(t)]m(\xi, \nu_F(\xi))$$

- As $\Delta t \rightarrow 0$,

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

SDSU

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**

SDSU

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:**

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

SDSU

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

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

SDSU

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

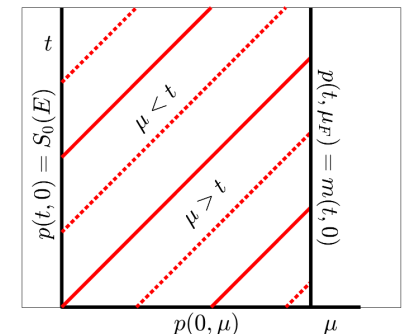
$$t(s) = s + t_0,$$

and

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

or

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



SDSU

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 **O₂**:

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

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 O₂ 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 maturation.
- 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

SDSU

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*:

$$\begin{aligned}\dot{x}_1(t) &= e^{\beta\mu_1} S'_0(\bar{E})x_2(t - \mu_F) - \gamma x_1(t), \\ \dot{x}_2(t) &= f'(\bar{M})x_1(t) - kx_2(t), \\ \dot{x}_3(t) &= \frac{1}{\bar{E}}x_2(t - \mu_F - \bar{\nu}_F) - \gamma x_3(t).\end{aligned}$$

SDSU

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:

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

SDSU

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 $\bar{A} \equiv -e^{\beta\mu_1} S'_0(\bar{E}) f'(\bar{M}) > 0$.

SDSU

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*

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

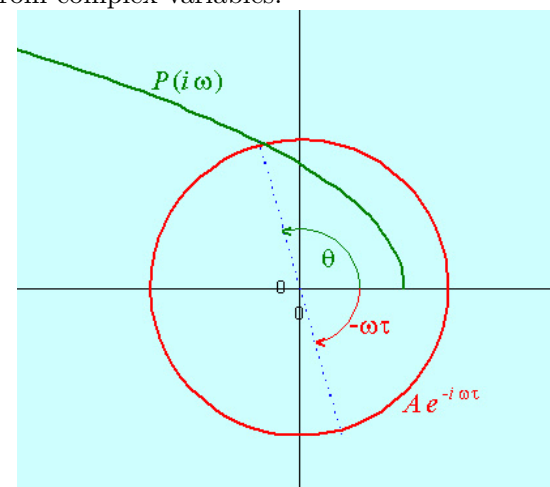
which has infinitely many solutions.

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



Constant Flux Boundary Condition

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



Constant Flux Boundary Condition

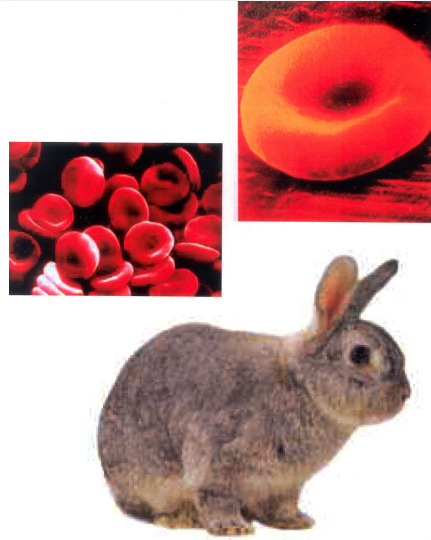
Experiment:

Give rabbits regular antibodies to **RBCs**.

This increases destruction rate γ .

Observe *oscillations* in **RBCs**.

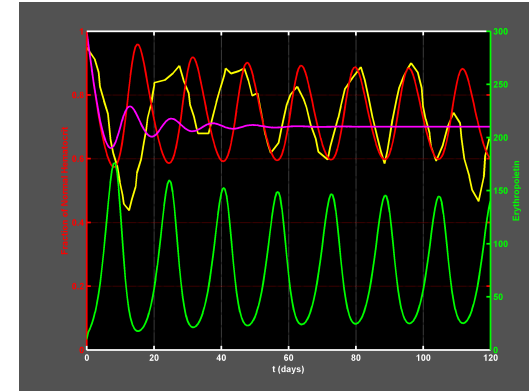
Model undergoes **Hopf bifurcation** with increasing γ .



SDSU

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.

SDSU