BLOOD GLUCOSE MODELLING AND CONTROL FOR PRE-TERM INFANTS

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Introduction: Hyperglycemia (high blood sugar levels) occurs in 40-80% of very low birth weight infants in the neonatal intensive care unit (NICU). This condition has been linked to mortality and morbidities including retinopathy of prematurity, osmotic diuresis, reduced immune system performance and sepsis. Insulin therapy can control hyperglycaemia and promote growth, but increases the risk of dangerous low levels of blood glucose.

The goal of this model is to provide a vehicle for real-time blood glucose control by accurately capturing the dynamic effect of insulin to provide dosing recommendations for attending clinicians. The model is used for two tasks: predict future blood glucose concentration for real-time control, and perform simulated trials to optimise control strategies.

Methods: The glucose regulatory system model is based upon a similar model employed successfully in adult intensive care, and modified to account for differing physiology in the neonate.

Insulin sensitivity is the driving parameter in the model. Stochastic modelling and time-series analysis methods provide confidence bands for blood glucose predictions. Retrospective data is used to generate patient-specific, time-varying insulin sensitivity profiles via integral-based parameter identification methods. The profiles are used to generate “virtual patients”, which are used to simulate patient responses to glucose and insulin inputs.

Results: Retrospective data for 25 episodes of insulin usage representing over 3,500 hours of patient data was used to validate the model in simulation. Median absolute prediction errors for the 25 virtual patients at 1 and 2 hour intervals were 5.8% and 9.9% respectively.

Stochastic modelling of the insulin sensitivity parameter averaged 59% of blood glucose predictions within the 0.98 mmol/L wide 25%-75% confidence range, and 91% of measurements within the 2.79 mmol/L wide 5%-95% confidence range.

Simulations using basic controllers over the 25 “virtual patients” resulted in 87% of hourly simulated measurements within the target 4-7 mmol/L band, compared to 31% for retrospective hospital control.

Mean blood glucose decreased 32% from 8.4 mmol/L to 5.7 mmol/L, and the standard deviation decreased 44% from 3.2 mmol/L to 1.8 mmol/L. Increased time in a target band and reduced standard deviation are robust measures of the tight control possible with model-based methods. Incorporating the stochastic model into simulated controllers resulted in a 17% decrease in simulated measurements below 4 mmol/L.

![Fig. 1: Blood glucose distribution for retrospective hospital control (left) and simulated model-based control (right).](image)

Discussion: Insulin sensitivity in the neonate was found to be higher than similar adult model due to higher metabolic clearance of insulin clearance and higher rates of glucose turnover. Endogenous glucose production may not be suppressed by exogenous glucose infusions in the neonate, exacerbating hyperglycaemia. Additionally, limited glycogen stores and low concentrations of enzymes for gluconeogenesis mark the importance of optimising glucose uptake.

Blood glucose control presents several challenges that are unique to this group of infants. Limited blood volume places restrictions on the frequency of blood glucose sampling achievable in practice. Virtual simulations allow testing of measurement frequency regimes in-silico and optimization during real-time control. Incorporating stochastic models provides extra assurance against hypoglycaemia.

Conclusions: Hyperglycaemia affects a large proportion of premature infants, and has been linked to worsened outcomes. A model that accurately captures the dynamics of neonatal metabolism can provide a vehicle for real-time blood glucose control and a platform to develop high-performance control algorithms in simulation. Reduced hyperglycaemia and tighter control in simulated results highlight the possibility for tight glucose control for improved outcomes in this fragile neonatal cohort. Clinical trials of this model are in progress.