Why Protocolised Care Works in My Unit

A case study in glycemic control

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A Well Known Story

- **Hyperglycaemia is prevalent in critical care**
  - Impaired insulin production + Increased insulin resistance = High BG
  - Average blood glucose values **> 10mmol/L** are not uncommon
  - Higher mean, median and variation of BG all increase odds risk of death by 2-4x vs lower levels around 6 mmol/L and low variability

- **Tight control → better outcomes:**
  - Reduced mortality ~17-43% (6.1-7.75 mmol/L) [van den Berghe, Krinsley]
  - SPRINT reduces mortality 32-45% depending on LoS in ICU (*details to come*)
  - Costly treatments & tests (mech. ventilation, transfusions, …) are also reduced

- **However, how to get this result w/o all the hypoglycemia and other difficult to repeat control issues**
  - SPRINT reduced hypoglycemia by 50%, others see 200-400% increases
  - **Model-based methods and engineering approach offer an answer**

Between a rock and a hard place: Pitfalls or just a hard problem?

- **Hypoglycaemia?**
  - Risk of neurological damage?
  - Fear of hypoglycaemia?
    - Lack of 'buy-in' by physicians and nursing staff

The "rock"

- **Hyperglycaemia?**
  - Patients evolve rapidly
  - High insulin resistance and insulin requirements
  - Insulin effect saturation
  - Infrequent measurement ← or → Burden

The "hard place"

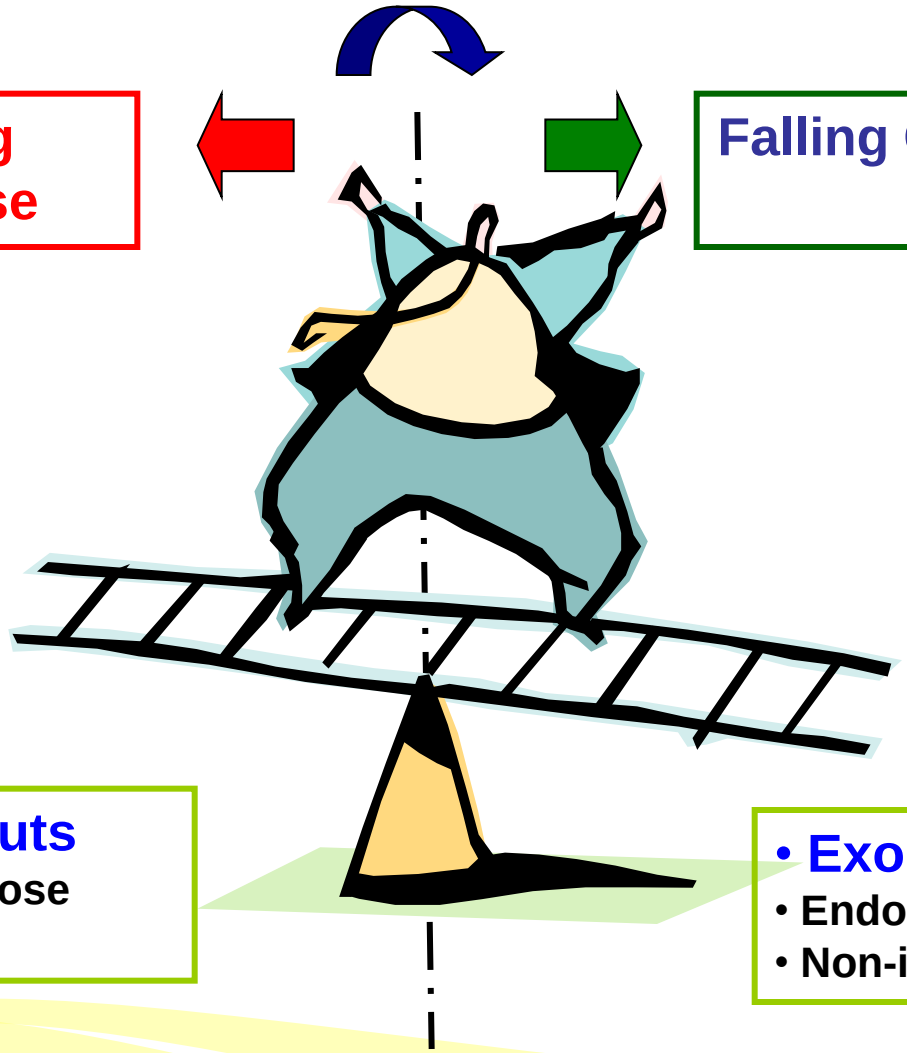
- **Not doing anything …? Too hard?**

The real question is how to manage the risk and reward in an optimal fashion for each patient.

Our Approach – A fat man on a see-saw

Rising Glucose

Falling Glucose



- **Nutritional Inputs**
- Endogenous Glucose Production

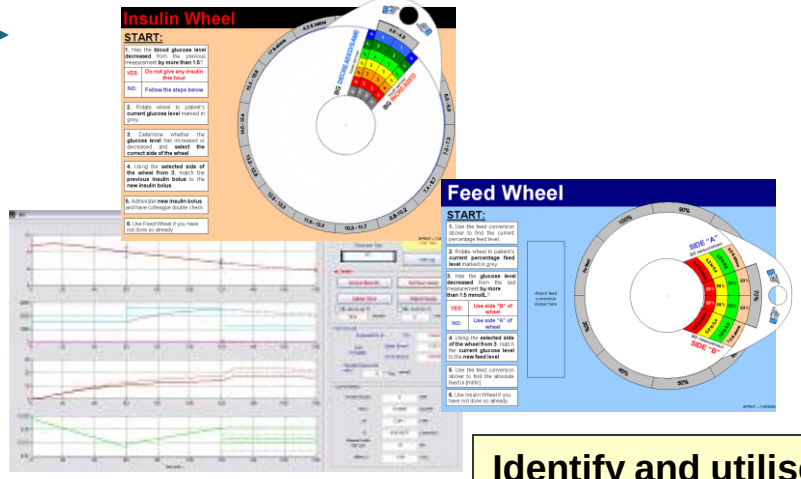
- **Exogenous Insulin**
- Endogenous Insulin
- Non-insulin Removal

Semi-Automated feedback control

Nursing Staff

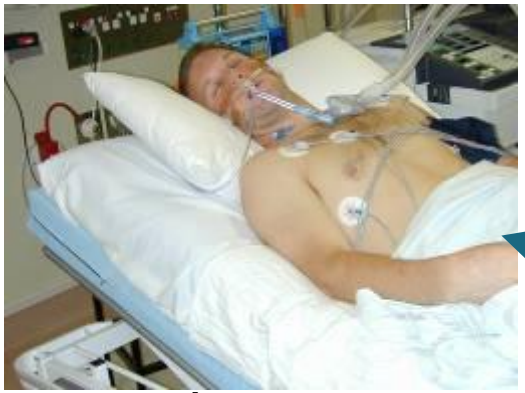
Measured data

Decision Support System



Identify and utilise patient specific parameters to optimise therapy

Standard infuser equipment



Patient management

Minimal time & training – Minimal interruption – Easy to understand

→ Transparent

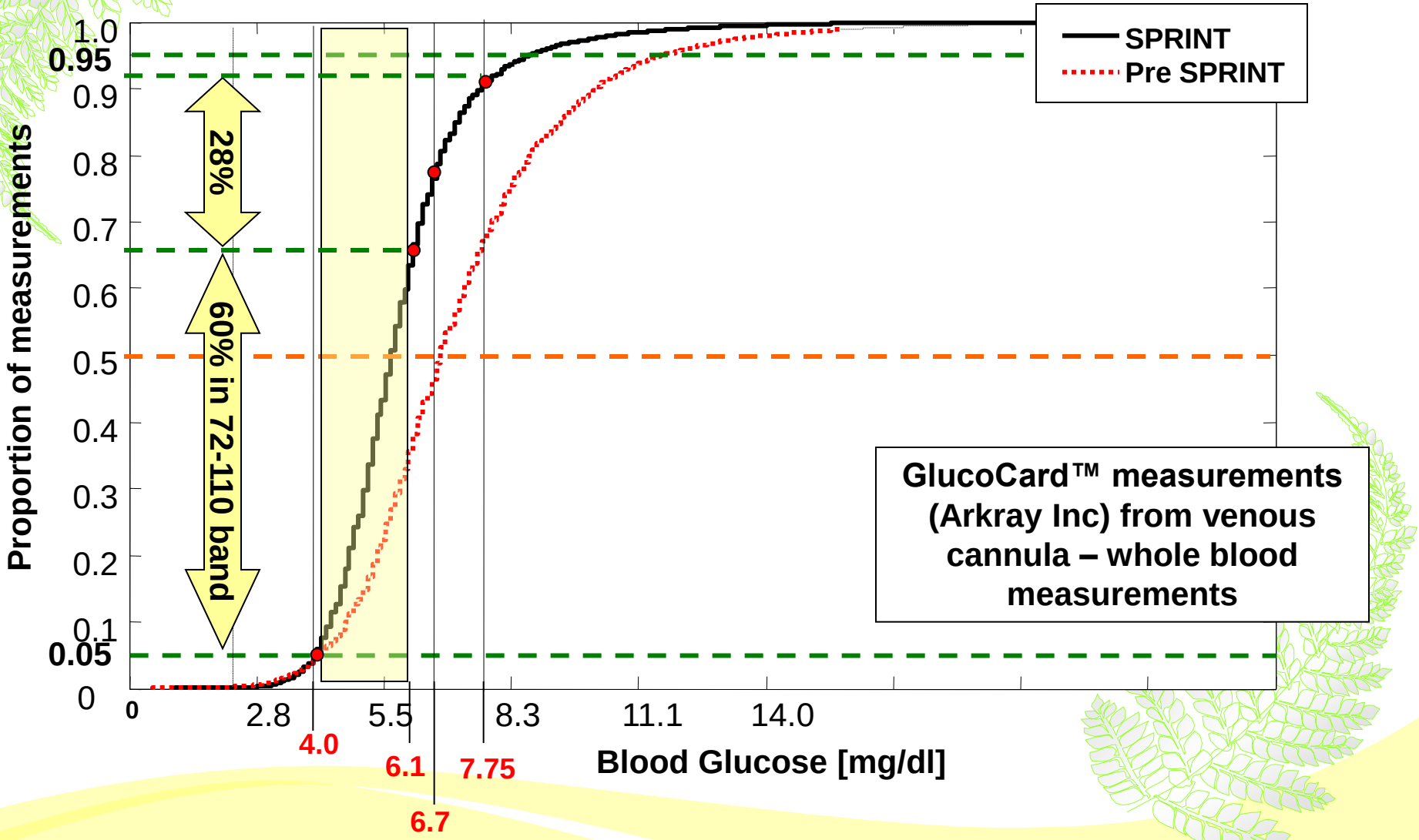
The Cohorts: Before/After Study

	Overall		
	Retrospective	*SPRINT*	
Total patients	516	394	
			p-value
Age (years)	65 [53 - 74]	65 [50 – 74]	0.22
% Male	60.1%	62.9%	0.38
APACHE II score	19 [15 - 24]	18 [14 – 24]	0.06
APACHE II risk of death	24.1% [11.2% - 45.3%]	25.7% [13.3% - 48.1%]	0.19

Admission: 2 BG > 8 mmol/L or 1 BG > 10 mmol/L
No exclusions

- **Retrospective before-after study – 1.2 yr SPRINT vs 2.5 yr past**
- **ROD is higher for SPRINT**
  - **Different case mix with retrospective cohort having much more cardiovascular surgery than recently** (non-clinical causes)
- **Otherwise statistically similar**
  - **Retrospective more cardiovascular surgery so ROD likely lower again**
  - **More similar for LoS > 2 days**

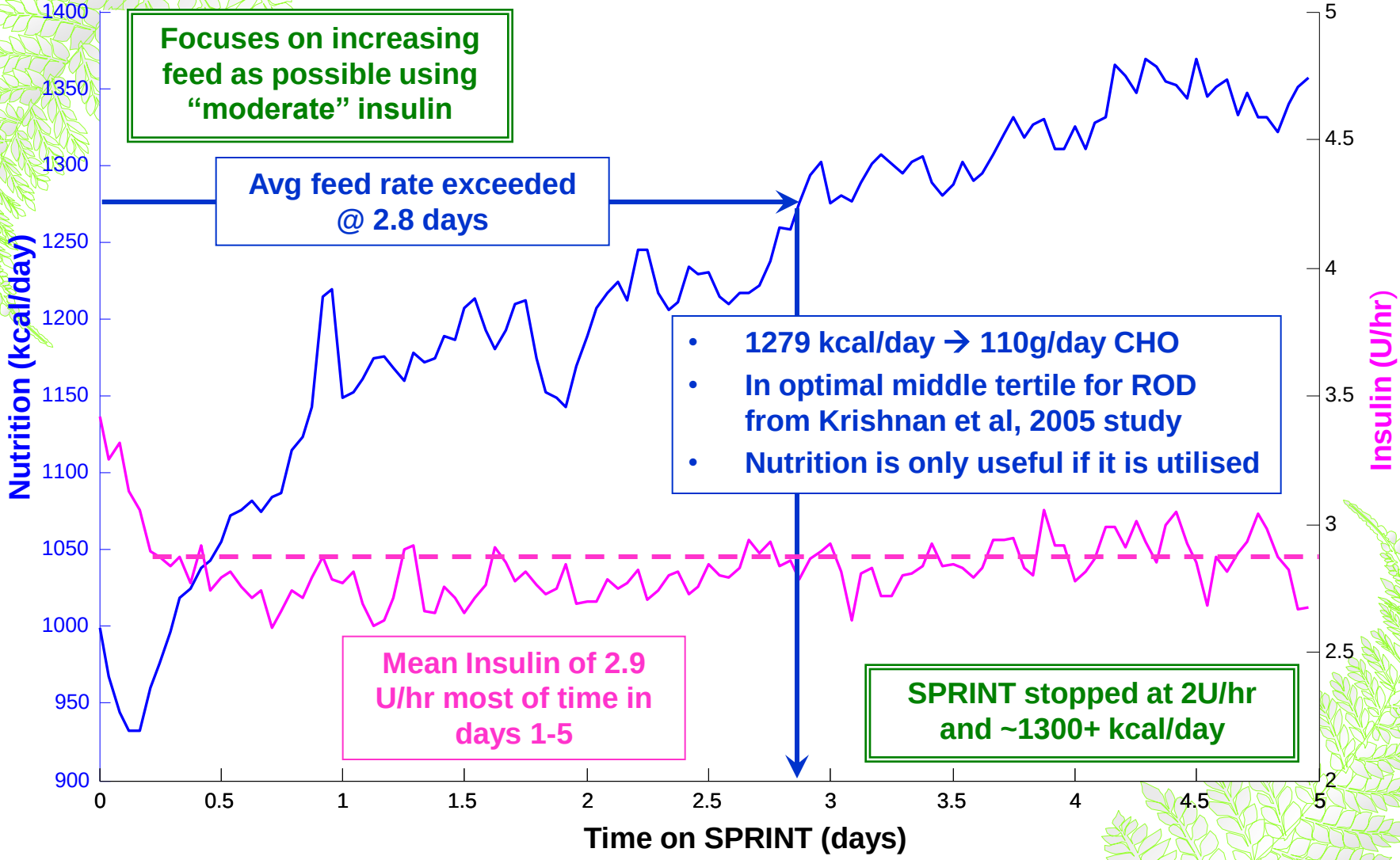
Cumulative Distribution of BG



Overall SPRINT Glycaemic control

Overall cohort data	*Retrospective*	*SPRINT*	
Number of patients	516	394	
Hours of control	62,769	47,290	hours
Total BG measurements	15,618	29,983	
BG mean (lognormal)	7.3	6.0	mmol/L
BG standard deviation (lognormal)	2.4	1.5	mmol/L
Percentage of measurements between:			
4.0 – 6.1 mmol/L	31.5%	59.2%	
4.0 – 7.0 mmol/L	50.3%	79.1%	
4.0 – 7.75 mmol/L	62.9%	86.5%	
Percentage of measurements less than:			
4.0 mmol/L	3.6%	3.9%	
2.2 mmol/L	0.2%	0.1%	
Mean insulin usage	1.0	2.9	U/hr
Mean nutrition rate			
During periods of feeding	1611	1279	kcal/day
Entire duration of SPRINT usage	-	1055	kcal/day
Mean % of goal feed	-	66%	

Nutrition and Insulin Concerns



Matches recent results where tight control via IIT decreased insulin required over days 2-7 and thus allows increased nutrition (Langouche et al, 2007)

SPRINT Glycaemic Control Per Patient

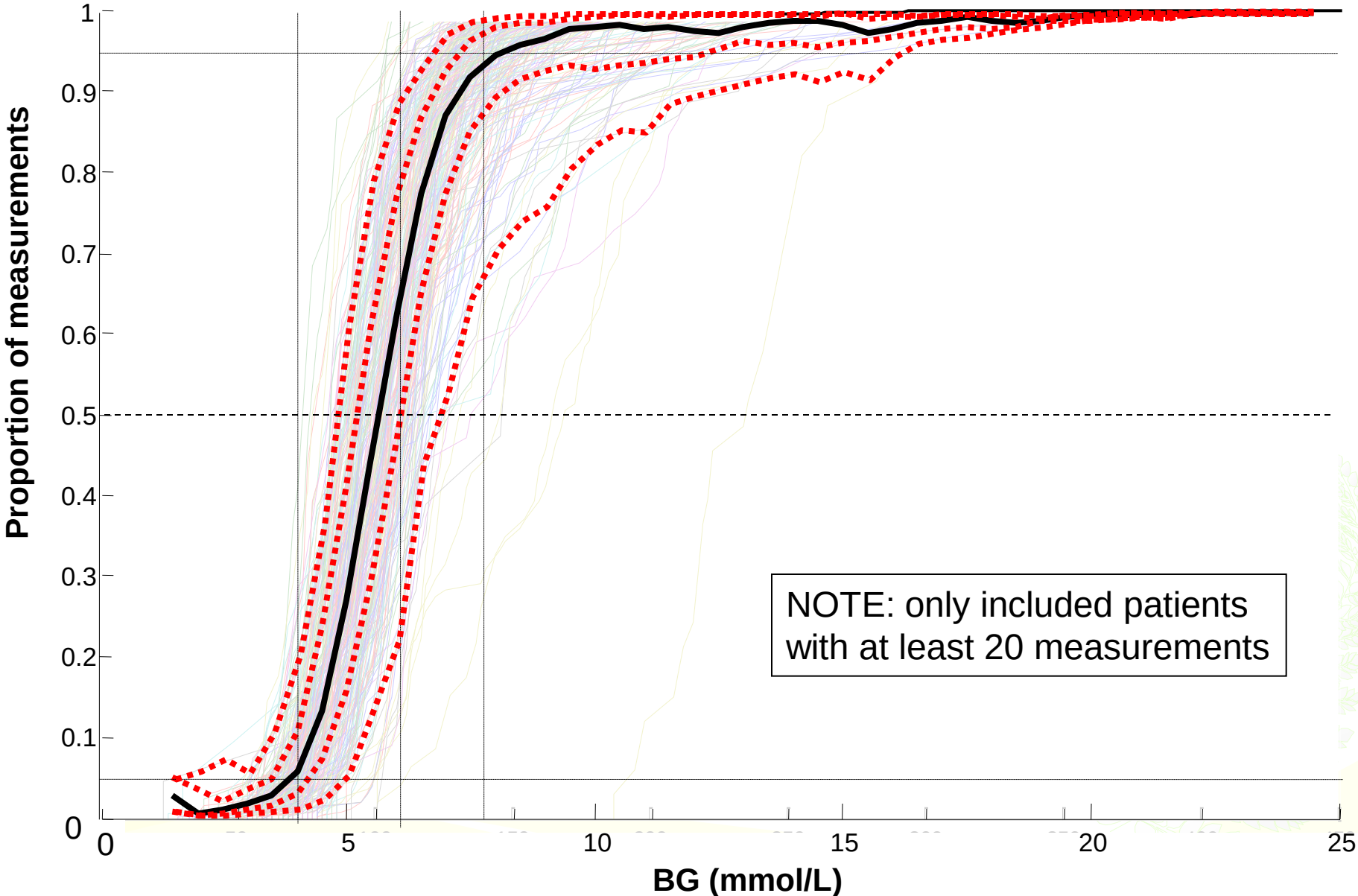
Per-patient data	Retrospective	SPRINT	
Hours of control	57 [25 – 162]	53 [19 – 147]	hours
Number of BG measurements	17 [8 – 40]	37 [16 – 97]	
BG mean (lognormal)	7.5 [6.7 – 8.4]	6.0 [5.5 – 6.6]	mmol/L
BG standard deviation (lognormal)	1.6 [1.2 – 2.4]	1.3 [1.0 – 1.8]	mmol/L
Percentage of patients < 7 mmol/L	82%	99%	
Percentage of patients < 6.1 mmol/L	73%	96%	
Insulin usage	0.9 [0.1 – 1.6]	2.6 [2.1 – 3.3]	U/hr
Nutrition rate			
During periods of feeding	724 [0 – 1596]	938 [0 – 1304]	kcal/day
Entire duration of SPRINT usage	-	708 [0 – 1174]	kcal/day
% of goal feed	-	50% [0% - 71%]	

- **Tighter per patient std deviation – indicates each patient is tighter than the cohort to their patient specific mean**
- **Variability (std deviation) is 20% lower/tighter than retrospective**
- **Nutrition is actually higher (due to tighter control and less shutoff?)**
- **Feed shutoff for other clinical reasons can skew results**

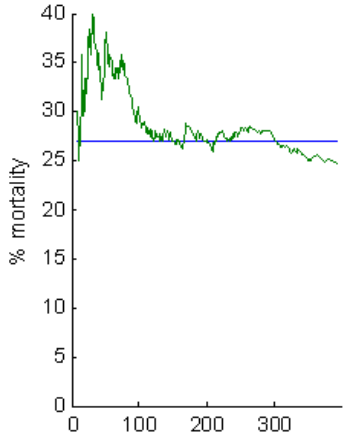
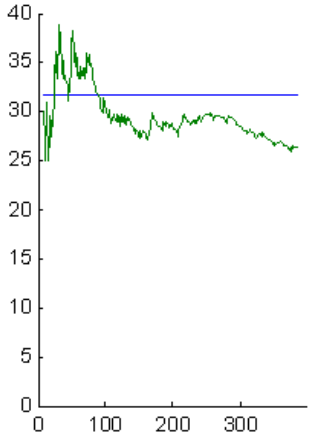
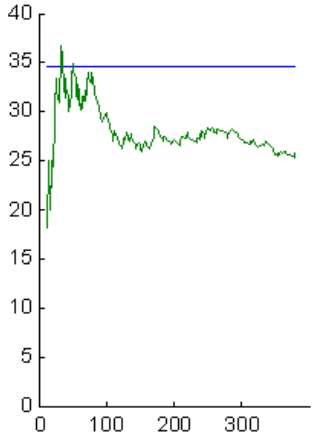
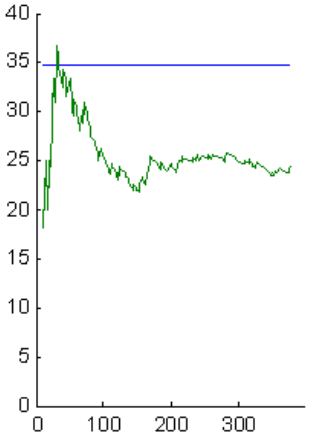
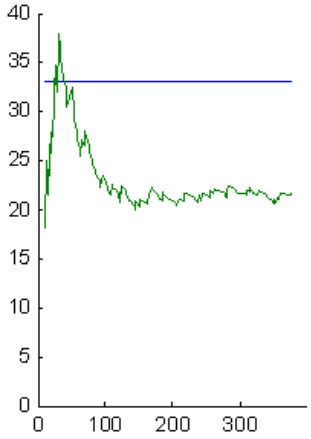
- **Effectively all patients are brought under 7 mmol/L and 96% under 6.1 mmol/L**

Per-Patient cumulative BG distribution: median, IQR & 90% CI

→ Each individual patient's BG cumulative distribution underneath

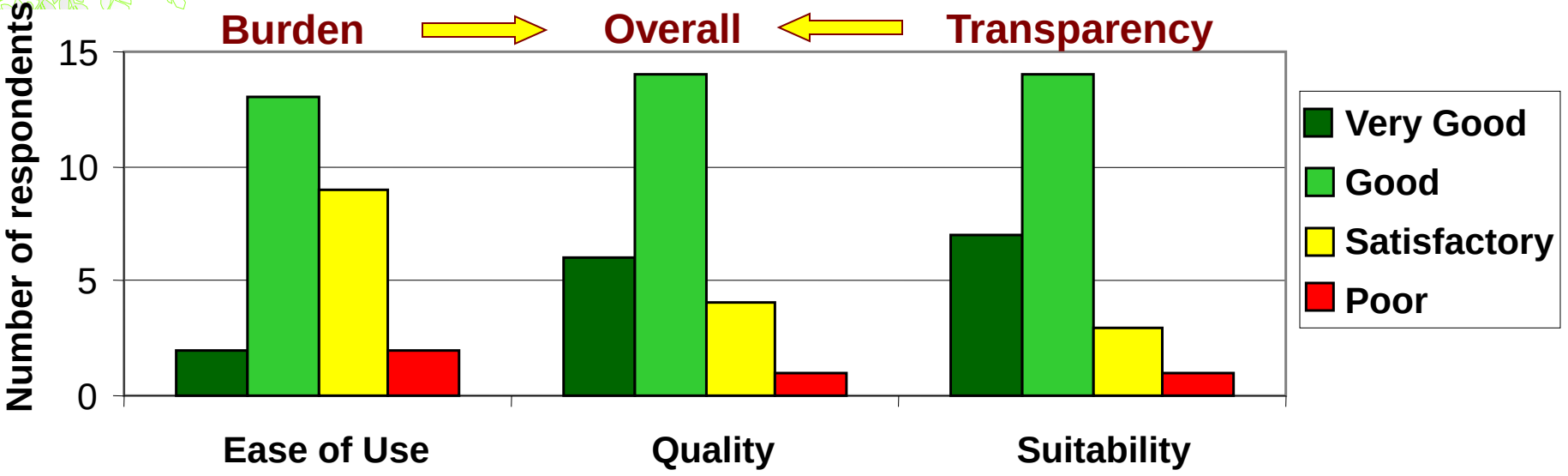


Hospital Mortality: SPRINT/Pre-SPRINT

LOS ≥ 1 day	LOS ≥ 2 days	LOS ≥ 3 days	LOS ≥ 4 days	LOS ≥ 5 days
				
P=0.244	P=0.077	P=0.023	P=0.012	P=0.010

The horizontal line shows the mortality for the retro cohort. The green line Is the total mortality of SPRINT patients against total number of patients Treated on the protocol

Nursing Feedback at 2 Months



Survey completed by 26 Christchurch Hospital ICU Nurses

Bottom line: Intuitive and easy for staff to use.

ICU staff workload reduced

Compliance over 97% (dose)

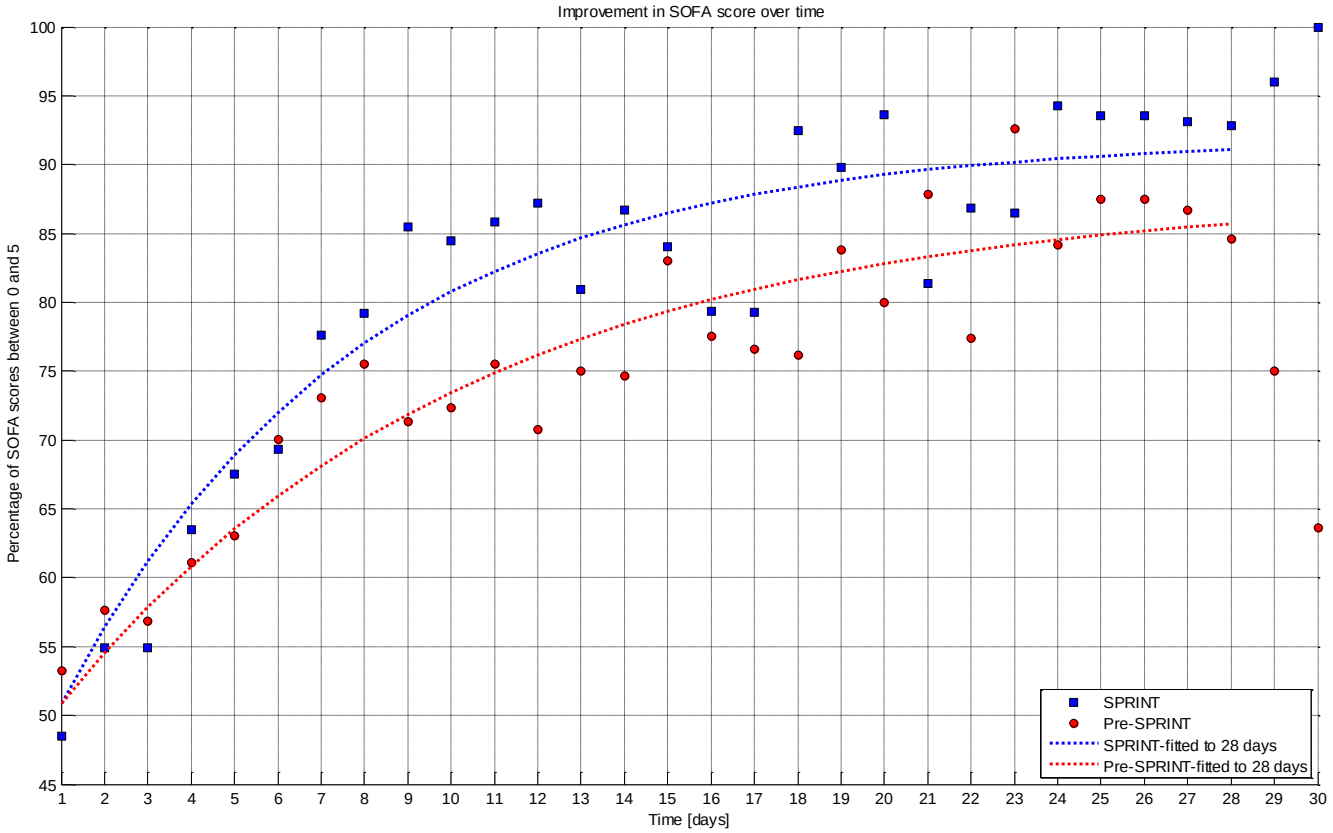
But Why? The answer is by the SOFA!

Table Day 1 and Maximum total SOFA score for each cohort plus percent mortality and number of patients [died, lived] by maximum SOFA score range.

	SPRINT	Pre-SPRINT	p-value
Day 1 SOFA (Mean ± SD)	5.6 ± 2.8	5.4 ± 3.0	0.20
Maximum SOFA (Mean ± SD)	6.8 ± 3.0	7.0 ± 3.2	0.76
Day of Maximum SOFA score (Median [IQR])	1 [1, 3]	1 [1, 3]	0.99
Mortality (%) [#Died, #Lived] by Maximum SOFA Range			
0-4	4.4% [4, 86]	5.2% [5, 92]	1.00
5-9	14.2% [30, 185]	15.3% [36, 199]	0.70
10-14	33.9% [21, 41]	40.9% [29,42]	0.47
15-19	75.0% [3, 1]	70.0% [7, 3]	1.00

- **We examined daily SOFA score for every patient (ignored CNS score)**
- **Initial SOFA and maximum SOFA are similar and in a similar number of days**
- **So, how did TGC affect reduction of organ failure as reflected by SOFA score? Does SPRINT get patients organ failure down faster providing a better platform for (later) survival?**

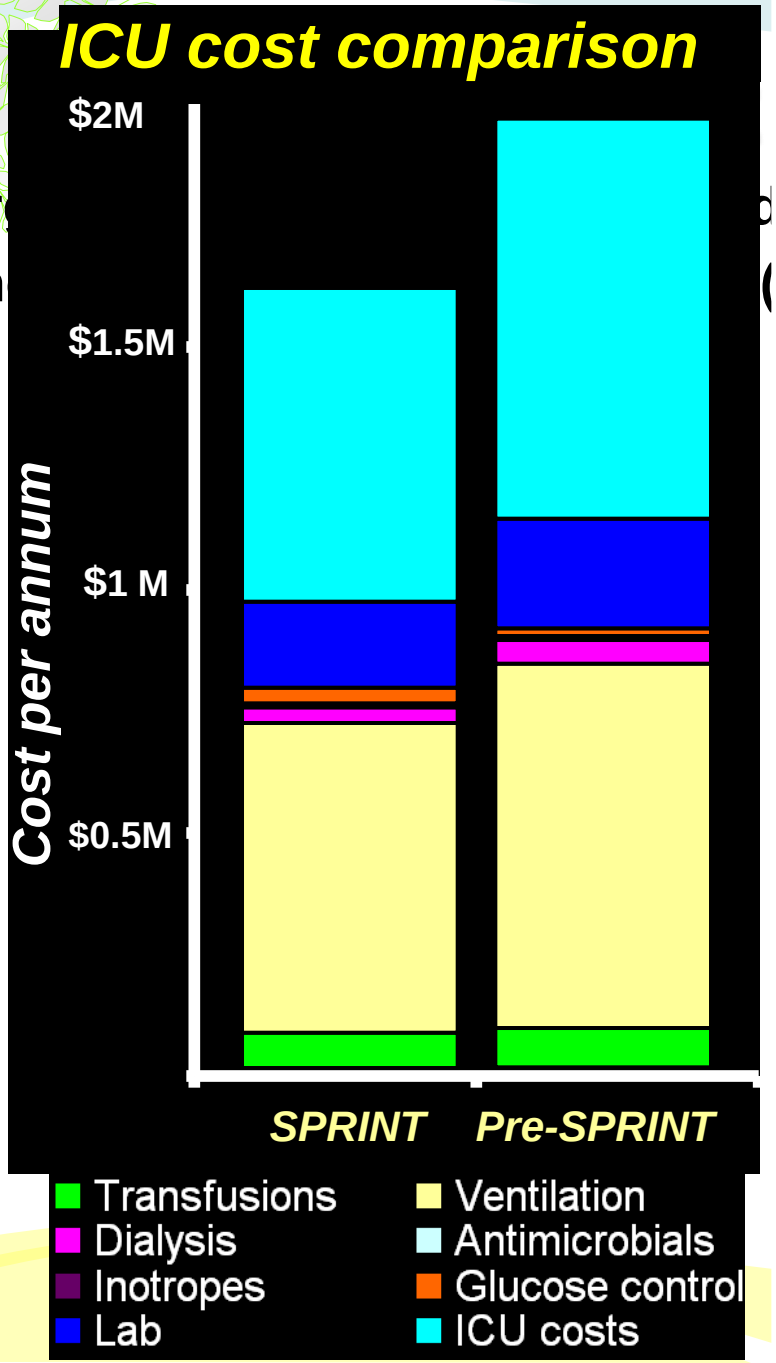
The Answer?

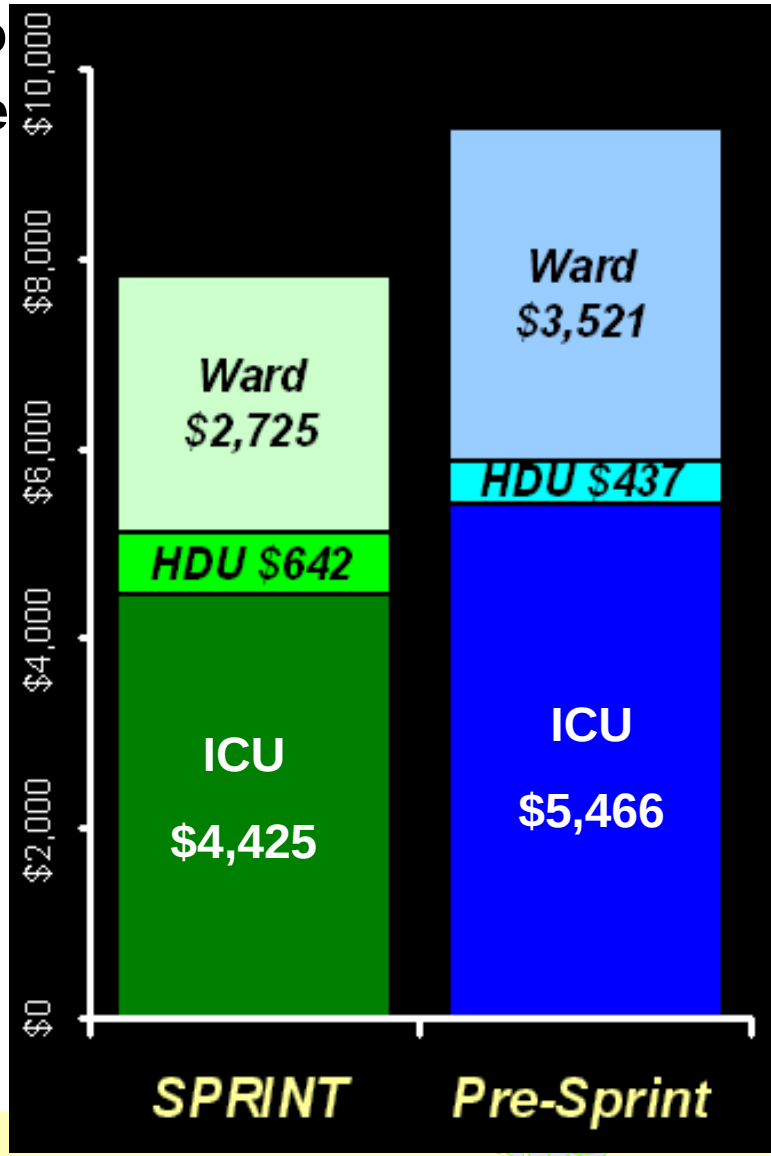


- **SOFA scores reduce faster with SPRINT and do so from day 2**
- **Organ failure free days: SPRINT = 41.6% > Retro = 36.6% (p<0.0001)**
- **Number of organ failures (% total possible) defined as SOFA > 2 for 1 SOFA score component: SPRINT = 16% < Retro = 19% (p<0.0001)**

on cost?

- O… due to
- Th… (as se…

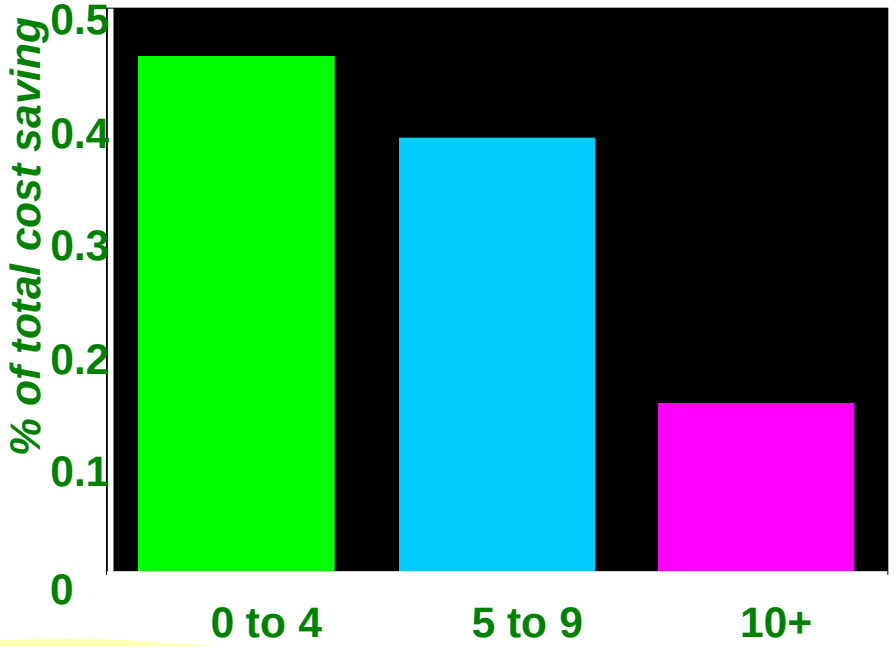




Cost was mostly saved in …

- Relatively well patients were most cost effective under SPRINT

SPRINT cost savings by max SOFA score

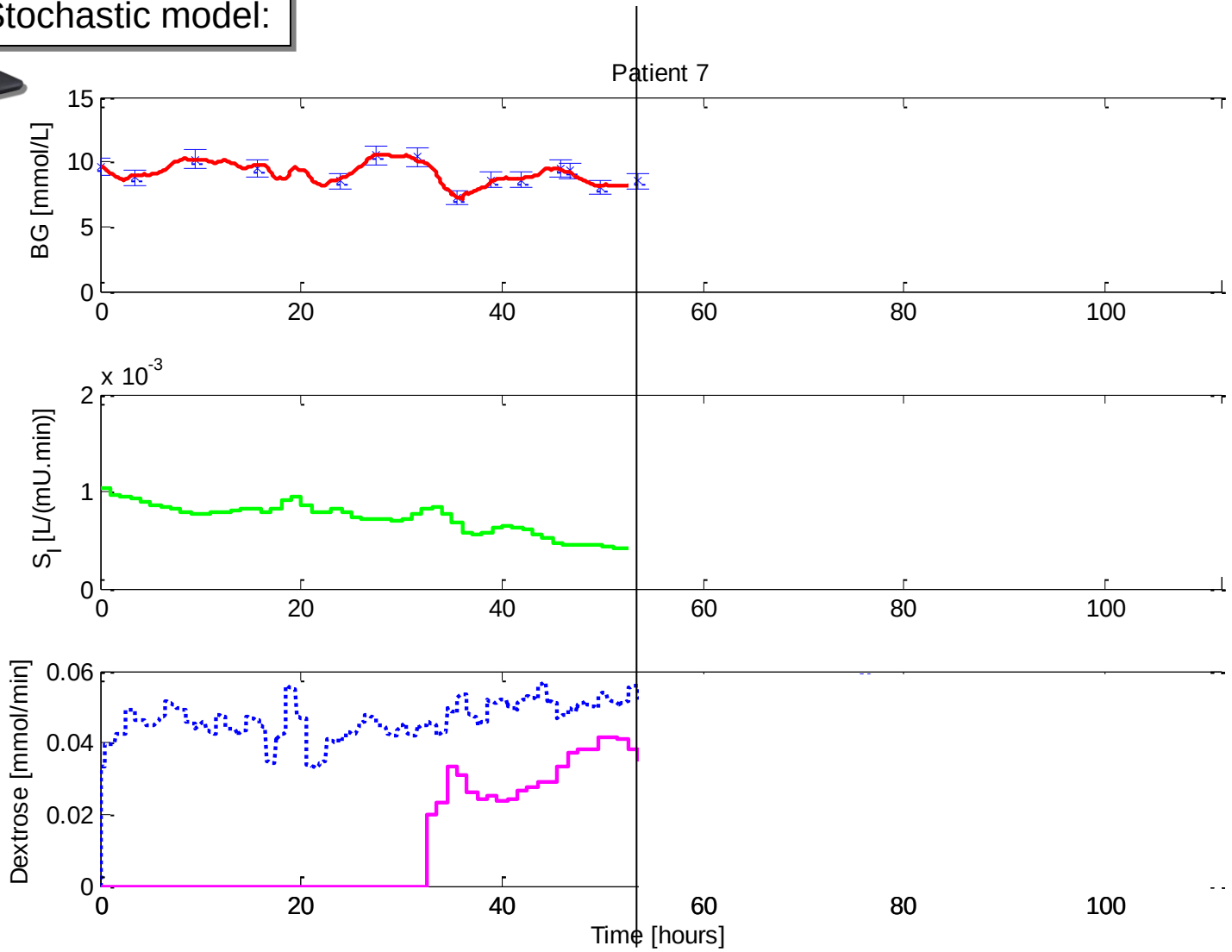


The Future?

- Stochastic Targeted (STAR) glycemic control
- Model-based and computer driven
- Forecasts changes in patient-specific behaviour using validated models to provide **guaranteed levels of safety from hypoglycemia**!
- To be trialled in Christchurch and Liege, Belgium in 2010.

Stochastic model in action

Stochastic model:



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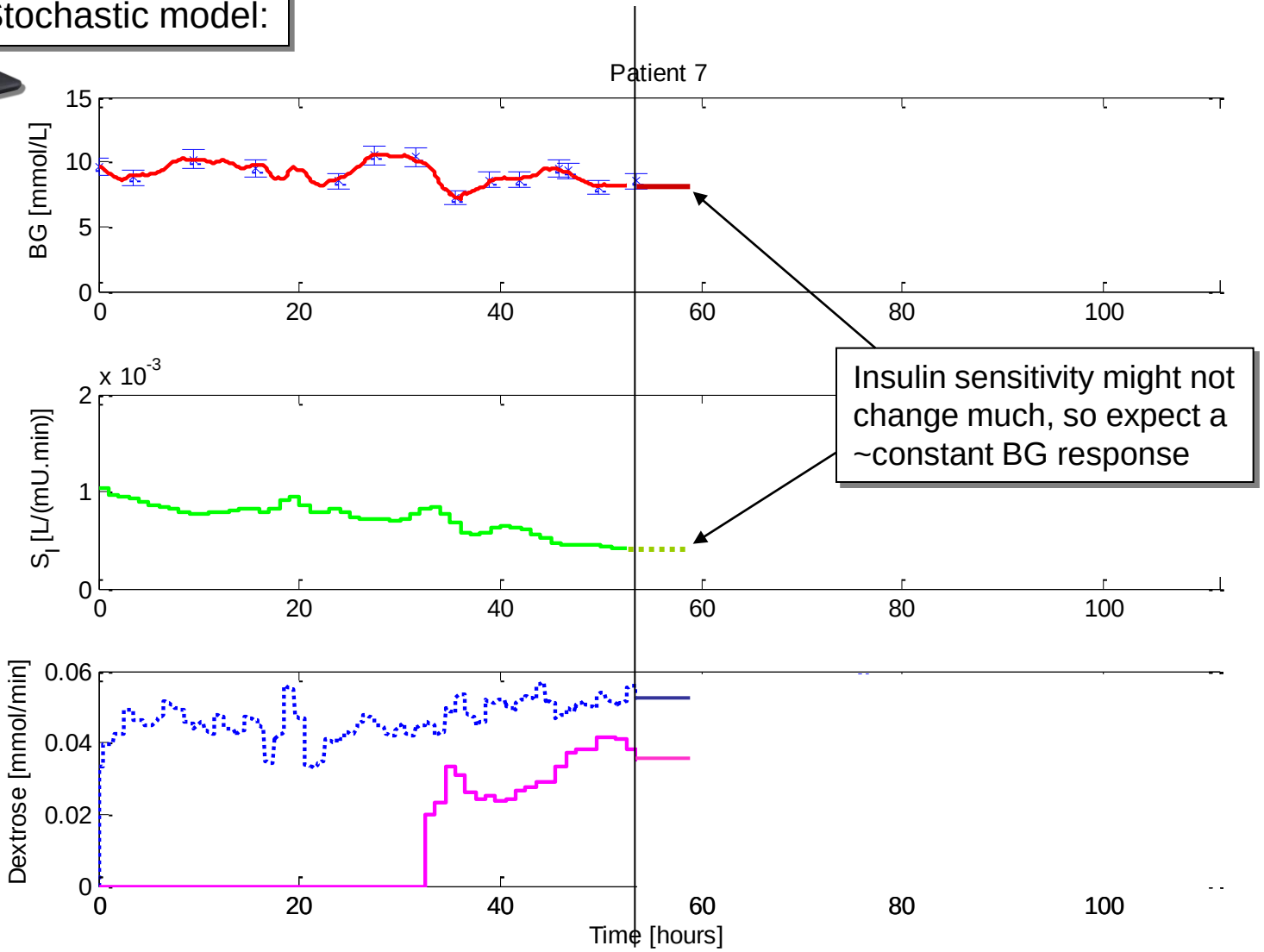

Stochastic model in action

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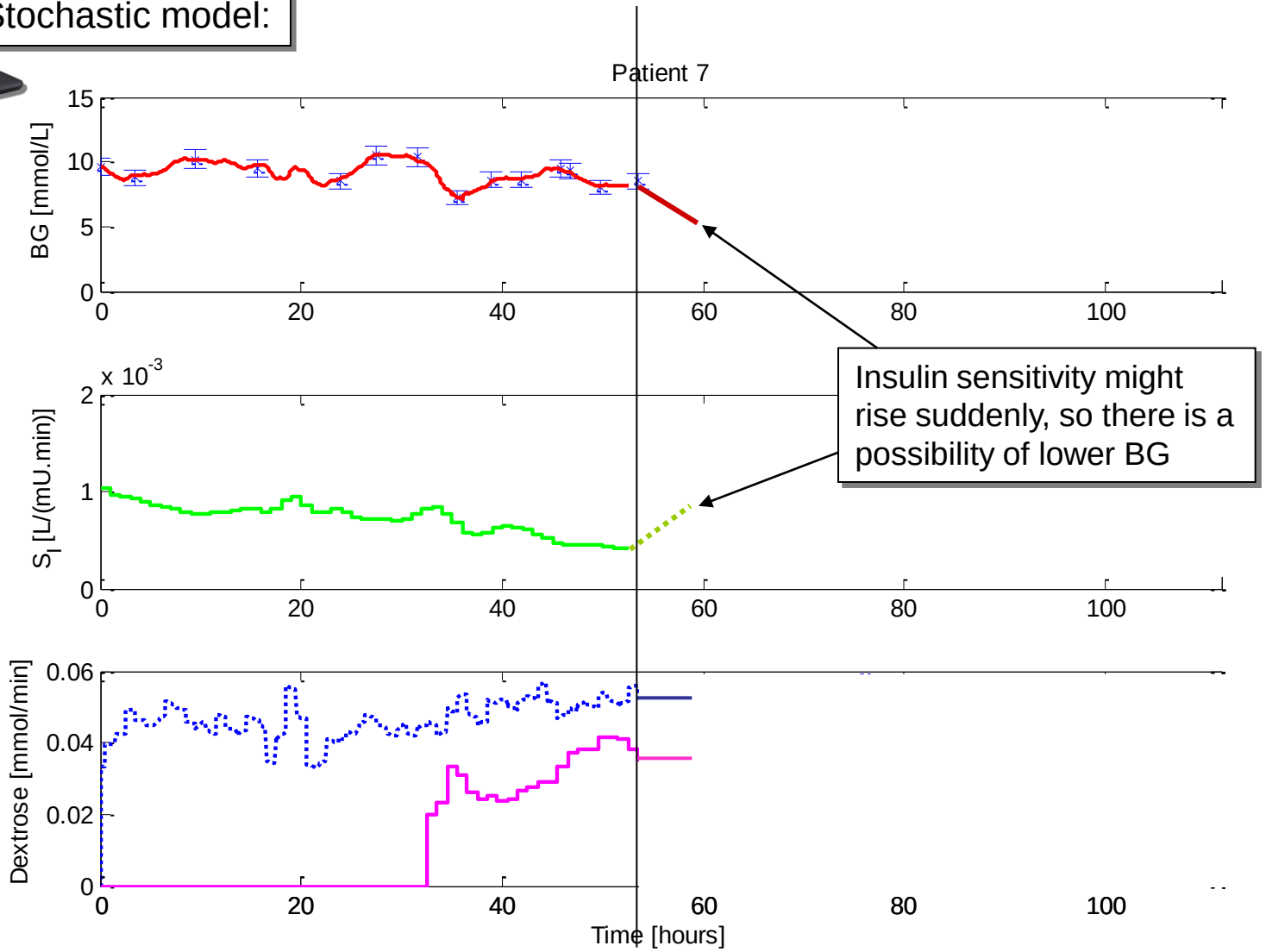

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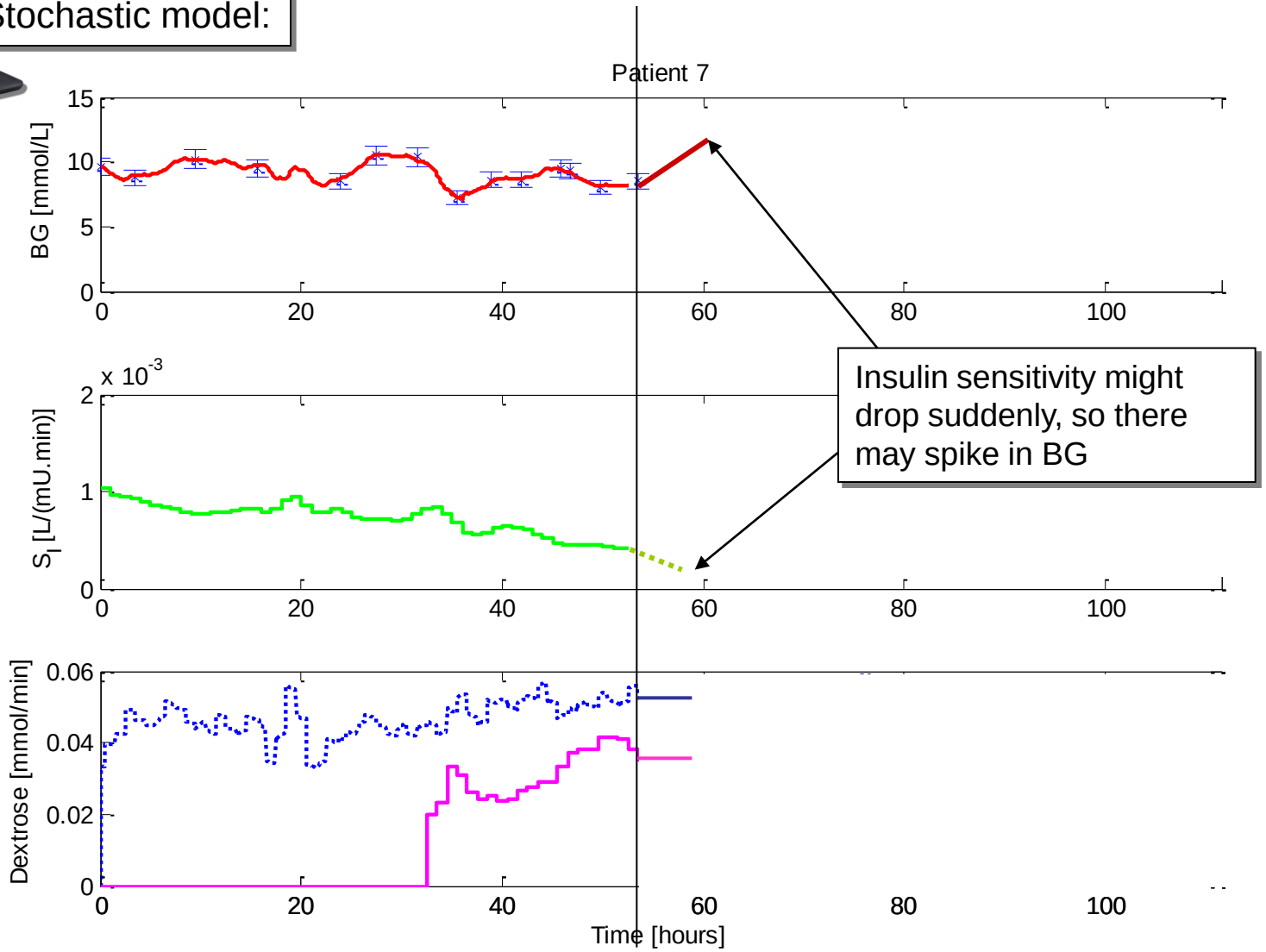

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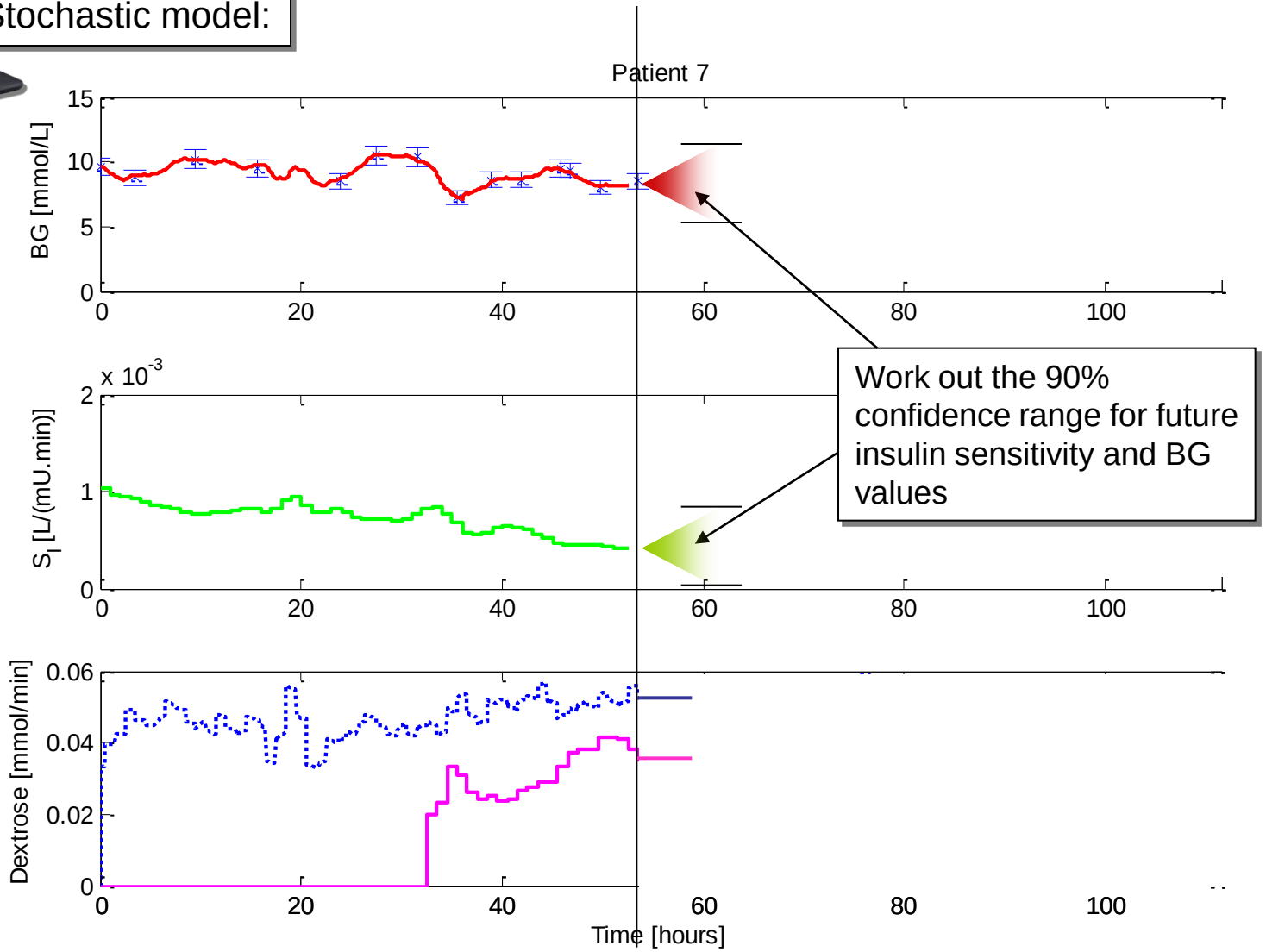

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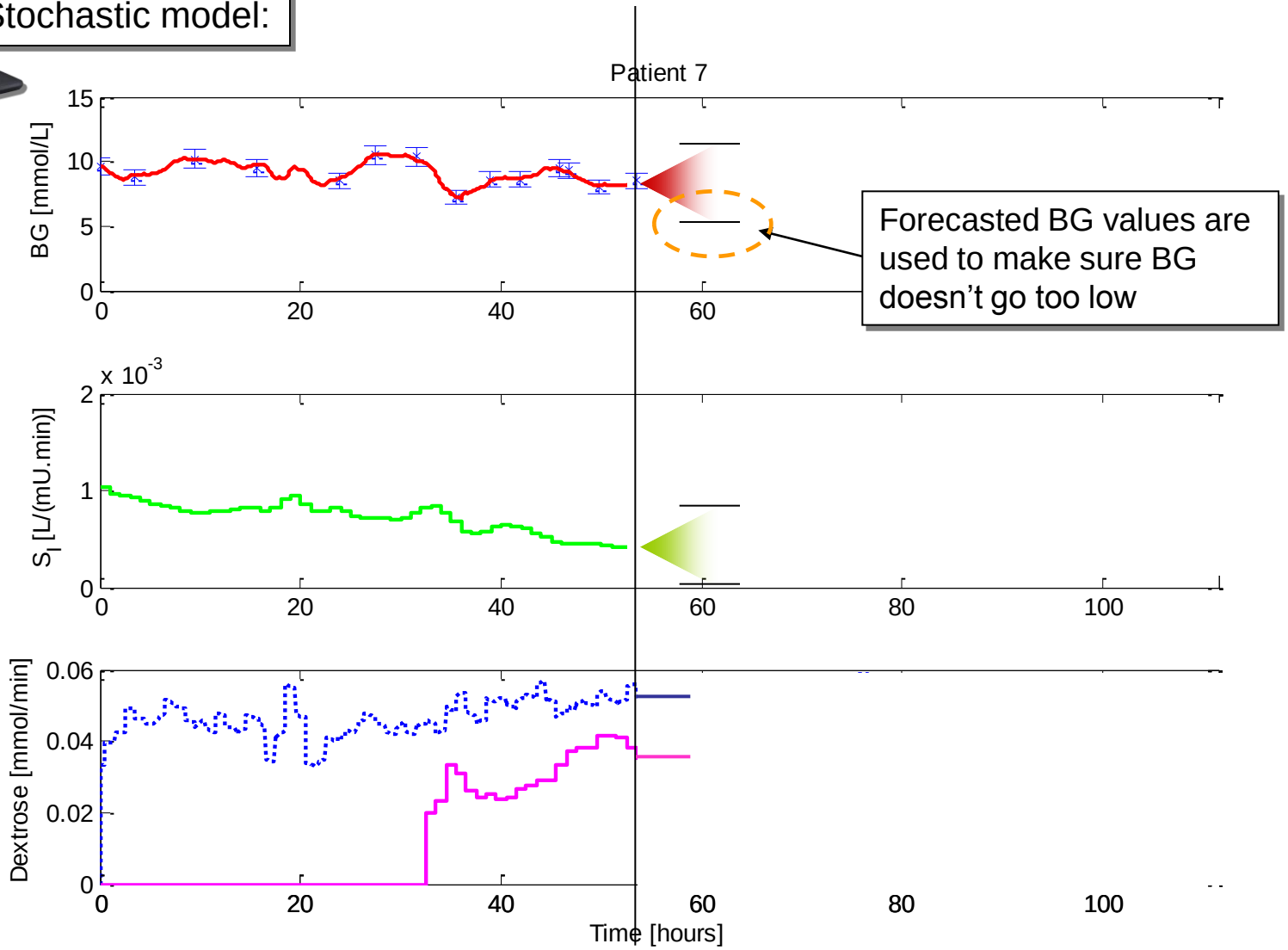
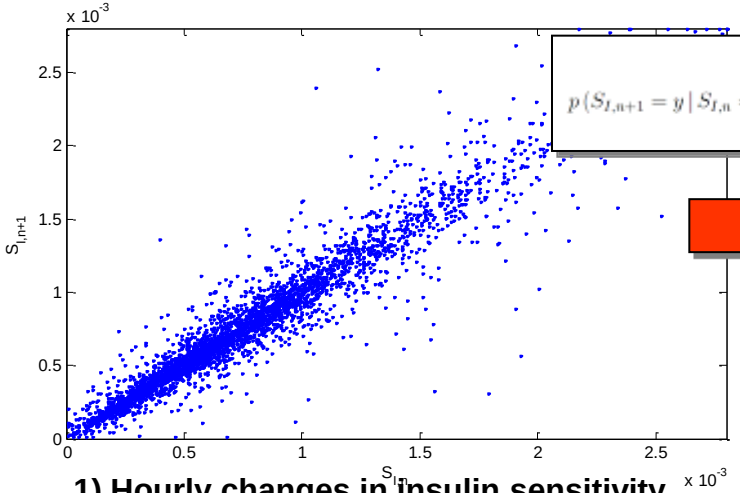


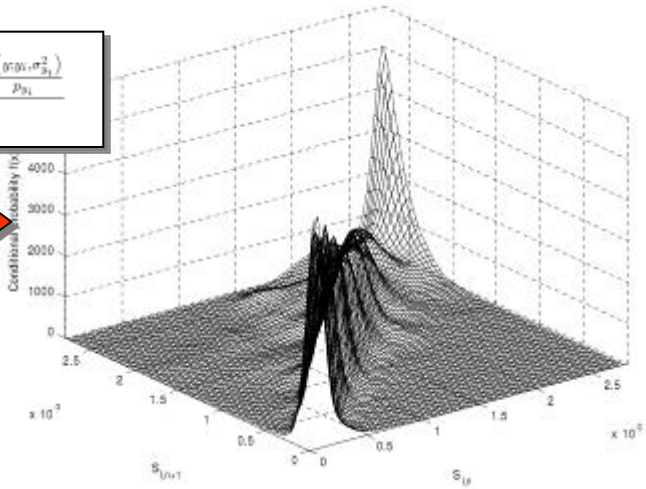
Forecasted BG values are used to make sure BG doesn't go too low

Kernel density model (lag-1)

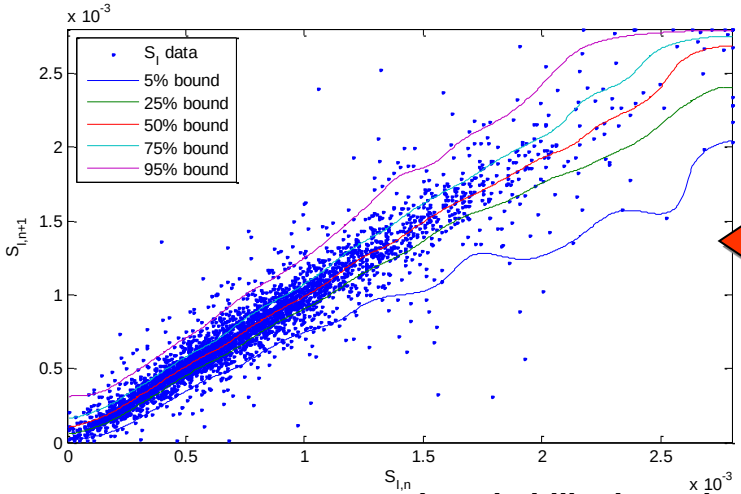


$$p(S_{I,n+1} = y \mid S_{I,n} = x) = \frac{\sum_{i=1}^{n} \frac{\phi(x;x_i,\sigma_{x_i}^2)}{p_{x_i}} \frac{\phi(y;y_i,\sigma_{y_i}^2)}{p_{y_i}}}{\frac{\phi(x;x_i,\sigma_{x_i}^2)}{p_{x_i}}}$$

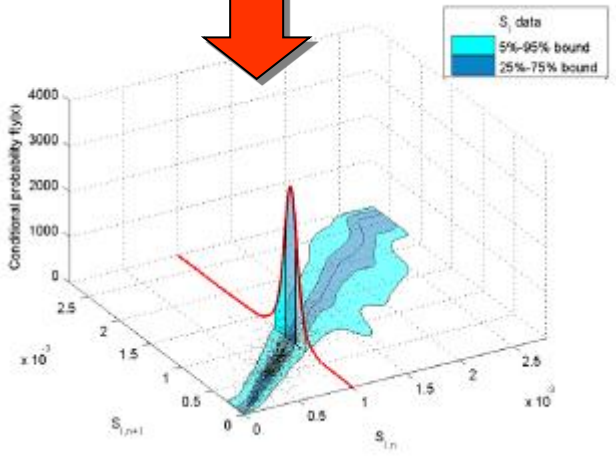
1) Hourly changes in insulin sensitivity



2) Kernel density model



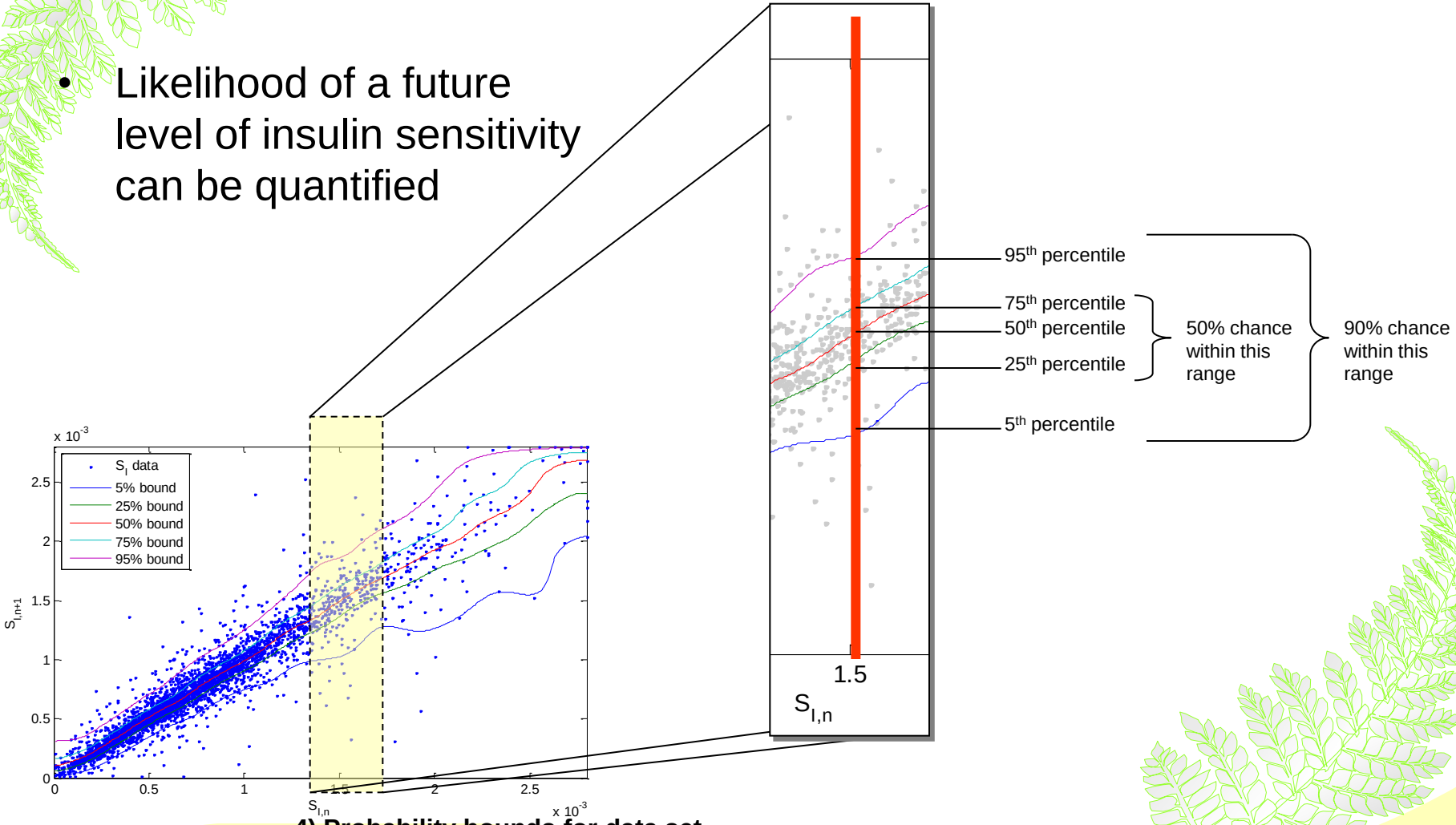
4) Probability bounds for data set



3) Conditional probability used for forecasting

Kernel density model (lag-1)

- Likelihood of a future level of insulin sensitivity can be quantified

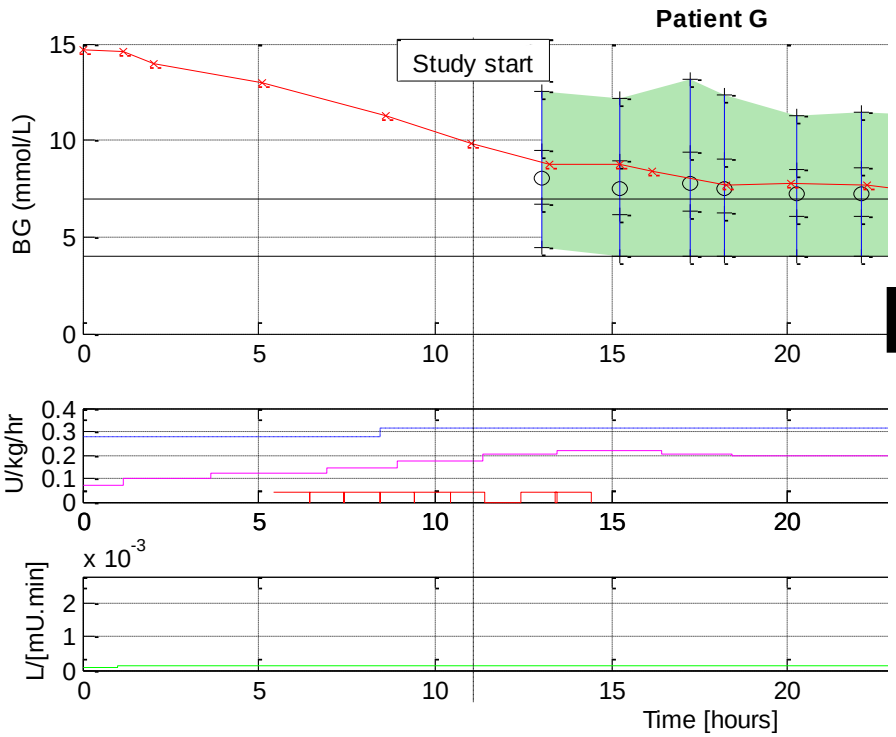


4) Probability bounds for data set

So, what does it look like in action?

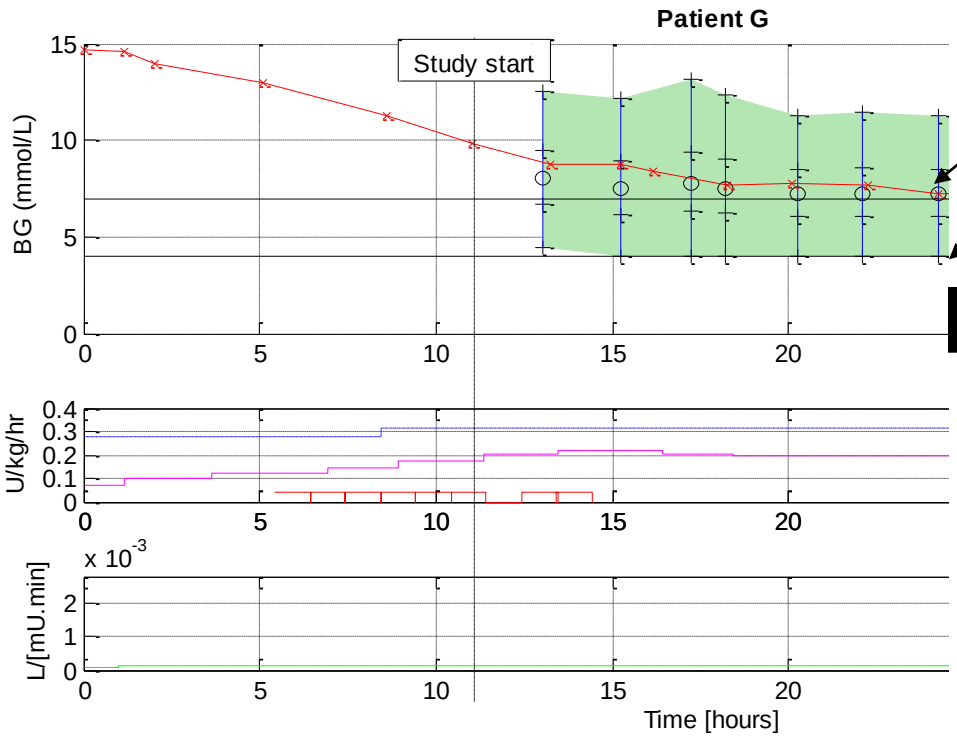
- **STAR was trialled with a neonate specific model in the Christchurch NICU**
- **8 patients have undergone 24 hour trials**
- **A further 8 have used system for entire length of hyperglycemia**
- **So, one example to show what a “STAR” glycemic controller can do…**

Patient G



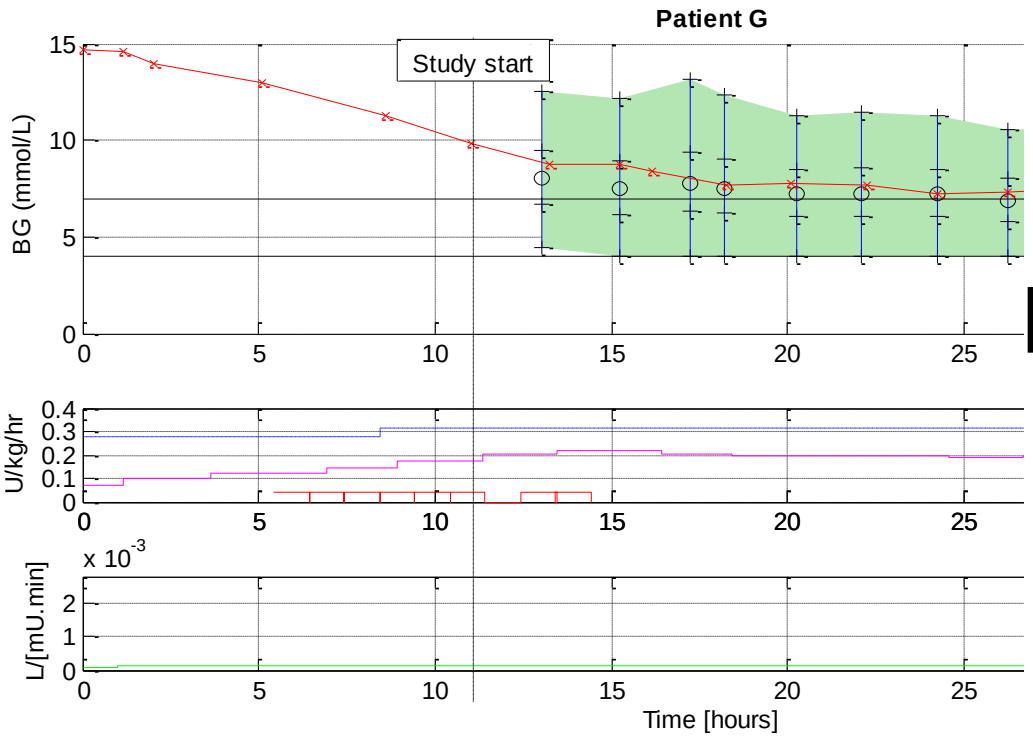
- Very insulin resistant →high insulin requirements (~2-3x other trial patients)
- High insulin rates → greater risk of hypo events, thus the stochastic model forecasts drove BG control
- Controller targeted ~7 mmol/L, based on possible change in insulin sensitivity in the future
- In essence, stochastic model said that 95th percentile rise in insulin sensitivity would lead to a BG < 4 mmol/L so target (median) was raised to ~7mmol/L to guarantee safety (5% max risk of BG < 4) → automatically
- Here we have the first ~10 hours of the trial…

Patient G



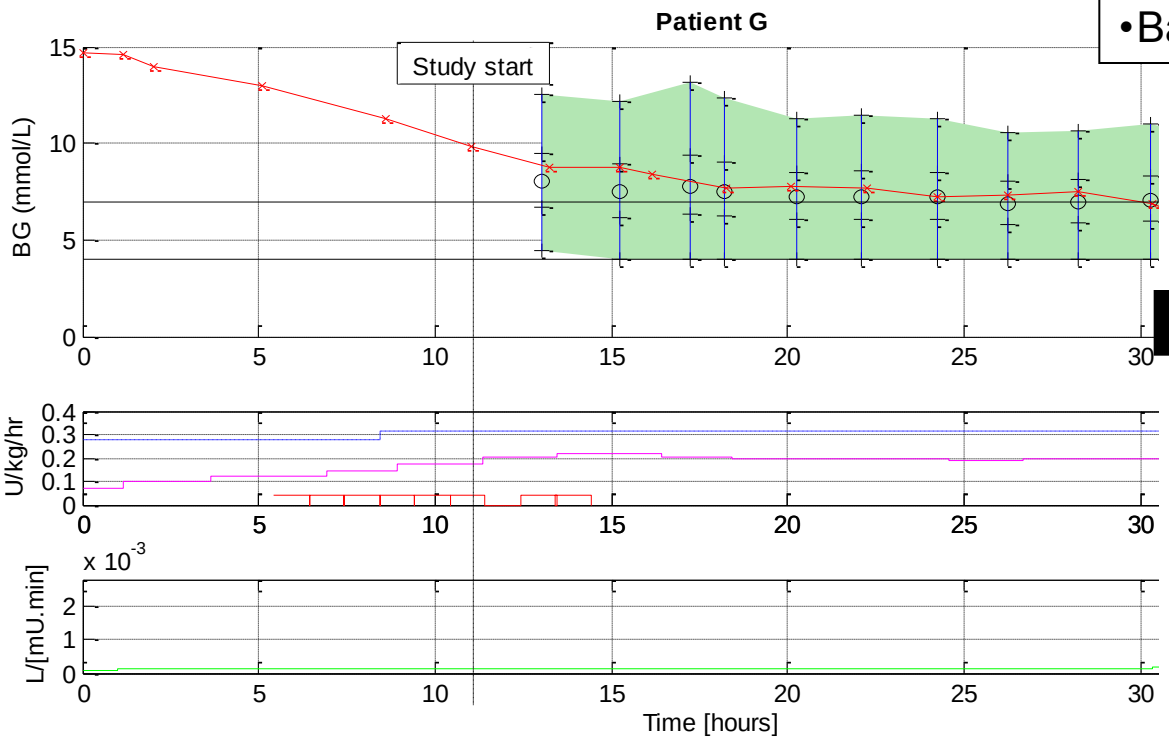
- Two hours later, and baby is still very insulin resistant.
- Controller targeting 7 mmol/L (to keep bottom of green shaded area at 4 mmol/L)…
- Thus, a 5% maximum risk of getting a BG < 4 mmol/L for a given 2-3 hourly intervention

Patient G



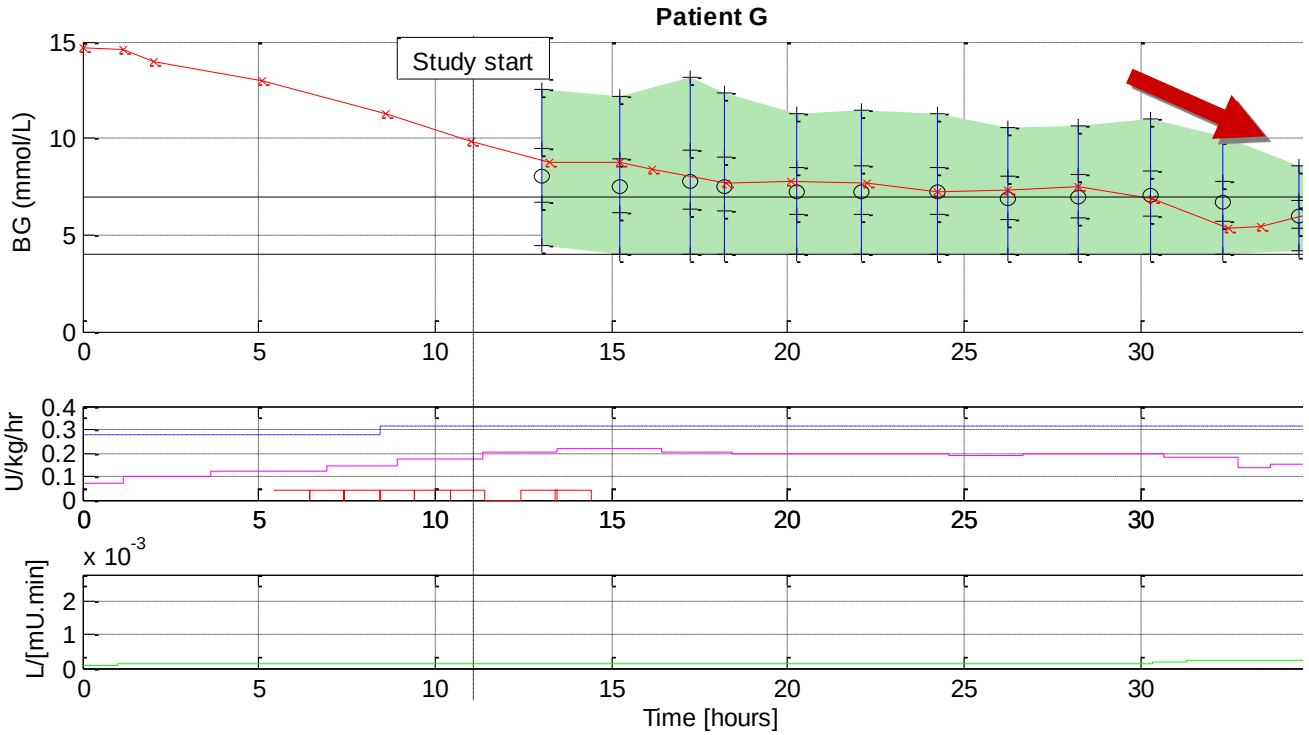
- Baby still very insulin resistant…

Patient G



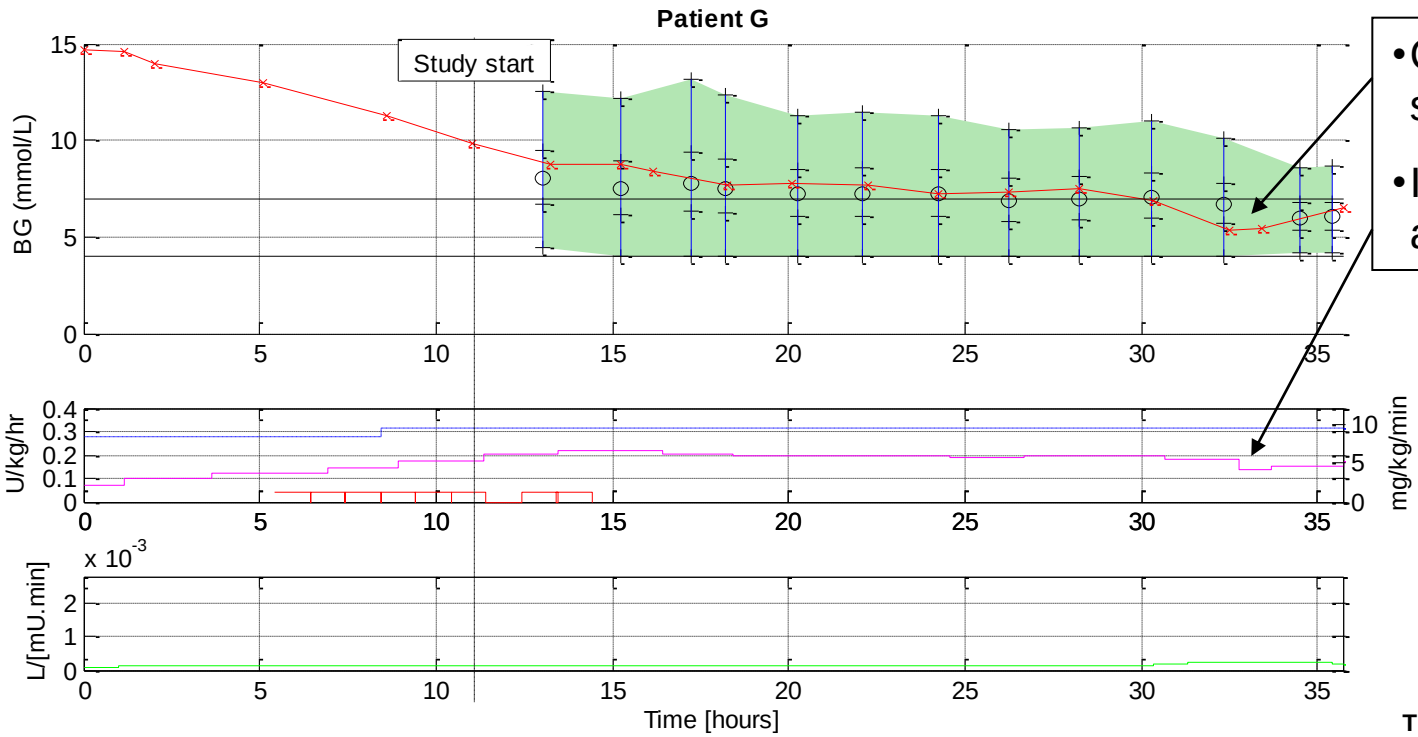
- Baby still very insulin resistant…

Patient G



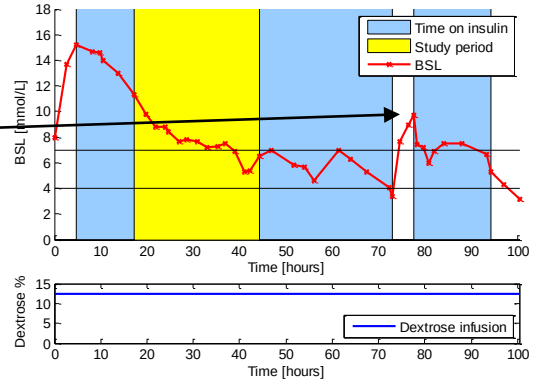
- Sudden BG drop of ~2 mmol/L
- If insulin infusions had been more 'aggressive', may have caused a hypo event → tolerated period of higher BG to create buffer against hypo.
- No clinically observable change in baby over this time → something inside 'switched on'
- Stochastic model forecasts to account for un-measurable and un-modelled effects

Patient G



- Change in insulin sensitivity contained
- Insulin infusion rate adjusted

- Rebound hyperglycaemia when insulin stopped



In Summary:

- **SPRINT**
  - Successful in reducing mortality, organ failure and cost = 240 lives and $2M over last 4 years
  - Model derived, but implemented in paper
  - Not adaptive to clinical needs or practice

- **The Future**: Flexible, stochastic, targeted and thus customisable across cohorts and practices
  - But, equally effective
  - Coming in 2010! (already here if you are a <1kg neonate in Chch)

- **The Moral**: It's not the car, it's how you drive it!
  - Anyone can drive a Ferrari F1 car, but only Michael Schumacher can control it and win world championships!
  - I.e. it's not the therapy or the target, it's the protocol or how you do it that defines success ➔ protocolised computer based TGC can make everyone an expert!

Acknowledgements

NEW ZEALAND HEALTH INNOVATION AWARDS

SUPREME WINNER 2006

Chronicle

UC UNIVERSITY OF CANTERBURY

Volume 41, No. 5 Thursday, March 30, 2006

UC students scoop award with life-saving device

Intensive Care Nursing Staff, Christchurch Hospital


Questions?