Computer Simulations in the Design and Evaluation of Anemia Management Protocols

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Objective

Simulation study to compare the performance of a current anemia management protocol (AMP) with an AMP adapted to responsiveness category.

Background

- Current anemia management protocols fail to achieve desired response.
- Anemia management should be viewed as a feedback control system, and new protocols designed using feedback control principles.

Methods

PK/PD Model

- Single pool of EPO in blood, intravenous (IV) dose as an impulsive input, and a Michaelis-Menten function capturing nonlinear clearance
- Stimulatory effects of EPO on differentiation, maturation, and proliferation of hematopoietic stem cells into reticulocytes modeled by nonlinear function of EPO concentration.
- Reticulocyte and RBC dynamics described by a compartmental model with given cellular lifespan distribution.

Clinical Data

- Retrospective data on 49 ESRD subjects having Hgb measured 3x-week and administered 3x-week EPO over a period of 18 months.

Parameter Estimation

- Simulink Design Optimization Toolbox (The MathWorks, Inc.) for estimating PK/PD parameters for 49 subjects.
- 83 sets of model parameters estimated. Figure 1 gives estimation results for subject #1. Note that erythropoiesis parameters changed at day 340 - estimated model parameters no longer predict Hgb response (red); new parameter estimates result in improved Hgb response (green). This resulted in multiple sets of parameters for most subjects.

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Results

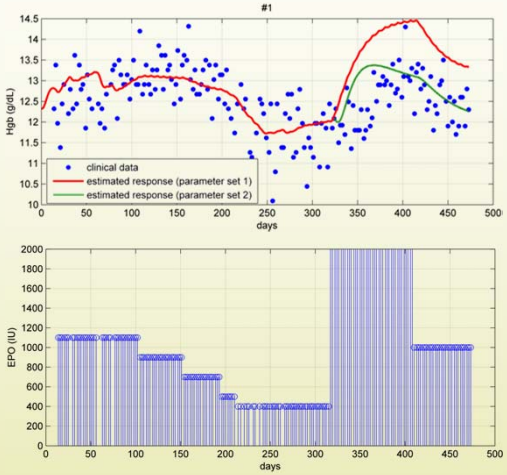

Figure 1: Parameter estimation results for subject #1

- Subjects grouped based on their "responsiveness" – the ratio of target Hgb to constant EPO dose required to achieve it.
- AMP adapted based on responsiveness categories – very hyper-, hyper-, intermediate-, and hypo-responsive subjects – based on the responsiveness levels shown in Figure 2.

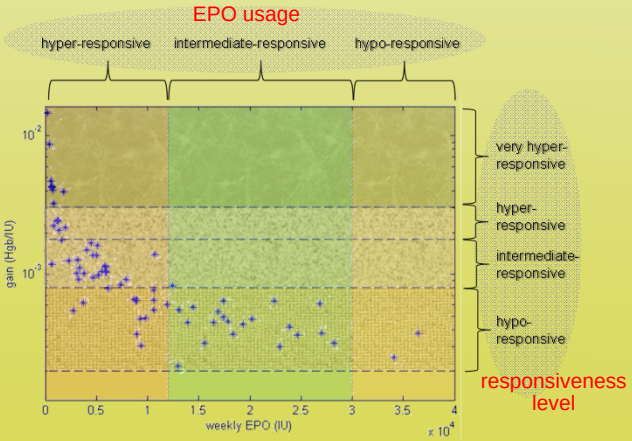

Figure 2: Subject categories based on responsiveness and EPO usage

- Simulated performance of current and new AMP based on 83 patient- models.
- Allowed simulations to reach equilibrium, then introduced random variations in the response to EPO stimulation (zero mean, 0.05 SD).
- Introduced a measure of variability, called *total variation*, as the sum of absolute consecutive Hgb changes divided by the number of data points; total variation measures variability while also accounting for the sequential evolution of the measurements.

Comparison of new and current AMP performance

Responsiveness Category	Protocol	Hgb Mean (SD) (g/dL)	Hgb Total Variation (SD) (g/dL/week)	Hgb in-Range [10-12] mean (SD) (%)	Weekly EPO Mean (SD) (IU)
All categories	New	11.08 (0.10)	5.81 (1.23)	80 (8)	12834 (10184)
	current	10.81 (0.39)	11.19 (6.78)	73 (17)	14492 (13726)
Very Hyper	New	11.08 (0.10)	6.80 (4.16)	79 (9)	2197 (764)
	current	10.81 (0.39)	8.34(4.16)	72 914)	2318 (1122)
Hyper	New	11.08 (0.08)	7.39 (1.28)	81 (7)	2878 (519)
	current	10.92 (0.45)	10.87 (4.90)	66 (9)	3491 (1305)
Intermediate	New	11.09 (0.05)	5.59 (1.10)	79 (10)	6650 (2649)
	current	10.79 (0.35)	11.27 (6.88)	74 (15)	7422 (2984)
Hypo	New	11.10 (0.12)	5.51 (0.92)	80 (7)	20703 (8870)
	current	10.83 (0.43)	11.82 (7.42)	73 (19)	23439 (14612)

Discussion

- One-size-fits-all AMPs are unlikely to achieve reasonable performance for the entire spectrum of ESRD patients.
- AMPs adapting to patient's qualitative response can be designed using model-based robust feedback control principles.
- Individualized AMPs can be tailored to fit categories of patients based on a patient's responsiveness.
- Simulations suggest that this new AMP offers better performance than current AMPs in terms of reduced Hgb total variation and standard deviation, increased in-range time, and decreased EPO usage.