Math 531 - Partial Differential Equations
Method of Characteristics for PDEs

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Spring 2020
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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**.
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

\[ u(x, t) = F(x - ct) + G(x + ct). \]
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\textsuperscript{st} order wave equations are given by:

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

$$x(t) = ct + x_0.$$
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 $t = 0$

\[
\begin{align*}
    w(x, 0) & = P(x), \\
    w(x, t) & = w(x_0, 0) = P(x_0),
\end{align*}
\]

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.
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 $c$. 

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**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*, \(x(t) = t^2 + x_0,\)

\[w(x(t), t) = ke^{\sin(t)}.\]
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 \(\xi\) implies that
\[
\frac{\partial u}{\partial \eta}(\xi, \eta) = \phi(\eta),
\]

which can be integrated with respect to \(\eta\) to give
\[
u(\xi, \eta) = \int \phi(\eta) \, d\eta + \psi(\xi) = \phi(\eta) + \psi(\xi).
\]

This is \textit{D’Alembert’s solution} for the wave equation.

Changing back the variables gives the form we have seen before
\[
u(x, t) = F(x - ct) + G(x + ct).
\]
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
\[ -cF(x) + cG(x) = \int_0^x g(s) \, ds + A. \]
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 \textit{D’Alembert’s solution} for the wave equation for \( x \in (-\infty, \infty). \)
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: 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*:

\[ n(0,a) = f(a). \]
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.
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*:

\[
\begin{align*}
  a < t : & \quad n(t, a) = n(t - a, 0) L(0, a), \\
  a > t : & \quad n(t, a) = n(0, a - t) L(a - t, a).
\end{align*}
\]
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:

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

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.
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**, \( n(t,a) = C n^*(a)e^{rt} \), gives

\[ Ce^{rt} = \int_{0}^{\infty} b(a)Ce^{r(t-a)}L(a)\ da, \]

\[ 1 = \int_{0}^{\infty} e^{-ra}L(a)b(a)\ da. \]

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

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

$$Ce^{rt}n^*(a) = Ce^{r(t-a)}n^*(0)L(a) = Ce^{r(t-a)}L(a),$$

$$n^*(a) = e^{-ra}L(a).$$
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*:

$$n(t, 0) = \int_0^\infty b(a)n(t, a) \, da.$$
In order to perform calculations (with the help of Maple), we take *birth and death functions*

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

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.
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

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

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 $r$:

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

and obtains

$$r = 0.02925985.$$

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

\[
n^*(a) = e^{-r a} L(a) = e^{-0.02926 a} e^{-0.08(e^{0.25 a} - 1)}.
\]
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.
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

Pluripotent Stem Cells
- IL-3
- IL-6
- IL-11
- HCS
- MPP

Multipotent Progenitors
- MEP
- CMP
- IL-3
- GATA-1
- GATA-2

Lineage-Committed Precursors
- BFU-MK
- BFU-E
- BFU-M
- BFU-G
- BFU-Eo
- Pro-B
- Pro-T
- NK

Precursors of Cells
- Megakaryoblast
- Erythroblast
- Monoblast
- Myeloblast
- Pro-B
- Pro-T

Mature Cells
- Platelet
- Erythrocyte
- Monocyte
- Neutrophil
- Eosinophil
- B Lymphocyte
- T Lymphocyte
- NK

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PDEs - Method of Characteristics — (31/54)
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
Age-Structured Model for Erythropoiesis

\[ V(E) \rightarrow \text{Aging Velocities} \]

\[ W \rightarrow \]

\[ S_0(E) \]

\[ p(t, \mu) \]

\[ \mu \]

\[ \mu_F \]

\[ E \]

\[ m(t, \nu) \]

\[ M(t) \]

\[ \nu_F \]

Cell Age

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Age-Structured Model viewed as a conveyor system
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 of macrophages.
  - Saturated consumption of **Erythrocytes**
    - Satiated predator eating a constant amount per unit time
  - Constant flux of **RBCs** being destroyed.
Constant Flux Boundary Condition

- Let $Q$ be rate of removal of erythrocytes.
- **Erythrocytes** lost are $Q\Delta t$.
- **Mean Value Theorem** - average number **RBCs**
  \[ m(\xi, \nu_F(\xi)) \text{ for } \xi \in (t, t + \Delta t) \]
- 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 $\Delta t \to 0$,
  \[ Q = [W - \dot{\nu}_F(t)]m(t, \nu_F(t)) \]
Constant Flux Boundary Condition

If macrophages consume a constant amount of \textbf{RBCs} at the end of their, we obtain the \textit{natural BC}

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

This results in the lifespan of the \textbf{RBCs} either lengthening or shortening from the normal 120 days.

This implies that the lifespan of the \textbf{RBCs} depends on the \textit{state of the system}.
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 $\beta$ satisfies:

$$\beta(\mu, E) = \begin{cases} 
\beta, & \mu < \mu_1, \\
0, & \mu \geq \mu_1, 
\end{cases}$$

- Assume that $\gamma$ is constant.

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

$$\frac{\partial p}{\partial t} + \frac{\partial p}{\partial \mu} = \beta(\mu)p,$$

$$\frac{\partial m}{\partial t} + \frac{\partial m}{\partial \nu} = -\gamma m.$$
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 \textbf{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

\( \mu(s) = s + \mu_0. \)
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 $O_2$:

$$p(t, \mu_F) = p(t_0, 0)e^{\int_0^t \beta(\mu(r))dr}$$

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

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 $\nu$:

$$M(t) = \int_0^{\nu_F(t)} m(t - \nu, 0)e^{-\gamma \nu} d\nu$$

$$= \int_0^{\nu_F(t)} e^{\beta \mu_1} S_0(E(t - \mu_F - \nu)) e^{-\gamma \nu} d\nu,$$

$$= e^{-\gamma(t - \mu_F)} e^{\beta \mu_1} \int_{t - \mu_F - \nu_F(t)}^{t - \mu_F} S_0(E(w)) e^{\gamma w} dw.$$

We apply Leibnitz’s rule for differentiating an integral:

$$\dot{M}(t) = -\gamma e^{-\gamma(t - \mu_F)} e^{\beta \mu_1} \int_{t - \mu_F - \nu_F(t)}^{t - \mu_F} S_0(E(w)) e^{\gamma w} dw,$$

$$+ e^{\beta \mu_1} \left[ S_0(E(t - \mu_F)) - S_0(E(t - \mu_F - \nu_F(t))) e^{-\gamma \nu_F(t)} (1 - \dot{\nu}_F(t)) \right]$$

$$= -\gamma M(t) + e^{\beta \mu_1} S_0(E(t - \mu_F)) - Q,$$
After reduction of PDEs, the state variables become *total mature erythrocytes,* $M$, *EPO, E*, and age of RBCs, $\nu_F$.

\[
\frac{dM(t)}{dt} = e^{\beta \mu_1} S_0(E(t - \mu_F)) - \gamma M(t) - Q
\]
\[
\frac{dE(t)}{dt} = f(M(t)) - kE(t)
\]
\[
\frac{d\nu_F(t)}{dt} = 1 - \frac{Q e^{-\beta \mu_1} e^{\gamma \nu_F(t)}}{S_0(E(t - \mu_F - \nu_F(t)))}
\]

This is a state-dependent delay differential equation.
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 $\mu_F$ 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*:

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

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

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 \textit{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 \textit{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 the Delay Model

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

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

which has one solution \(\lambda = -\gamma\).

This shows the stability of the \(\nu_F\) 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 $\omega$, 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 $\omega$ by varying parameters such as $\gamma$ or $\mu_F$. 

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

Give rabbits regular antibodies to **RBCs**.

This increases destruction rate $\gamma$.

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

**Model** undergoes **Hopf bifurcation** with increasing $\gamma$. 

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**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.