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

Outline

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**

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

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

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

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**.

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:

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

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 1^{st} ***order wave equations*** are given by:

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

Characteristics - Wave Equation

Consider the 1^{st} ***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***.

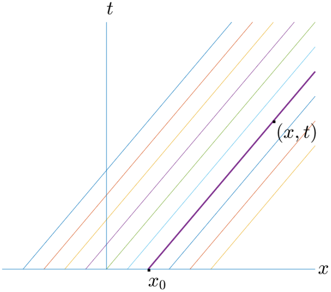
Thus, the observer sees no change in the solution if the observer is moving with constant speed c, so

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

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.

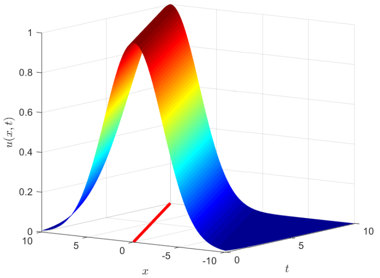
Characteristics - Wave Equation

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

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

The **ODE** is

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

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

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

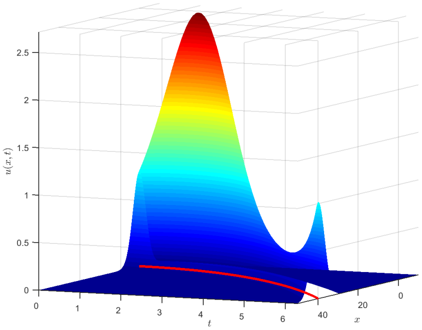
Characteristics - Example

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

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

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

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

which can be integrated with respect to η to give

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

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

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

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:

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

and

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

It follows that

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

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:

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

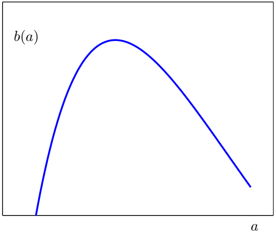
with the ***birth boundary condition*** (Malthusian):

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

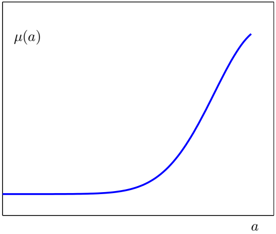
and the ***initial condition***:

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

Birth Function



Death Function



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***:

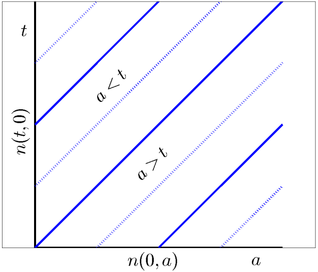
$$\frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} = -\mu(a)n(t,a).$$

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***:

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

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***:

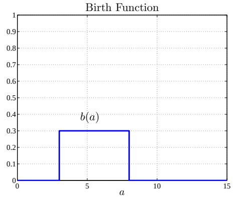
$$n(t,0) = \int_0^{\infty} b(a)n(t,a)\,da.$$

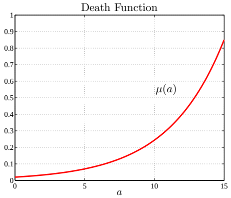
Age-Structured Model

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.





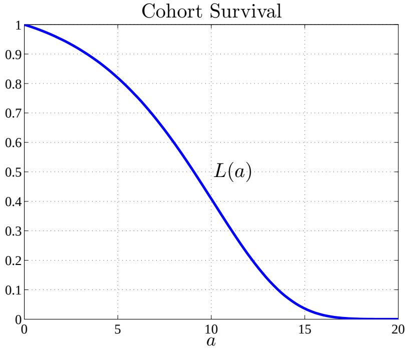
Note: These functions are very crude approximations to the forms displayed earlier.

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

$$r = 0.02925985.$$

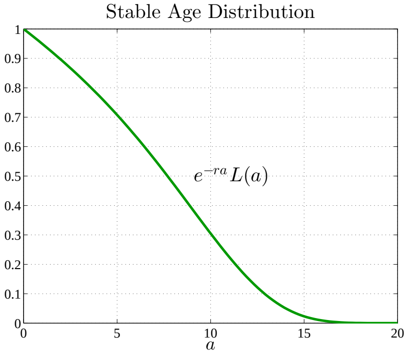
This shows the overall population is growing about 3% per unit time.

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,

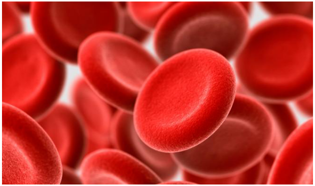
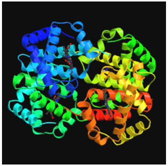
$$T = \frac{1}{R_0}\int_0^\infty aL(a)b(a)\,da = \frac{1}{1.1678}\int_3^8 0.3a\,e^{-0.08(e^{0.25a}-1)}da = 5.33205,$$

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.

Erythropoiesis

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

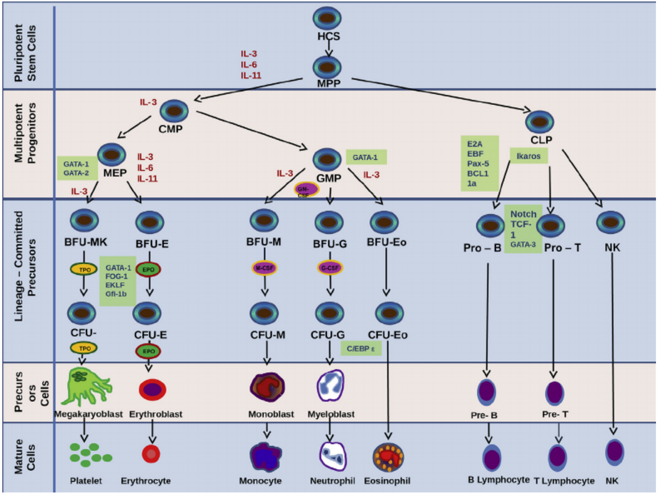
- **RBCs** are the most numerous cells that we produce in our bodies, accounting for almost 85% by numbers.
- Critical for carrying O_2 to our other cells, using the protein hemoglobin.
- By volume, **RBCs** are about 40% of blood.

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 though 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



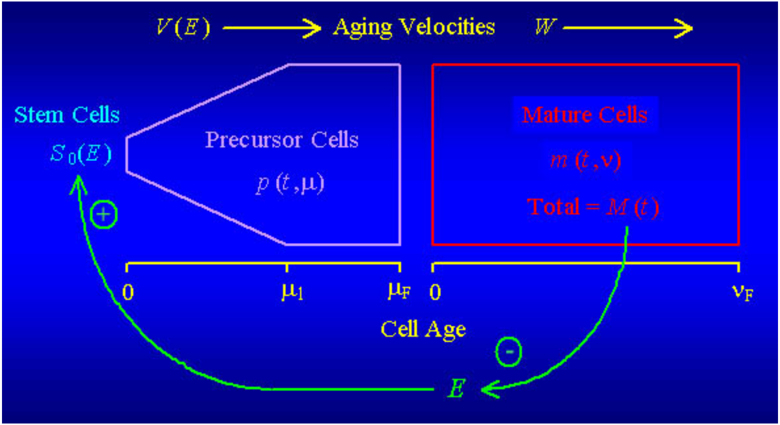
Model for Erythropoiesis

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

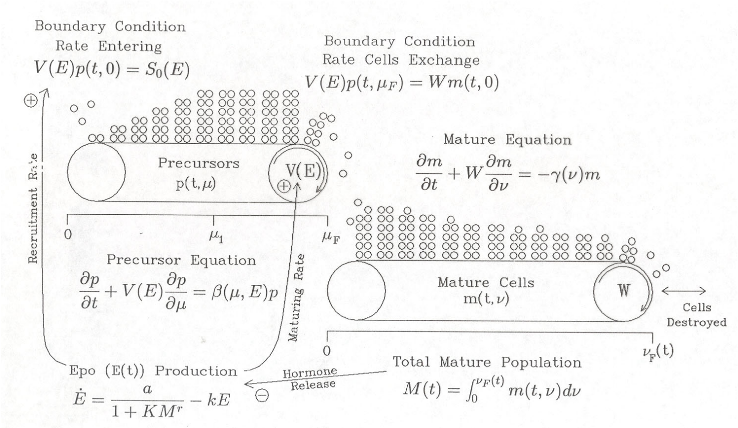
Model for Erythropoiesis

Age-Structured Model for Erythropoiesis



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**

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

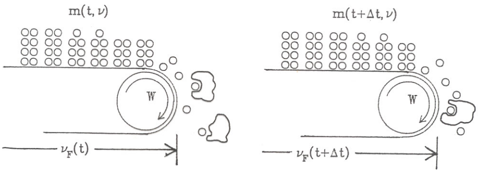
- Balance law

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

- 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

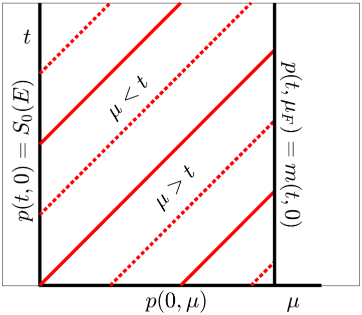
$$t(s) = s + t_0,$$

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.

$$\frac{dM(t)}{dt} = e^{\beta\mu_1} S_0(E(t-\mu_F)) - \gamma M(t) - Q$$

$$\frac{dE(t)}{dt} = f(M(t)) - kE(t)$$

$$\frac{d\nu_F(t)}{dt} = 1 - \frac{Qe^{-\beta\mu_1} e^{\gamma\nu_F(t)}}{S_0(E(t-\mu_F-\nu_F(t)))}$$

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

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

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

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***

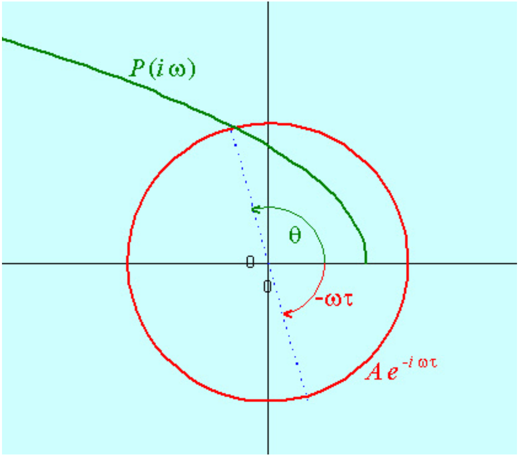
$$\Theta(\omega) \equiv \arctan\left(\frac{\omega}{\gamma}\right) + \arctan\left(\frac{\omega}{k}\right) = \pi - \omega\mu_F,$$

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

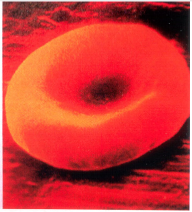
Experiment:

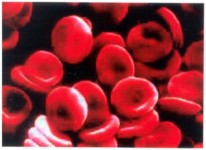
Give rabbits regular antibodies to **RBCs**.

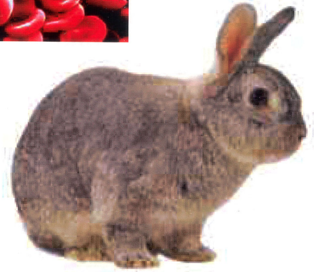
This increases destruction rate γ.

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

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

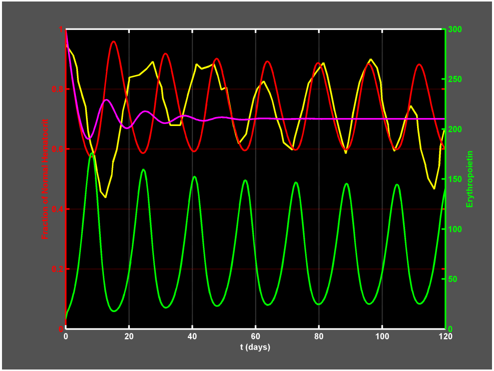






Model for Erythropoiesis

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.