The Engineering of Anemia Management Protocols in Chronic Kidney Disease

MJ Germain[1], WC Vogt[2], RP Shrestha[3], B Nichols[3], CV Hollot[4], J Horowitz[5], and Y Chait[3]

[1]Western New England Renal & Transplant Associates, PC, Springfield, MA, [2]Biomedical Engineering & Sciences, Virginia Polytechnic Institute & State University, Blacksburg, VA, [3]Mechanical & Industrial Engineering, University of Massachusetts, Amherst, MA, [4]Electrical & Computer Engineering, University of Massachusetts, Amherst, MA, [5]Mathematics & Statistics, University of Massachusetts, Amherst, MA

Objective

To design a new, patient-specific anemia management protocol using feedback control principles by explicitly considering the dynamic structure of the erythropoiesis, together with models of the biosystem's uncertainties.

Background

- In chronic kidney disease (CKD), endogenously produced erythropoietin (EPO) is inappropriately low for the level of anemia. In addition there is EPO resistance so that EPO that is produced works less effectively. A shortened RBC life-span further contributes to the anemia of CKD.

- The discovery of recombinant human EPO has shifted the treatment of anemia for patients on dialysis away from blood transfusions.

- Erythropoiesis is a nonlinear, dynamic biosystem. However, its interaction with an anemia management protocol results in a *new* nonlinear system, whose behavior can be very different from that observed in pharmacokinetic/pharmacodynamic (PK/PD) studies.

- Current anemia management protocols fail to achieve desired response.

- Current protocols can be analyzed and new protocols can be designed through the principles of feedback control systems.

Anemia Management as Feedback Control System

anemia management protocol

exogenous EPO pharmacokinetics

erythropoiesis

red blood cell pool

pharmacodynamics

Hgb sensor
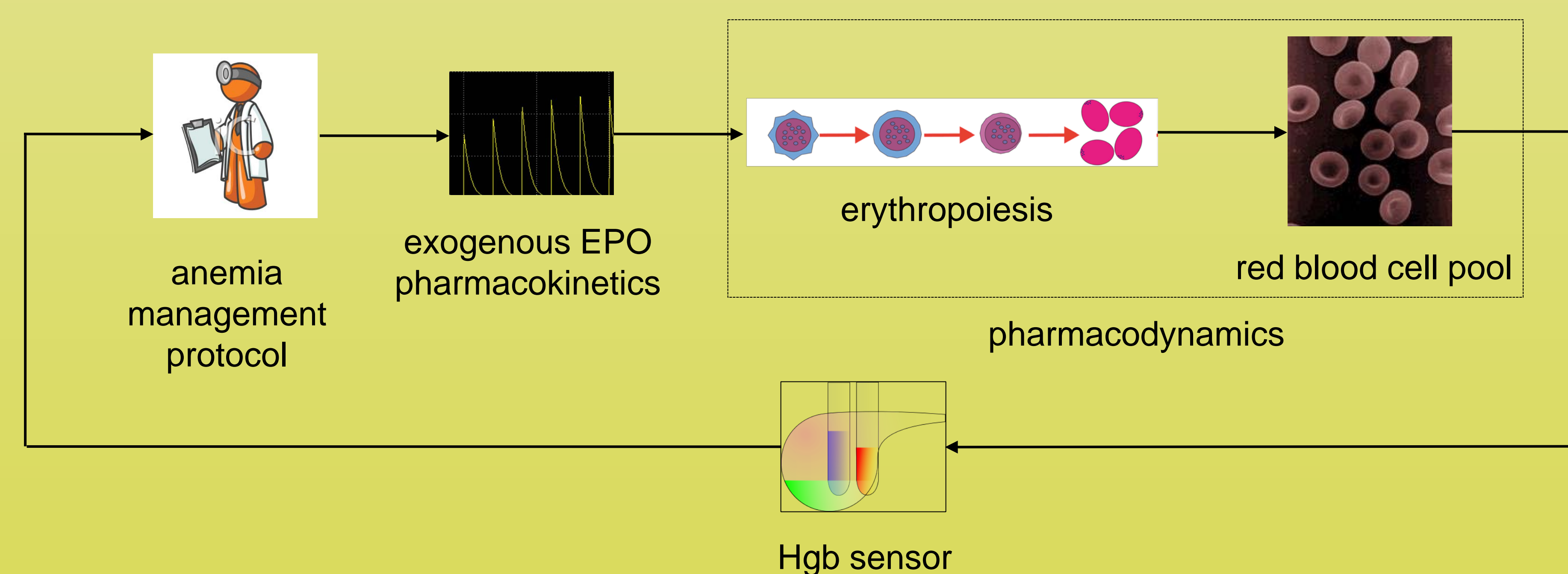
Methods

Pharmacokinetics Model

- A single pool of EPO in blood, intravenous (IV) dose as an impulsive input, and a Michaelis-Menten function capturing nonlinear clearance.

Pharmacodynamics Model

- Stimulatory effects of EPO on differentiation, maturation, and proliferation of hematopoietic stem cells into reticulocytes is described using a nonlinear, time-delayed function of EPO concentration.

- Reticulocyte and RBC dynamics are described using cellular lifespan distribution functions.

Clinical Data

- Retrospective data set consisting of 49 subjects having Hgb measured 3x-week, 3x-week IV EPO administration, over a period of 18 months.

PK/PD Parameter Estimation

- Simulink Design Optimization Tool (The MathWorks, Inc.) for estimating nominal PK/PD parameters.

- Quantify uncertainty in PK/PD parameters.
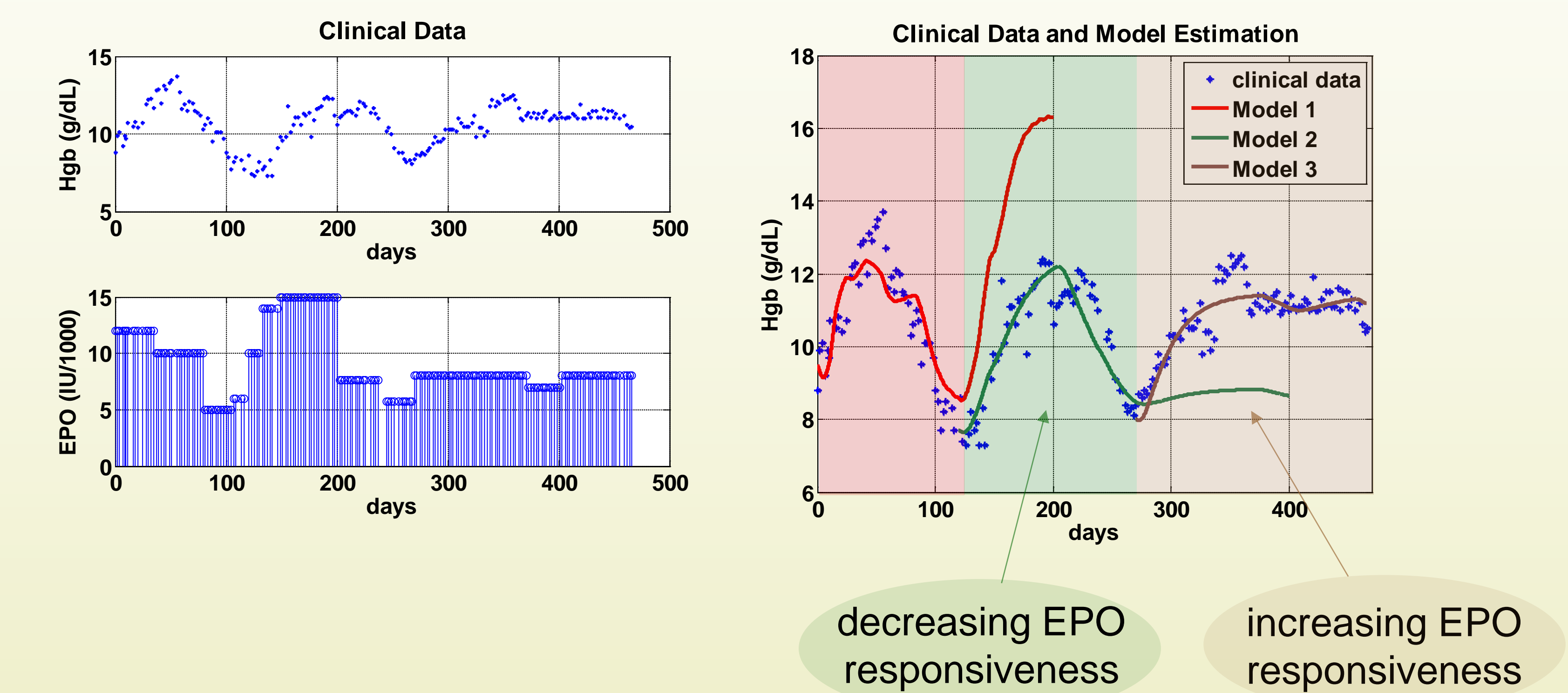
Model Simplification

- Pharmacokinetics and cell production represented as nonlinear function of EPO dose.

Design of New Anemia Management Protocol

- Apply feedback control principles (Quantitative Feedback Theory) to protocol design to maintain target Hgb level.

- Assess protocol performance with regard to Hgb variations in the face of uncertainty.
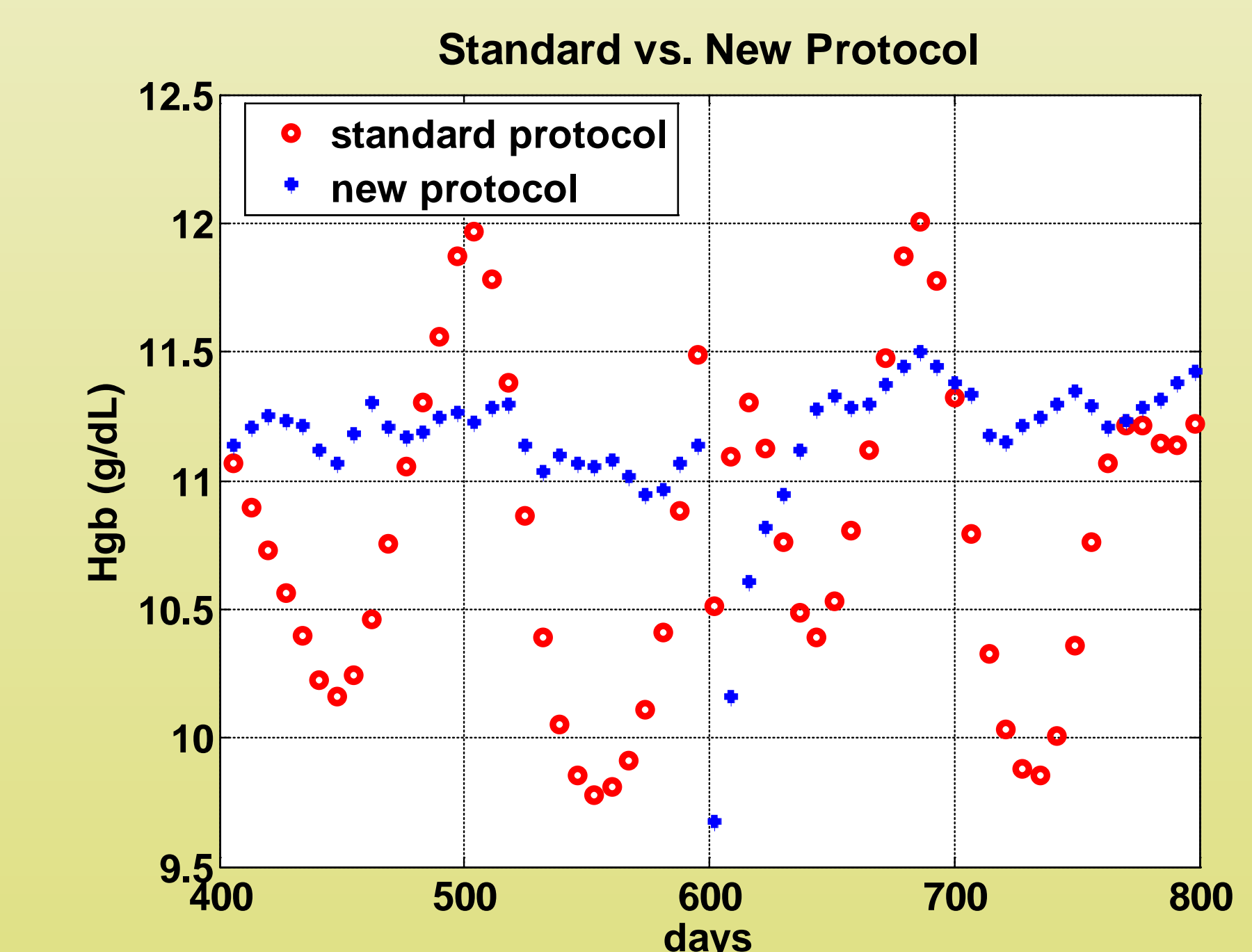
Results

Model Parameter Estimation (subject #14)

Clinical Data

Clinical Data and Model Estimation

decreasing EPO responsiveness

increasing EPO responsiveness

New vs. Standard Protocol

- Hgb measurement noise (std=0.8)

- Bleeding (1.5 g/dL at day 600)

Standard vs. New Protocol

Discussion

- Model-based, feedback control principles offer an improved approach for designing anemia management protocols.
- Intercurrent events (e.g., iron status, infection) and uncertainty in endogenous EPO levels complicate the design of protocols.
- Real-time adaptation of such protocols to variations in EPO responsiveness should further improve results.
- Inclusion of iron administration in the protocol may be necessary; lack of iron PK/PD models is presently a hurdle.