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 appropriately 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 d₀ that would achieve the specified mean target Hb value, Hbₜarget, for that individual.
- If the dose d₀ 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 = ΔHb/Δd.
- 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 d₀, the dose that produces long-term target mean Hb level of 11.25 g/dL.

<table>
<thead>
<tr>
<th>PSG (g/dL IU)</th>
<th>Min</th>
<th>Max</th>
<th>Mean</th>
<th>SD</th>
<th>Max/Min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.21x10⁻¹</td>
<td>5.23x10⁻¹</td>
<td>1.12x10⁻²</td>
<td>1.07x10⁻⁴</td>
<td>43</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Mean (SD)</th>
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<tr>
<td>Total weekly EPO</td>
</tr>
<tr>
<td>RBC lifespan:</td>
</tr>
<tr>
<td>time periods over which patient models did not require updating</td>
</tr>
</tbody>
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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.