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 120-160mg/dL (Yale 2009). The safety and efficacy of the Yale 2009 protocol was evaluated *in silico* and compared with the earlier Yale 2005 protocol[2] that targeted 90-120mg/dL.

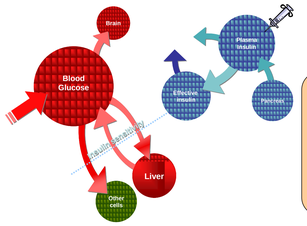
METHODS

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 protocol[2]

• Virtual patients generated from 40 New Zealand cardiac surgery patients treated with the SPRINT insulin-dextrose infusion protocol[3]

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[4]. 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.



$$\dot{G} = -p_G.G - S_I.G.\frac{Q}{1+\alpha_G Q} + \frac{P(t) + (P_{END} * m_{body}) - CNS}{(V_{G,frac}(t) * m_{body})}$$

$$\dot{Q} = -kQ + kI$$

$$\dot{I} = -\frac{nI}{1+\alpha_I I} + \frac{u_{ii}(t)}{(V_{I,frac} * m_{body})} + e^{-(k_e u_{ii}(t))} I_B$$

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

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

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.

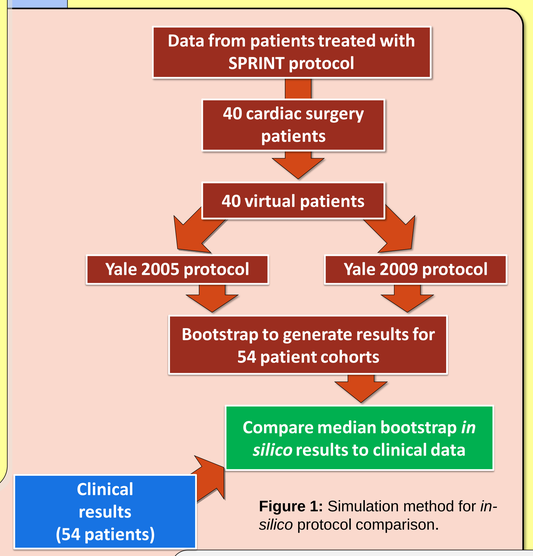


Figure 1: Simulation method for *in-silico* protocol comparison.

Yale 2009 simulations

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

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

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

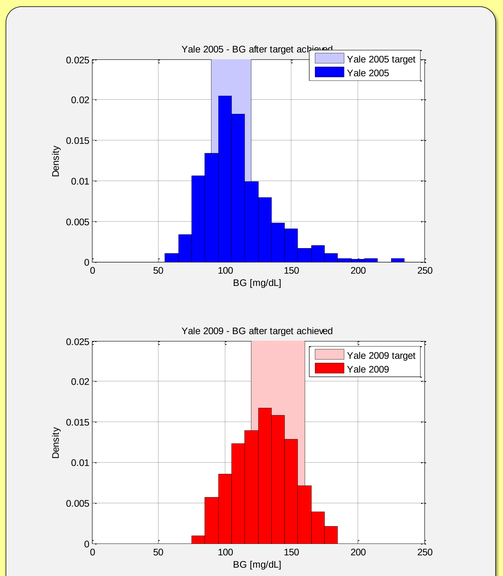


Figure 3: Distribution of simulated BG measurements for Yale 2005 (top panel, blue) and Yale 2009 (bottom panel, red).

Comparison of Results for the Yale 2005 and Yale 2009 Protocols

	Yale 2005 (90 – 120 mg/dL)		Yale 2009 (120 – 160 mg/dL)
	Clinical	Simulated	Simulated
Number of patients	54	54	54
Mean initial BG level (mg/dL)	189	188	185
SD Initial BG level (mg/dL)	44	35	30
Median time on protocol (hours)	15	15	18
Median time to target (<120 mg/dL)	6 hours	4 hours	-
Median time to target (<160 mg/dL)	-	-	2 hours
Median time to < 140 mg/dL (hours)	5 hours	3 hours	3 hours
Following highlighted results are after respective target achieved:			
% BGs within 80 - 139 mg/dL	86	78	66
% BGs within 80 - 199 mg/dL	95	90	99.8
% BGs within 90 - 119 mg/dL	60	50	27
% BGs within 100 - 139 mg/dL	66	51	56
Mean BG (per-patient) (mg/dL)	109	109	130
Mean BG (cohort) (mg/dL)	112	110	130
Hypoglycemia (BG < 60 mg/dL)			
% of BG measurements	0.3	0.6	0.0
# of patients	3	4	0
# of ICU patient days	3.7	4.0	0.0
Number of measurements after target	679	708	866
Measurements per hour		0.961	0.938
Median BG (overall) (mg/dL)		117	135
Mean BG (overall) (mg/dL)		124	137
% BGs within target range			
After target achieved		51	56
Overall		37	48

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[2]. 'Overall' indicates data used for entire simulated protocol usage

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

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