**In silico** Analysis and Optimization of the Yale Insulin Infusion Protocol

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**INTRODUCTION**

Due to the risk of hypoglycemia, safe, effective and reproducible tight glycemic control (TGC) has proven challenging in the intensive care unit (ICU). Hence, based on recent clinical trials, there is a trend toward less rigid blood glucose (BG) targets.¹

Based on new guidelines for inpatient glycemic management, the Yale ICU insulin infusion protocol was revised to achieve a higher BG target of 120-160 mg/dL. (Yale 2009). The safety and efficacy of the Yale 2009 protocol was evaluated in silico and compared with the earlier Yale 2005 protocol² that targeted 90-120 mg/dL.

**METHODS**

Insulin-glucose modeling was used to create ‘virtual patients’ and simulate expected glycemic responses to different insulin protocols. To validate the simulation system for the Yale Protocol, simulation results were compared to reported clinical results for the Yale 2005 protocol (Figure 1):

- Clinical data from 54 US cardiac surgery patients treated with the Yale 2005 protocol²
- Virtual patients generated from 40 New Zealand cardiac surgery patients treated with the SPRINT insulin-dextrose infusion protocol²

Next, the Yale 2009 protocol was simulated on the virtual cohort and compared to the Yale 2005. The system model (Figure 2) has been previously validated in silico, versus the euglycemic clamp and in several real-time clinical TGC trials in adults and neonates.³ To aid direct comparison to the 54-patient clinical results, the 40 patient virtual cohort was re-sampled to create 1,000 54-patient cohorts using the bootstrapping method with replacement.

**RESULTS**

Clinical vs. simulated results

BG outcomes for the Yale 2005 clinical results and simulations on the virtual patient cohort were very similar (Table 1):

- Mean BG levels within 1-2 mg/dL
- Hypoglycemia rates closely matched to the observed clinical incidence.

The New Zealand SPRINT clinical patients and, as a result, the in silico cohorts, exhibited some differences to US Yale clinical patients:

- Higher sensitivity to insulin
- Reduced time to BG target
- Lower BMI

Overall, the well-matched results demonstrate the ability of the in silico model to capture Yale 2005’s fundamental glycemic dynamics and outcomes.

Yale 2009 simulations

The Yale 2009 simulation results predict expected shifts in glucose control (Table 1):

- Median BG of 135 mg/dL (128 mg/dL after reaching target)
- Essentially no hypoglycemia.
- Possible reduction in BG fluctuations per hour

Additionally, distributions of simulated BG measurements indicate that the Yale 2009 protocol will effectively shift glycemic levels to the new higher target range (Figure 3).

**CONCLUSIONS**

- The in silico analysis indicates that the Yale 2009 protocol will reduce hypoglycemia without increasing BG measurement burden, and will maintain glycemia within a new higher target range.

- In silico simulation and analysis is a highly effective tool to design, evaluate and optimize protocols prior to clinical implementation.

**REFERENCES**


**Figure 1:** Simulation method for in-silico protocol comparison.

**Figure 2:** Overall insulin-glucose model employed in this study.

Model-fitted insulin sensitivity parameter ($S$) indicates influence of insulin on glucose concentration ($G$) via uptake by insulin-dependent mechanisms. Simulated insulin levels are governed by the model equations for $S$ and $G$, plasma and interstitial insulin.

**Figure 3:** Distribution of simulated BG measurements for Yale 2005 (top panel, blue) and Yale 2009 (bottom panel, red).

**Table 1:** Clinical results for Yale 2005 compared to simulated glycemic outcomes for Yale 2005 and 2009 protocols. Highlighted results indicate metrics are computed once patient has reached target BG band for consistency with reported clinical results. Overall indicates data used for entire simulated protocol usage.

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