A New Measure of Patient Responsiveness for Improving Anemia Management Protocols

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Objective

- **Introduce the concept of patient-specific gain (PSG), a measure of EPO responsiveness, adapted from feedback control theory.**
- **Demonstrate the impact of interpatient variability of PSG on performance of anemia management protocols.**

Background

- Anemia of end-stage kidney disease (ESRD) is characterized by multiple factors including:
- Endogenously produced erythropoietin (EPO) is inappropriately low for the level of anemia, reduced red blood cell lifespan, EPO resistance, inflammation, and loss of blood.
- The interaction of anemia management protocols (AMPs) with erythropoiesis in end-stage renal disease (ESRD) patients can often lead to undesired behavior, such as increased variability, cycling, and inability to reach and maintain target hemoglobin (Hb).
- Various classifications of patient responsiveness (or resistance) have been introduced.
- When defined correctly, EPO responsiveness corresponds to the concept of *gain*, which is classical in feedback control.

Methods

Study Data

- Retrospective data from an observational study of 44 unselected ESRD patients at one dialysis facility that started in March 2007 and lasted for 16 months.

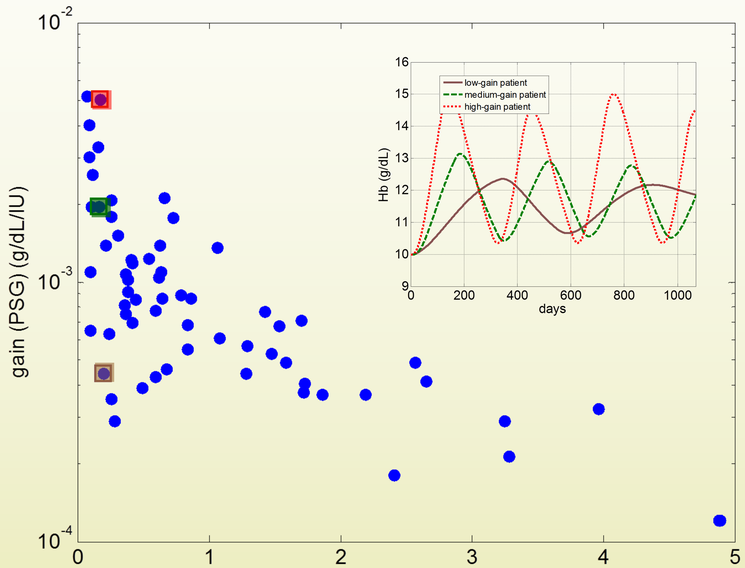
Patient-Specific Models

- An erythropoiesis model was estimated from each patient's data using nonlinear least squares.
- The model consisted of a pharmacokinetic model with linear and nonlinear clearance of EPO, a pharmacodynamic model describing nonlinear production of red blood cells (RBCs) by EPO, and a compartmental model describing RBC pool dynamics using cellular lifespan probability distribution.

Patient-Specific Gain

- For a given constant EPO dose d administered periodically, the erythropoiesis model gives a corresponding long-run mean hemoglobin value $Hb(d)$.
- Using each patient's identified erythropoiesis model, we determined the dose d_0 that would achieve the specified mean target Hb value, Hb_{target}, for that individual.
- If the dose d_0 is changed (up or down) by a small amount Δd, the resulting long-run mean Hb will change by an amount ΔHb.
- Patient-specific gain is then defined as the *ratio of the change in Hb to the change in dose*; more concisely, $PSG = \Delta Hb/\Delta d$.
- PSG can be calculated once the patient's model has been identified.

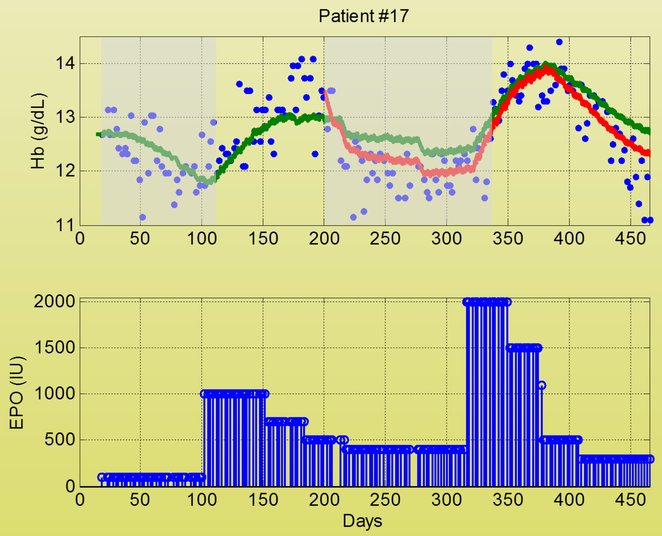
Results



Patient-specific gains for 41 patients. Gain (*PSG*), on log scale, plotted against total weekly EPO dose d_0, the dose that produces long-term target mean Hb level of 11.25 g/dL.

(insert) **Simulated results of AMP applied to 3 virtual patients.** The low-gain patient's Hb level (solid) settles just above Hb_{target}, whereas the medium-gain (dash) and high-gain (dotted) patients' Hb levels show sustained cycling.

	Min Max	Mean SD	Max/Min
PSG (g/dL/IU)	1.21×10^{-4} 5.23×10^{-3}	1.12×10^{-3} 1.07×10^{-4}	43



Re-identification of patient's gain parameter. (top) Clinical Hb data (dots); model A (green) trained over data from days 14 to 115 (shaded area) shows an emerging mismatch to actual Hb response around day 200; re-identification of patient's gain over days 200-340 leads to model B (red) whose response provides better match; (bottom) Administered EPO doses.

	Mean (SD)
Total weekly EPO	10256 (11266) IU
RBC lifespan:	70.2 (17.1) days
time periods over which patient models did not require updating	225 (98.7) days

Conclusions

- Patient gain has large interpatient variability, even among patients requiring less than 10000 IU EPO weekly.
- From a feedback control viewpoint, fixed AMPs, such as used in virtually all clinics, would be expected not to work satisfactorily for a population having a large interpatient gain variability.
- Thus, AMPs should be individualized, and patient-specific gains should play a role in their design.