To derive a physiologically-motivated erythropoiesis model that can be used for anemia management protocol (AMP) design based on formal feedback control methods.

Background

- In end-stage renal disease (ESRD), endogenously produced erythropoietin (EPO) is inappropriately low for the level of anemia; EPO resistance is often observed. A shortened RBC life-span further contributes to the anemia of ESRD.
- The discovery of recombinant human EPO has shifted the treatment of anemia for patients on dialysis away from blood transfusions.
- Current anemia management protocols fail to achieve desired response.

Methods/Results

Schematic of erythropoiesis stages.

Pharmacokinetics/Pharmacodynamics Model

- Successive exogenous EPO doses \( d_i \), \( i = 0,..., n \), are modeled as impulses into the blood pool \( E \) of EPO (endogenous, \( E_{en} \), plus exogenous), with Michaelis-Menten clearance.
- \( k_{in} \) represents the stimulatory effect of EPO on RBC production, and is the output of a saturating function of pool \( E \).

\[
\frac{d}{dt} E(t) = -\frac{V_{max} E(t)}{K_m + E(t)} + \sum_{i=0}^{n} d_i \delta(t - T_i); \quad (1)
\]

RBC Pool

- The RBC pool \( R \) is described by the compartment model

\[
\frac{d}{dt} R(t) = k_{in}(t - D) - \int_{0}^{t} i(t - \tau) k_{in}(\tau - D) d\tau \quad (2)
\]

where \( D \) is the time required for pluripotent hematopoietic stem cells to become RBCs, and \( i(t) \) is the probability density function of the RBC lifespan \( \tau \) - taken as a second-order gamma distribution.

Discussion

- A physiologically-relevant erythropoiesis model with estimated parameters can be derived to match clinical results.
- The nonlinear dynamics can be accurately converted into a nonlinear function of EPO which should facilitate the design of robust anemia management protocols based on control techniques.
- These concepts are presently being tested in a clinical setting, with successful preliminary results.