# CLINICAL DATA VALIDATION OF A NEW, PHYSIOLOGICALLY RELEVANT CRITICAL CARE GLYCAEMIC CONTROL MODEL

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**Introduction:** Hyperglycaemia is prevalent in critical care due to the stress of condition, even without a previous history of diabetes. Tight glycaemic control is associated with significantly improved patient outcomes. However, providing tight control is difficult due to evolving patient condition and interactions with common drug therapies resulting in recurring hyperglycaemic episodes. Model-based and model-derived tight control methods, such as the SPRINT system in Christchurch, have shown significant reductions in mortality. However, as computational capability and access improve, there are still avenues of further improvement to be made – if better models and/or methods were available. This research presents an updated control model, and its predictive virtual patient validation for use in real-time glycaemic control.

**Methods:** The model is based on prior work in this area by the authors' research group and defines a simple pharmacokinetic and pharmacodynamic system model:

$$\dot{G} = -p_G \cdot G - S_I \cdot G \cdot \frac{Q}{1+\alpha_G Q} + \frac{P(t) + EGP_{\max} - CNS}{V_G(t)} \quad (1)$$

$$\dot{Q} = -kQ + kI \quad (2)$$

$$\dot{I} = -\frac{nI}{1+\alpha_I I} + \frac{u_{ex}(t)}{V_I} + e^{-(k_I u_{ex}(t))} I_B \quad (3)$$

In the model, $G$ is the blood glucose level, $I$ is the plasma insulin, and $Q$ is the interstitial insulin. $EGP_{max}$ is the theoretical maximum endogenous glucose production for a patient under no presence of glucose or insulin. Endogenous glucose production ($EGP$) is suppressed with increasing $G$ and $Q$. Insulin independent glucose removal (excluding central nervous system uptake $CNS$) and the suppression of $EGP$ from $EGP_{max}$ with respect to $G$ are represented with $p_G$. In contrast, insulin mediated glucose removal and the suppression of $EGP$ from $EGP_{max}$ due to GLUT4 (which action is associated with the compounding effect of receptor-binding insulin and blood glucose) is represented with $S_I$.

Both $p_G$ and $S_I$ are time varying, with $p_G$ to a much lesser degree, reflecting evolving patient condition. Exogenous inputs are glucose appearance $P(t)$ and insulin administration $u_{ex}(t)$. All other associated parameters are physiologically defined transport rates ($n$, $\alpha_I$, $k$) or volumes ($V_G$, $V_I$). Overall, this model relates more directly to the specific physiology than prior models, which should offer better prediction and control in clinical application.

Virtual patients are created by fitting to retrospective data from 394 critical care patients (42,000 hours of data) at Christchurch Hospital under the SPRINT glycaemic control protocol. The model is prediction validated by fitting the model value of $S_I(t)$ to each intervention point (hourly) and then using it to predict the intervention blood glucose outcome. Performance is measured in absolute percentage error (APE) and compared to measurement error.

**Results:** Three main results emerged:

1. The model fit error with time-varying (hourly) $S_I(t)$ is 3-6% average APE
2. Prediction APE is within measurement error of 7-10% for over 93% of predictions
3. Prediction differences outside measurement error are due to outlying measurement errors or sensor failures.

**Discussion:** The new more physiologically based model is presented and validated on over 40,000 hours of clinical data. Validation includes both model fitting error, as well as more clinically relevant model prediction validation. The errors in both cases are within tolerable values for using the model in real-time glycaemic control or for designing newer or more advanced algorithms.

**Conclusion:** Model-based tight glycaemic control is primarily a function of model quality. A new, more physiologically relevant model is presented and validated. The results indicate its suitability for further use in control design and analysis in this area.