Mathematical Models for Red Blood Cell Production

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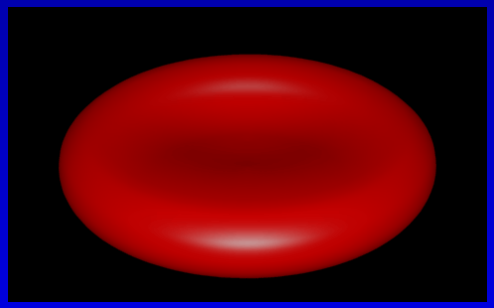
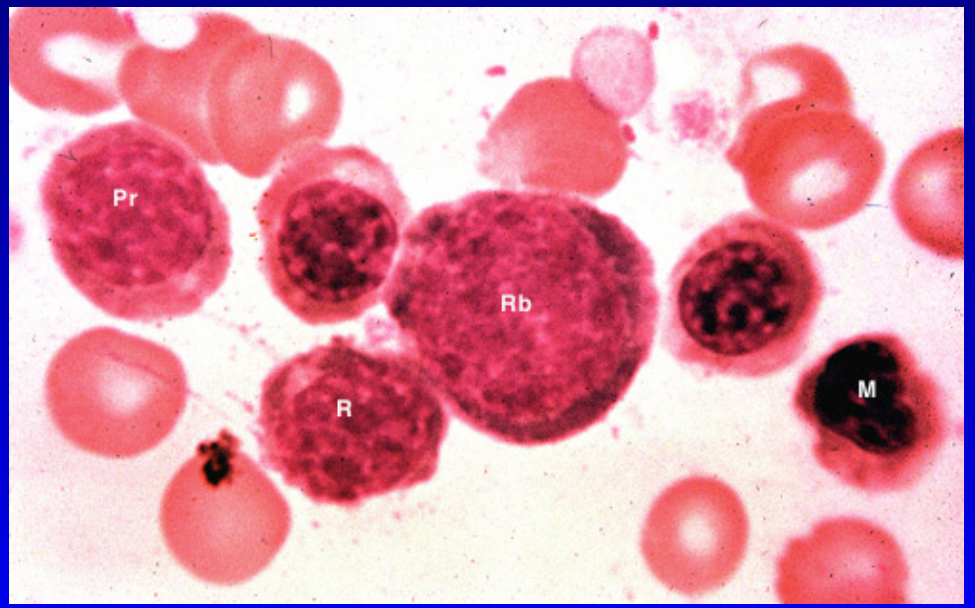


Collaborators

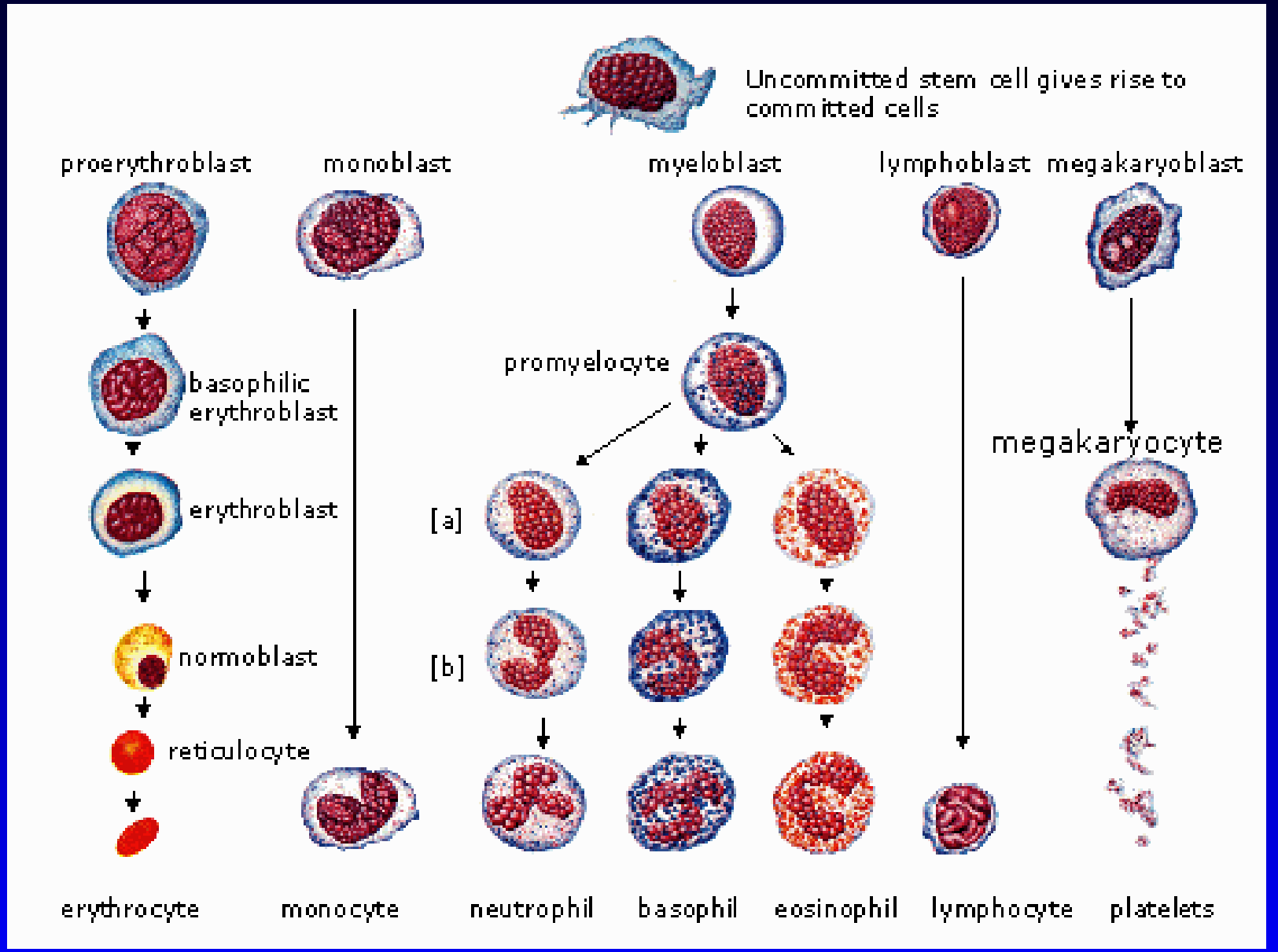
- Jacques Bélair - Université de Montréal
- Mike Mackey - McGill University
- NSF-REU Students
  - Sam Polk
  - Roland Roeder



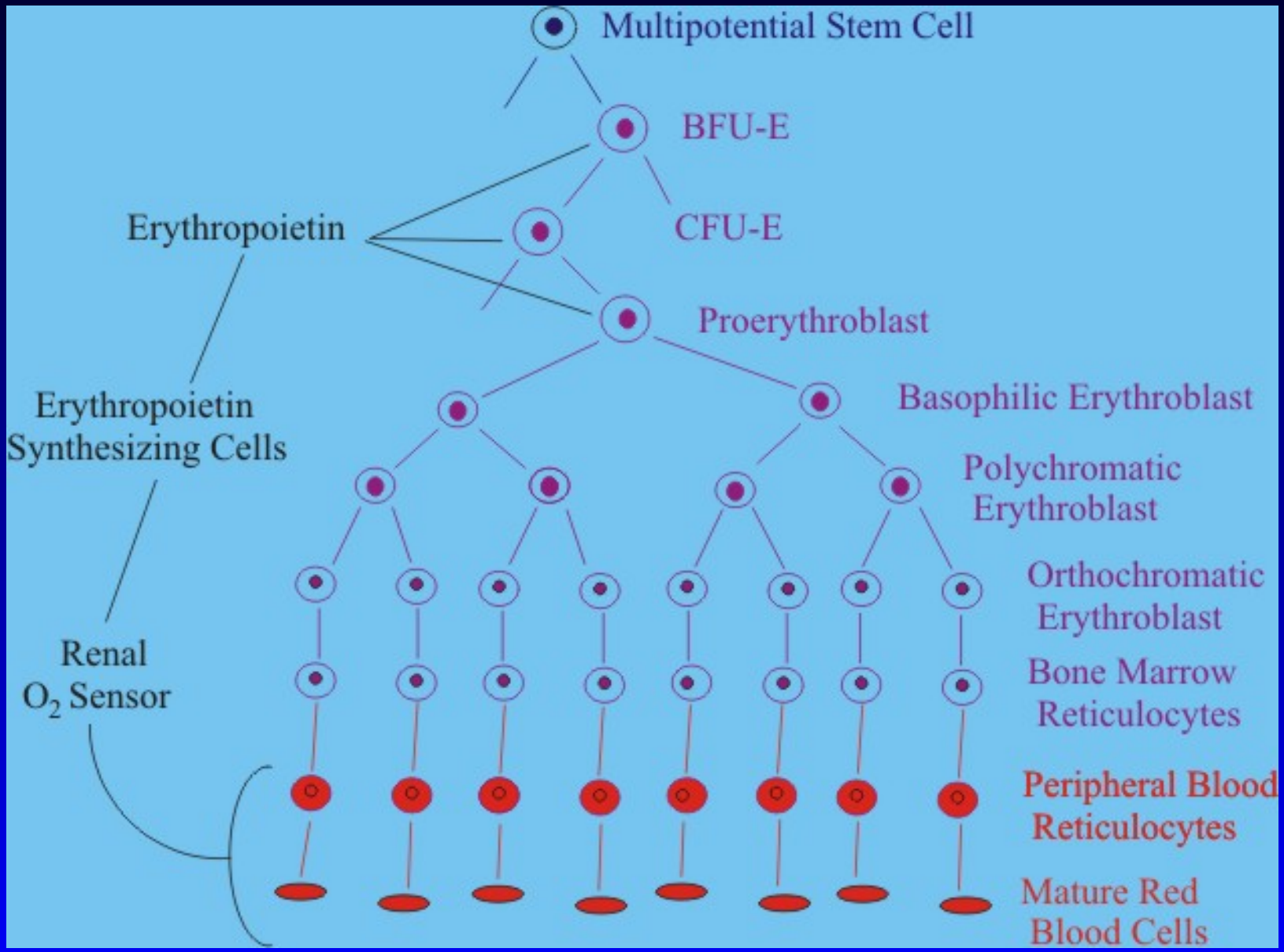
Outline

- 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



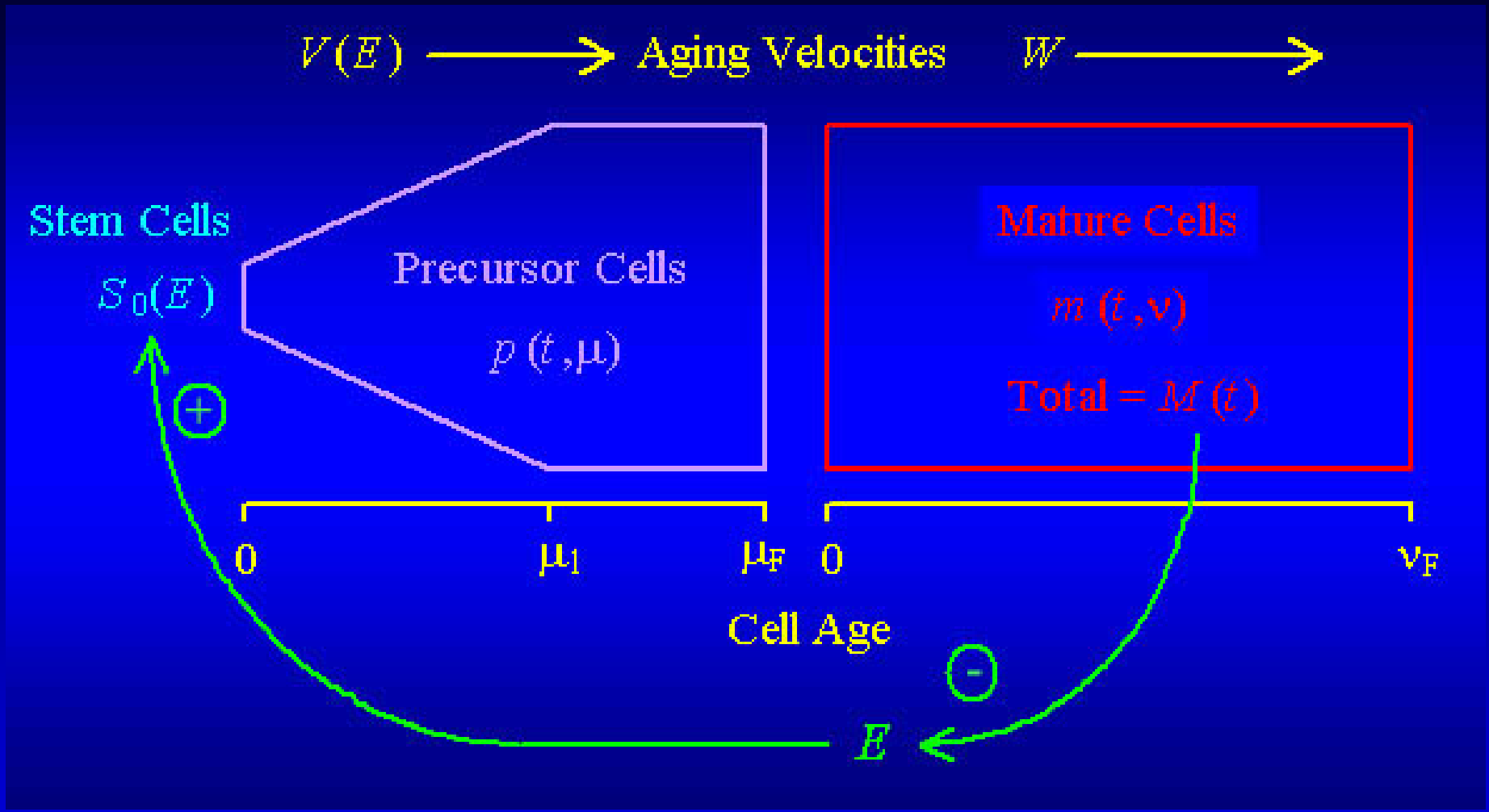
Erythropoiesis



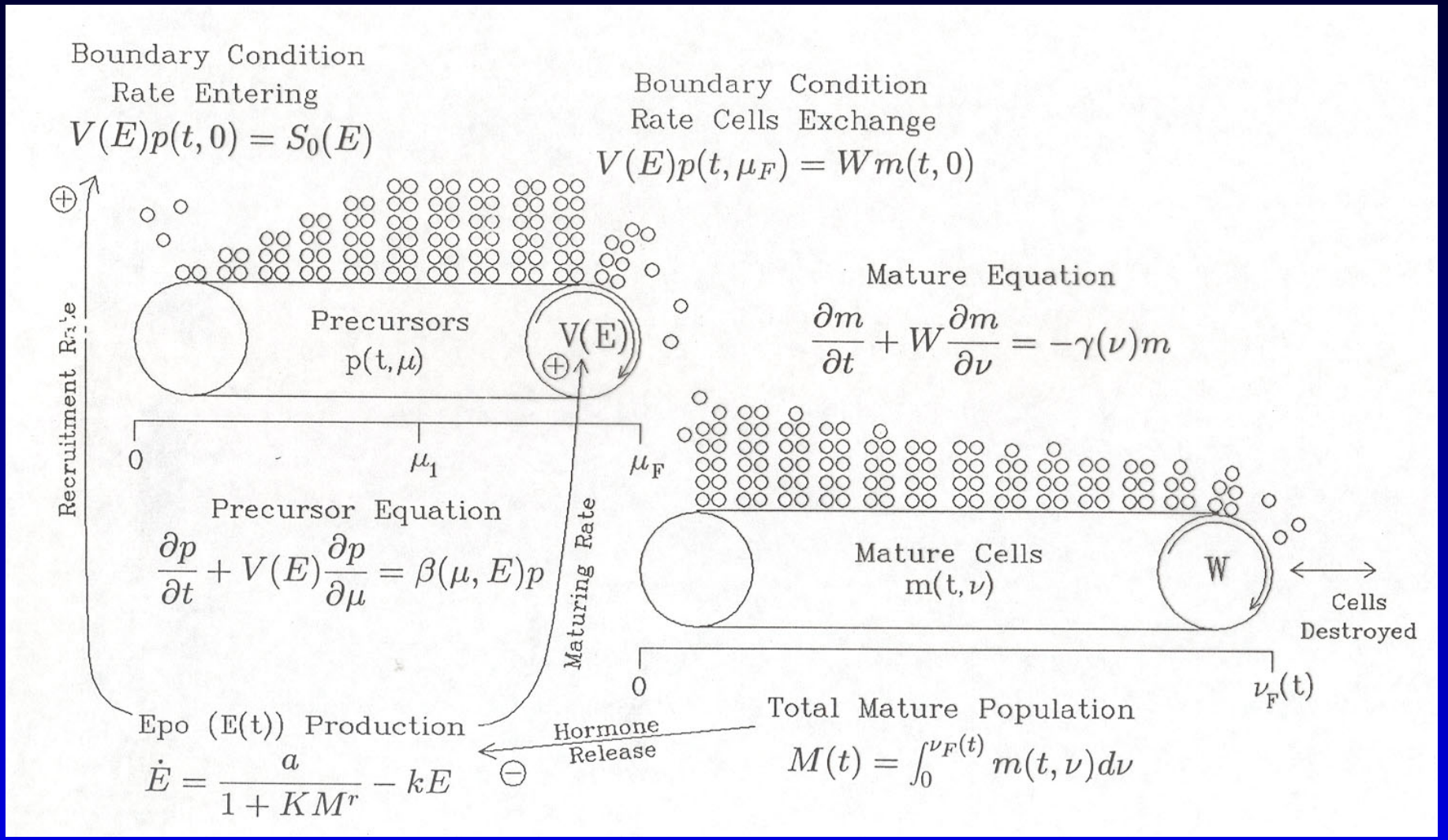
Features of Erythropoiesis

- 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



Detailed Model



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

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

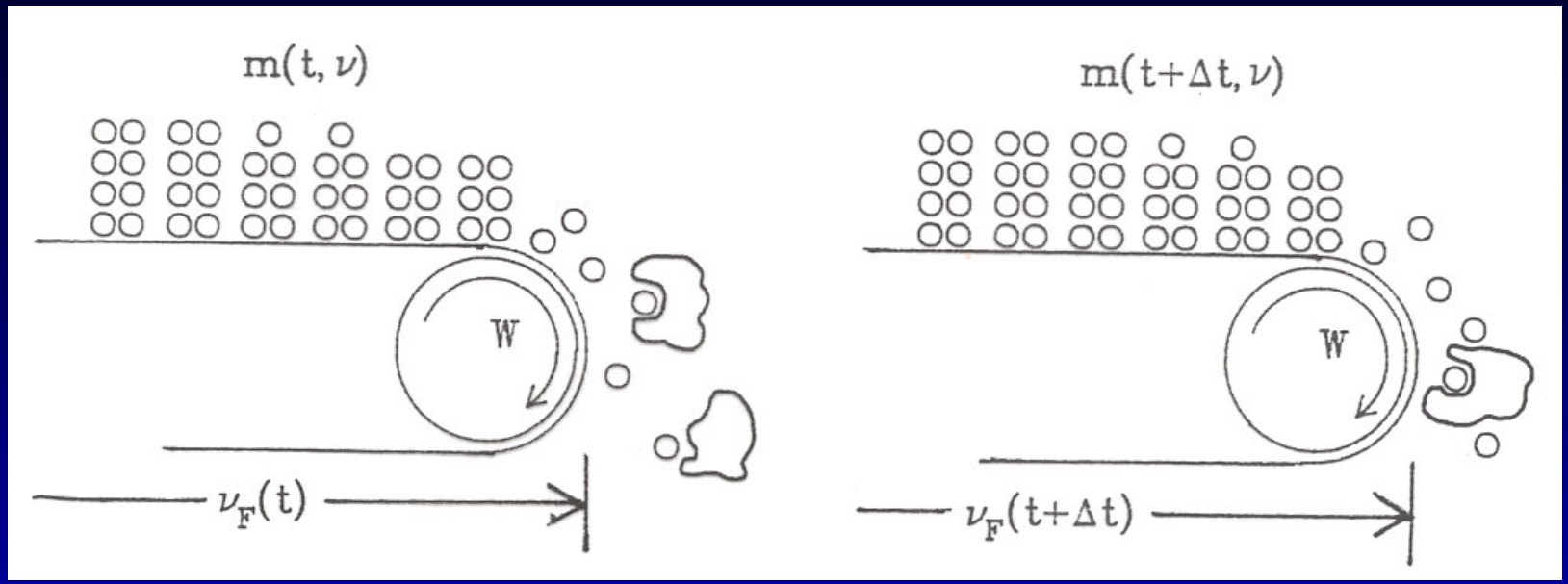
- Balance law

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

- As $\Delta t \to 0$,

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

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 β satisfies:

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

- Assume that γ 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:

$$p(t,0) = S_0(E) \qquad \text{and} \qquad p(t,\mu_F) = m(t,0)$$

$$(1 - \dot{\nu}_F(t)) m(t,\nu_F(t)) = Q$$

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 $P(s) = p(t(s), \mu(s))$,

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

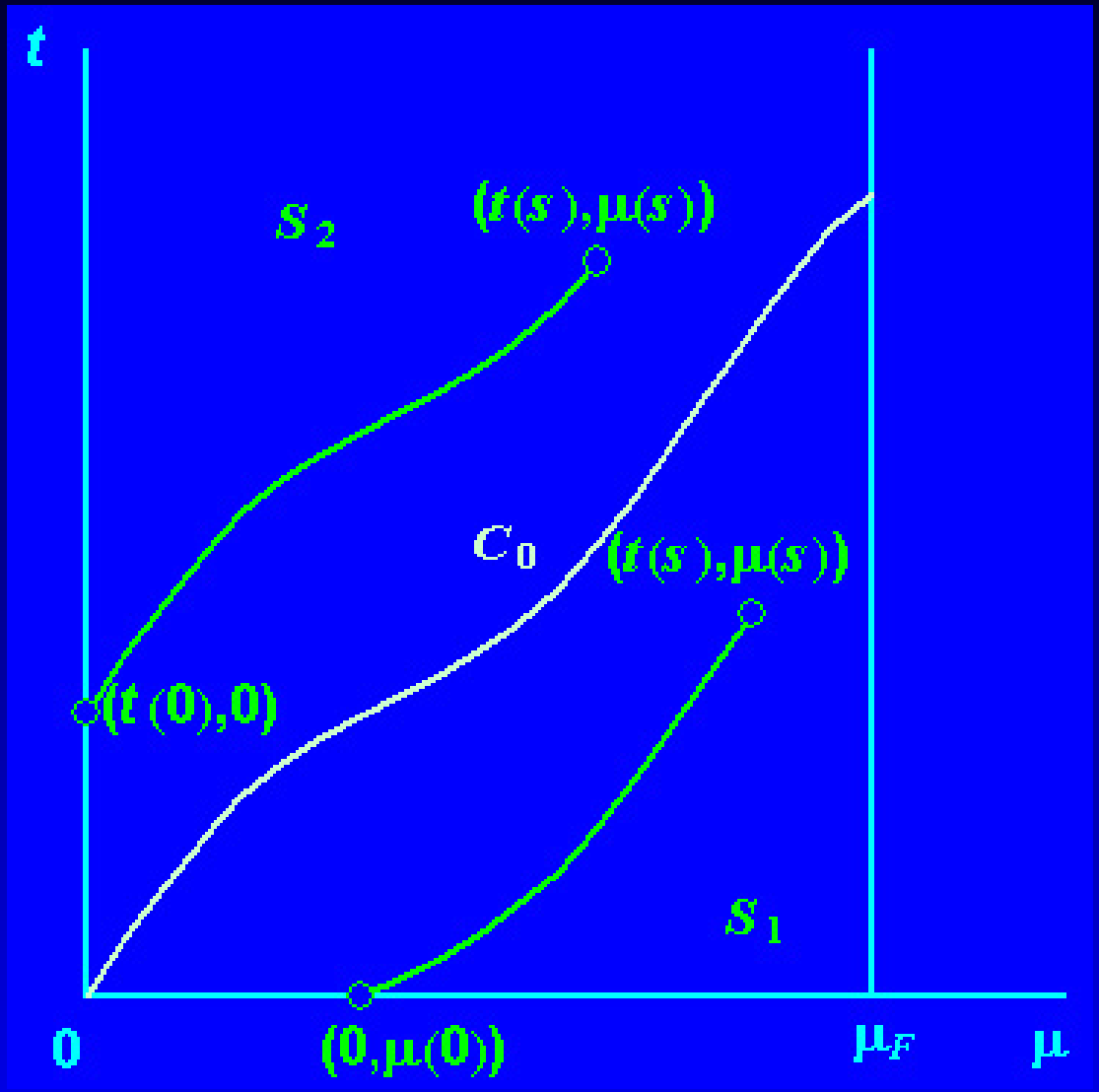
which has the solution,

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

provided

$$\frac{dt}{ds} = 1 \qquad \text{and} \qquad \frac{d\mu}{ds} = V(E(t(s))) = 1$$

Characteristics Diagram



Evaluating $p(t,\mu)$ and $m(t,\nu)$

To find p at μ_F,

$$\begin{aligned} p(t,\mu_F) &= p(t_0,0)exp\left[\int_0^{\mu_F}\beta(r)dr\right] \\ &= p(t-\mu_F,0)e^{\beta\mu_1} = e^{\beta\mu_1}S_0(E(t-\mu_F)) \end{aligned}$$

Similar use of the characteristics gives

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

Finding $M(t)$

$$
\begin{aligned}
M(t) &= \int_0^{\nu_F(t)} m(t-\nu,0)e^{-\gamma\nu}d\nu \\
&= \int_0^{\nu_F(t)} p(t-\mu_F-\nu,0)e^{-\gamma\nu}d\nu \\
&= \int_0^{\nu_F(t)} e^{\beta\mu_1}S_0(E(t-\mu_F-\nu))e^{-\gamma\nu}d\nu, \\
&= e^{-\gamma(t-\mu_F)}e^{\beta\mu_1}\int_{t-\mu_F-\nu_F(t)}^{t-\mu_F} S_0(E(w))e^{\gamma w}dw,
\end{aligned}
$$

Leibnitz's Rule

We apply Leibnitz's rule for differentiating an integral:

$$\begin{aligned}
\dot{M}(t) &= -\gamma e^{-\gamma(t-\mu_F)} e^{\beta\mu_1} \int_{t-\mu_F-\nu_F(t)}^{t-\mu_F} S_0(E(w)) e^{\gamma w} dw \\
&\quad + e^{\beta\mu_1} \left[S_0(E(t-\mu_F)) - \right. \\
&\quad \left. S_0(E(t-\mu_F-\nu_F(t))) e^{-\gamma\nu_F(t)} (1-\dot{\nu}_F(t)) \right] \\
&= -\gamma M(t) + e^{\beta\mu_1} S_0(E(t-\mu_F)) - Q,
\end{aligned}$$

Model with Delays

After reduction of PDEs, the state variables become total mature erythrocytes, M, EPO, E, and age of RBCs, ν_F.

$$\begin{aligned}
\frac{dM(t)}{dt} &= e^{\beta\mu_1} S_0(E(t-T_1)) - \gamma M(t) - Q \\
\frac{dE(t)}{dt} &= f(M(t)) - kE(t) \\
\frac{d\nu_F(t)}{dt} &= 1 - \frac{Qe^{-\beta\mu_1} e^{\gamma\nu_F(t)}}{S_0(E(t-T_1-\nu_F(t))}
\end{aligned}$$

where $T_1 = \mu_F$.

This is a state-dependent delay differential equation.

Properties of the Model

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- State-dependent delay in equation for ν_F, the varying age of maturation
- The ν_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{aligned}
\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) - kE(t) \\
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The characteristic equation is given by

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

where $A \equiv -e^{\beta\mu_1} S_0'(\bar{E}) f'(\bar{M}) > 0$.

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where $A \equiv -e^{\beta\mu_1} S_0'(\bar{E}) f'(\bar{M}) > 0$. One solution is $\lambda = -\gamma$, which shows the stability of the ν_F equation.

Analysis of Characteristic Equation

- Remains to analyze

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

$$|(i\omega + \gamma)(i\omega + k)| = A$$

$$\Theta(\omega) \equiv \arctan\left(\frac{\omega}{\gamma}\right) + \arctan\left(\frac{\omega}{k}\right) = \pi - \omega T_1$$

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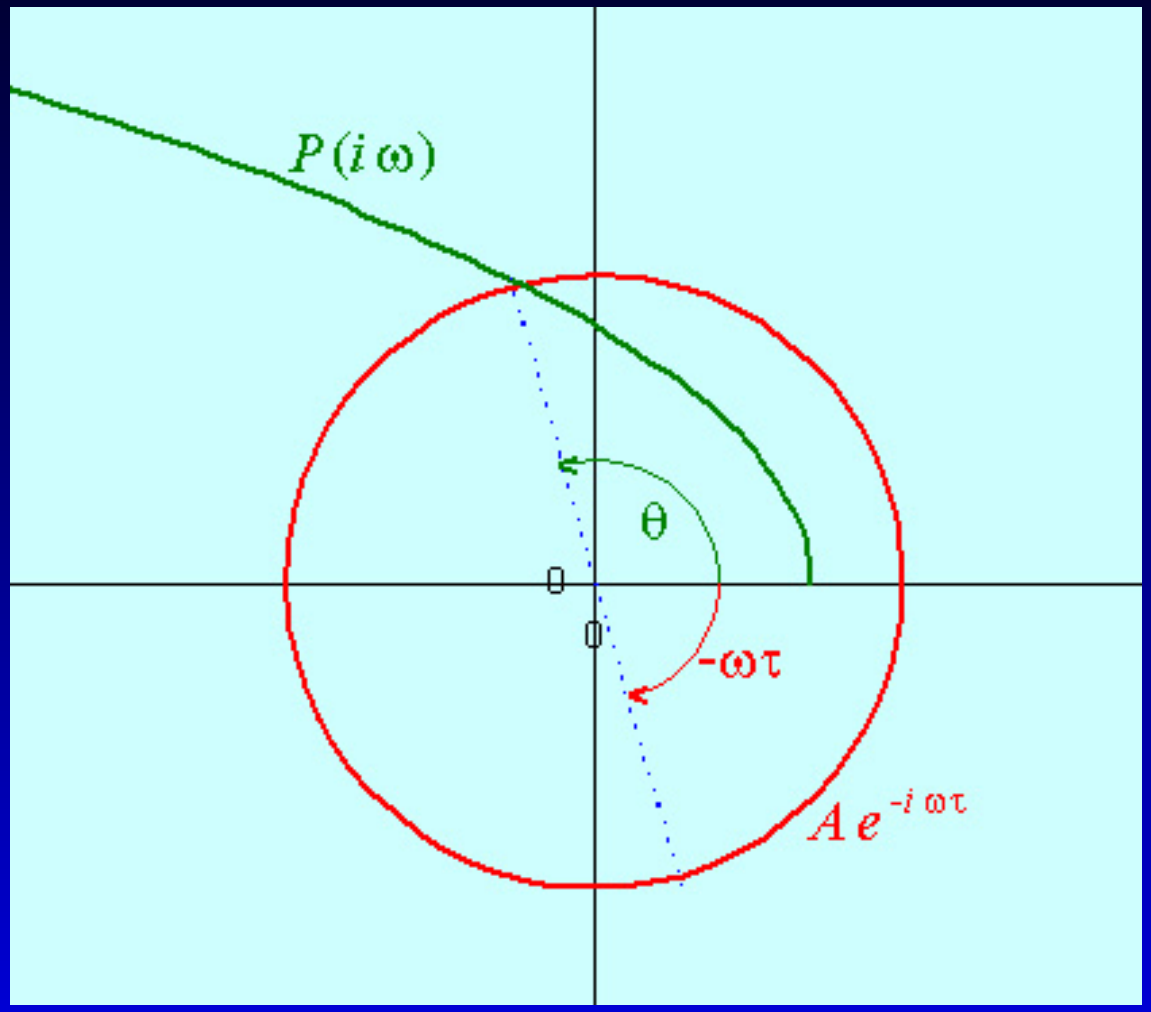
- Solve for ω by varying parameters such as γ

Hopf - Argument Principle



Link to Var. Vel. Anal.

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- 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

$$(\lambda+\gamma)(\lambda+k)-e^{\beta\mu_1}f'(\bar{M})(V_1+V_2e^{-\lambda\mu_F})=0$$

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 α_2 positive.

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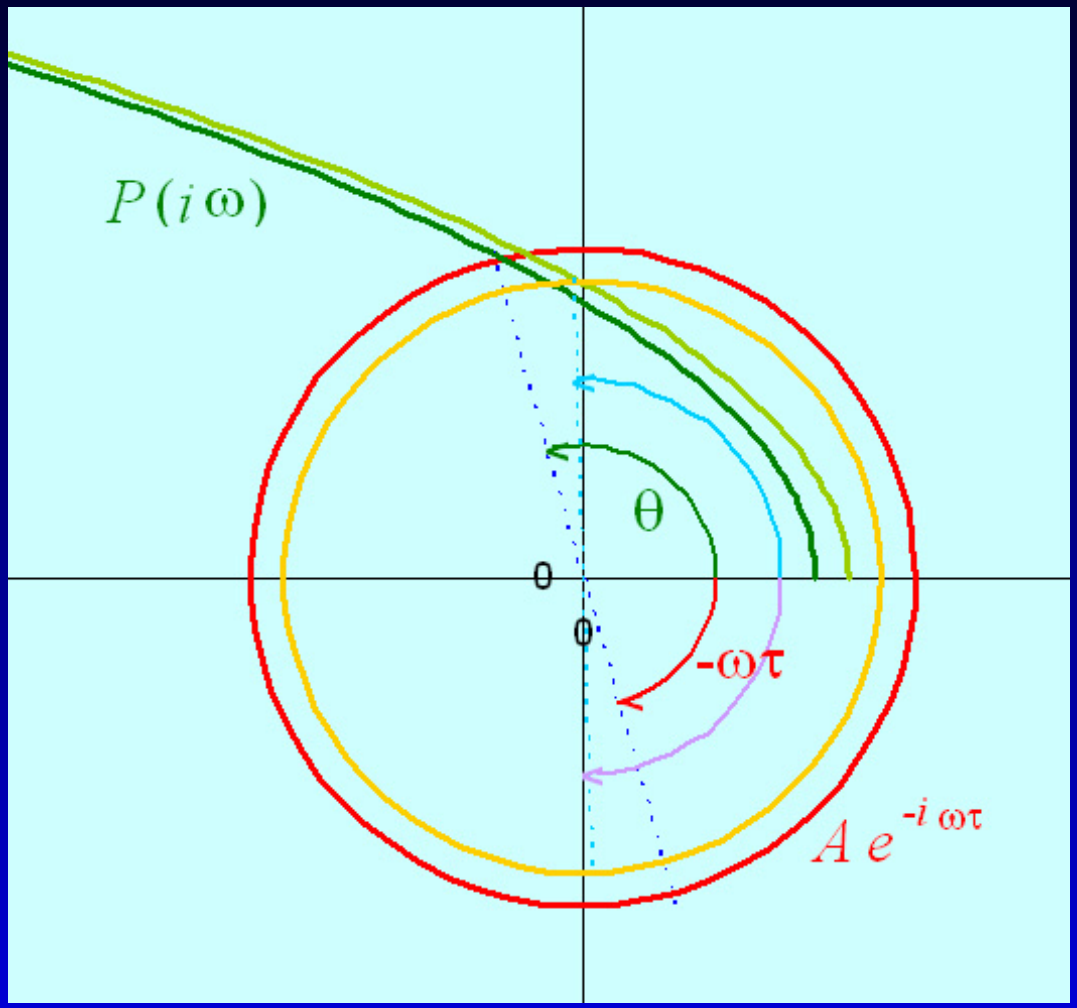
- This can be readily seen to stabilize the model.

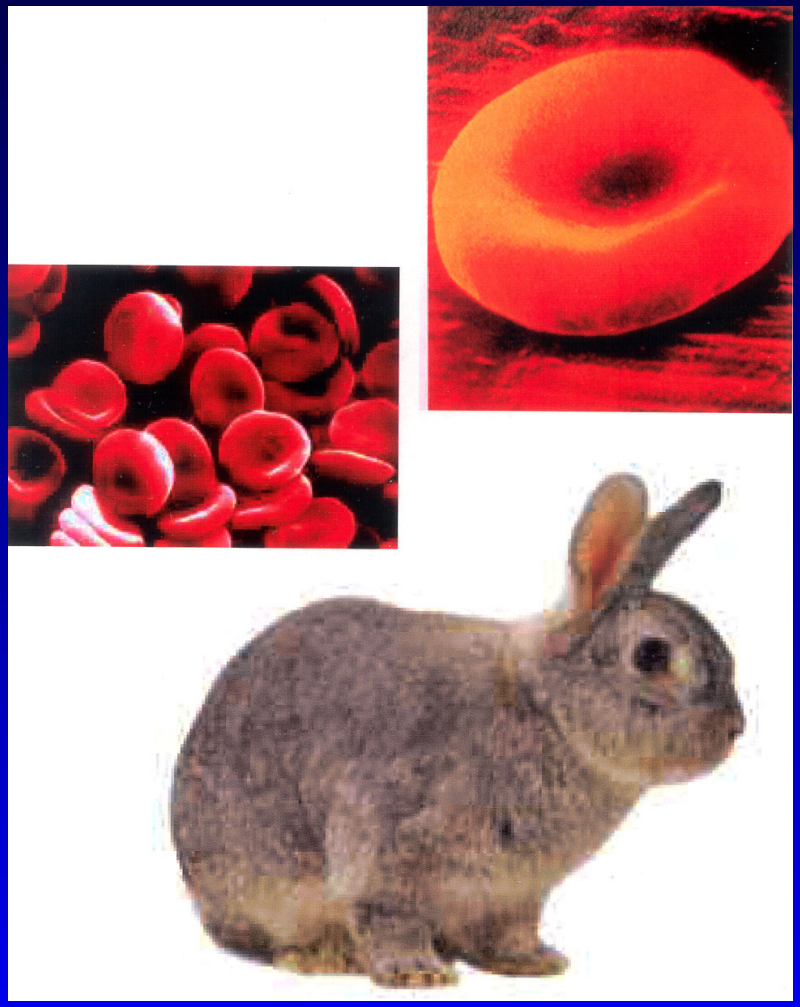
Hopf - Variable Velocity



Link to Anal. Link to Hopf

Auto-Immune Induced Anemia

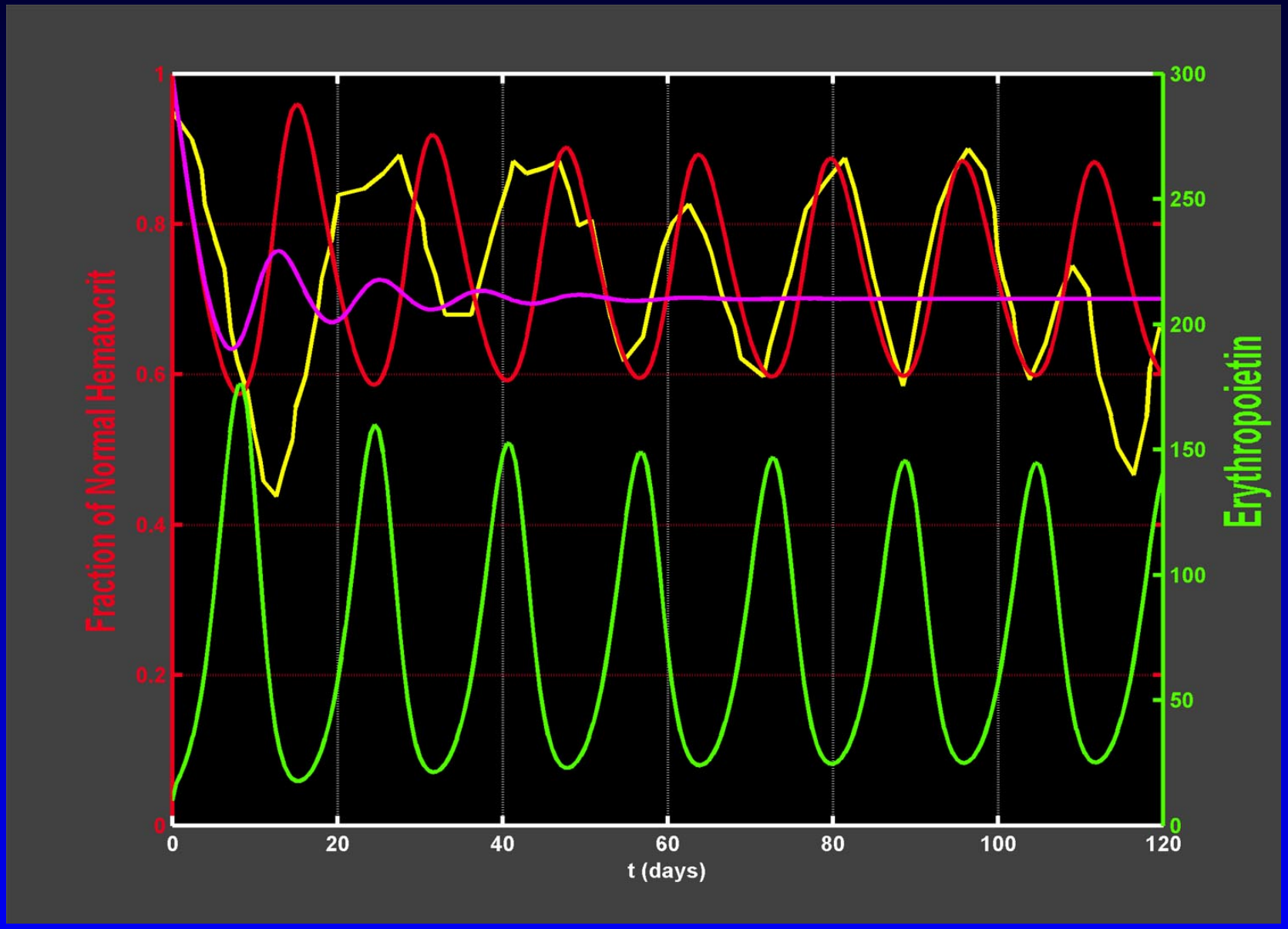
Rabbits were injected with antibodies to their Red Blood Cells



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, γ, causes a Hopf Bifurcation
- Model most sensitive to parameters γ and μ_F
- Variable velocity of maturation stabilizes the model

Simulation


Fraction of Normal Hematocrit
Erythropoietin
t (days)
0
0.2
0.4
0.6
0.8
1
0
50
100
150
200
250
300
0
20
40
60
80
100
120

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

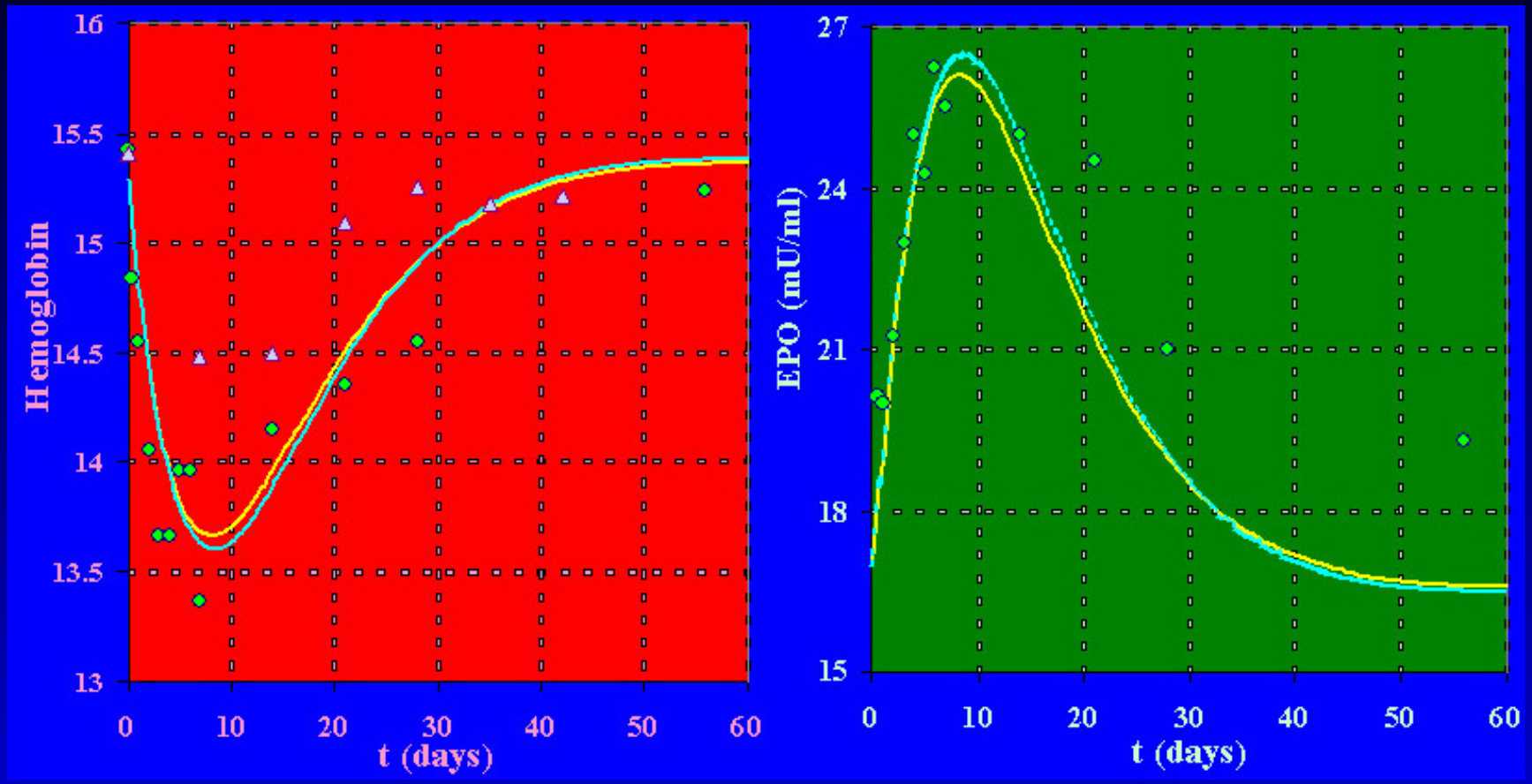
$$\rho(t) = \alpha\left[1 + (\beta_1 t - 0.08)e^{-\beta_2 t}\right]$$

- The age-structured model remains the same except

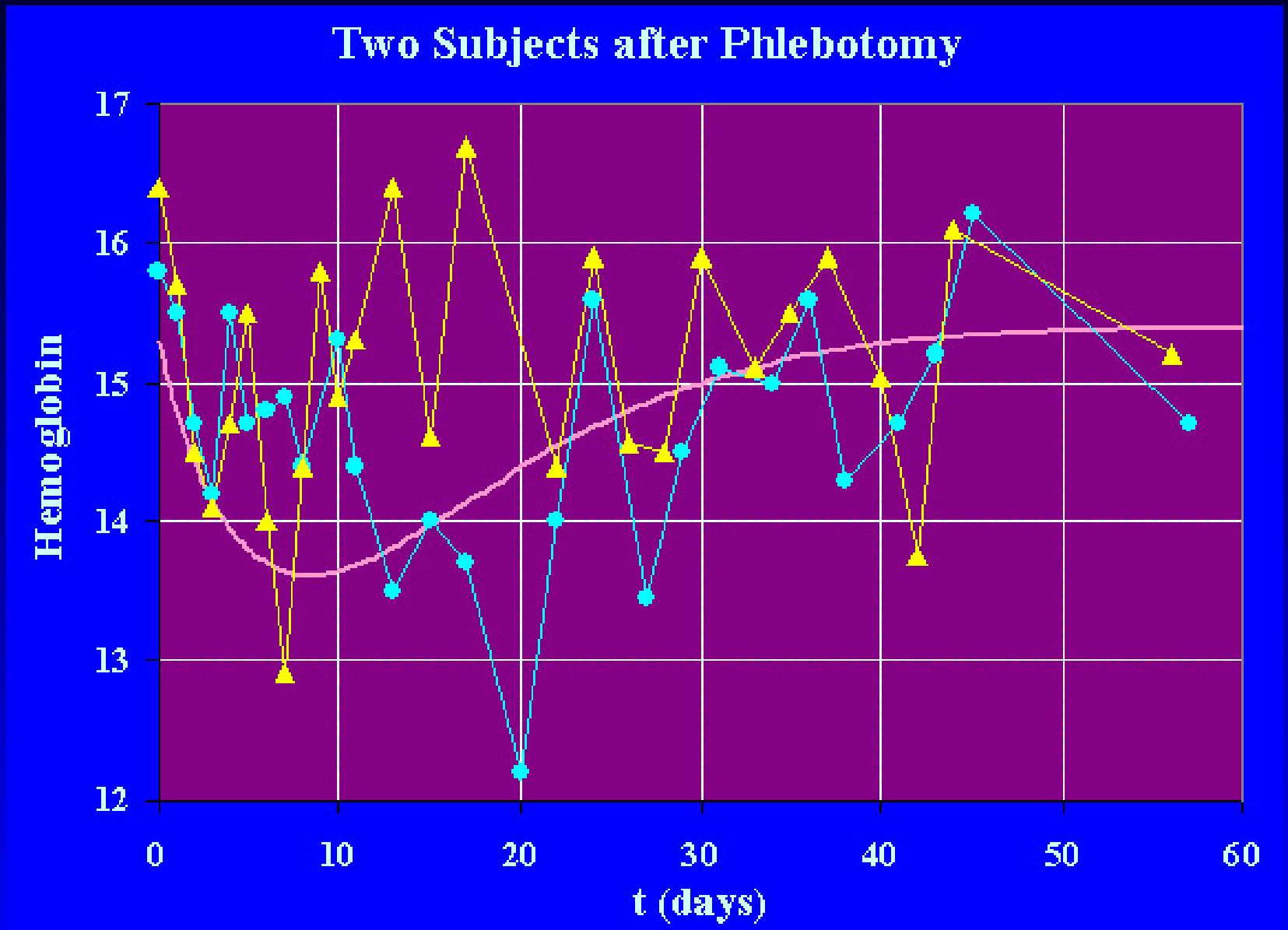
$$\dot{E}(t) = f(h(t)) - kE(t)$$

- Fit model to data of Maeda et al and Wadsworth

Model a Phlebotomy



Model Compared to Data



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.