Mathematical Models for Erythropoiesis

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Outline

• Discuss the Physiology
• Develop the Age-Structured Model
• Reduce the Model to Delay Equations
• Bifurcation Analysis
• Compare to Examples
  • Rabbit with Induced Auto-Immune Hemolytic Anemia
  • Human Subject following a Phlebotomy
• Summary
Hematopoiesis
Erythropoiesis
Features of 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 degrade RBCs
- EPO released near kidneys with half-life of 6 hours
Age-Structured Model

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

- Stem Cells
  - \( S_0(E) \)
- Precursor Cells
  - \( p(t, \mu) \)
- Mature Cells
  - \( m(t, \nu) \)
  - Total = \( M(t) \)

Cell Age

Cell Age

\( E \)
Detailed Model

Boundary Condition
Rate Entering
\[ V(E)p(t, 0) = S_0(E) \]

Boundary Condition
Rate Cells Exchange
\[ V(E)p(t, \mu_F) = Wm(t, 0) \]

Precursors
\[ p(t, \mu) \]

Mature Equation
\[ \frac{\partial m}{\partial t} + W \frac{\partial m}{\partial \nu} = -\gamma(\nu)m \]

Recruitment Rate
\[ \mu_1 \]

Maturity Rate
\[ \mu_F \]

EPO (E(t)) Production
\[ \dot{E} = \frac{a}{1 + KM_r} - kE \]

Total Mature Population
\[ M(t) = \int_0^{\nu_F(t)} m(t, \nu) d\nu \]
Active Degradation of RBCs

- RBCs age - Cell membrane breaks down
- Membrane marked with antibodies
- Macrophages destroy least pliable cells
- Model assumes constant supply macrophages
- Saturated consumption of Erythrocytes - Satiated predator
- 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 - Diagram
Simplifying Assumptions

Several simplifying assumptions allow reduction of the age-structured model to delay differential equations

- Assume that $V(E) = W = 1$.
- 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.
Reduced PDEs

The model satisfies the partial differential equations:

\[
\frac{\partial p}{\partial t} + \frac{\partial p}{\partial \mu} = \beta(\mu)p
\]

\[
\frac{\partial m}{\partial t} + \frac{\partial m}{\partial \nu} = -\gamma m
\]
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\]

with the boundary conditions:

\[ p(t, 0) = S_0(E) \quad \text{and} \quad p(t, \mu_F) = m(t, 0) \]

\[(1 - \nu_F(t)) m(t, \nu_F(t)) = Q \]
Negative Control

The negative feedback by EPO satisfies the equation:

\[ \dot{E} = \frac{a}{1 + KM^r} - kE \]

where the total mature erythrocyte population is

\[ M(t) = \int_0^{\nu_F(t)} m(t, \nu) d\nu \]
Method of Characteristics
Applied to a Simplified Model

The method of characteristics can be used to simplify the partial differential equations given above. Let

\[ P(s) = p(t(s), \mu(s)), \]

\[
\frac{dP}{ds} = \frac{\partial p}{\partial t} \frac{dt}{ds} + \frac{\partial p}{\partial \mu} \frac{d\mu}{ds} = \beta(\mu(s), E(t(s))) P(s),
\]

which has the solution,

\[ P(s) = p(t, \mu) = P(0) \exp \left[ \int_0^s \beta(\mu(r), E(t(r))) dr \right], \]

provided

\[
\frac{dt}{ds} = 1 \quad \text{and} \quad \frac{d\mu}{ds} = V(E(t(s))) = 1.
\]
Characteristics Diagram
Evaluating $p(t, \mu)$ and $m(t, \nu)$

To find $p$ at $\mu_F$,

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

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

Similar use of the characteristics gives

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

\[
M(t) = \int_0^{\nu_F(t)} m(t - \nu, 0) e^{-\gamma \nu} d\nu \\
= \int_0^{\nu_F(t)} p(t - \mu_F - \nu, 0) e^{-\gamma \nu} d\nu \\
= \int_0^{\nu_F(t)} e^{\beta \mu_1} S_0(E(t - \mu_F - \nu)) e^{-\gamma \nu} d\nu, \\
= e^{-\gamma(t - \mu_F)} e^{\beta \mu_1} \int_{t - \mu_F - \nu_F(t)}^{t - \mu_F} S_0(E(w)) e^{\gamma w} dw,
\]
Leibnitz’s Rule

We apply Leibnitz’s rule for differentiating an integral:

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

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

\[ = -\gamma M(t) + e^{\beta \mu_1} S_0(E(t - \mu_F)) - Q, \]
Model with Delays

After reduction of PDEs, the state variables become total mature erythrocytes, \( M \), EPO, \( E \), and age of RBCs, \( \nu_F \).

\[
\frac{dM(t)}{dt} = e^{\beta \mu_1} S_0(E(t - T_1)) - \gamma M(t) - Q
\]

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

\[
\frac{d\nu_F(t)}{dt} = 1 - \frac{Q e^{-\beta \mu_1} e^{\gamma \nu_F(t)}}{S_0(E(t - T_1 - \nu_F(t)))}
\]

where \( T_1 = \mu_F \).

This is a state-dependent delay differential equation.
Properties of the Model

- State-dependent delay model has a unique positive equilibrium
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- Delay $T_1$ accounts for maturing time
- State-dependent delay in equation for $\nu_F$, the varying age of maturation
- The $\nu_F$ differential equation is uncoupled from the differential equations for $M$ and $E$
- Stability determined by equations for $M$ and $E$
Linear Analysis of the Model

Linearizing about the unique equilibrium \((\bar{M}, \bar{E}, \bar{\nu}_F)\),

\[
\begin{align*}
\dot{M}(t) & = e^{\beta \mu_1} S'_0(\bar{E}) E(t - T_1) - \gamma M(t) \\
\dot{E}(t) & = f'(\bar{M}) M(t) - k E(t) \\
\dot{\nu}_F(t) & = \frac{1}{\bar{E}} E(t - T_1 - \bar{\nu}_F) - \gamma \nu_F(t)
\end{align*}
\]

The characteristic equation is given by

\[
(\lambda + \gamma) \left[ (\lambda + \gamma)(\lambda + k) + \bar{A} e^{-\lambda T_1} \right] = 0,
\]

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

One solution is \(\lambda = -\gamma\), which shows the stability of the \(\nu_F\) equation.
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The characteristic equation is given by

\[
(\lambda + \gamma) \left[ (\lambda + \gamma)(\lambda + k) + A e^{-\lambda T_1} \right] = 0,
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Analysis of Characteristic Equation

- Remains to analyze

\[(\lambda + \gamma)(\lambda + k) = -Ae^{-\lambda T_1}\]
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\[(\lambda + \gamma)(\lambda + k) = -Ae^{-\lambda T_1}\]

• A Hopf bifurcation occurs when \(\lambda = i\omega\) solves the characteristic equation

• From complex variables, we match the magnitudes and arguments:

\[| (i\omega + \gamma)(i\omega + k) | = A \]

\[\Theta(\omega) \equiv \arctan \left( \frac{\omega}{\gamma} \right) + \arctan \left( \frac{\omega}{k} \right) = \pi - \omega T_1 \]
Analysis of Characteristic Equation

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- Solve for \(\omega\) by varying parameters such as \(\gamma\)
Hopf - Argument Principle

$P(i\omega)$

$Ae^{-i\omega \tau}$
Variable Velocity of Maturing

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$$V(E) = \frac{\kappa_1 E}{\kappa_2 + E}$$

- Method of characteristics leaves a threshold-type functional equation rather than simpler delay equation
- Linear analysis of the age-structured model relatively simple
Linear Analysis with Variable Velocity

The modified characteristic equation for the threshold-type functional equation becomes

\[(\lambda + \gamma)(\lambda + k) - e^{\beta \mu_1} f'(\bar{M})(V_1 + V_2 e^{-\lambda \mu_F}) = 0\]

where

\[V_1 \equiv \frac{V'(\bar{E})S_0(\bar{E})}{V(\bar{E})}\]

\[V_2 \equiv \frac{V(\bar{E})S'_0(\bar{E}) - V'(\bar{E})S_0(\bar{E})}{V(\bar{E})}\]
Linear Analysis (continued)

- This has the form

\[(\lambda + \gamma)(\lambda + k) + \alpha_1 + (\alpha_2 - \alpha_1)e^{-\lambda \mu F} = 0\]

with \(\alpha_1 = V_1\) and \(\alpha_2\) positive.
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• Since \(\alpha_2 = A\) from previous characteristic equation, the \(\alpha_1\) shifts our geometric diagram above to the right with a smaller radius circle.
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• Since \(\alpha_2 = A\) from previous characteristic equation, the \(\alpha_1\) shifts our geometric diagram above to the right with a smaller radius circle.

• This can be readily seen to stabilize the model.
Hopf - Variable Velocity

\[ P(i\omega) \]

\[ A e^{-i\omega\tau} \]

\[ \theta \]

\[ -\omega\tau \]

Link to Anal.  Link to Hopf
Auto-Immune Induced Anemia

Rabbits were injected with antibodies to their Red Blood Cells
Identify Parameters

- Physiological parameters found for rabbit
  - Extensive literature search
  - Some gaps using other species studied
  - Difficult, but essential process
- Increasing the destruction of Erythrocytes, $\gamma$, causes a Hopf Bifurcation
- Model most sensitive to parameters $\gamma$ and $\mu_F$
- Variable velocity of maturation stabilizes the model
Simulation
Phlebotomy (Blood Donation)

- Normal blood donation is about 8% of blood
- \(O_2\) sensors near kidneys probably sense concentration, not \(M(t)\)
- Blood donation loses erythrocytes and plasma, no concentration change
- Plasma recovers quickly
Model for Phlebotomy

• Define the hemoglobin concentration

\[ h(t) = H \frac{M(t)}{M(t) + \rho(t)} \]

• The plasma function chosen to fit data

\[ \rho(t) = \alpha \left[ 1 + (\beta_1 t - 0.08)e^{-\beta_2 t} \right] \]

• The age-structured model remains the same except

\[ \dot{E}(t) = f(h(t)) - kE(t) \]

• Fit model to data of Maeda et al and Wadsworth
Model a Phlebotomy
Model Compared to Data

Two Subjects after Phlebotomy

Hemoglobin vs. t (days) graph showing data points and a trend line for two subjects after phlebotomy.
Summary

• The mathematical model provides a good example of how age-structured models are related to models with delays.

• The modeling of satiation for destruction of erythrocytes could prove valuable in other population models.

• The model for erythropoiesis can be fit to existing data and can hopefully provide insight into the study of some hematopoietic diseases. It is unlikely to aid in the study of normal individuals for improved blood donation schemes.
Summary (cont)

• Our numerical simulations and analytical study show how a variable velocity of maturation stabilizes the model. This implies that plasticity in the precursor compartment may be an important evolutionary adaptation.

• Current studies have identified the most significant parameters in the model, which could give insight to the likely causes of the disease states and possible therapeutic approaches.

• New studies examine thrombopoietic systems using a multi-compartment model to account for size structures of megakaryocytes.