STAR GRYPHON

Glycaemic Control for Neonatal Intensive Care Units

Performance and safety of STAR glycaemic control in the NICU : clinical results, including results from a new protocol implementation

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MŰEGYETEM 1782

A glycaemic control fairy tale?

The damsel in distress

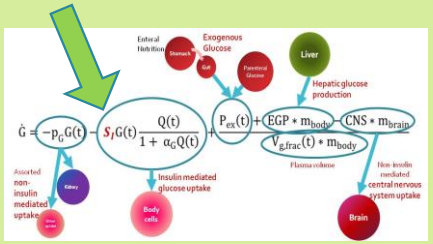
The evil Stepmother

Abnormal Blood sugar

The Hero

GRYPHON

The Noble Steed



SI: Insulin Sensitivity!

The Happy Ending

A STAR glycaemic control framework

The very premature infant: a damsel in distress

The damsel in distress

The damsel :

- Very premature infant (<31 weeks GA)
- Extremely premature infant (<28 weeks GA)

The distress (and there is a lot of it):

- Not fully developed
- High risk of:
  - sever infection (sepsis)
  - Brain haemorrhage
  - Retinopathy of prematurity
- High dependence on
  - Intensive care
  - Mechanical Ventilation
  - Intravenous nutrition

Abnormal blood sugar: the evil step mother

The evil Stepmother

Abnormal Blood sugar

Abnormal Blood Glucose:

- **Hyperglycaemia** (Elevated blood glucose concentrations)
- **Hypoglycaemia** (Low blood glucose concentrations)

Associated effects of hyperglycaemia in neonates

- Worsened outcomes
- Increased mortality
- Increased :
  - hospital length of stay
  - dependence on mechanical ventilation
- Increased risk of:
  - sepsis
  - brain haemorrhaging
  - retinopathy of prematurity

Abnormal blood sugar: the evil step mother

The evil Stepmother

Abnormal Blood sugar

Why is glycaemic control hard?

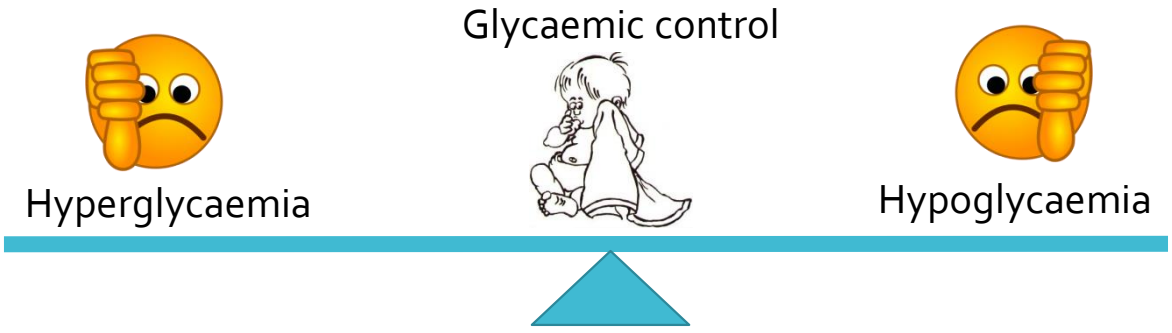
Hypoglycaemia (low blood sugar) is also dangerous

- Brain damage
- Developmental delays
- Higher mortality and morbidity

"Humans are horribly variable"

Variation in glycaemic metabolics:

- Over time
- Between patients



The Quest: GLYCAEMIC CONTROL

The evil Stepmother

Abnormal Blood sugar

Common treatments for hyperglycaemia:

Reduce Nutrition → at cost of weight gain and development

Use Insulin → at risk of driving blood sugar levels too low!

THE QUEST:

→ Dose insulin in a way that is safe and allows the infants nutritional needs to be met!

→ Personalised, predictive, and preventative medicine

-accounting for the differences between patients, and changing patient condition over time

The Hero: STAR-GRYPHON

The Hero

GRYPHON

Model-based glycaemic control protocol for intensive care patients

- → Glycaemic control: Targeting a blood glucose range of 4-8 mmol/L
- → Model-based: use mathematics to describe and predict glucose and insulin response to therapy
- → Interface: touch screen bedside tablet computer

STAR – Stochastic TARgeted glycaemic control:

Applications in

- →Adult intensive care
- →**GRYPHON**: specialized application for neonatal intensive care

(Glucose Regulation sYstem to Prevent Hyper- and hypO-glycaemia in Neonates)

Getting to know the HERO

The Hero

GRYPHON

The next few slides outline:

→ The basics of the physiological model

→ What insulin sensitivity is

→ How insulin sensitivity is used to predict changes in BG

Common abbreviations:

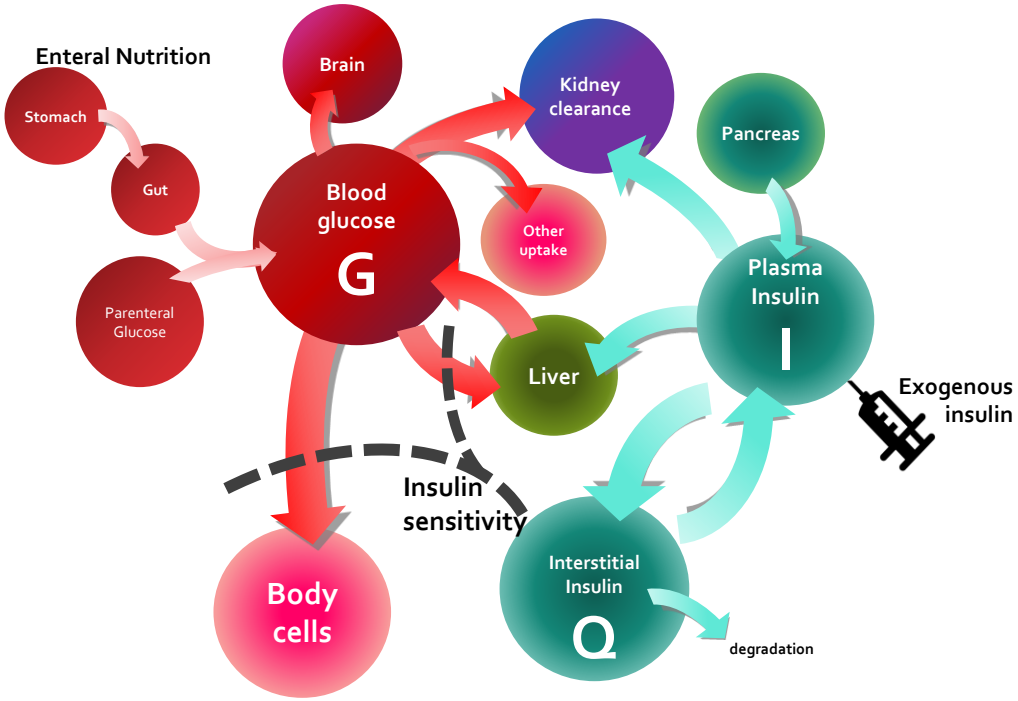
- BG: Blood Glucose concentration
- SI: insulin sensitivity

Not just a pretty face: The Physiological Model

Using mathematics to describe physiological changes in insulin and glucose

The Hero

GRYPHON



The Model – INSULIN

Model describes both peripheral and plasma insulin…..

The Hero

GRYPHON

PERIPHERAL INSULIN

$$\dot{Q} = n_I\big(I(t) - Q(t)\big) - n_C \frac{Q(t)}{1 + \alpha_G Q(t)}$$

degradation

Diffusion between plasma and periphery

PLASMA INSULIN

Exogenous insulin

Pancreas

Pancreatic Insulin Secretion

$$\dot{I} = -n_K I(t) - \frac{n_L I(t)}{1 + \alpha_I I(t)} - n_I\big(I(t) - Q(t)\big) + \frac{u_{ex}(t)}{V_{I,frac} * m_{body}} + \big(1 - x_L\big) u_{en}$$

Kidney clearance

Kidney

Liver clearance

Liver

First pass hepatic extraction

The Model – BLOOD GLUCOSE

The Hero

GRYPHON

Insulin sensitivity!

Exogenous Glucose

Enteral Nutrition

Stomach

Gut

Parenteral Glucose

Liver

Hepatic glucose production

$$\dot{G} = -p_G G(t) - S_I G(t) \frac{Q(t)}{1 + \alpha_G Q(t)} + \frac{P_{ex}(t) + EGP * m_{body} - CNS * m_{brain}}{V_{g,frac}(t) * m_{body}}$$

Plasma volume

Assorted **non-insulin mediated uptake**

Kidney

Other uptake

Insulin mediated glucose uptake

Body cells

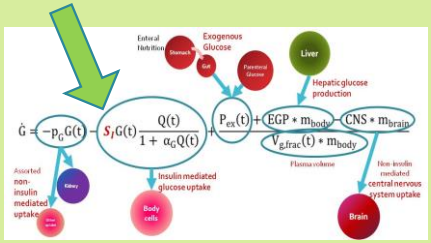
Non-insulin mediated **central nervous system uptake**

Brain

The Noble Steed: INSULIN SENSITIVITY

S_I

The
Noble Steed



SI: Insulin Sensitivity!

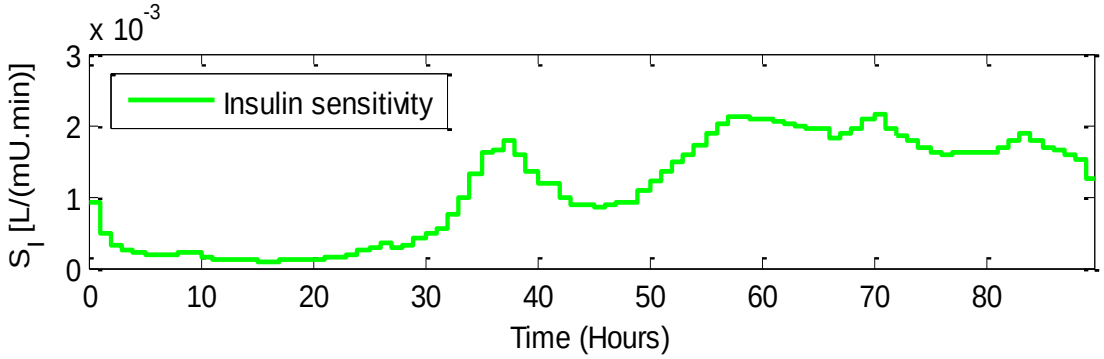
"Whole-body" insulin sensitivity

Fitted from clinical data - hour to hour

→ **Varies over time and between patients**

Captures the bodies overall blood glucose response to nutrition and insulin treatments

→ **Treatment independent**

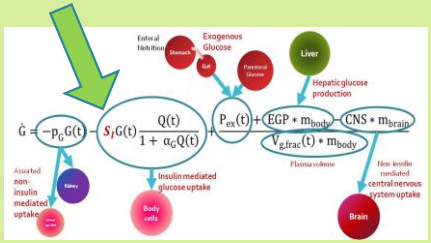


SI profile from recent Christchurch NICU patient

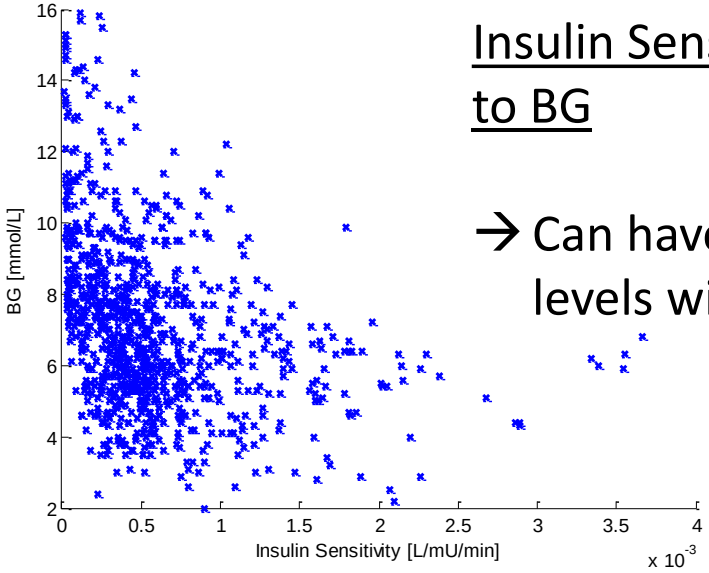
The Noble Steed: INSULIN SENSITIVITY

S_I

The Noble Steed



SI: Insulin Sensitivity!



<u>Insulin Sensitivity is NOT proportional to BG</u>

→ Can have **same SI** and **different BG** levels within and between patients

Insulin sensitivity describes r**esponsiveness to insulin**

Typically:

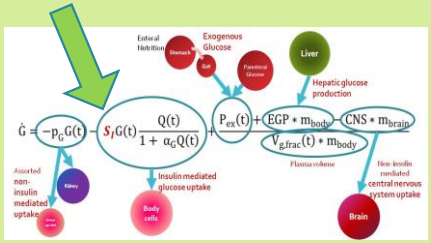
SI ↑ - BG ↓ SI ↓ - BG ↑

→ **Therefore it is safer to dose insulin based on BG and SI, than on BG alone**

INSULIN SENSITIVITY - Forecasting

S_I

The Noble Steed

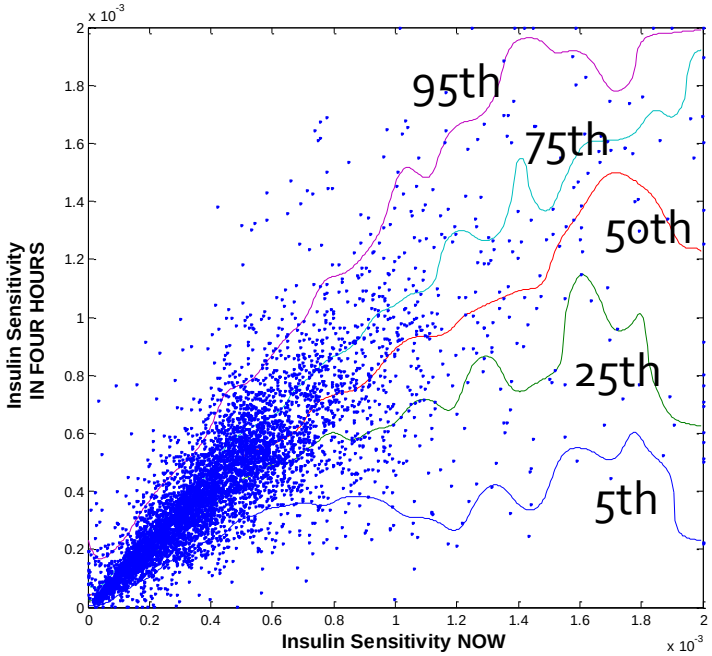


SI: Insulin Sensitivity!

Use population data to forecast

→Insulin sensitivity can change hour to hour

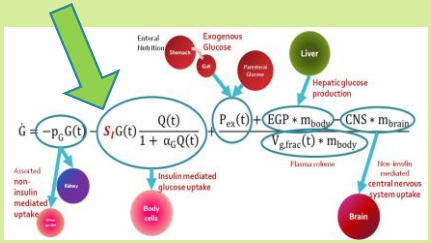
→ Median likely outcome being approximately no change



INSULIN SENSITIVITY - Forecasting

S_I

The Noble Steed

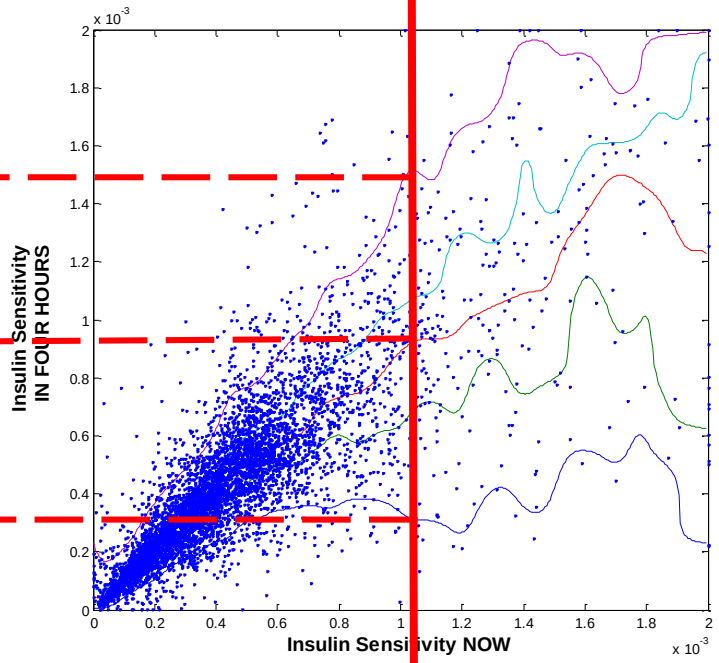


SI: Insulin Sensitivity!

95th SI

50th

5th SI



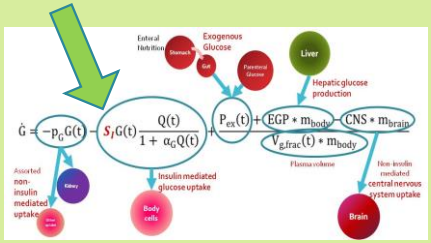
SI NOW

The 95th percentile of SI in particular is useful for quantifying risk of increase in sensitivity

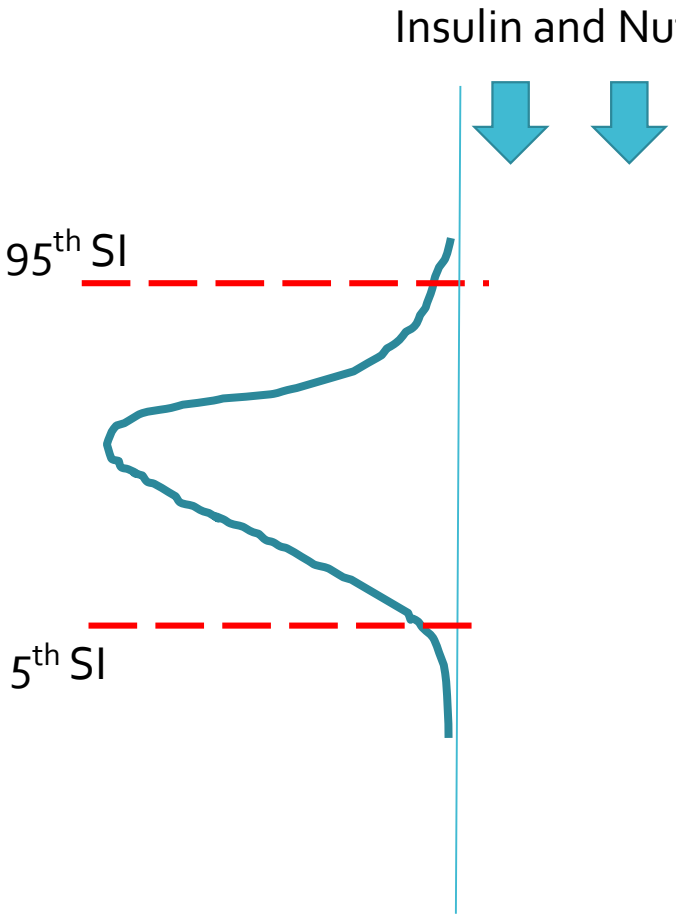
INSULIN SENSITIVITY - Forecasting

S_I

The Noble Steed



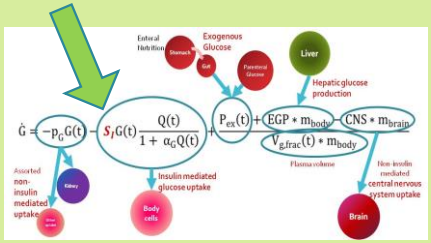
SI: Insulin Sensitivity!



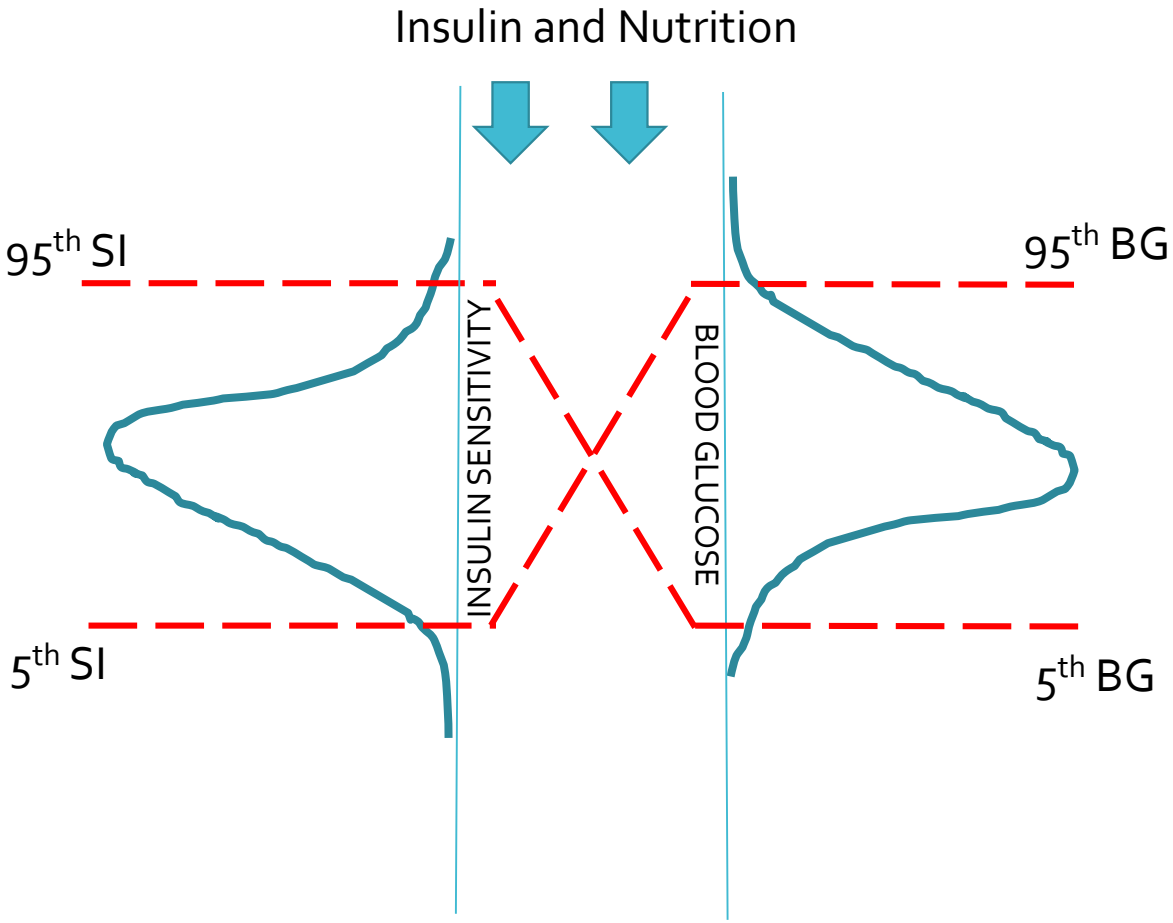
INSULIN SENSITIVITY - Forecasting

S_I

The Noble Steed



SI: Insulin Sensitivity!



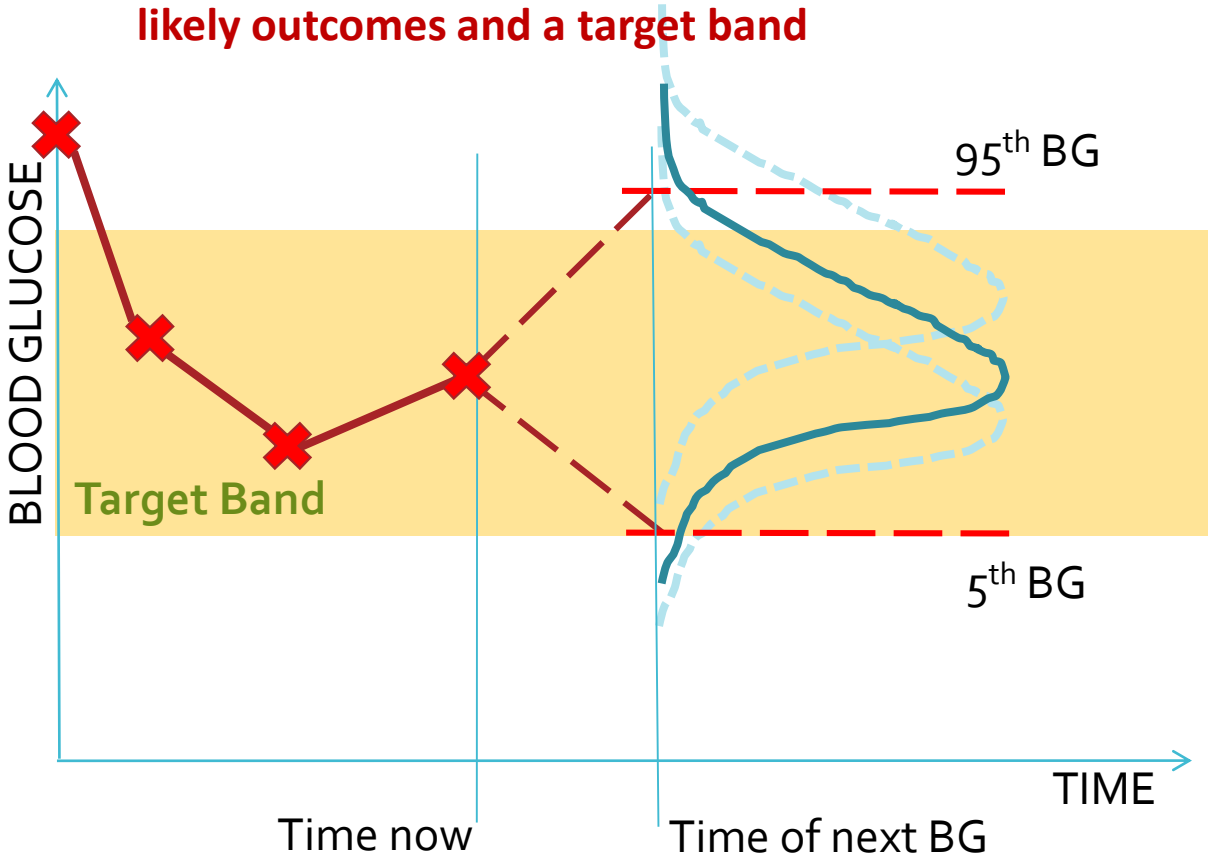
Using the 95th percentile of SI we can calculate the 5th percentile of BG for a given treatment

INSULIN SENSITIVITY – Selecting Treatments

The Hero

GRYPHON

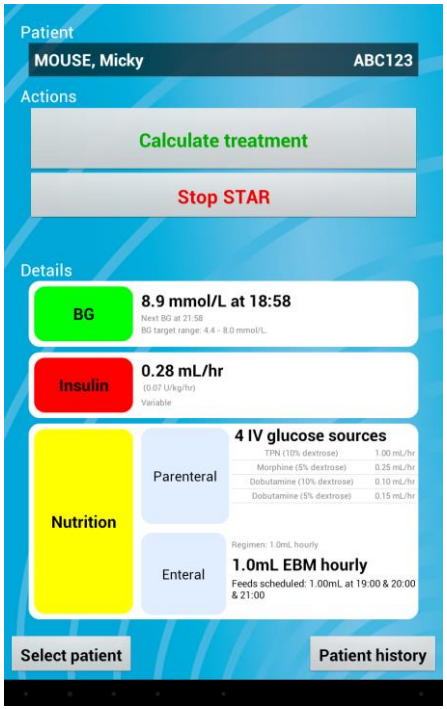
Thus we can directly quantify risk of hypo glycaemia *and* select a treatment that manages this risk and maximizes the overlap between likely outcomes and a target band

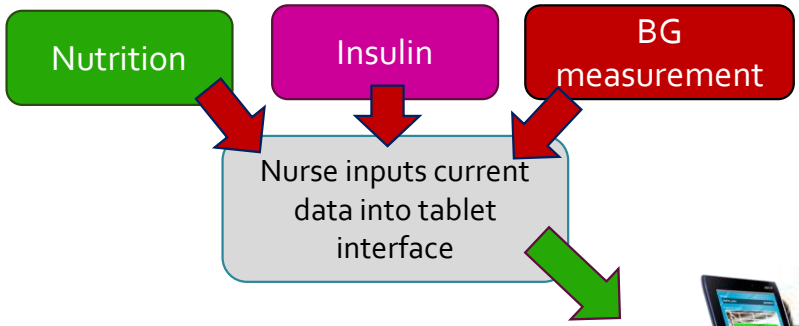


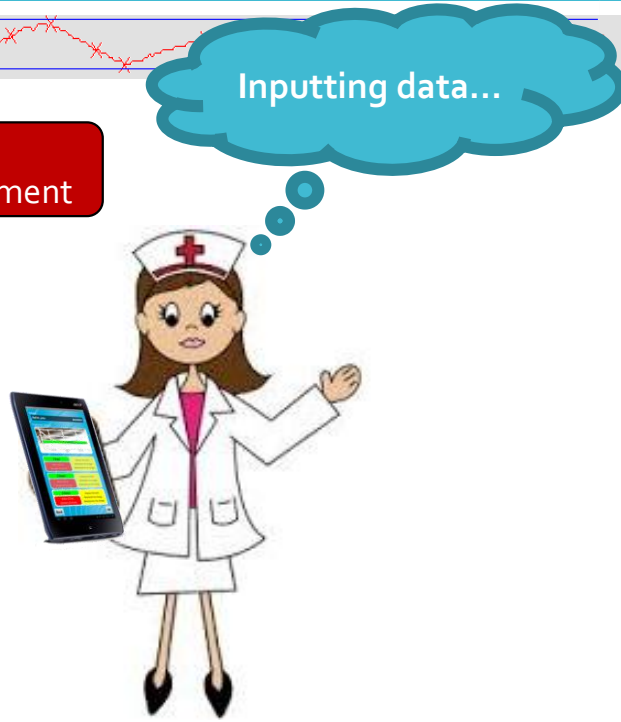
How do we use GRYPHON clinically?

The Hero

GRYPHON







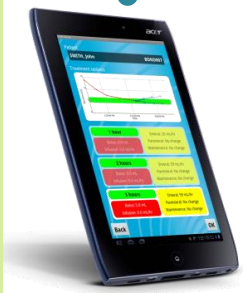
- **Tablet computer** interface
- Interface designed for clarity and ease of use
- Minimal data entry

How do we use GRYPHON clinically?

Calculating …

The Hero

GRYPHON



Nutrition

Insulin

BG measurement

Nurse inputs current data into tablet interface

Work out how sensitive to insulin the patient is

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

$$\dot{I} = -\frac{n_L I(t)}{1+\alpha_I I(t)} - n_K I(t) - n_I(I(t) - Q(t)) + \frac{u_{ex}(t)}{V_{I,frac} * m_{body}} + (1 - x_L)\frac{u_{en}}{V_{I,frac} * m_{body}}$$

$$\dot{Q} = n_I(I(t) - Q(t)) - n_C\frac{Q(t)}{1+\alpha_G Q(t)}$$

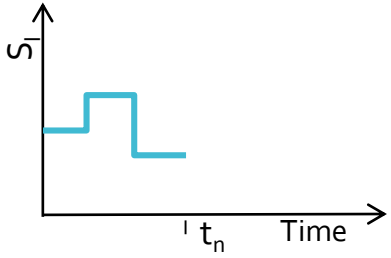
$$\dot{P}_1 = -d_1 P_1 + P(t)$$

$$\dot{P}_2 = -\min(d_2 P_2, P_{max}) + d_1 P_1$$

$$P(t) = \min(d_2 P_2, P_{max}) + PN(t)$$

$$u_{en} = I_B e^{\frac{-x_L u_{ex}}{V_I}}$$

MODEL



For each treatment **insulin sensitivity over the last few hours is calculated** based on BG response to nutrition and insulin inputs

How do we use GRYPHON clinically?

Calculating more stuff…

The Hero

GRYPHON

Nutrition

Insulin

BG measurement

Nurse inputs current data into tablet interface

Work out how sensitive to insulin the patient is

Predict how that sensitivity is going to change over the next few hours

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

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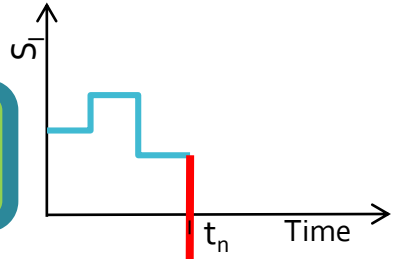
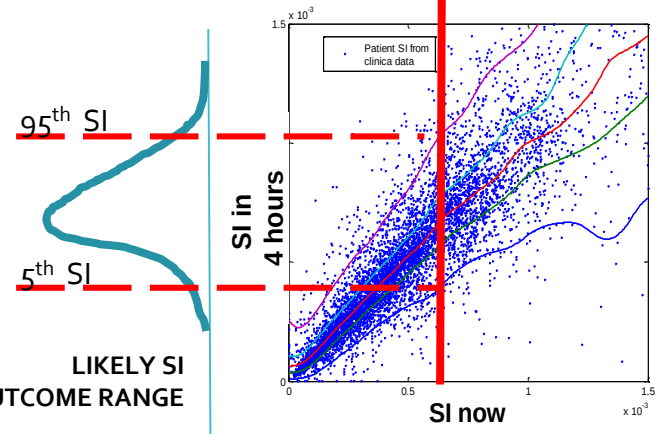
$$P(t) = \min(d_2 P_2, P_{max}) + PN(t)$$

$$u_{en} = I_B e^{\frac{-x_L u_{ex}}{V_I}}$$

MODEL



Statistical forecasts a **range of likely insulin sensitivity changes**



How do we use GRYPHON clinically?

Still calculating …

The Hero

GRYPHON

Nutrition

Insulin

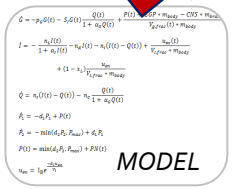
BG measurement

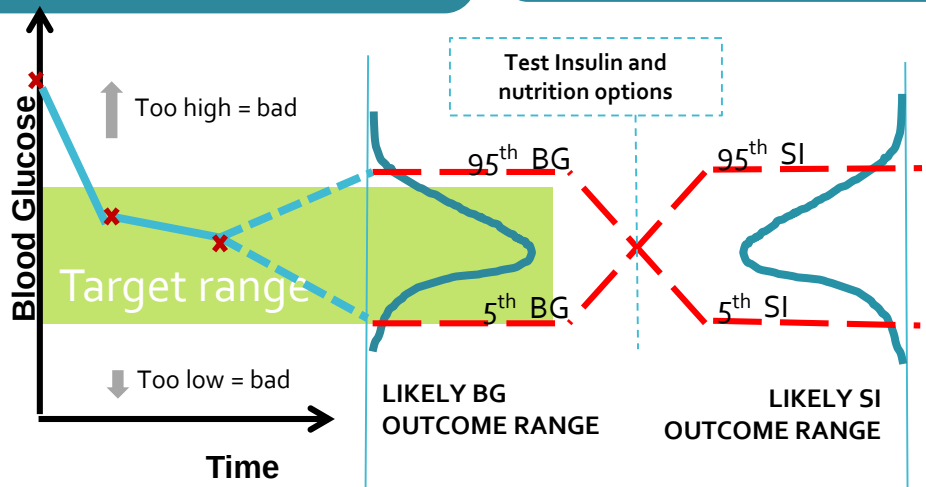
Nurse inputs current data into tablet interface

Work out how sensitive to insulin the patient is

Predict how that sensitivity is going to change over the next few hours

Predicted changes in SI used to guide the **CONTROL PROTOCOL** to select an optimum insulin treatment





Predicted changes in Insulin Sensitivity are used to **choose an insulin treatment** such that **95% of BG outcomes are** likely to be **greater than a lower target**

How do we use GRYPHON clinically?

The Hero

GRYPHON

Nutrition

Insulin

BG measurement

Nurse inputs current data into tablet interface

Work out how sensitive to insulin the patient is

Predict how that sensitivity is going to change over the next few hours

Predicted changes in SI used to guide the **CONTROL PROTOCOL** to select an optimum insulin treatment

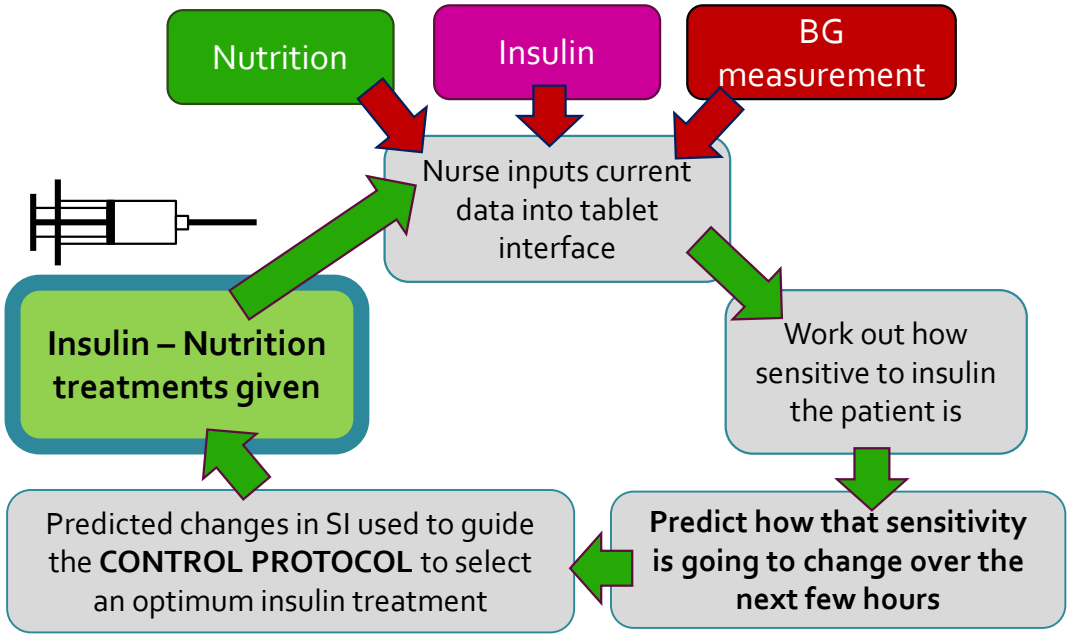
Now I make recommendations

Reviewing treatments

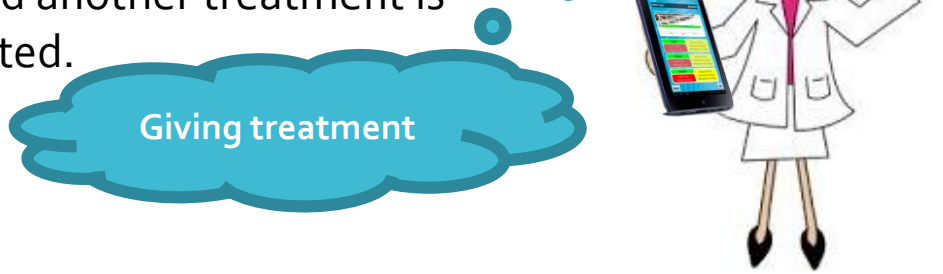
How do we use GRYPHON clinically?

The Hero

GRYPHON



Treatments are given.
After a chosen measurement interval, another BG measurement is taken, and another treatment is calculated.



Christchurch Women's Hospital, NICU

Starting Criteria:

- 2 sequential BG greater than 10 mmol/L

BG measures

- Measures BG approximately every 4 hours
- Max time between measurements while on STAR is 6 hours
- Blood drawn from umbilical arterial line or heel prick
- Blood glucose is measured using blood gas

Christchurch Women's Hospital, NICU

Nutrition

- Is clinically determined and not modified by STAR
- Predominantly TPN, some medications are combined with a 5% Dextrose solution
- Start EBM (Expressed Breast Milk) as soon as it is available at a rate of 0.5mL every 4 hours

Insulin

- Shares a IV line with main dextrose fluids
- Insulin typically totals 1-5mL/day and is not considered in fluid targets

Christchurch Women's Hospital, NICU

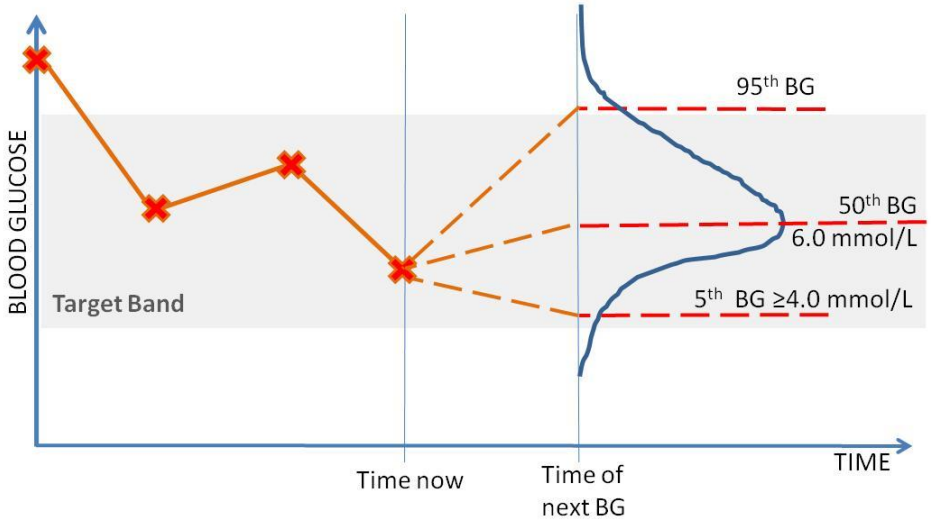
STAR-NICU
Initial protocol implementation

STAR-GRYPHON
Optimised protocol

August 2008 — August 2010 — January 2013 — Present

STAR used as a standard of care

STAR GRYPHON: optimizing the framework



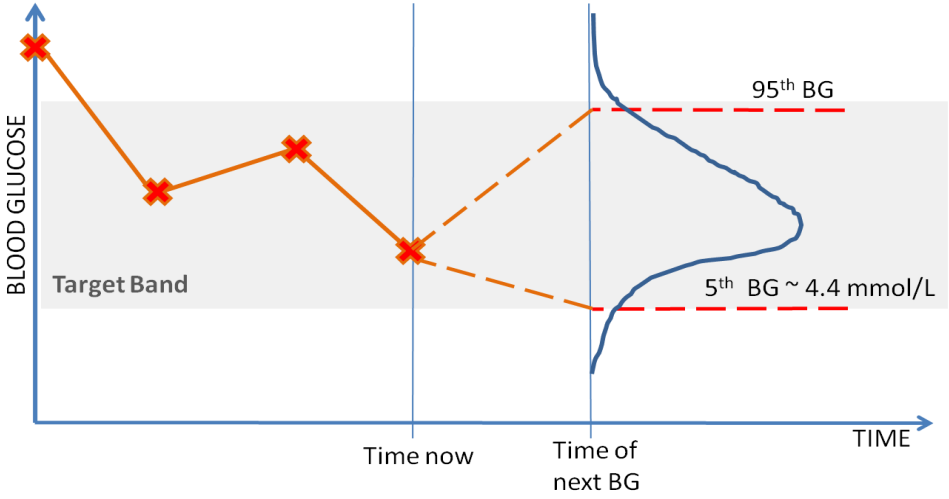
First Implementation: STAR-NICU

- Target median to 6.0 mmol/L, with checks on the lower 5th
- Pilot trials
- Implemented as a standard of care

Optimised protocol:

STAR-GRYPHON

- Target 5th percentile of BG to ~4.4 mmol/L
- Maximum overlap of outcomes with target range



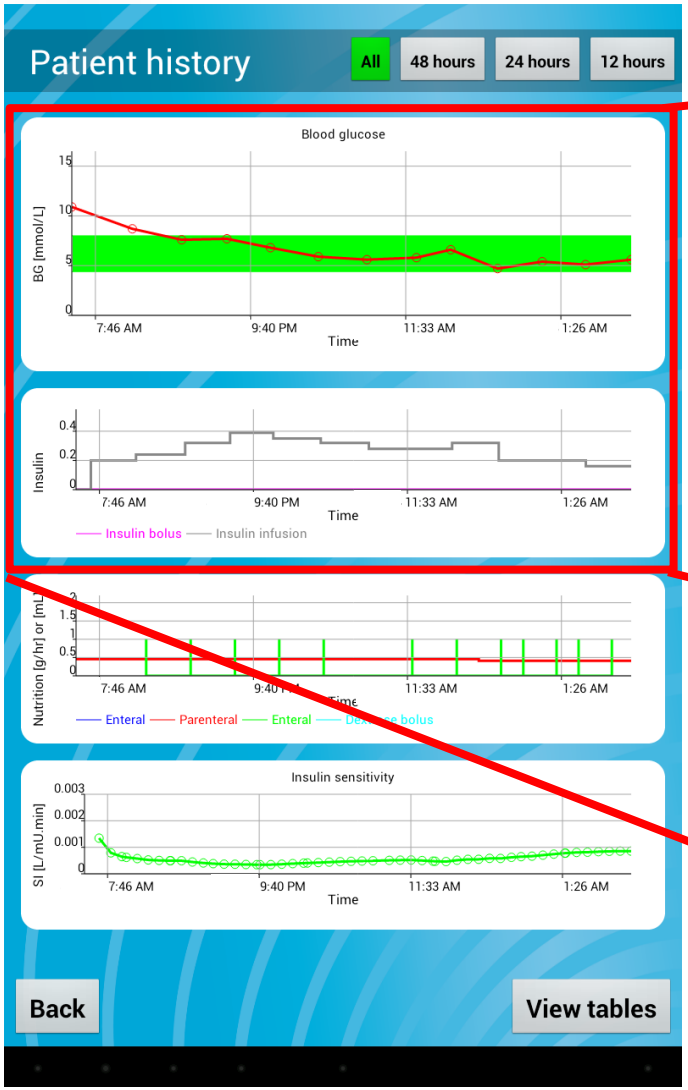
Christchurch – Clinical Results

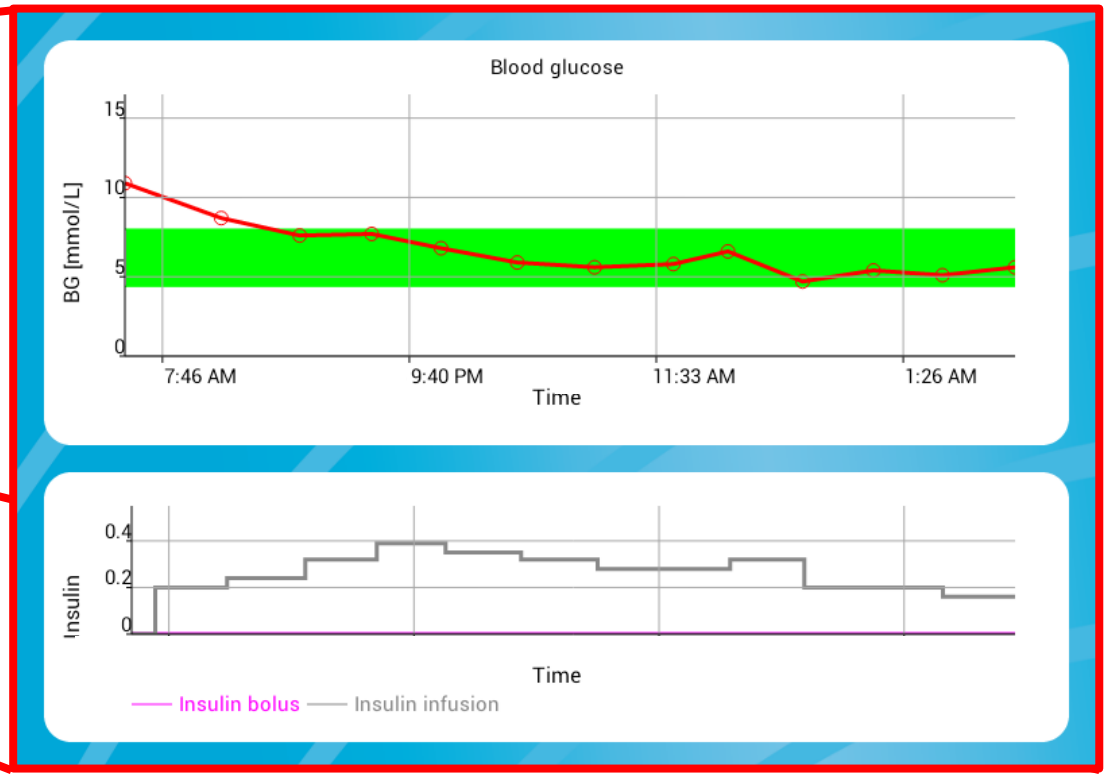
The Happy Ending

	CCH - Retrospective	CCH – STAR NICU	CCH – STAR GRYPHON
Num episodes	25	61	14
Total hours	3098 s	5104	965
Measurement Interval (hrs)	3.2 [2.7 - 3.8]	3.2 [2.6 - 3.9]	4.0 [3.9 - 4.1]
Median insulin rate [IQR] (U/kg/hr)	0.031 [0.015 - 0.060]	0.044 [0.017 - 0.080]	0.05 [0.04 - 0.07]
Median Glucose rate [IQR] (mg/kg/hr)	8.1 [5.7 - 9.7]	7.4 [5.2 - 8.6]	7.6 [7.1 - 8.4]
Median BG [IQR] (mmol/L)	7.8 [6.5 - 9.1]	6.6 [5.5 - 8.1]	6.9 [6.1 - 7.7]
% BG within 4.0 - 8.0 mmol/L	51.9	69. 8	80
% BG > 10 mmol/L	16.3	10.0	3.8
% BG < 4.0 mmol/L	2.1	3. 5	0.1
% BG < 2.6 mmol/L	0.1	0.2	0
Num patients < 2.6 mmol/L	1	8	0

Christchurch – now receiving **better control with fewer BG measurements**
Low rates of hypoglycaemia – severe hypos of BG<2.0 mmol/L are never seen

Christchurch –our most recent patient…





Christchurch – Clinical Results

The Happy Ending

	STAR-NICU	STAR-GRYPHON	NIRTURE Beardsall et al	HINT Alsweiler et al	Comparing birth weights Ng et al
			Early insulin	Tight control	ELBW vs. LBW
Median BG [IQR]	6.6 [5.5- 8.2]	6.9 [6.1 - 7.7]	6.2±1.4	5.8 [4.8-6.7]	12 [6-24] and 11 [7-19]
% patients < 2.6 mmol/L	13%	0%	29%	58%	11-15%

→Comparison difficult due to

- Differing definitions of hyper glycaemia
- Differing protocols and targets

However, **GRYPHON shows less hypoglycaemia than other studies, and tighter BG around the median**

Christchurch – Clinical Results

The Happy Ending

Better control → Improved outcomes and survival rates

→ Healthier patients → Happier doctors & parents!

A glycaemic control fairy tale?

The damsel in distress

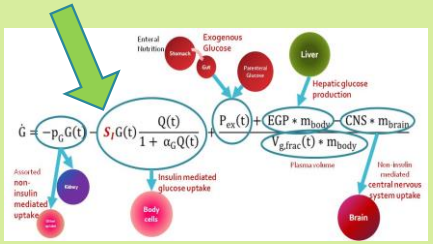
The evil Stepmother

Abnormal Blood sugar

The Hero

GRYPHON

The Noble Steed



SI: Insulin Sensitivity!

The Happy Ending

A STAR glycaemic control framework

Acknowledgements: The cast of extras

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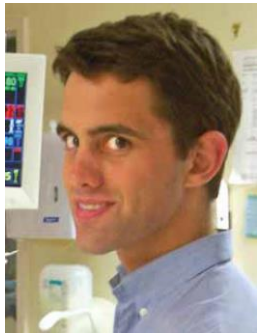

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Dr Chris Pretty

UC BIOMEDICAL ENGINEERING

The UC BioEng Crew

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Any Questions?