STAR GRYPHON

Glycaemic Control for Neonatal Intensive Care Units

UC BIOMEDICAL ENGINEERING

UC UNIVERSITY OF CANTERBURY
Te Whare Wānanga o Waitaha
CHRISTCHURCH NEW ZEALAND

UNIVERSITY of OTAGO
Te Whare Wānanga o Otāgo

Canterbury District Health Board
Te Poari Hauora ō Waitaha

MŰEGYETEM 1782

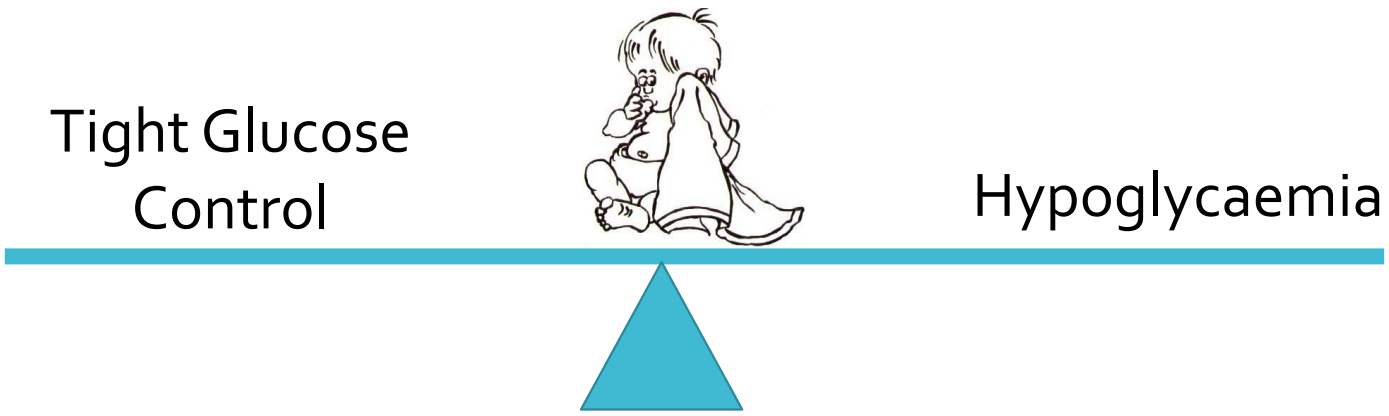
What is STAR?

Model based glycaemic control for intensive care patients

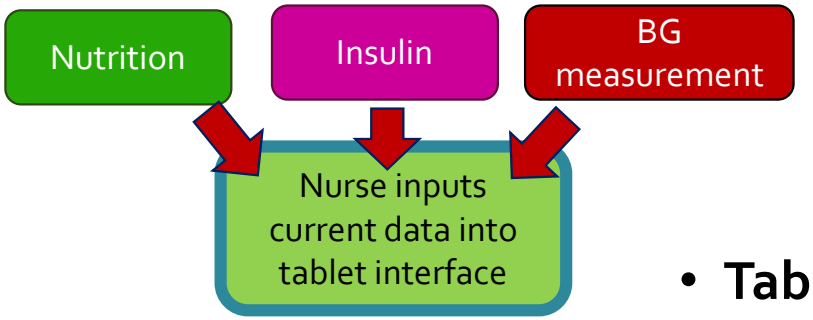
→ Glycaemic control: Targeting a blood glucose range of 4-8 mmol/L

→ Model based: use mathematics to describe and predict glucose and insulin response to therapy

→ STAR-GRYPHON: Specifically designed for the NICU environment

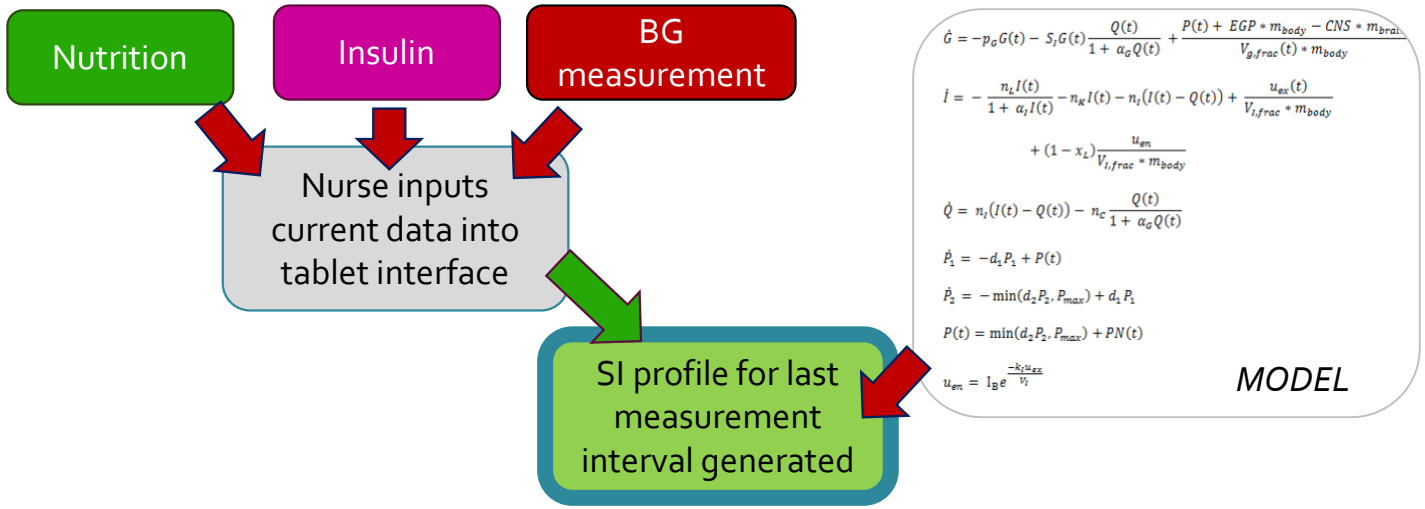


How does STAR work?



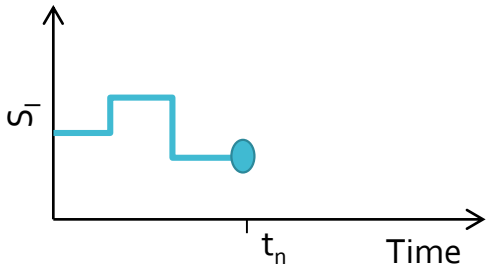
- **Tablet computer** interface
- Interface designed for clarity and ease of use
- Minimal data entry

How does STAR work?



Model based **Insulin Sensitivity** describes response to insulin

For each treatment **a SI profile from the last few hours is calculated** based on BG response to nutrition and insulin inputs



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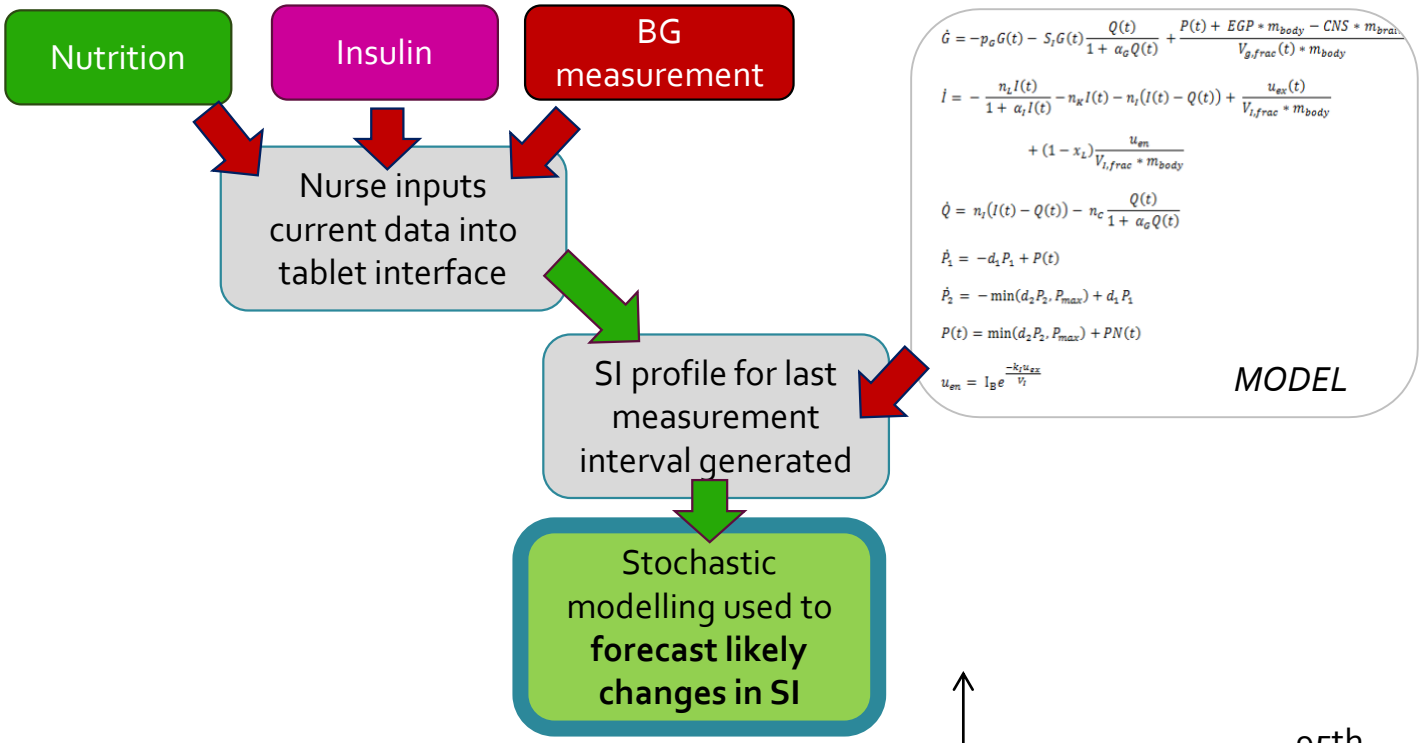
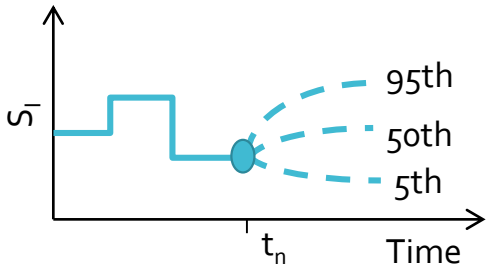


Statistical modelling utilizing population data is used to determine a **range of likely insulin sensitivity changes**



How does STAR work?

Nutrition

Insulin

BG measurement

Nurse inputs current data into tablet interface

SI profile for last measurement interval generated

Stochastic modelling used to forecast likely changes in SI

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

$$\dot{G} = -p_G G(t) - S_I G(t)\frac{Q(t)}{1+\alpha_G Q(t)} + \frac{P(t)+\dots}{\dots}$$

$$\dot{I} = -\frac{n_L I(t)}{1+\alpha_I I(t)} - n_K I(t) - n_I(I(t)-Q(t)) + \dots$$

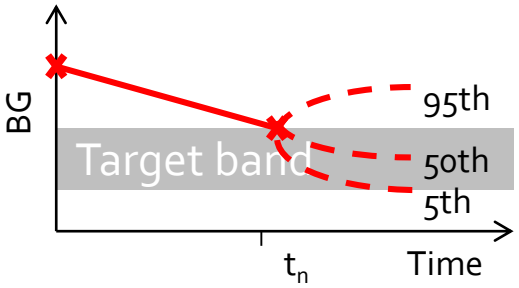
$$+ (1-x_L)\frac{u_{en}}{V_{I,frac} * m_{body}}$$

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

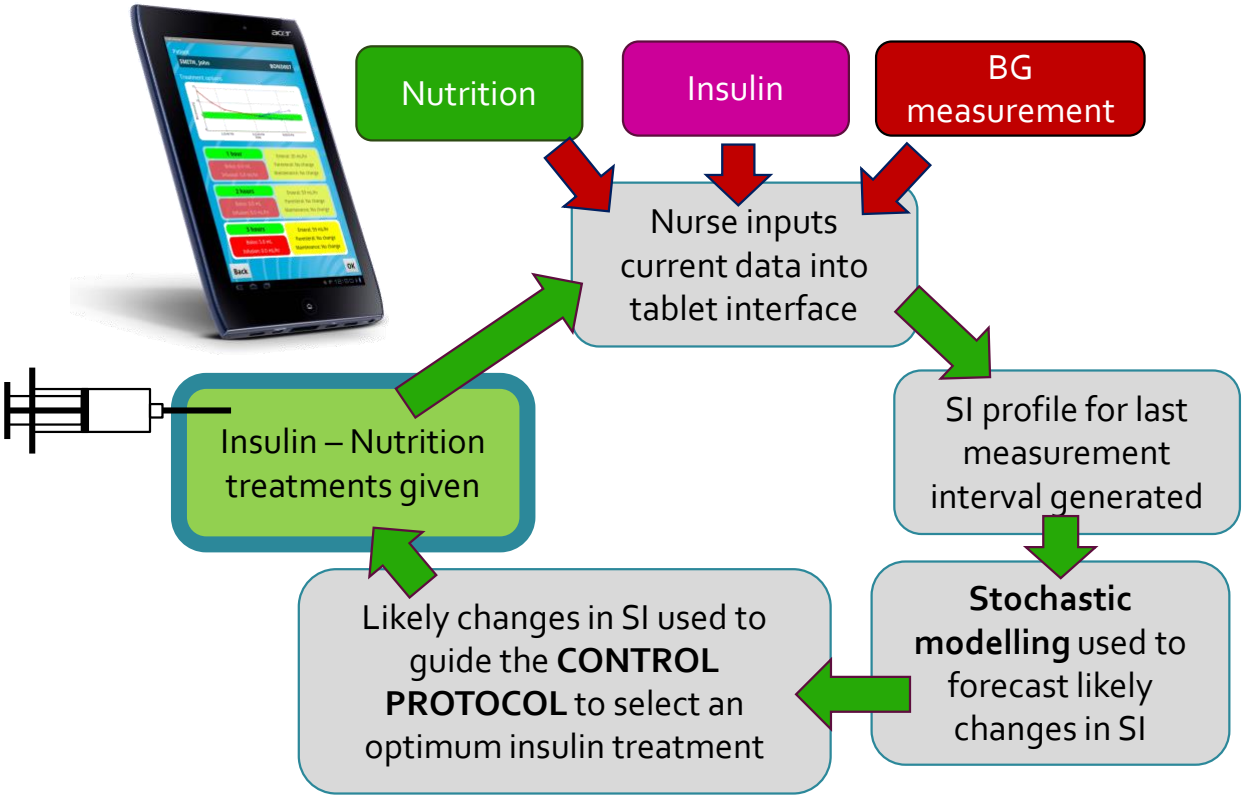
$$\dot{P}_1 = -d_1 P_1 + P(t)$$

MODEL

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 does STAR work?



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

How does STAR work?

Clinical actions

Nutrition

Insulin

BG measurement

Nurse inputs current data into tablet interface

SI profile for last measurement interval generated

$$\dot{G} = -p_G G(t) - S_I G(t)\frac{Q(t)}{1 + \alpha_G Q(t)} + \frac{P(t) + \cdots}{\cdots}$$

$$\dot{I} = -\frac{n_L I(t)}{1 + \alpha_I I(t)} - n_K I(t) - n_I(I(t) - Q(t)) + \cdots$$

$$+ (1 - x_L)\frac{u_{en}}{V_{I,frac} * m_{body}}$$

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

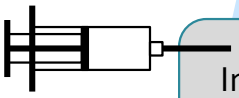
$$\dot{P}_1 = -d_1 P_1 + P(t)$$

MODEL

Stochastic modelling used to forecast likely changes in SI

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

Insulin – Nutrition treatments given



$$\dot{G} = -p_G G(t) - S_I G(t)\frac{Q(t)}{1 + \alpha_G Q(t)} + \frac{P(t) + \cdots}{\cdots}$$

$$\dot{I} = -\frac{n_L I(t)}{1 + \alpha_I I(t)} - n_K I(t) - n_I(I(t) - Q(t)) + \cdots$$

$$+ (1 - x_L)\frac{u_{en}}{V_{I,frac} * m_{body}}$$

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

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

MODEL

Under the tablet "hood"

Under the hood

The next few slides outline:

→ The basics of the physiological model

→ What insulin sensitivity is

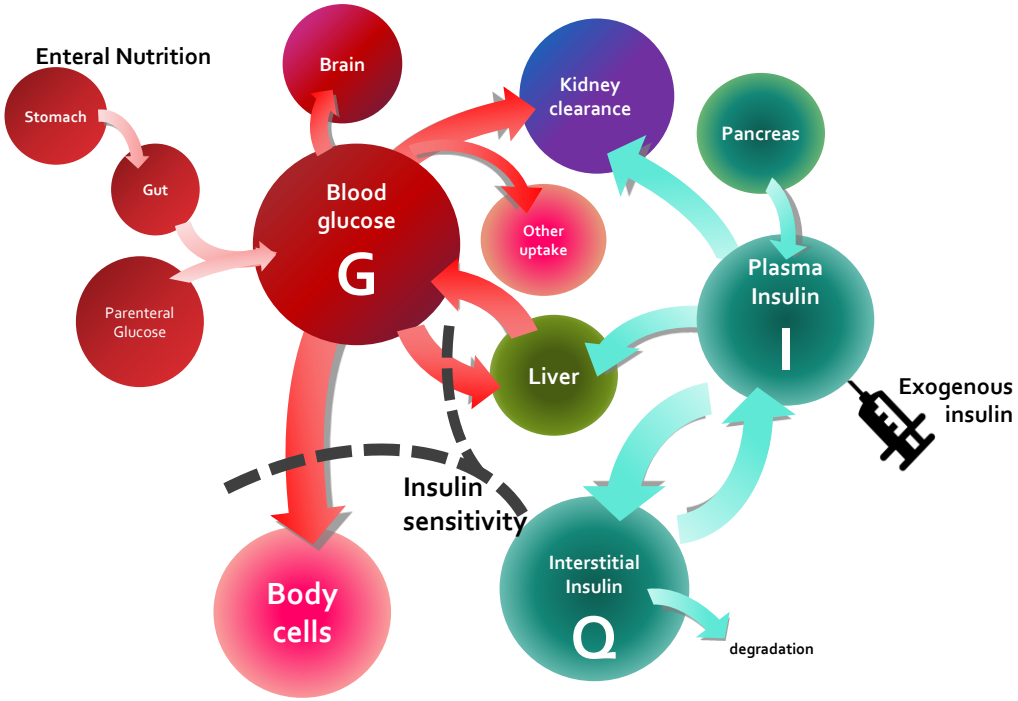
→ How insulin sensitivity is used to predict changes in BG

Common abbreviations:

- BG: Blood Glucose concentration
- SI: insulin sensitivity

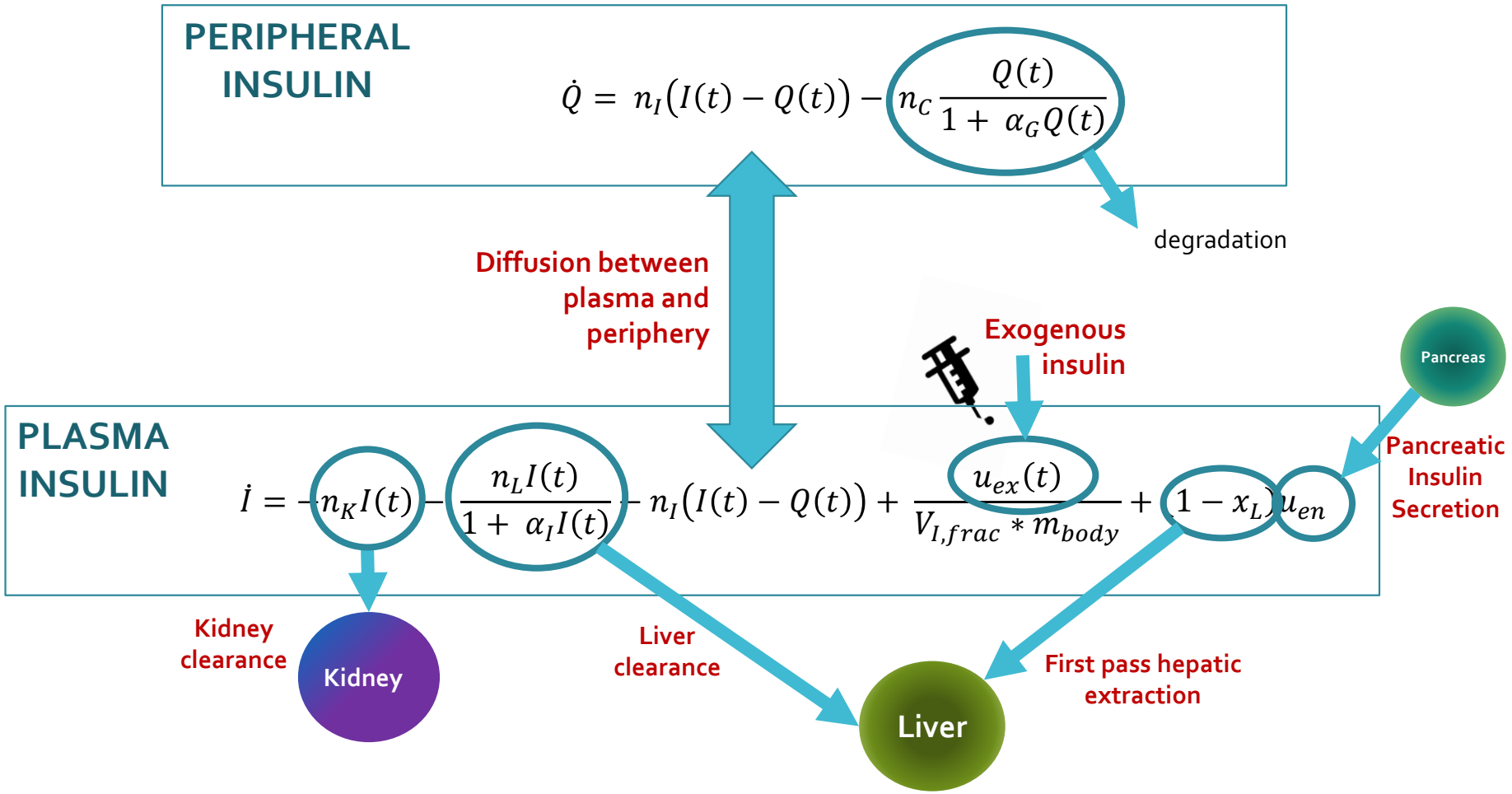
The Physiological Model

Using mathematics to describe physiological changes in insulin and glucose



The Model – INSULIN

Model describes both peripheral and plasma insulin…..



The Model – BLOOD GLUCOSE

Insulin sensitivity!

Enteral Nutrition

Stomach

Exogenous Glucose

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

INSULIN SENSITIVITY

S_I

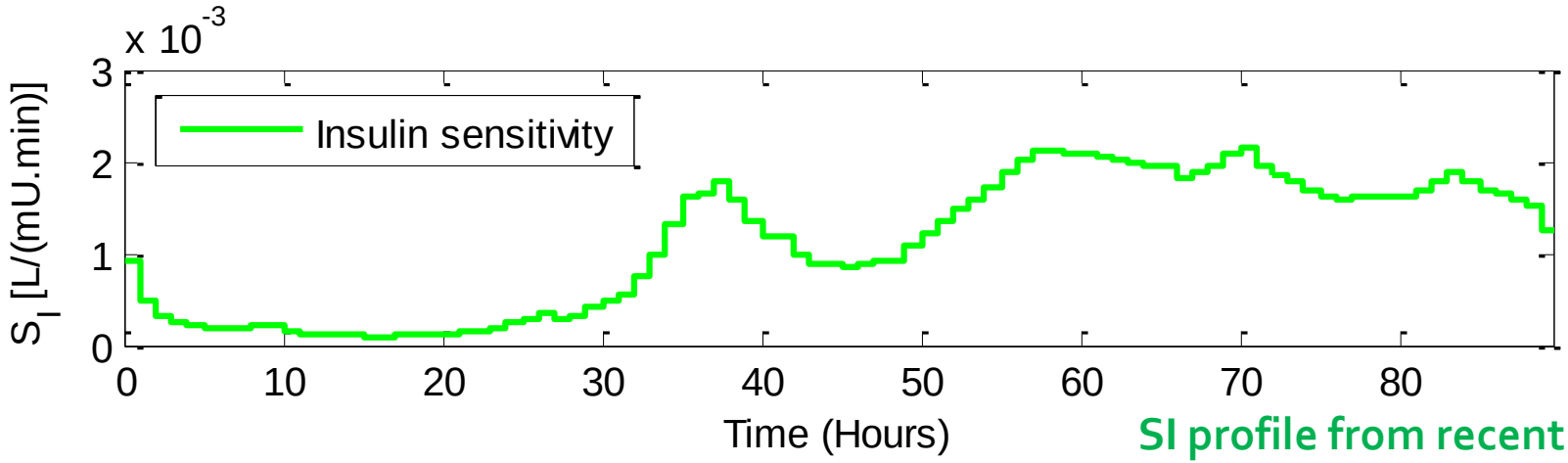
"Whole-body" insulin sensitivity

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

INSULIN SENSITIVITY

S_I

Captures overall metabolic balance, including the relative net effect of :

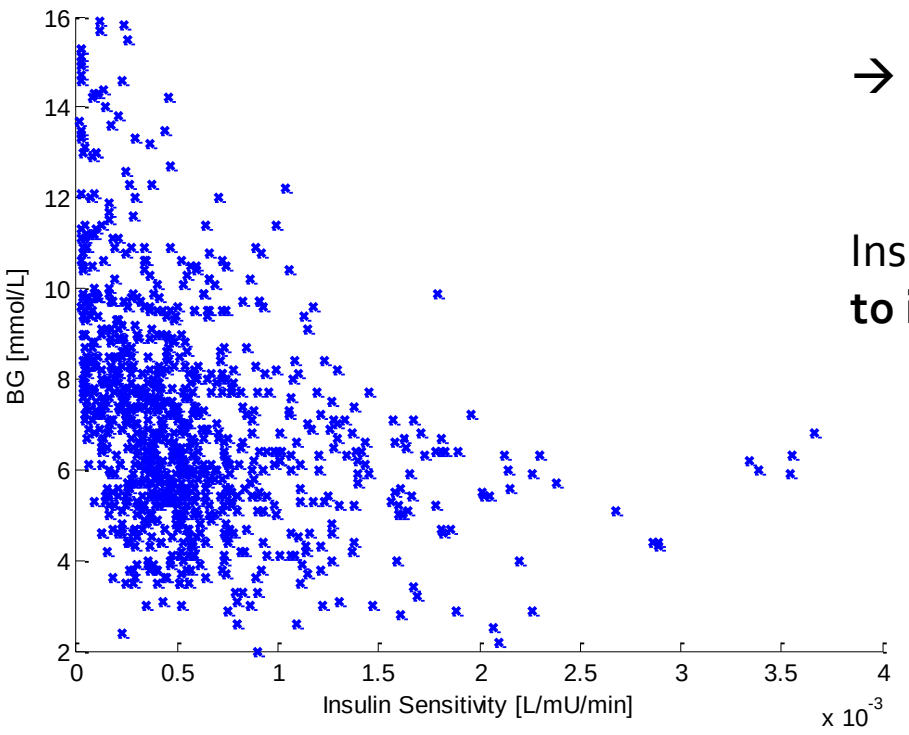
→ **Peripheral Insulin Sensitivity**

→ Patient-specific deviations from models of

- **Endogenous glucose production**
- **Peripheral and hepatic insulin mediated glucose uptake**
- **Endogenous insulin secretion**

SI captures **changes in patient behavior** and makes the system **robust** to deviations from modelled metabolics

INSULIN SENSITIVITY



Insulin Sensitivity is NOT proportional to BG

→ 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**

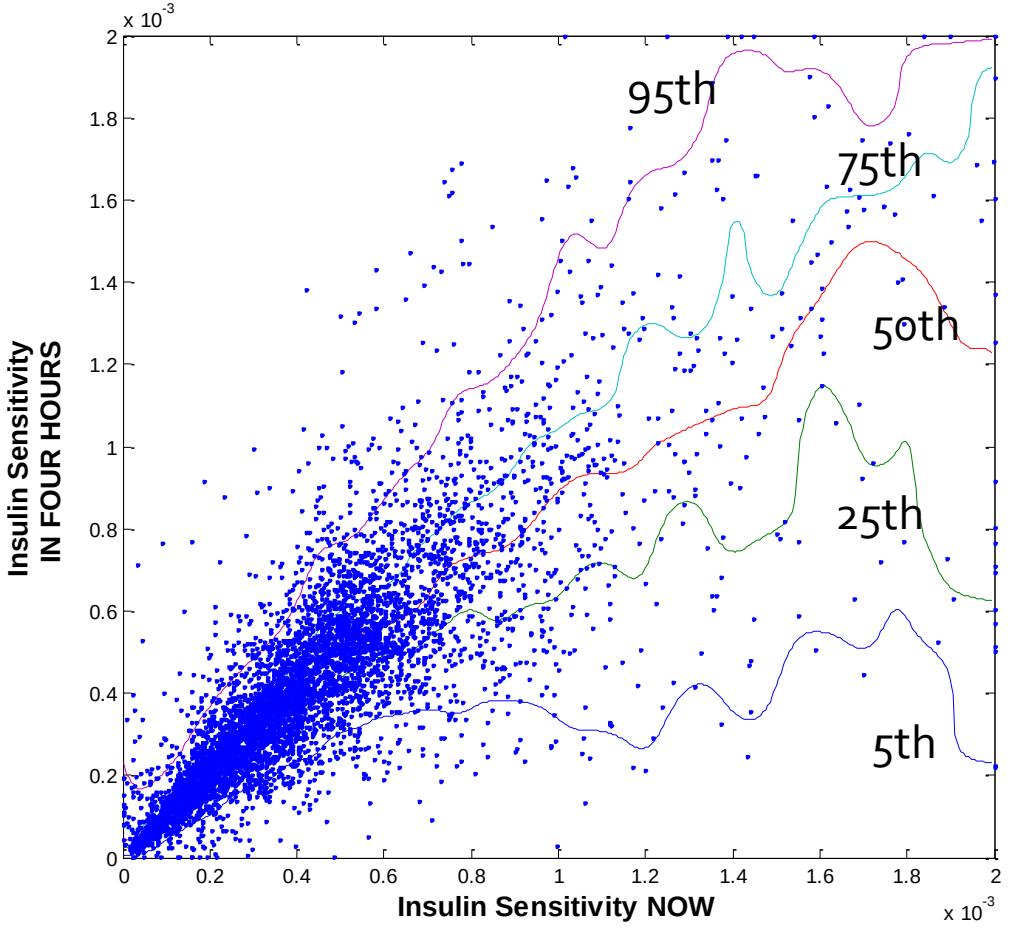
INSULIN SENSITIVITY - Forecasting

S_I

Use population data to forecast

→ Insulin sensitivity can change hour to hour

→ Median likely outcome being roughly no change



INSULIN SENSITIVITY - Forecasting

S_I

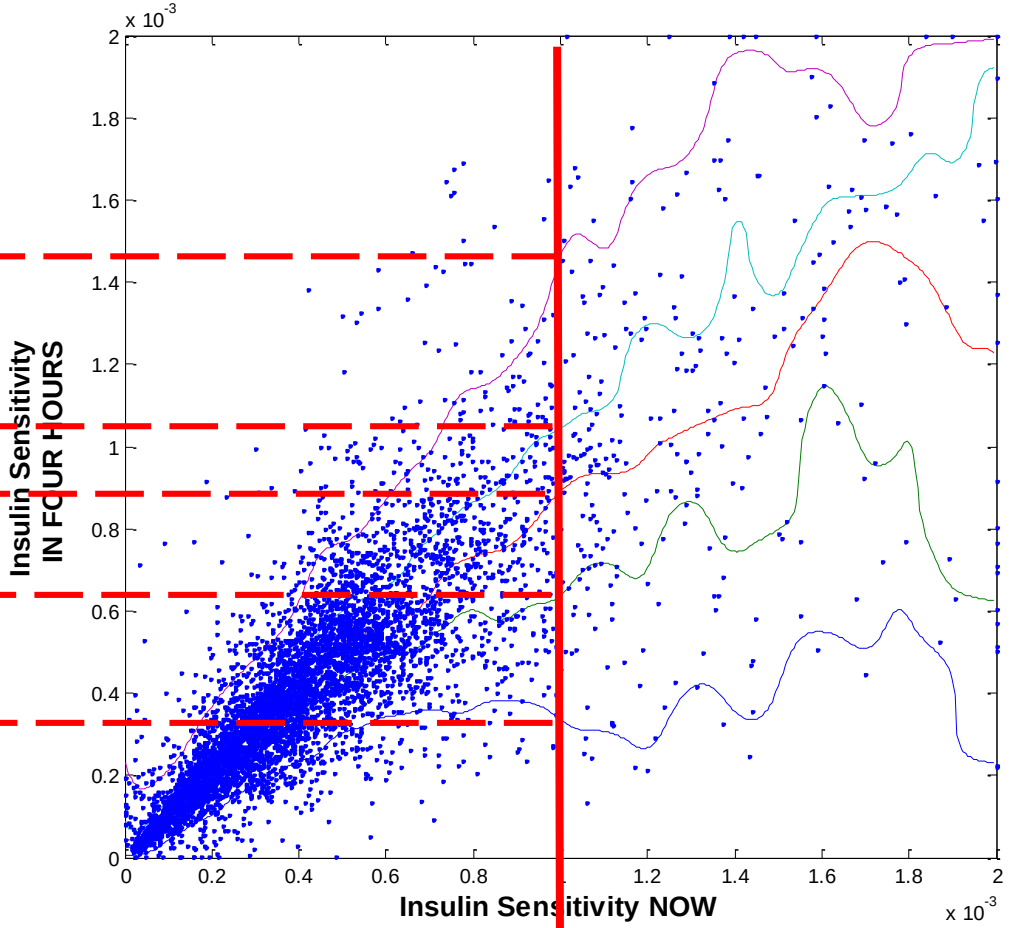
95th SI

75th

50th

25th

5th SI

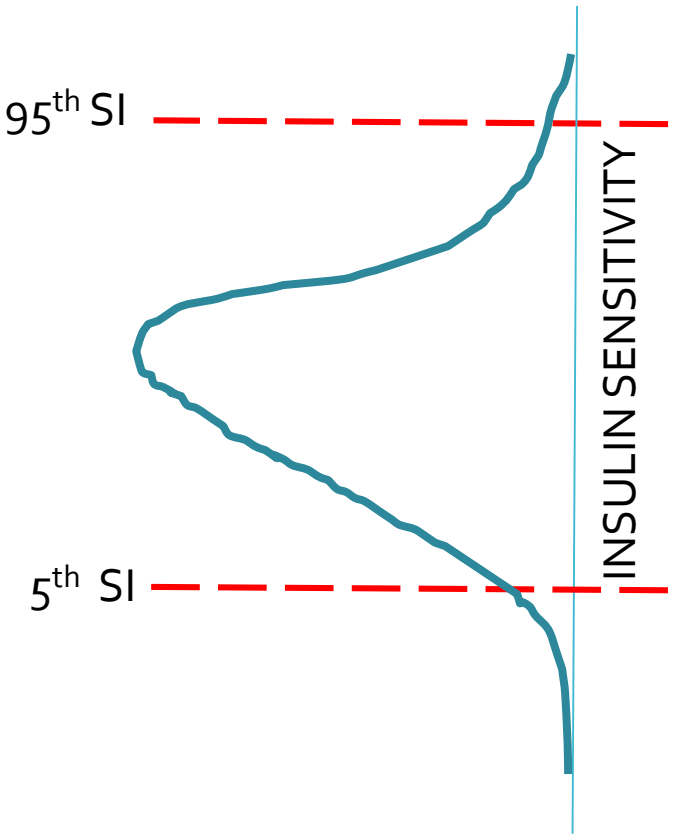


SI NOW

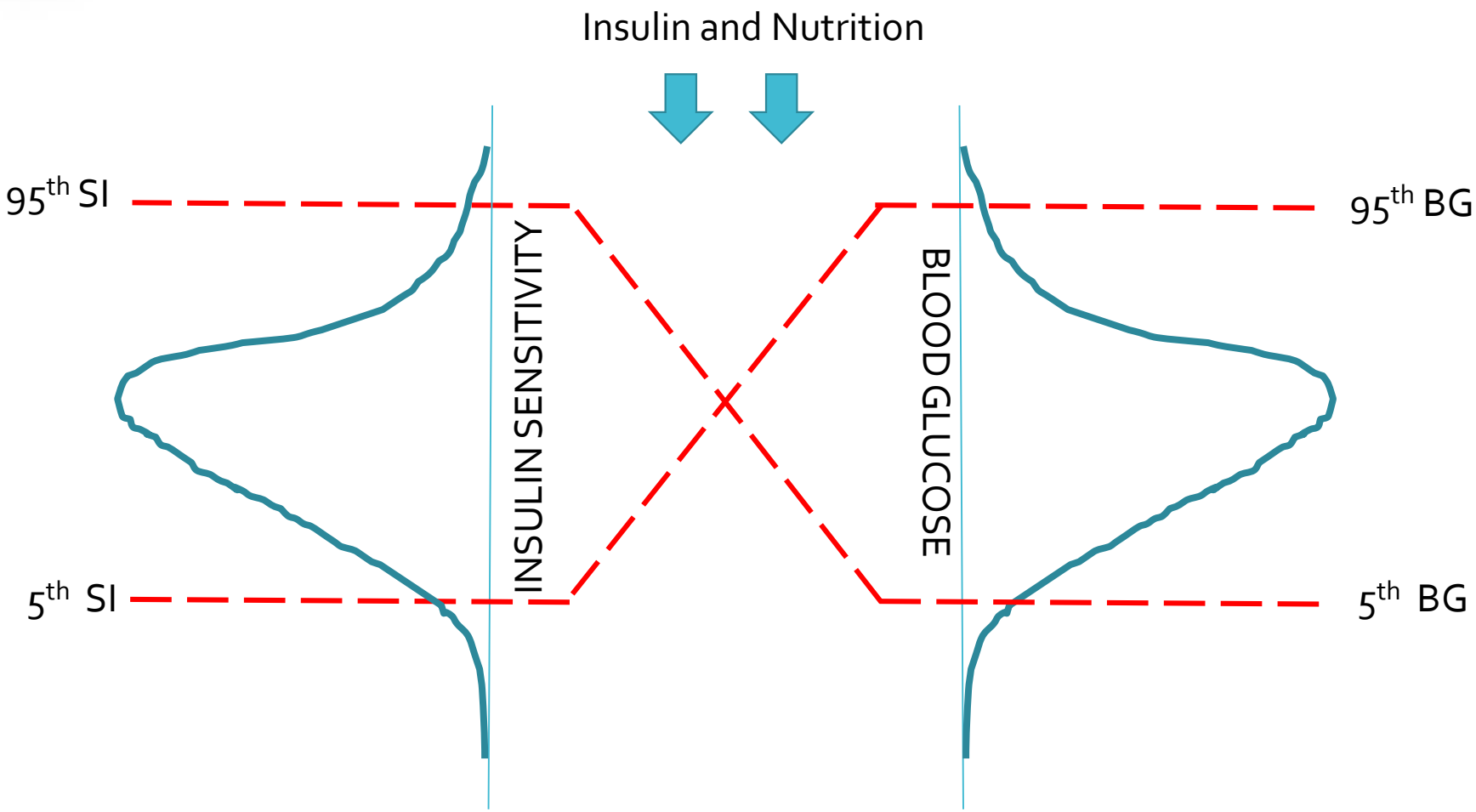
The 95th percentile of SI in particular is useful for quantifying risk of increase in sensitivity

INSULIN SENSITIVITY – Forecasting BG

Insulin and Nutrition



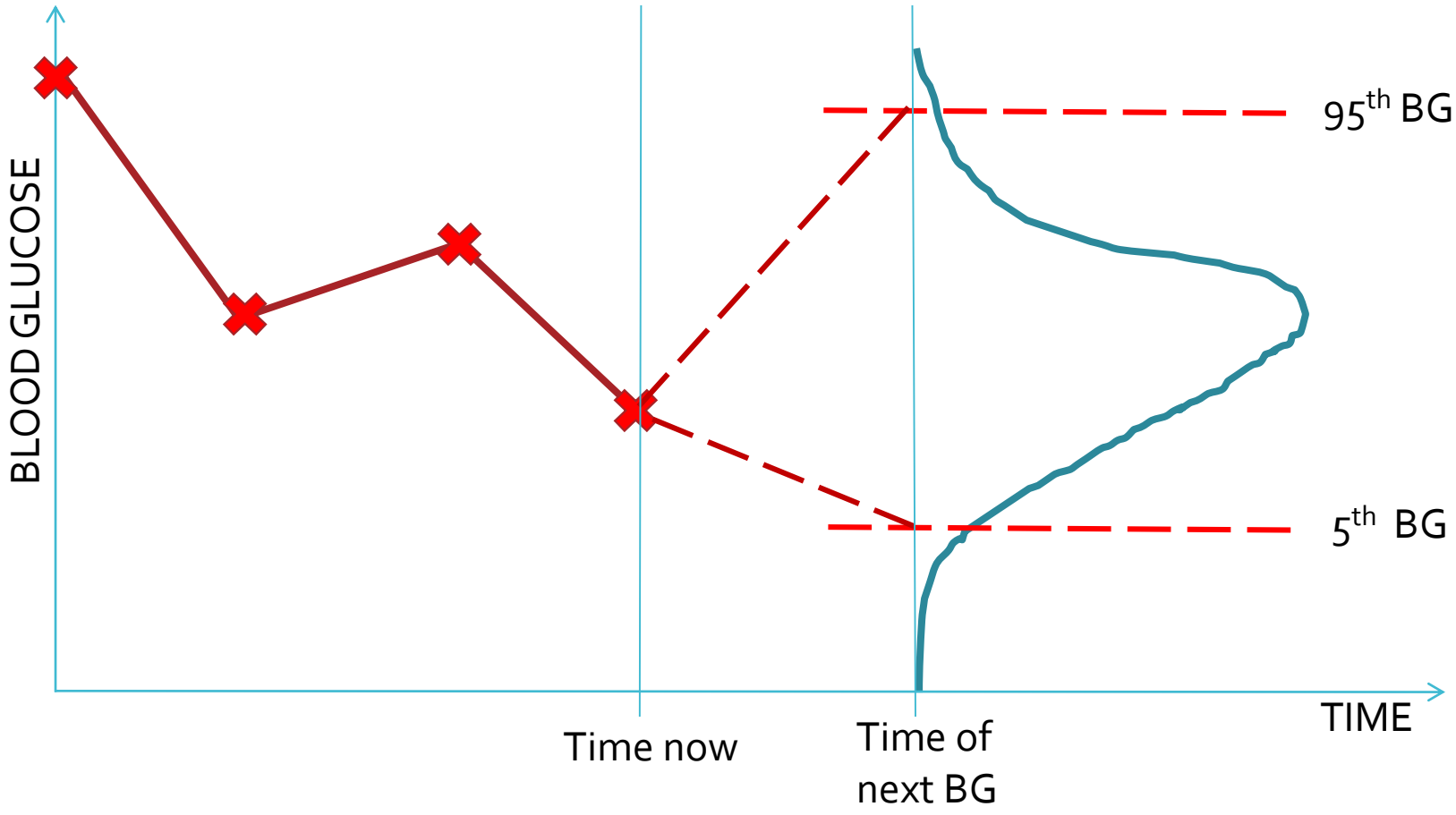
INSULIN SENSITIVITY – Forecasting BG



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

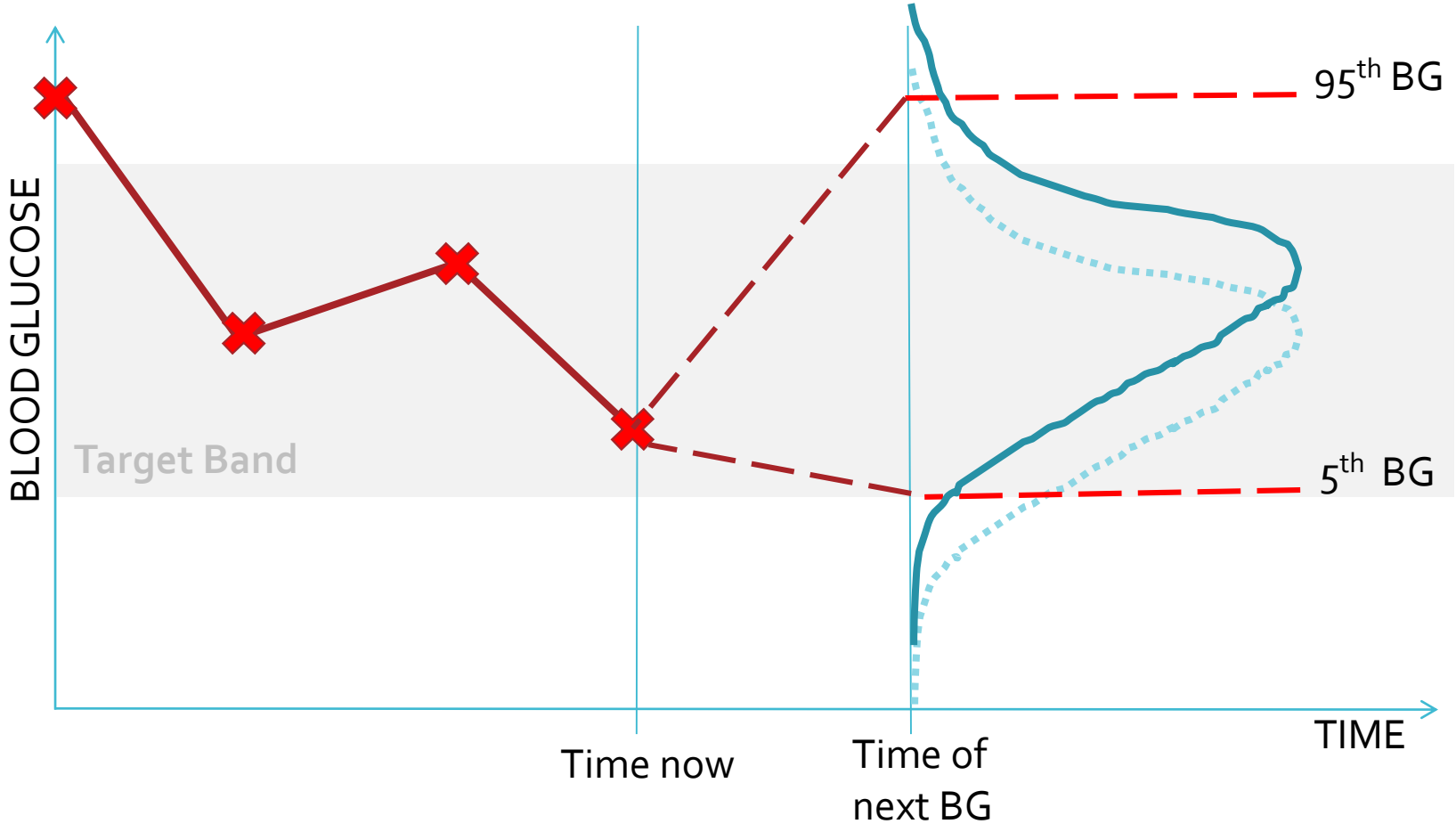
INSULIN SENSITIVITY – Forecasting BG

For any given treatment we can calculate the range of likely blood glucose outcomes



INSULIN SENSITIVITY – Selecting Treatments

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



That is the theory… how does Christchurch implement it?

- When do they start?
- What is general practice for delivering insulin and nutrition?
- What kind of control do they achieve in practice?

Christchurch

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

Christchurch

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

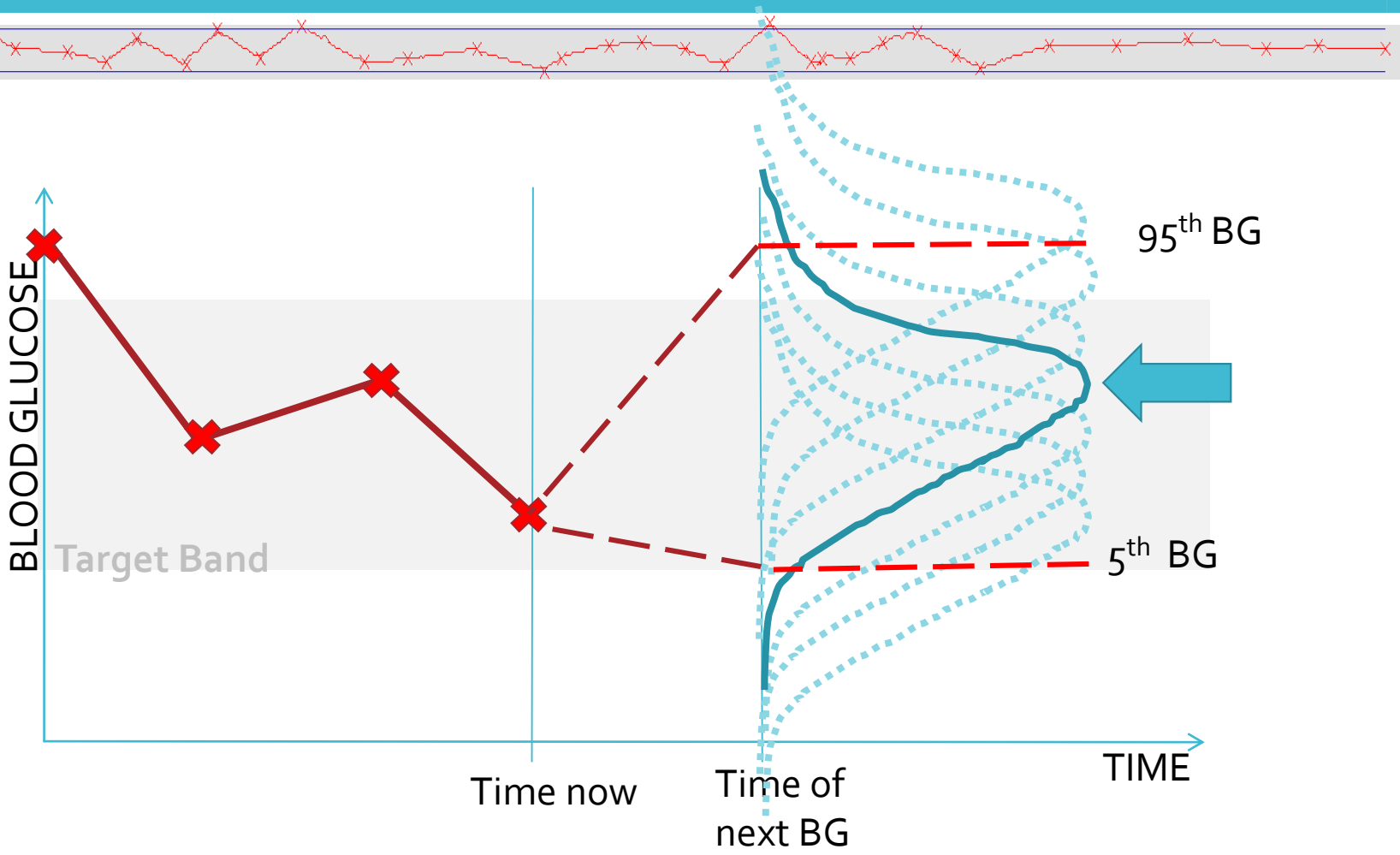
Insulin

- Shares a IV line with main dextrose fluids
- Concentration is set such that

  X U/kg/hr = Y mL/hr

  for all babies
- Work in step sizes of 0.01 U/kg/hr
- Insulin typically totals 1-5mL/day and is not considered in fluid targets

Protocol



Protocol:

- **choose insulin dose that puts the 5th percentile BG prediction on a lower target of 4.4 mmol/L**
- **Limits on how much an insulin infusion can increase by between treatments**

Christchurch – Clinical Results

	CCH - Retrospective	CCH – STAR 1	CCH – STAR 2
Num episodes:	25	61	5
Total hours:	3098 hours	5104 hours	457 hours
Measurement Interval	3.2 [2.7 - 3.8]	3.2 [2.6 - 3.9]	4.0 [3.8 - 4.0]
Median insulin rate [IQR] (U/kg/hr):	0.031 [0.015 - 0.060]	0.044 [0.017 - 0.080]	0.040 [0.030 - 0.059]
Median BG [IQR]	7.8 [6.55 - 9.14]	6.6 [5.53 - 8.15]	6.7 [6.13 - 7.50]
% BG within 4.0 - 8.0 mmol/L	51.9	69. 8	87.2
% BG > 10 mmol/L	16.3	10.0	1.5
% BG < 4.0 mmol/L	2.1	3. 5	0
% BG < 2.6 mmol/L	0.1	0.2	0
Num patients < 2.6 mmol/L	1	5	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

How can it be used in Miskolc?

- What are the differences between Christchurch and Miskolc infants?
- Some simulation results…

Christchurch vs. Miskolc

Patient data given to us

- 10 Patients

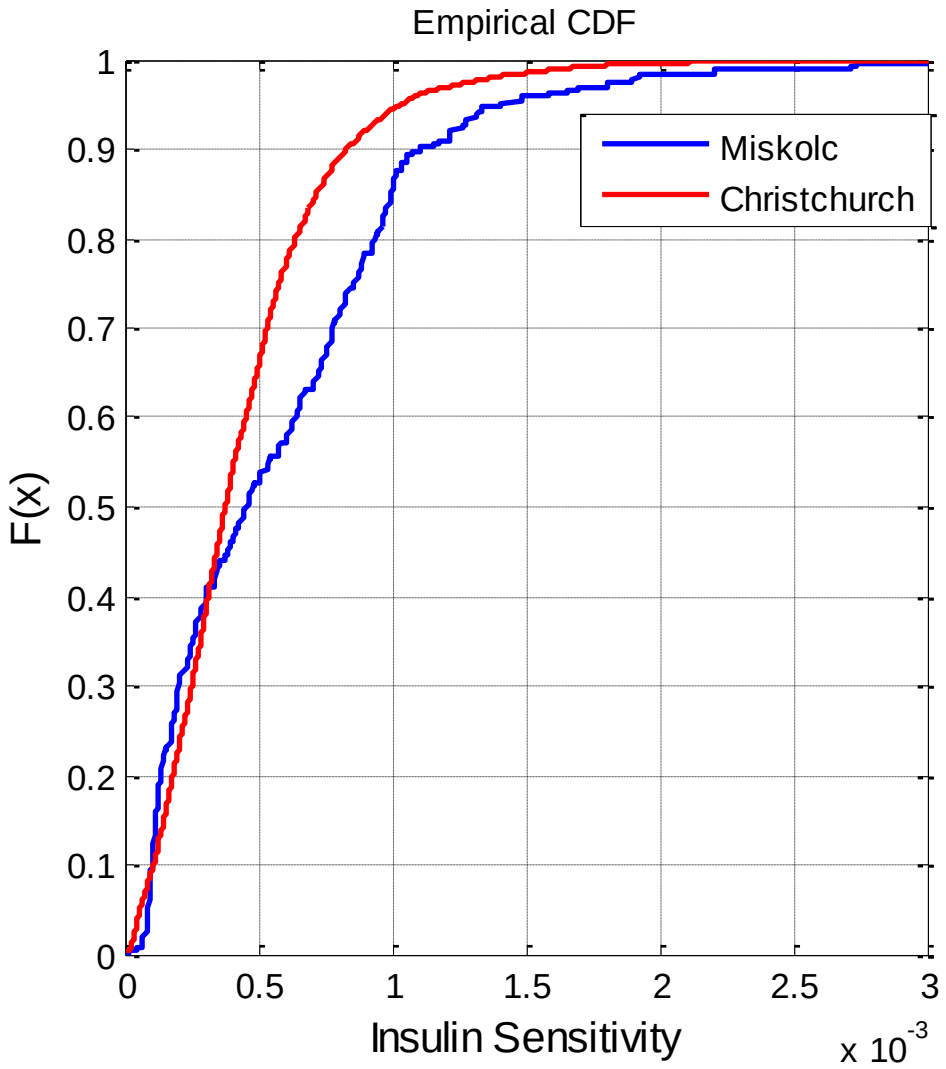
After extracting insulin treatment episodes of 12 hours or longer with less than 6 hours between BG measurements

- 15 Patient Episodes
- 359 hours of data
- 37% time in 4-8.0 mmol/L band
- 10% BG<2.6 mmol/L
- 25% BG<4.0 mmol/L

Miskolc

Patients

- Similar in range of SI values, a little more resistant than Christchurch patients



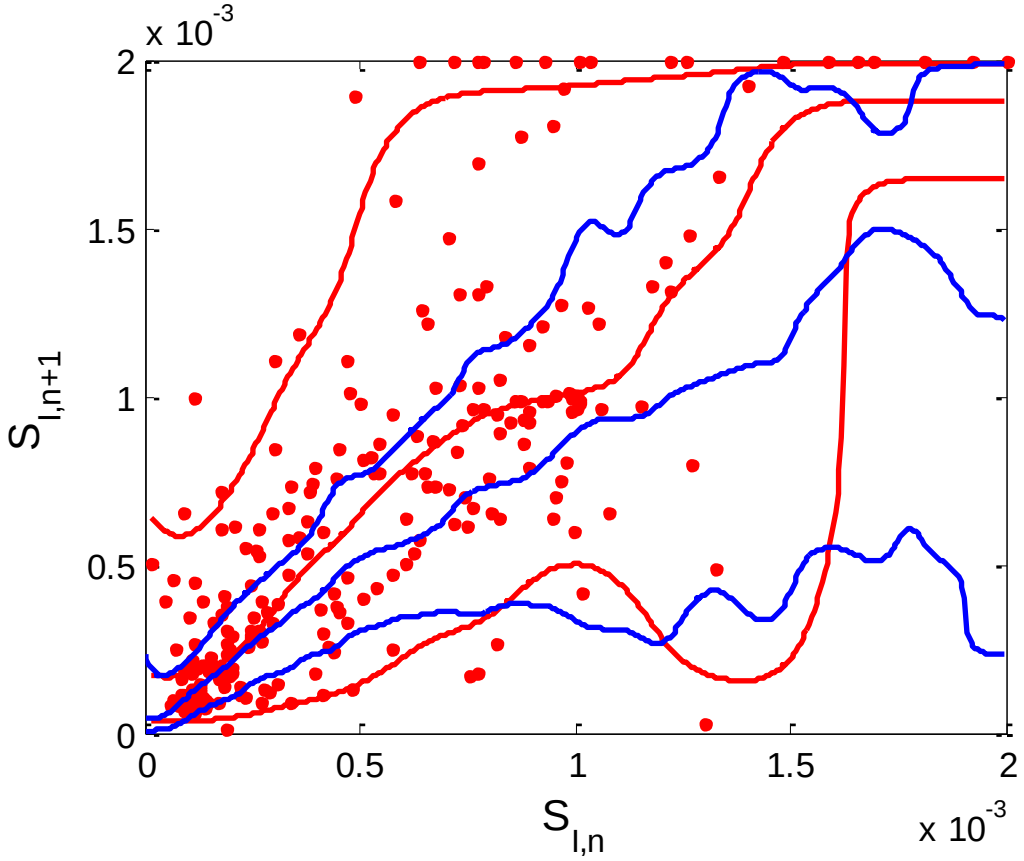
Miskolc

Patients

- Similar in range of SI values, a little more resistant than Christchurch patients

- More variable than Christchurch Patients – wider 5th to 95th band

→ BUT, low data density widens percentiles based on data extremes



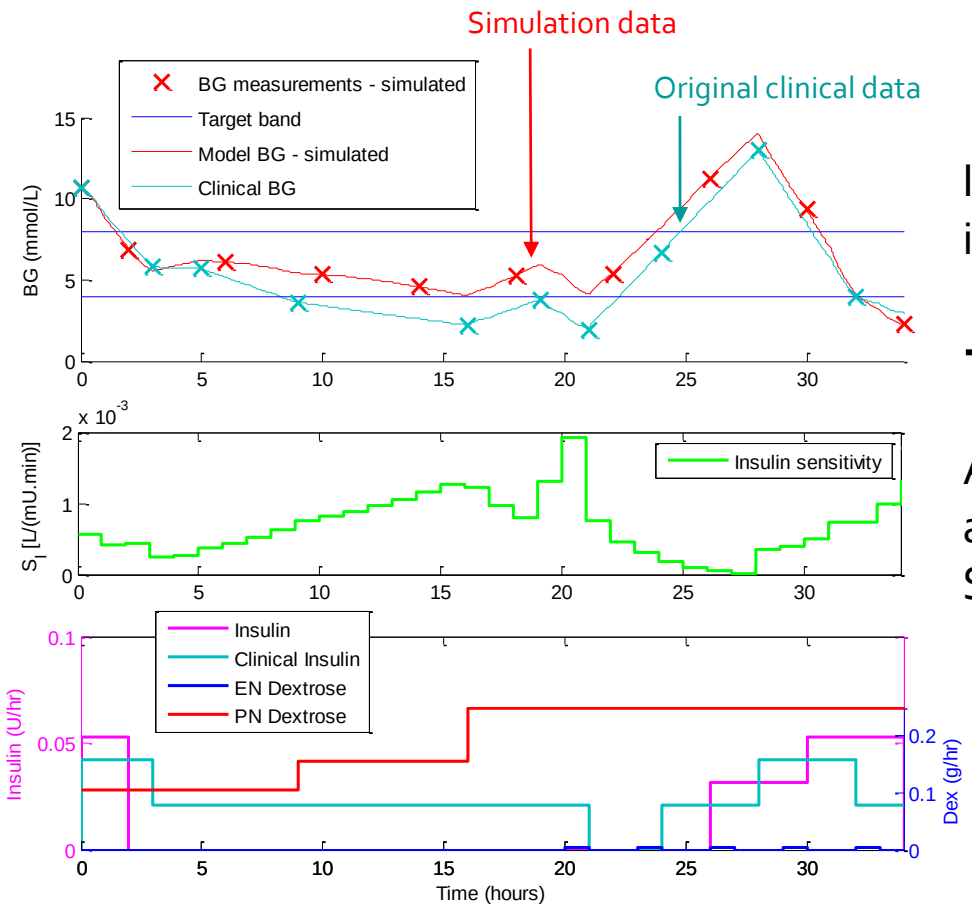
- Miskolc 5th, 50th and 95th percentiles
- Christchurch 5th, 50th and 95th percentiles

Miskolc

→ Currently, we don't have enough data from Miskolc to generate hospital-specific population models of insulin sensitivity

→ Using Christchurch population models in simulation with Miskolc patients has proven effective…

Miskolc – Simulations



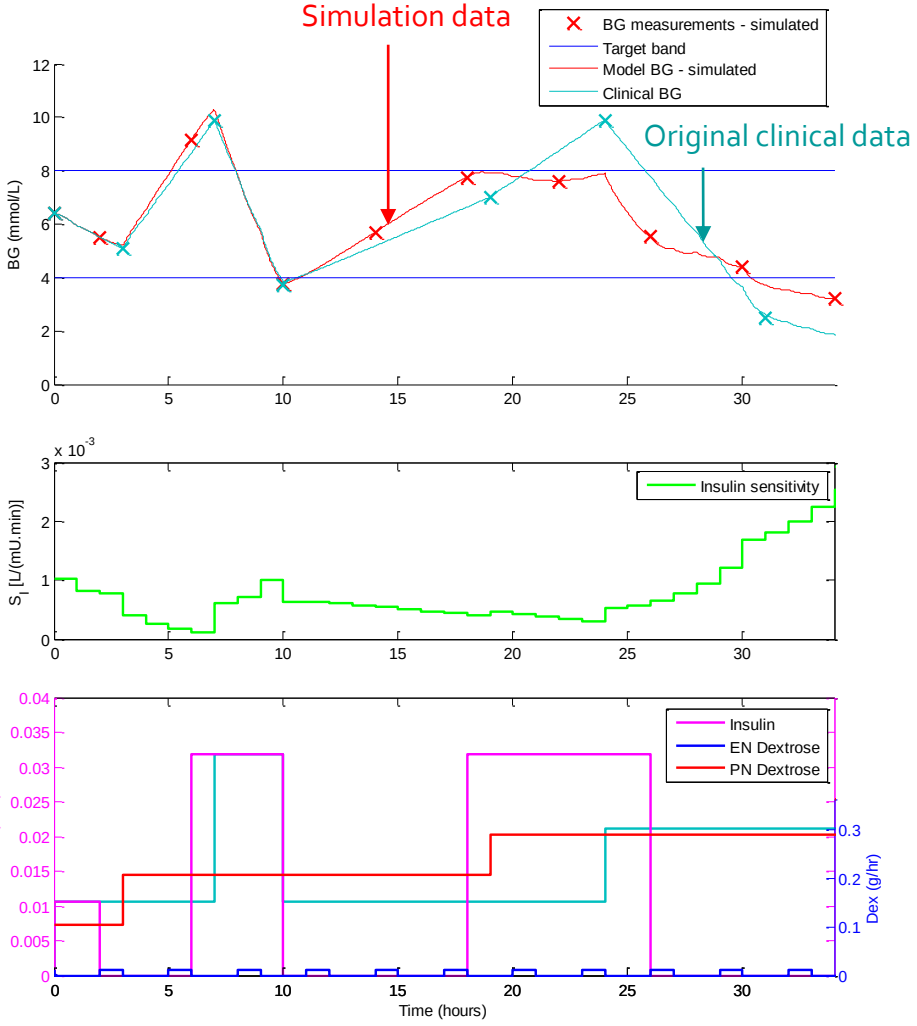
Insulin turned off early when BG stabilizes in the target band

→ **Much less hypo glycaemia**

A large drop in insulin sensitivity results in a large BG spike, and a later sharp rise in SI causes BG to drop

→ Population models say that the treatment at BG≈10 mmol/L was reasonable

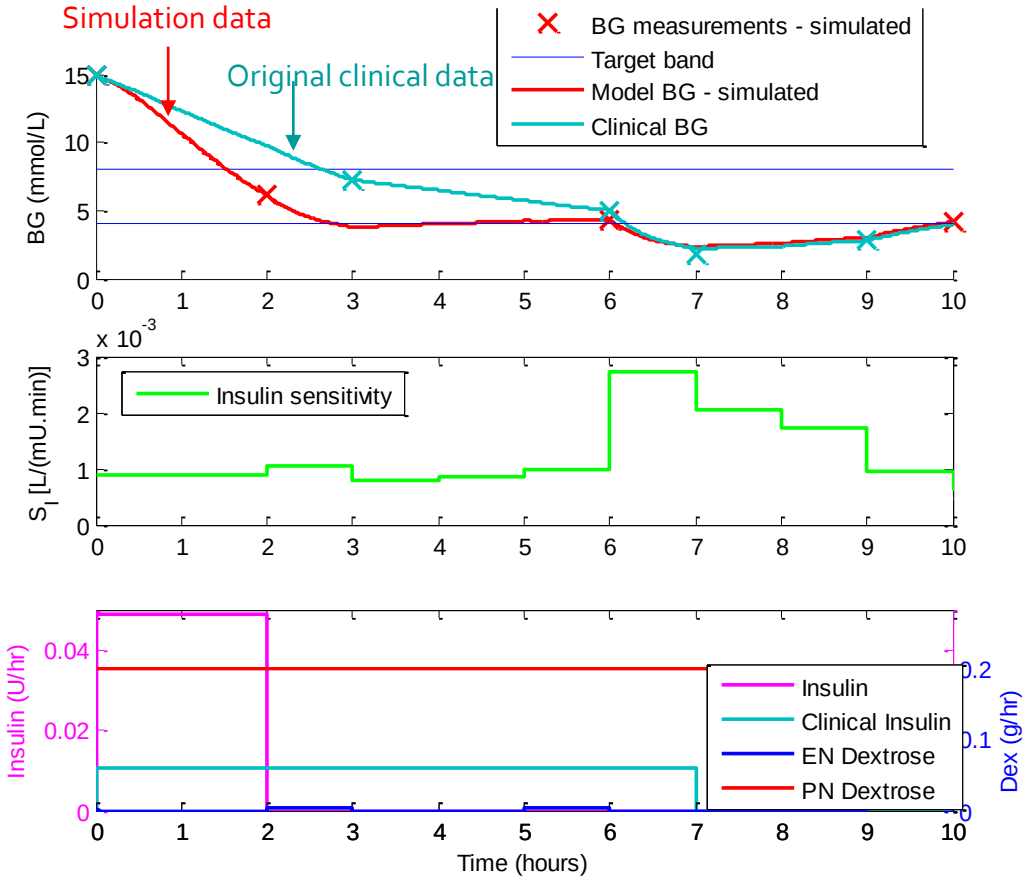
Miskolc – Simulations



→ **More time in band**

→ No severe Hypo glycaemia
– Insulin turned off as SI rises

Miskolc – Hypo's in simulation – Avoidable?



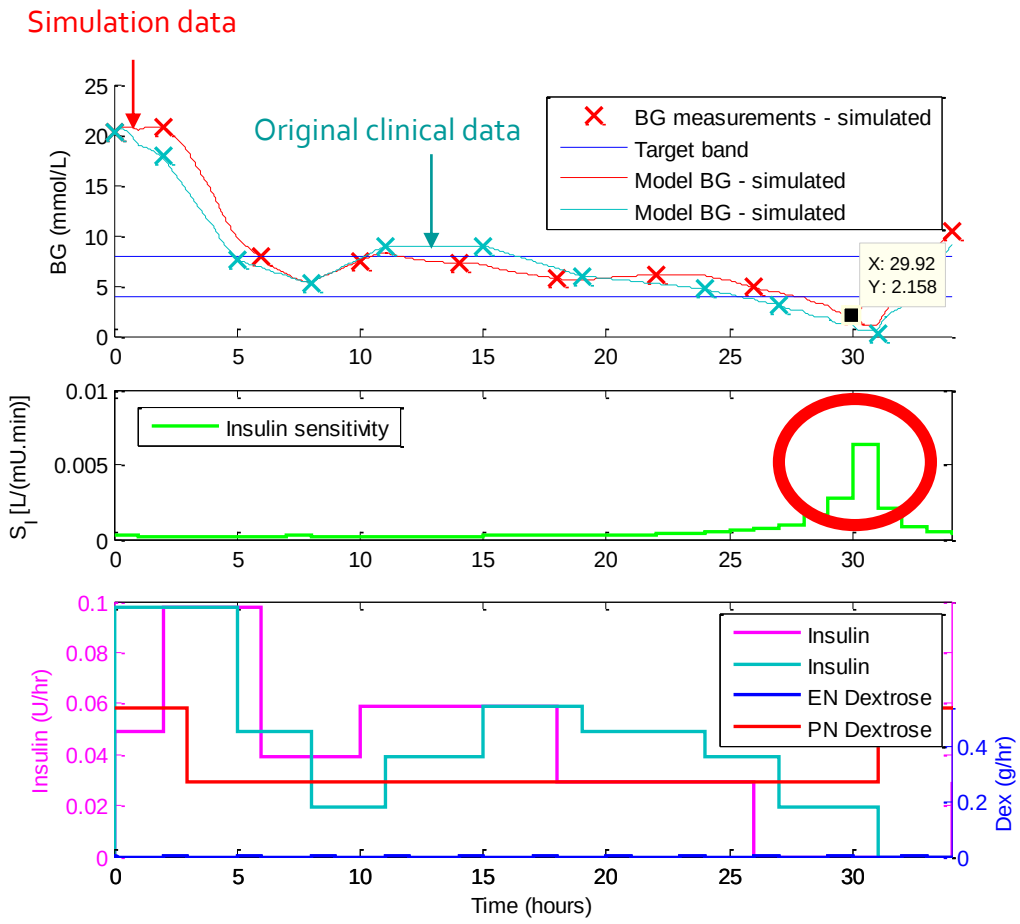
See a large unexpected rise in SI at hour 6

In simulation, insulin is turned off long before hour 6, indicating that the hypo at hour 7 is unavoidable

→ 4 other cases like this

→ Likely some amplification of low BG by noise in data

Miskolc – Hypo's in simulation – Avoidable?



See an extremely large unexpected rise in SI at hour 30

→Because of this, even when insulin is turned off and BG is "normal," BG continues to drop

→ The magnitude of this rise is more than 4 times larger than most other SI across the cohort. It occurs round a shut off in insulin in the original clinical data

This spike is likely not real, but results from noise in the data

Simulation results

BG measurement interval – 4 hours

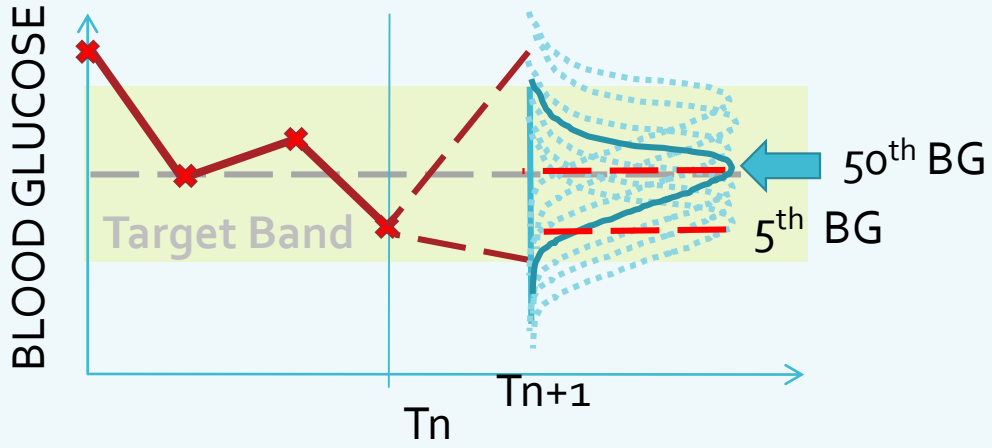
	Clinical Data	STAR Christchurch Protocol	Median protocol
Median BG [IQR]	6.4 [4.00 - 9.60]	7.0 [4.86 - 8.87]	7.0 [5.10 - 8.84]
% BG within 4.0 - 8.0 mmol/L	36.6	48.4	57.8
% BG > 10 mmol/L	21.4	16.0	15.9
% BG < 4.0 mmol/L	24.9	15.8	9.3
% BG < 3.0 mmol/L	14.2	5.8	3.7
% BG < 2.6 mmol/L	10.4	2.0	2.4
Num patients < 2.6 mmol/L	11	6	6

Simulations predict an increased time in band of at least 20% and a 5 fold decrease in BG<3.0 mmol/L

Note: → % time in band likely to be higher as with the limited Miskolc data available for simulation the first few hyperglycaemic hours represent a higher proportion of total time

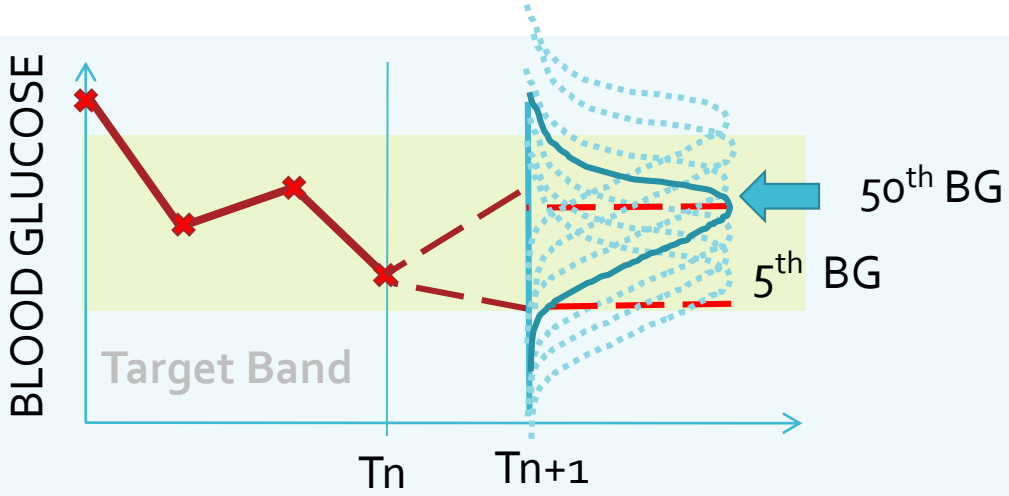
* All stats are resampled – simulation results were "re-sampled" every hour to give statistics independent of measurement interval

Protocol design



Best Protocol – as seen in simulation

- **choose insulin dose that puts the 50th percentile BG prediction on 6.5 mmol/L**



- **Check the 5th percentile BG prediction to ensure it is equal to or greater than a lower value of 4.5 mmol/L. If lower, then reduce insulin to put lower 5th on 4.5 mmol/L**

When the 5th-95th BG prediction intervals are narrower the 5th percentile of BG outcomes is higher → SAFER

Miskolc – Challenges

Differences in implementation – the challenge of fluid balancing

- Christchurch and Miskolc:
  - Differences in pump rates and insulin concentration protocols
  - Differences in the way fluid balance is approached

→ What does Christchurch do and why?

Miskolc – Insulin increments

Simulations are based on step sizes of 0.01 U/kg/hr

1kg baby, starting at 1 mL/hr and 0.05 U/kg/hr

mL/hr	U/kg/hr
0.2	0.01
0.4	0.02
0.6	0.03
0.8	0.04
1	0.05
1.2	0.06
1.4	0.07
1.6	0.08
1.8	0.09
2	0.1

Christchurch

mL/hr	U/kg/hr
0.05	0.01
0.1	0.02
0.15	0.03
0.2	0.04
0.25	0.05
0.3	0.06
0.35	0.07
0.4	0.08
0.45	0.09
0.5	0.1

Christchurch uses the same increments of insulin, but much lower fluid volumes

Christchurch – Insulin and fluid targets

Postnatal age (days)	Fluid Target (mL/kg/day)	
	Christchurch	Miskolc
1	90	50
2	90	80
3	120	100
4	120	120
5	150	150
6	165	150

According to what data we have…

*possibly missing some medications

	Christchurch	Miskolc
Number patient episodes	45	12
Christchurch daily fluid **guideline target** , [mL/kg/day]	165 [120–180]	100 [80–150]
Patient specific daily target, [mL/kg/day]	150 [150–150]	
Fluids given, [mL/kg/day]	152 [126–165]	94 [56–120]
→ % of daily target	104 [100–110] %	
→ % of guideline target	99 [90–109] %	82 [73–100] %

Christchurch does not include insulin in its fluid balance calculations, but still meets fluid targets

→ insulin usually totals only 2-5mL/day

Christchurch – Insulin and fluid targets

Christchurch uses the same increments of insulin, but much lower fluid volumes

→ Higher concentrations mean that volumes of insulin given are negligible in comparison to fluid targets

→ Insulin not included in fluid targets

→ Insulin therapy not complicated or biased by competing fluid balance targets

→ Simpler clinical implications for Christchurch

→ Not modifying nutrition volumes to compensate for insulin (complicated by a rise in insulin and a drop in glucose having similar effects)

→ Not modifying nutrition concentrations to maintain nutrition volume targets