Size-Structured Population Models and Their Applications to Erythropoiesis

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The Classical Size-Structured Model

- In 1926, A.G. Mckendrick derived a first order PDE model for an age-structured ($g = 1$) population as follows:

- Let $u(x,t)$ be the density of individuals of size x at time t.
- Let $g(x,t)$ be the growth rate of individuals of size x at time t.
- Let $m(x,t)$ be the mortality rate of individuals of size x at time t.
- Let $\beta(x,t)$ be the birth rate of individuals of size x at time t.
- Let $u_0(x)$ be the initial distribution of the population.

The Classical Size-Structured Model

- It also follows that the model satisfies the boundary condition:

$$g(0,t)u(0,t) = C(t) + \int_0^{x_{\max}} \beta(y,t)u(y,t)dy.$$

- Hence, along with an initial condition, the model takes the form:

$$\begin{aligned} & u_t + (g(x,t)u)_x = -m(x,t)u, && 0 < x < x_{\max},\ 0 < t < T, \\ & g(0,t)u(0,t) = C(t) + \int_0^{x_{\max}} \beta(y,t)u(y,t)dy, && 0 < t < T, \\ & u(x,0) = u_0(x), && 0 < x < x_{\max}. \end{aligned} \tag{1}$$

Nonlinear Variations of the Size-Structured Model

- In 1974, M. Gurtin and R. MacCamy introduced the first nonlinear age structured ($g = 1$) population model. They did so by allowing the mortality and birth rates to depend on the total population $P(t) = \displaystyle\int_0^{x_{\max}} u(x,t)dx$. The model has the following form:

$$
\begin{aligned}
&u_t + u_x = -m(x, P(t))u, && 0 < x < x_{\max},\ 0 < t < T,\\
&u(0,t) = C(t) + \int_0^{x_{\max}} \beta(y, P(t))u(y,t)dy, && 0 < t < T,\\
&u(x,0) = u_0(x), && 0 < x < x_{\max}.
\end{aligned}
\tag{2}
$$

Nonlinear Variations of the Size-Structured Model

- In 1995, Calsina and Saldana proved that the problem

$$
\begin{aligned}
&u_t + (g(x,P(t))u)_x = -m(x,P(t))u, && 0 < x < x_{\max},\ 0 < t < T,\\
&g(0,P(t))u(0,t) = C(t) + \int_0^{x_{\max}} \beta(y,P(t))u(y,t)dy, && 0 < t < T,\\
&u(x,0) = u_0(x), && 0 < x < x_{\max}.
\end{aligned} \tag{3}
$$

has a unique solution.

Numerical Approximations of the Nonlinear Size-Structured Model

- In 1997, Ackleh and Ito presented the first numerical method for approximating solutions to the fully nonlinear size-structured population model. The method took the form of the following finite difference scheme:

$$\begin{aligned} &\frac{u_i^{k+1} - u_i^k}{\Delta t} + \frac{g_i^k u_i^{k+1} - g_{i-1}^k u_{i-1}^{k+1}}{\Delta x} - m_i^k u_i^{k+1} = 0 \\ &g_0^k u_0^{k+1} = \sum_{i=1}^{n} \beta_i^k u_i^{k+1} \end{aligned} \tag{4}$$

with the initial conditions

$$u_i^0 = \frac{1}{\Delta x} \int_{(i-1)\Delta x}^{i\Delta x} u_0(x) dx \quad i = 1, 2, \cdots, n,$$

Erythropoiesis

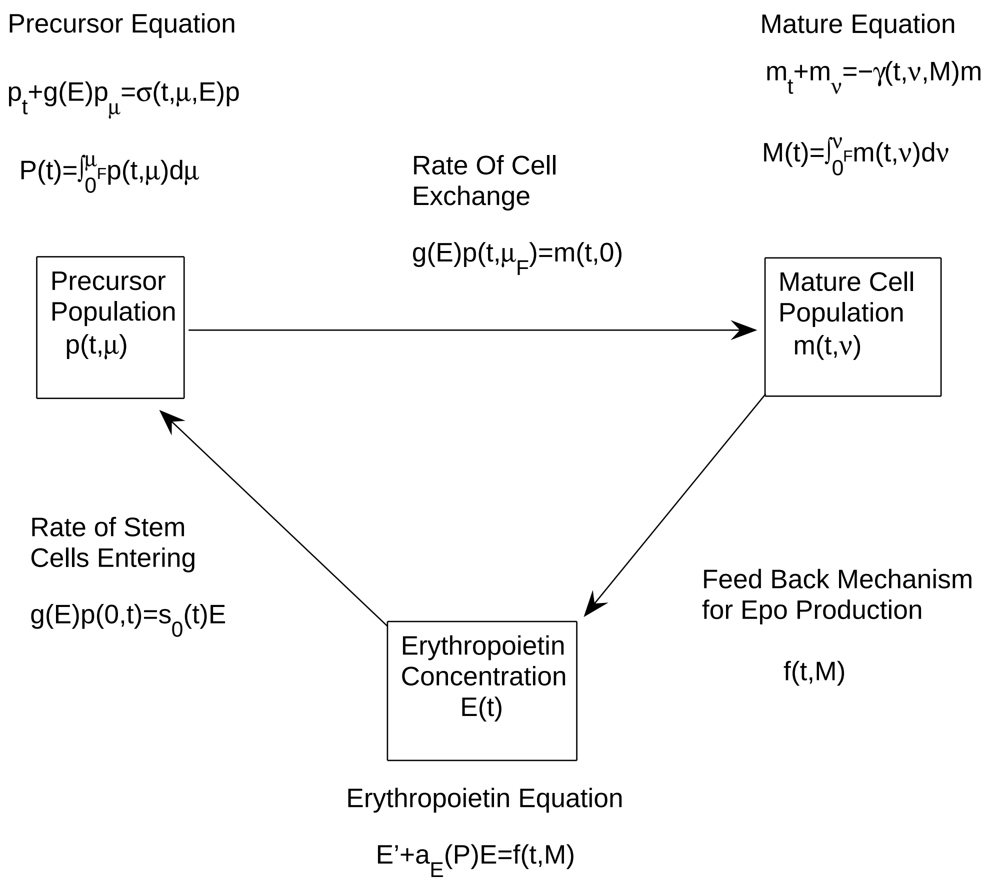
- Erythropoiesis is the process in which red blood cells are developed. The three major components of the process are:

  1) Precursor Cells
  The density of these cells is denoted by $p(t, \mu)$. These cells are structured by the variable μ, which is relative to their hemoglobin content.

  2) Mature Red Blood Cells
  The density of these cells is denoted by $m(t, \nu)$. These cells are structured by the variable ν, which is simply their age.

  3) The Hormone Erythropoietin
  The concentration of this hormone in the body is given by $E(t)$. This hormone is responsible for the recruitment of stem cells into the precursor population.

Erythropoiesis Models (1991-present)(Grabosch, Heijmans, Mahaffy, Bèlair)



The Erythropoiesis Model (2006)(J. Thibodeaux)

$$
\begin{aligned}
&\frac{\partial p(t,\mu)}{\partial t} + g(E(t))\frac{\partial p(t,\mu)}{\partial \mu} = \sigma(t,\mu,E(t))p(t,\mu), && 0 < t < T, \quad 0 < \mu < \mu_F, \\
&\frac{\partial m(t,\nu)}{\partial t} + \frac{\partial m(t,\nu)}{\partial \nu} = -\gamma(t,\nu,M(t))m(t,\nu), && 0 < t < T, \quad 0 < \nu < \nu_F, \\
&\frac{dE(t)}{dt} + a_E(P(t))E(t) = f(t,M(t)), && 0 < t < T, \\
&g(E(t))p(t,0) = s_0(t)E(t), && 0 < t < T, \\
&m(t,0) = g(E(t))p(t,\mu_F), && 0 < t < T, \\
&p(0,\mu) = p_0(\mu), && 0 \le \mu \le \mu_F, \\
&m(0,\nu) = m_0(\nu), && 0 \le \nu \le \nu_F, \\
&E(0) = E_0,
\end{aligned}
\tag{5}
$$

The Finite Difference Approximation

$$
\begin{aligned}
&\frac{p_i^{k+1} - p_i^k}{\Delta t} + g^k \frac{p_i^{k+1} - p_{i-1}^{k+1}}{\Delta \mu} - \sigma_i^k p_i^{k+1} = 0, \quad 1 \le i \le n_1, \;\; 1 \le k \le l \\
&\frac{m_j^{k+1} - m_j^k}{\Delta t} + \frac{m_j^{k+1} - m_{j-1}^{k+1}}{\Delta \nu} + \gamma_j^k m_j^{k+1} = 0, \;\; 1 \le j \le n_2, \;\; 1 \le k \le l \\
&\frac{E^{k+1} - E^k}{\Delta t} + a_E^k E^{k+1} = f^k, \qquad 1 \le k \le l \\
&g^k p_0^{k+1} = s_0^k E^k \\
&m_0^{k+1} = g^k p_{n_1}^{k+1} \\
&M^{k+1} = \sum_{j=1}^{n_2} m_j^{k+1} \Delta \nu \\
&P^{k+1} = \sum_{i=1}^{n_1} p_i^{k+1} \Delta \mu
\end{aligned}
\tag{6}
$$

The Finite Difference Approximation

$\vec{p}^{k+1} = [p_0^{k+1}, p_1^{k+1}, \cdots, p_{n_1}^{k+1}]^T \in \mathbb{R}^{n_1+1}$

$$A_1^k \vec{p}^{k+1} = \vec{b_1}^k, \tag{7}$$

where $\vec{b_1}^k = [s_0^k E^k, p_1^k, \cdots, p_{n_1}^k]^T$ and A_1^k is the following lower triangular matrix

$$A_1^k = \begin{pmatrix} g^k & 0 & 0 & \cdots & 0 & 0 \\ -\frac{\Delta t}{\Delta \mu} g^k & d_{1,1}^k & 0 & \cdots & 0 & 0 \\ 0 & -\frac{\Delta t}{\Delta \mu} g^k & d_{1,2}^k & \cdots & 0 & 0 \\ \cdots & \cdots & \cdots & \cdots & \cdots & \cdots \\ 0 & 0 & 0 & \cdots & -\frac{\Delta t}{\Delta \mu} g^k & d_{1,n_1}^k \end{pmatrix},$$

The Finite Difference Approximation

$\vec{m}^{k+1} = [m_0^{k+1}, m_1^{k+1}, \cdots, m_{n_2}^{k+1}]^T \in \mathbb{R}^{n_2+1}$

$$A_2^k \vec{m}^{k+1} = \vec{b_2}^k, \tag{8}$$

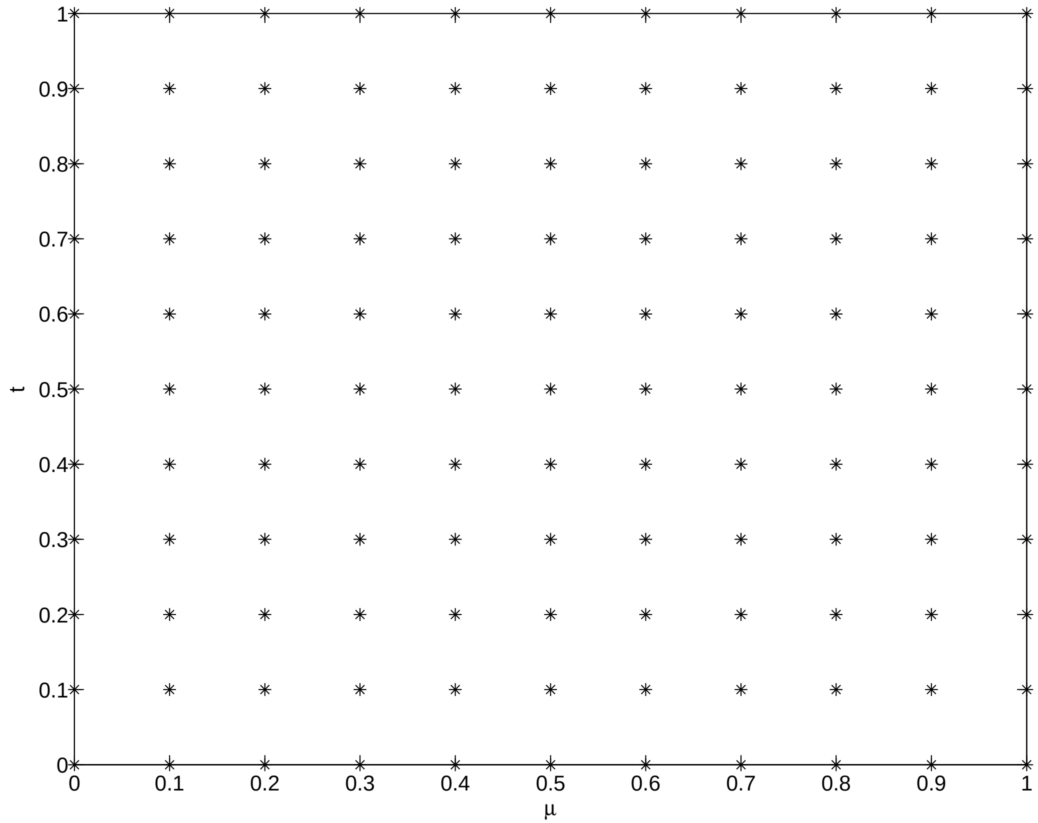
where $\vec{b_2}^k = [g^k p_{n_1}^{k+1}, m_1^k, \cdots, m_{n_2}^k]^T$ and A_2^k is the following lower triangular matrix

$$A_2^k = \begin{pmatrix} 1 & 0 & 0 & \cdots & 0 & 0 \\ -\dfrac{\Delta t}{\Delta \nu} & d_{2,1}^k & 0 & \cdots & 0 & 0 \\ 0 & -\dfrac{\Delta t}{\Delta \nu} & d_{2,2}^k & \cdots & 0 & 0 \\ \cdots & \cdots & \cdots & \cdots & \cdots & \cdots \\ 0 & 0 & 0 & \cdots & -\dfrac{\Delta t}{\Delta \nu} & d_{2,n_2}^k \end{pmatrix},$$

and

$$E^{k+1} = (1 + a_E^k \Delta t)^{-1} E^k + \triangle t (1 + a_E^k \Delta t)^{-1} f^k \tag{9}$$

A Typical Grid



Results Concerning the Finite Difference Scheme

- The l_1 bound:

Let $\|p^k\|_1 = \sum_{i=1}^{n_1} |p_i^k| \Delta\mu$ and $\|m^k\|_1 = \sum_{j=1}^{n_2} |m_j^k| \Delta\nu$.

Lemma 0.1 *Assume that* $2c\Delta t \le 1$ *(A1). Then there exists a positive constant* B_1 *such that* $\|p^k\|_1 + \|m^k\|_1 + |E^k| \le B_1$.

Results Concerning the Finite Difference Scheme

- The l_∞ bound:

Let $\|p^k\|_\infty = \max_i |p_i^k|$ and $\|m^k\|_\infty = \max_j |m_j^k|$.

Lemma 0.2 *Assume that (A1) holds. Then there exists a constant* B_2 *such that* $\|p^k\|_\infty + \|m^k\|_\infty \le B_2$.

Results Concerning the Finite Difference Scheme

- The approximations are of bounded total variation

Lemma 0.3 *Assume (A1) holds. Then there exists a constant B_3 such that*

$$\sum_{i=1}^{n_1} |p_i^k - p_{i-1}^k| + \sum_{j=1}^{n_2} |m_j^k - m_{j-1}^k| \leq B_3.$$

- **Motivation**: Recall that the set of functions of bounded total variation is a compact subset of the set of L^1 functions. So for each fixed k, we can construct a sequence of functions from our approximations that converges to an L^1 function, in the L^1 norm.

Results Concerning the Finite Difference Scheme

- A Lipschitz-type condition

Lemma 0.4 *There exists an* $A > 0$ *such that for any* $r > q$

$$\sum_{i=1}^{n_1} \left| \frac{p_i^r - p_i^q}{\Delta t} \right| \Delta\mu \leq A(r-q)$$

$$\sum_{j=1}^{n_2} \left| \frac{m_j^r - m_j^q}{\Delta t} \right| \Delta\nu \leq A(r-q)$$

$$\left| \frac{E^r - E^q}{\Delta t} \right| \leq A(r-q).$$

Results for the Finite Difference Scheme (L^1 Convergence)

Theorem 0.5 *There exist sequences* $\{\mathbb{P}_{\Delta t_i,\Delta\mu_i}\} \subset \{\mathbb{P}_{\Delta t,\Delta\mu}\}, \{\mathbb{M}_{\Delta t_i,\Delta\nu_i}\} \subset \{\mathbb{M}_{\Delta t,\Delta\nu}\}$*, and* $\{\mathbb{E}_{\Delta t_i}\} \subset \{\mathbb{E}_{\Delta t}\}$ *which converge to* $BV([0,T]\times[0,\mu_F]), BV([0,T]\times[0,\nu_F])$ *and* $C[0,T]$ *functions* $p(t,\mu), m(t,\nu)$ *and* $E(t)$*, respectively, in the sense that for all* $t > 0$

$$\int_0^{\mu_F} |\mathbb{P}_{\Delta t_i,\Delta\mu_i}(t,\mu) - p(t,\mu)|\, d\mu \to 0,$$

$$\int_0^{\nu_F} |\mathbb{M}_{\Delta t_i,\Delta\nu_i}(t,\nu) - m(t,\nu)|\, d\nu \to 0,$$

$$\int_0^{T}\int_0^{\mu_F} |\mathbb{P}_{\Delta t_i,\Delta\mu_i}(t,\mu) - p(t,\mu)|\, d\mu dt \to 0,$$

$$\int_0^{T}\int_0^{\nu_F} |\mathbb{M}_{\Delta t_i,\Delta\nu_i}(t,\nu) - m(t,\nu)|\, d\nu dt \to 0,$$

and

$$\max_{t\in[0,T]} |\mathbb{E}_{\Delta t_i}(t) - E(t)| \to 0,$$

as $i \to \infty$*. Furthermore, there exists a constant* Γ *such that the limit functions satisfy*

$$\|p\|_{BV([0,T]\times[0,\mu_F])} \le \Gamma, \qquad \|m\|_{BV([0,T]\times[0,\nu_F])} \le \Gamma, \qquad \|E\|_{C[0,T]} \le \Gamma.$$

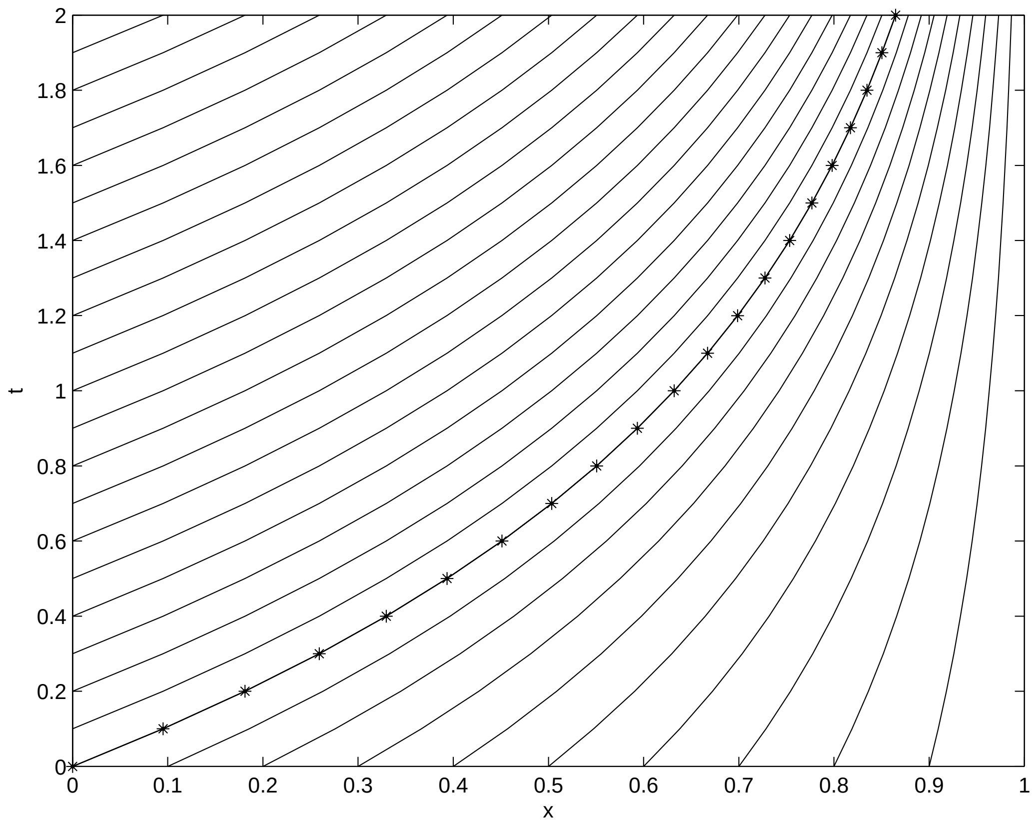
Main Theoretical Result

There exist unique functions $p(t,\mu) \in BV([0,T] \times [0,\mu_F])$, $m(t,\nu) \in BV([0,T] \times [0,\nu_F])$, and $E(t) \in C[0,T]$ that satisfy (1) in the sense that

$$\begin{aligned}
&\int_0^{\mu_F} p(t,\mu)\xi(t,\mu)d\mu \\
&\quad = \int_0^{\mu_F} p_0(\mu)\xi(0,\mu)d\mu - \int_0^t g(E(\tau))p(\tau,\mu_F^-)\xi(\tau,\mu_F)d\tau + \int_0^t s_0(\tau)E(\tau)\xi(\tau,0)d\tau \\
&\qquad + \int_0^t \int_0^{\mu_F} [\xi_\tau(\tau,\mu) + g(E(\tau))\xi_\mu(\tau,\mu)]p(\tau,\mu)d\mu d\tau \\
&\qquad + \int_0^t \int_0^{\mu_F} \sigma(\tau,\mu,E(\tau))p(\tau,\mu)\xi(\tau,\mu)d\mu d\tau \\
&\int_0^{\nu_F} m(t,\nu)\zeta(t,\nu)d\nu \\
&\quad = \int_0^{\nu_F} m_0(\nu)\zeta(0,\nu)d\nu - \int_0^t m(\tau,\nu_F^-)\zeta(\tau,\nu_F)d\tau + \int_0^t g(E(\tau)p(\tau,\mu_F^-)\zeta(\tau,0)d\tau \\
&\qquad + \int_0^t \int_0^{\nu_F} [\zeta_\tau(\tau,\nu) + \zeta_\nu(\tau,\nu)]m(\tau,\nu)d\nu d\tau \\
&\qquad - \int_0^t \int_0^{\nu_F} \gamma(\tau,\nu,M(\tau))m(\tau,\nu)\zeta(\tau,\nu)d\nu d\tau \\
&E(t) = \exp\left(-\int_0^t a_E(P(\tau))d\tau\right)\left(E_0 + \int_0^t f(\tau,M(\tau))\exp\left(\int_0^\tau a_E(P(s))ds\right)d\tau\right)
\end{aligned} \tag{10}$$

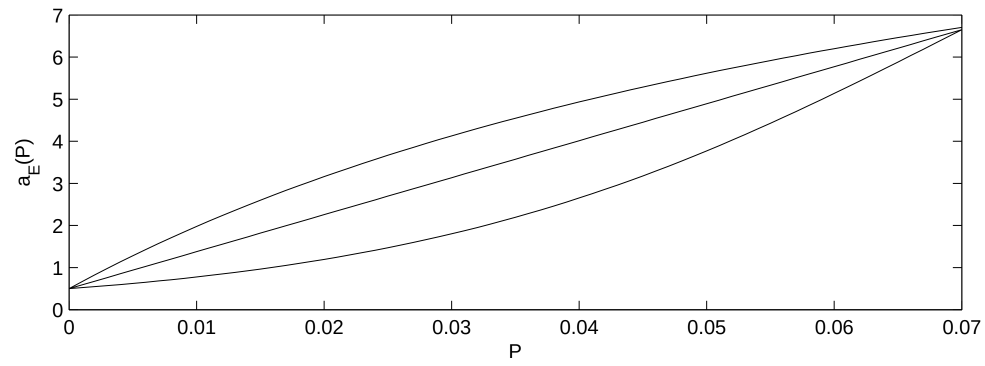
for each $t \in (0,T)$, every $\xi \in C^1([0,T] \times [0,\mu_F])$, and every $\zeta \in C^1([0,T] \times [0,\nu_F])$, where $p(t,\mu_F^-) = \lim_{\mu \to \mu_F^-} p(t,\mu)$ and $m(t,\nu_F^-) = \lim_{\nu \to \nu_F^-} m(t,\nu)$.

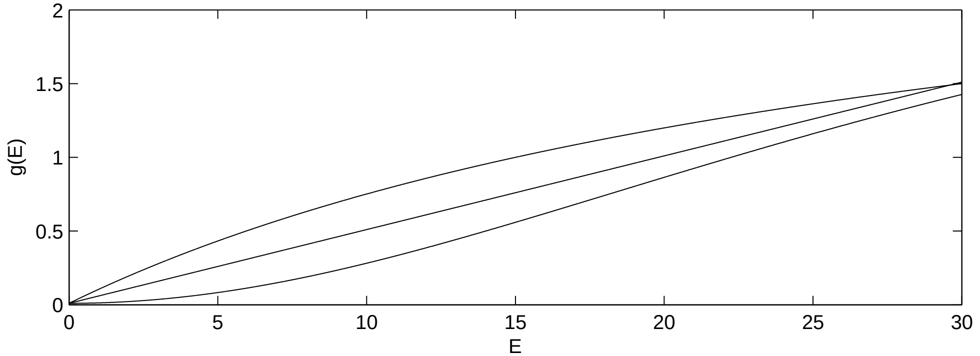
Characteristics



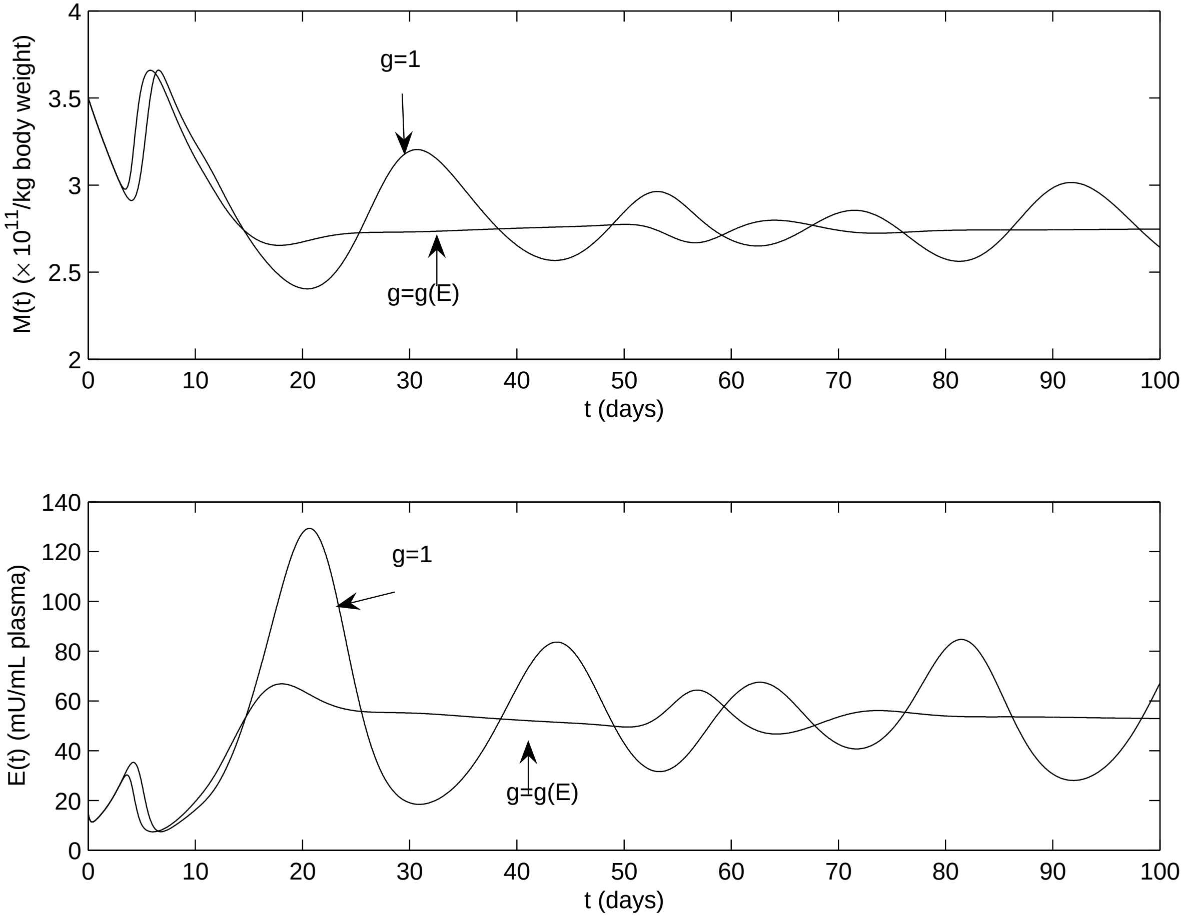
Effects of $g(E)$ and $a_E(P)$

- Since we do not have data on the functions $a_E(P)$ and $g(E)$ in the model, we would like to see what kind of effects these functions have on model output.
- To be biologically reasonable, these functions should both be nondecreasing.

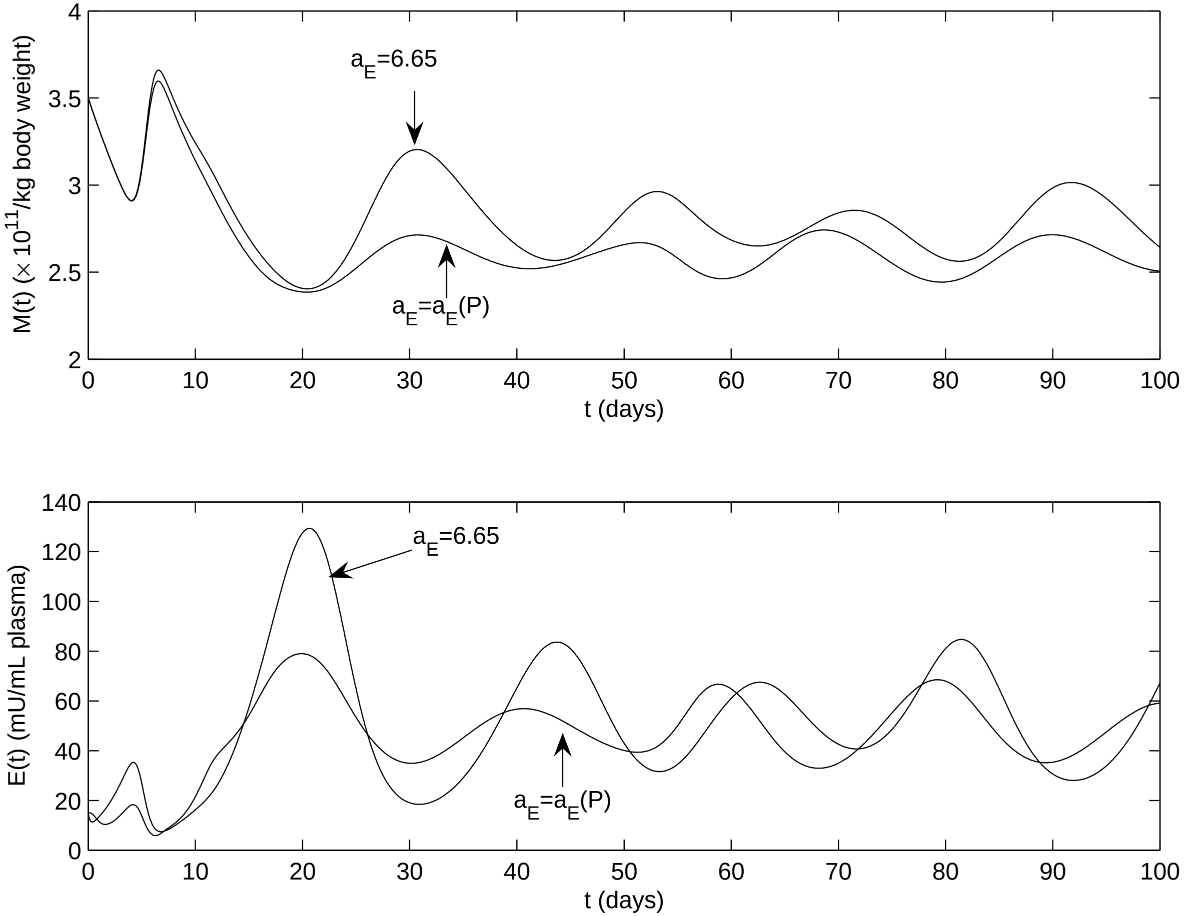




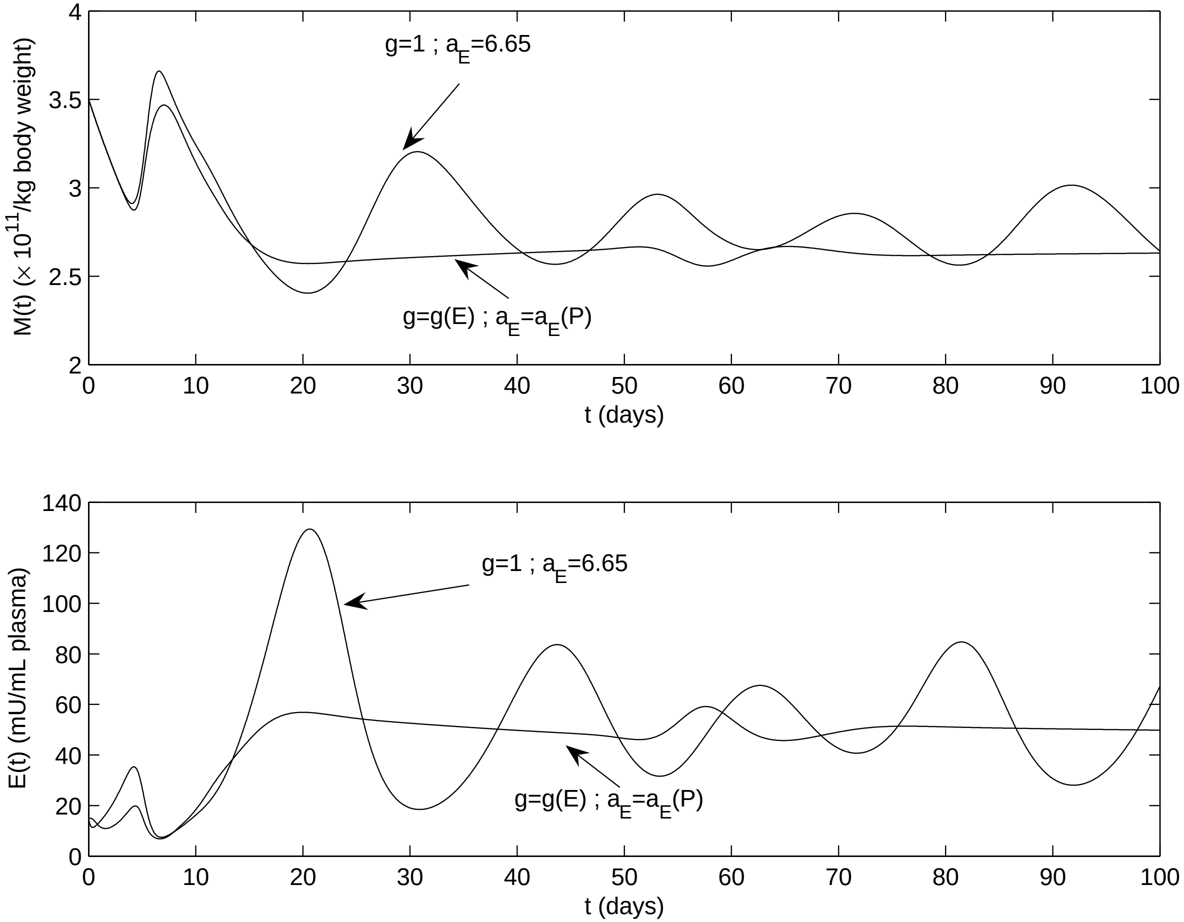
Variable vs. Constant Maturation Velocity



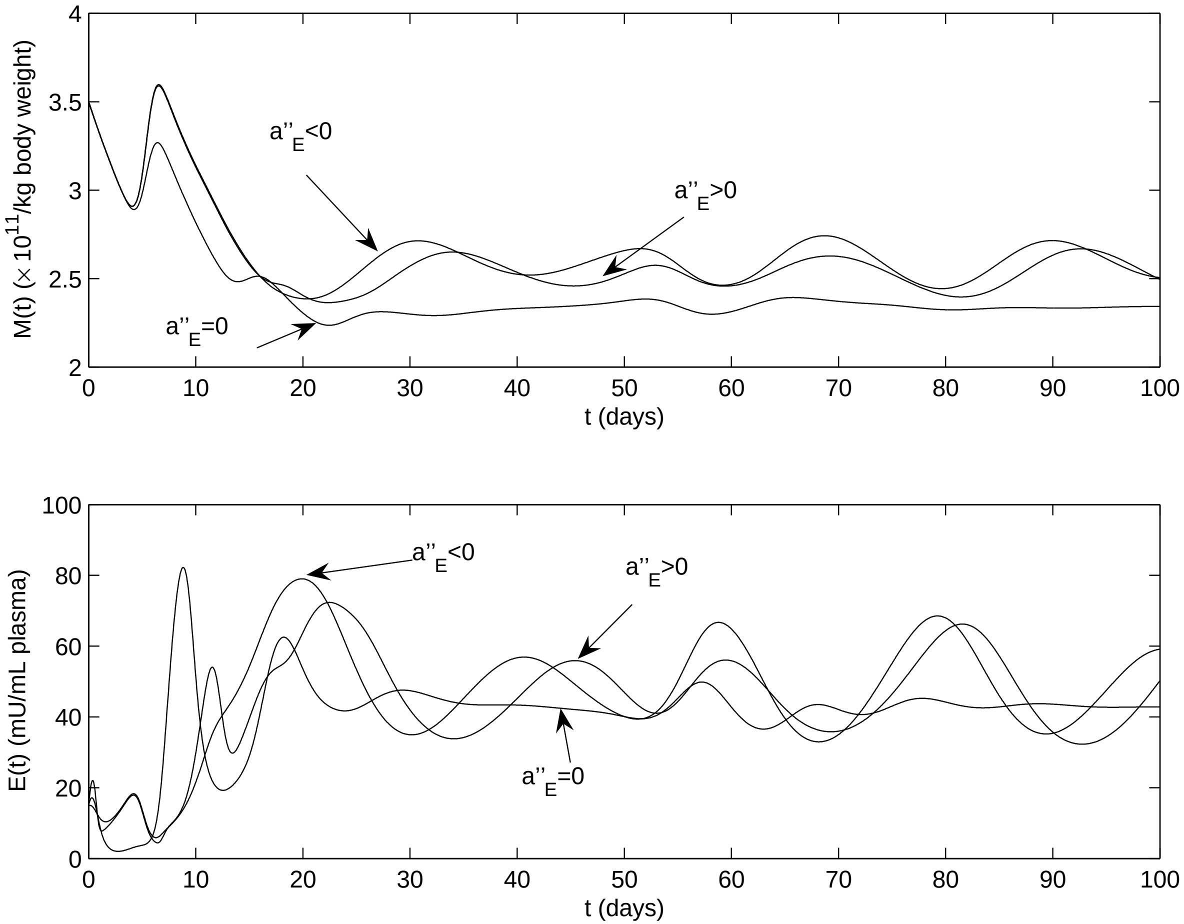
Variable vs. Constant Erythropoietin Decay Rate



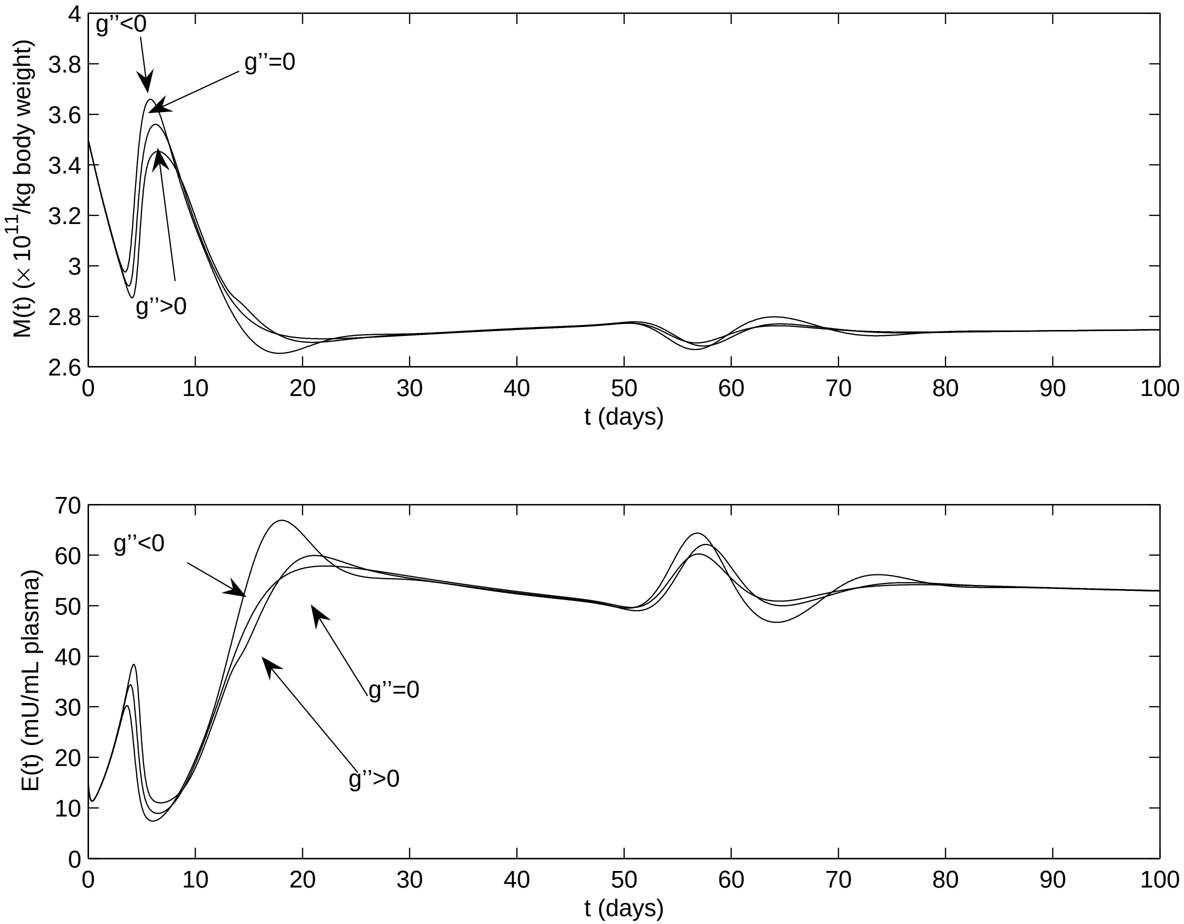
Variable Maturation Velocity and Erythropoietin Decay Rate



Robustness with Respect to the Forms of $a_E(P)$ and $g(E)$



Robustness with Respect to the Forms of $a_E(P)$ and $g(E)$

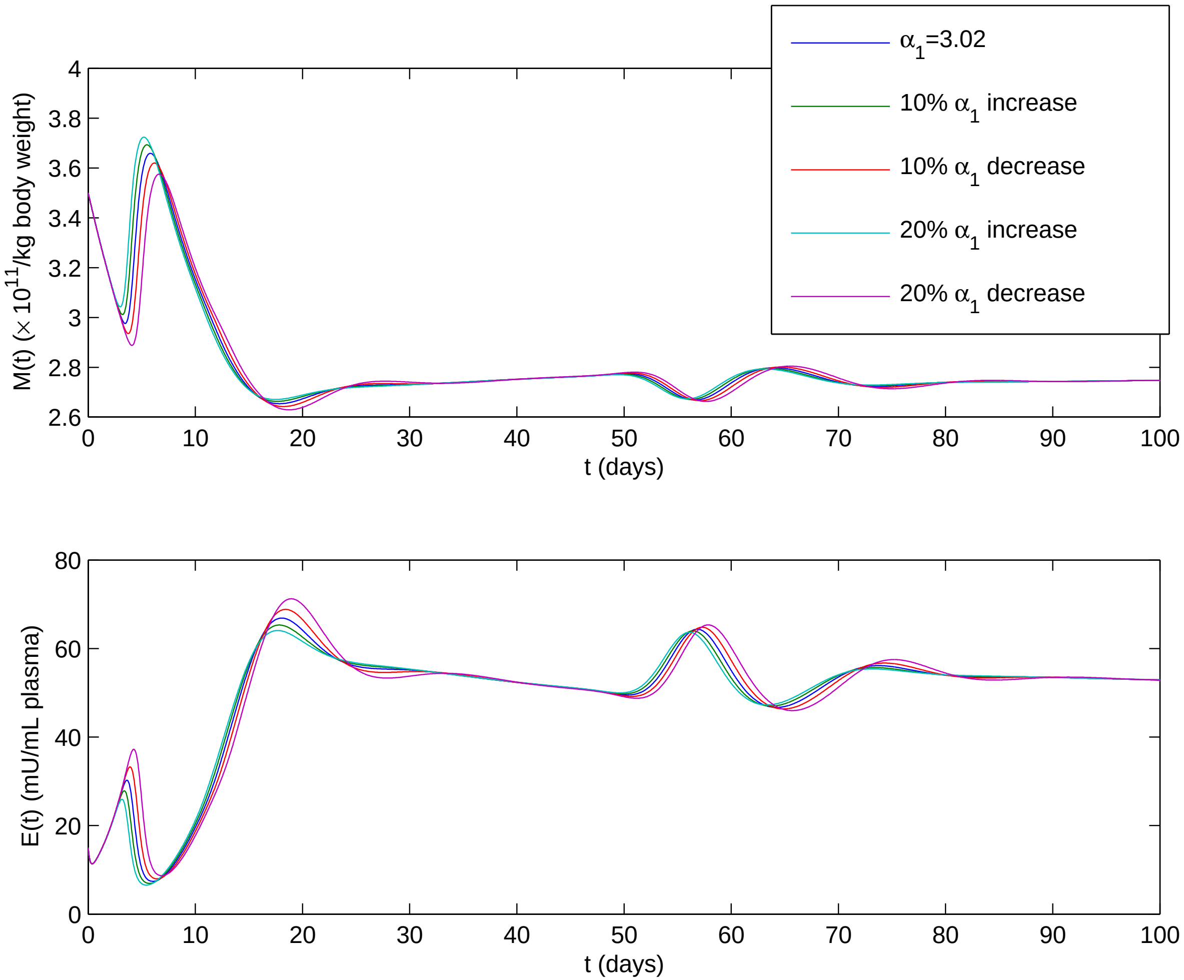


Sensitivity Analysis

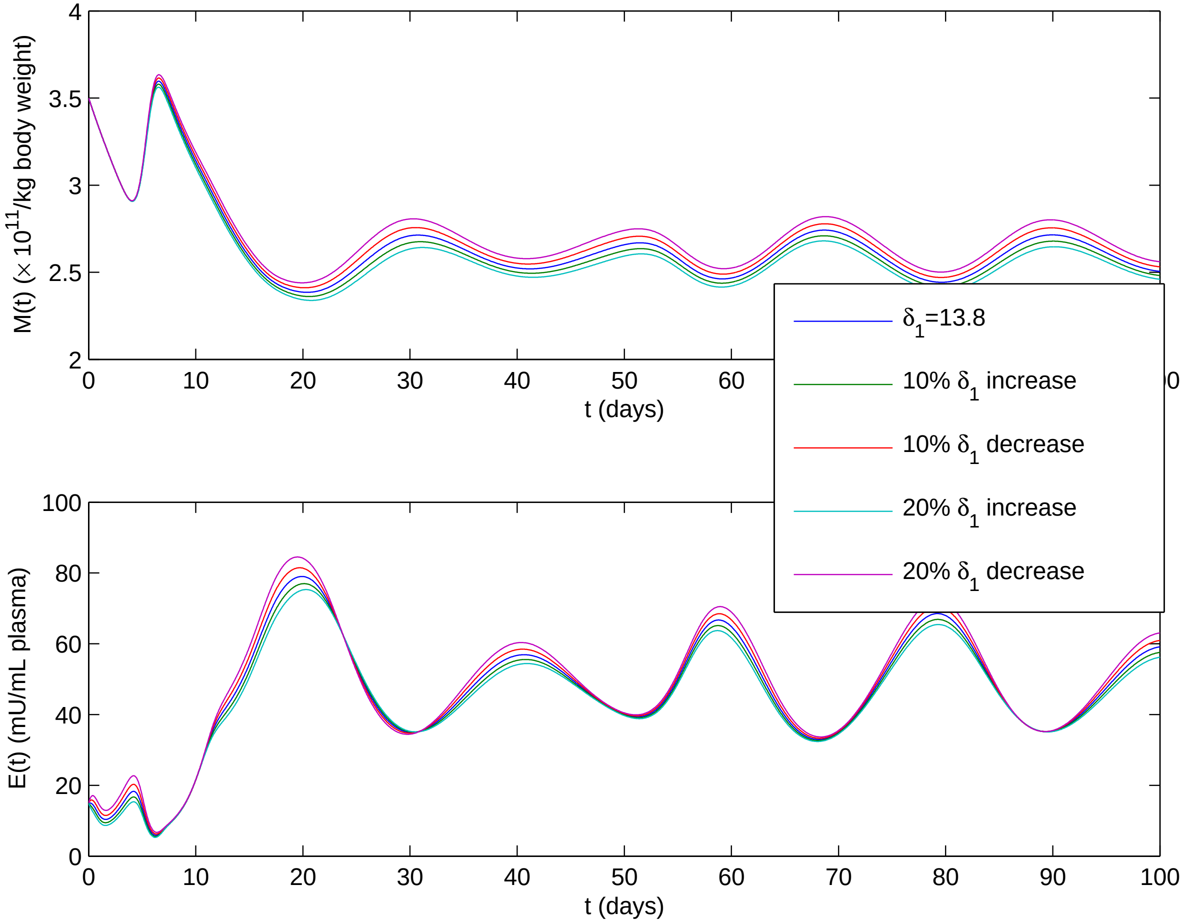
- Once particular forms of $g(E)$ and $a_E(P)$ are chosen, one wonders how sensitive the model is to the parameters in these functions.
- We assumed $g(E)$ and $a_E(P)$ to be of the following forms:

$$g(E) = \frac{\alpha_1 E + \alpha_2}{\alpha_3 + E} \qquad a_E(P) = \frac{\delta_1 P + \delta_2}{\delta_3 + P}$$

Sensitivity Analysis



Sensitivity Analysis



Conclusion and Future Research

- We have established existence-uniqueness for what is presently the most general erythropoiesis model.
- We have provided a practical numerical scheme which converges to the solution.
- Numerical investigations show that a nonconstant growth rate and a nonconstant erythropoietin decay rate have a stabilizing effect on the model.
- A. Ackleh, K. Deng, K. Ito, and J. Thibodeaux, A Structured Erythropoiesis Model with Nonlinear Cell Maturation Velocity and Hormone Decay Rate, *Math. Biosci.*, **204** (2006), 21-48.
- Future research on this topic will include an investigation of the stability properties of possible stationary solutions.