STAR GRYPHON

Glycaemic Control for Neonatal Intensive Care Units

Gender and glycaemia: Insulin sensitivity and secretion in premature neonates

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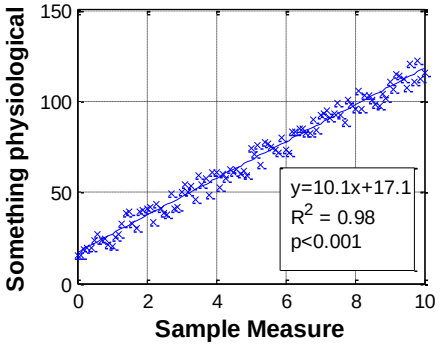
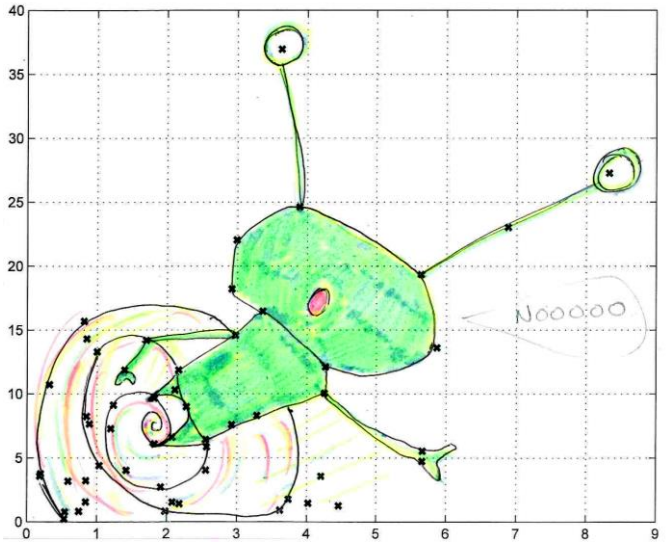
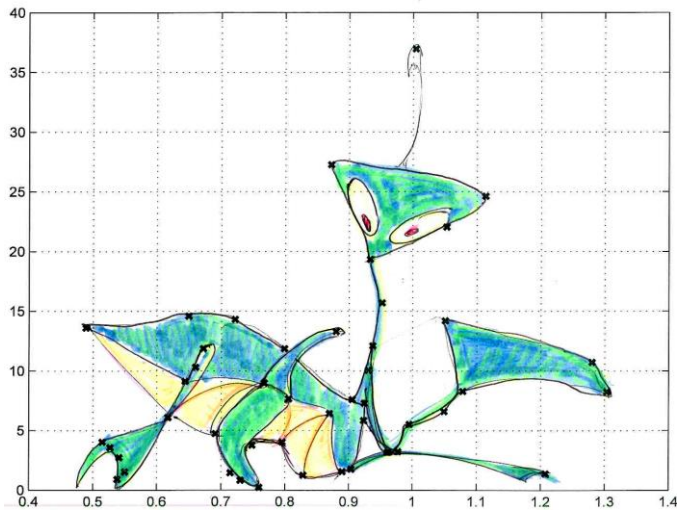
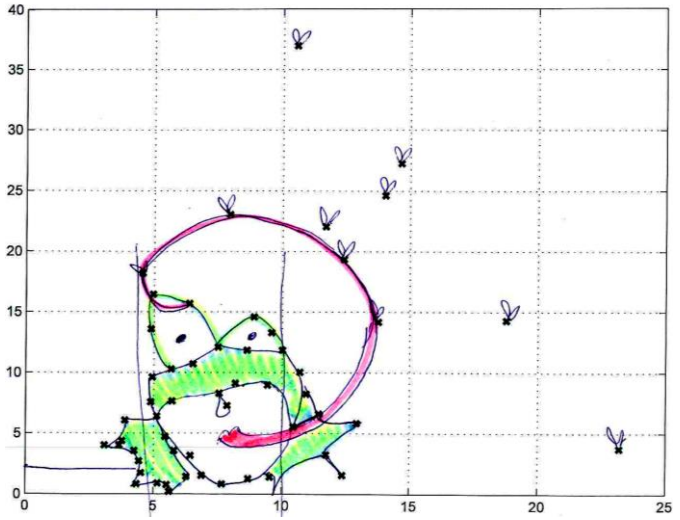
Introduction: Humans are horribly variable



Optimism vs. actuality







Can we quantify some of this variability?

Should gender equality affect intensive care?

… should we treat boys and girls in the same way?

It is well known that extremely/very premature male infants tend to be sicker and have higher mortality rates than their female counterparts.

Our research suggests that metabolic differences between boys and girls exist, even in a extremely premature cohort

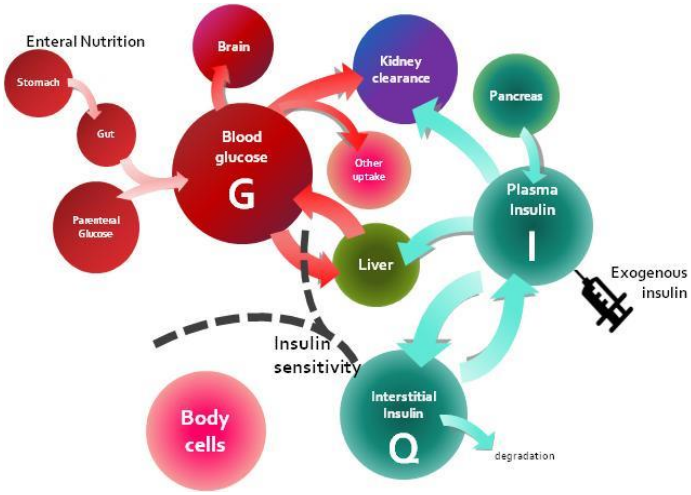
→ The focus here is improvement of glycaemic control protocols by better accounting for differences between patients

Background: Glycaemic control

What is STAR-GRYPHON?

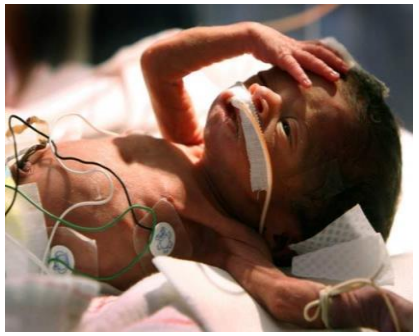
STAR – GRYPHON is a model-based protocol for dosing insulin in **very premature infants**.

- → Model-based: use mathematics to describe glucose-insulin dynamics
- → Insulin Sensitivity: describes the patient-specific and time-varying glycaemic response to insulin
- → Interface: touch screen bedside tablet computer



Background: The preterm infant

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



Associated medical issues:

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

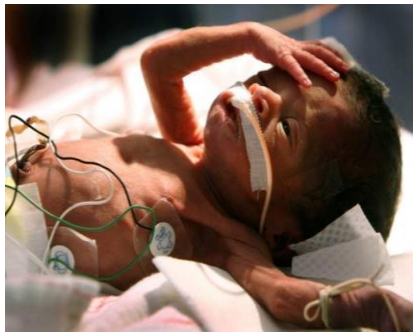
Further complicating features:

- Extremely fragile – minimise invasive procedures
- Low blood volume - ~50 mL

Why control blood glucose in this cohort?

Abnormal Blood Glucose:

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



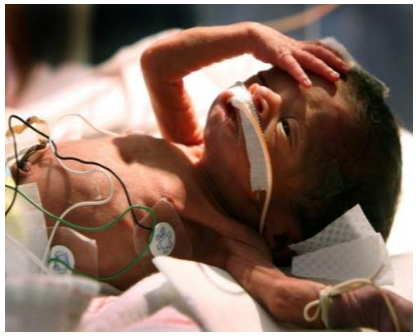
Associated effects of hyperglycaemia in neonates

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

Why is glycaemic control hard?

Hypoglycaemia is also dangerous

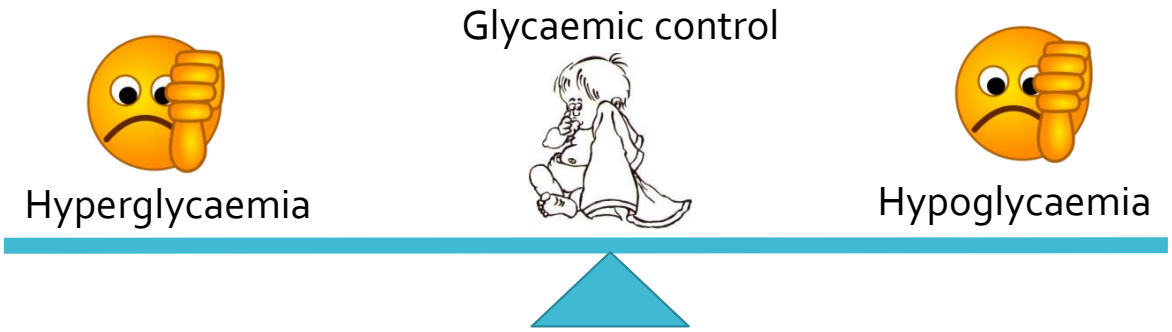
- Brain damage
- Developmental delays
- Higher mortality and morbidity



"Humans are horribly variable"

Variation in glycaemic metabolics:

- Over time
- Between patients

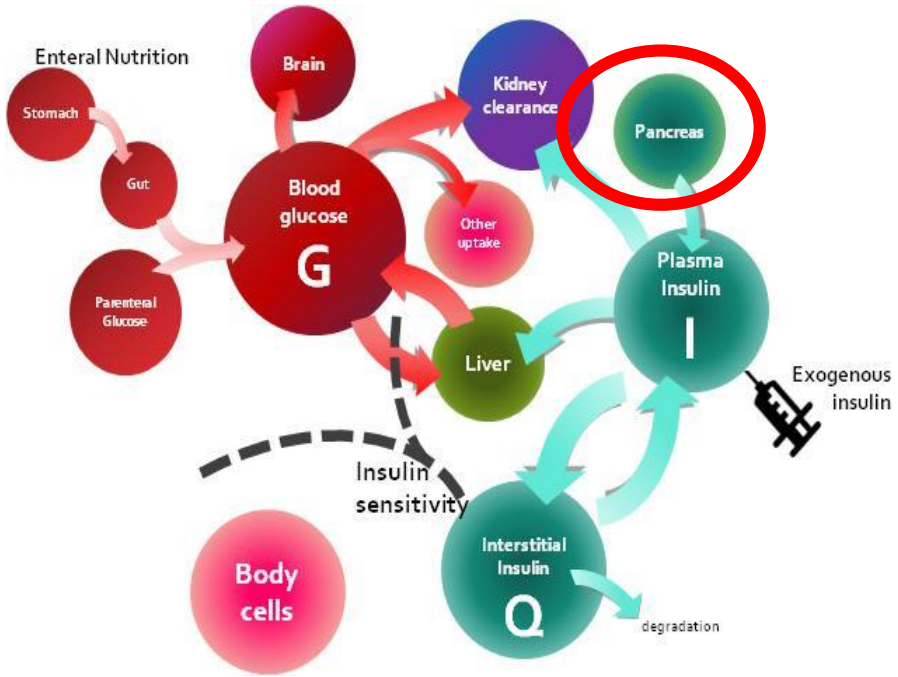


Study objective: model insulin secretion

Why is quantification of insulin secretion in this cohort important?

→ Improve the mathematical model used by STAR-GRYPHON

→ Better quantification of sources of variability within and between patients



A small term in a big equation, but better modelling can have a big effect...

The scope of other work in this area:

EFFECT OF THEOPHYLLINE, GLUCAGON AND THEOPHYLLINE PLUS GLUCAGON ON INSULIN SECRETION

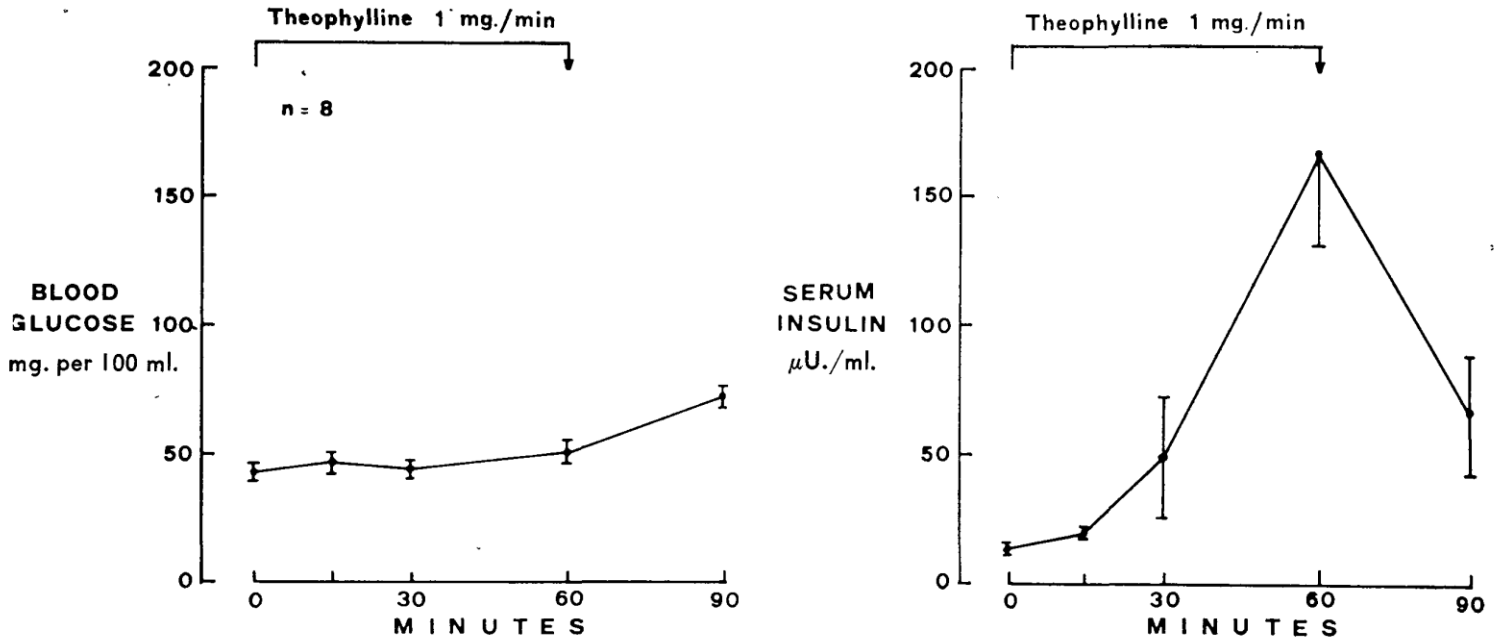


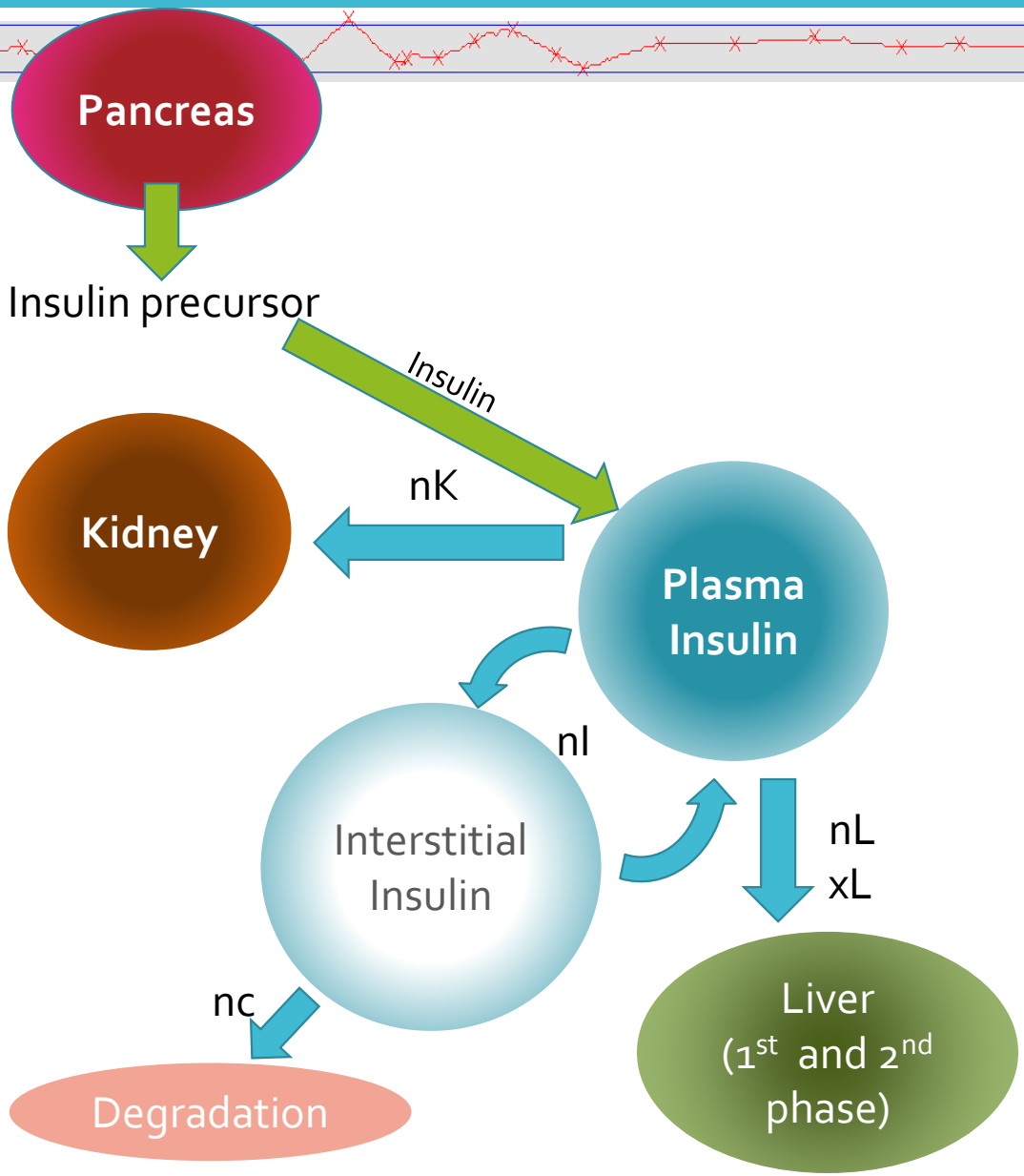
FIG. 1. Levels of blood sugar and serum insulin in premature infants following a sixty minute infusion of theophylline (1 mg. per min.).

Grasso et al (1970), *Effect of Theophylline, Glucagon and Theophylline plus Glucagon on Insulin Secretion n the Premature Infant.* Diabetes. 19(11). P. 837041

Insulin secretion in premature infants has previously been indirectly analysed via plasma insulin concentrations .

Why is plasma insulin insufficient?

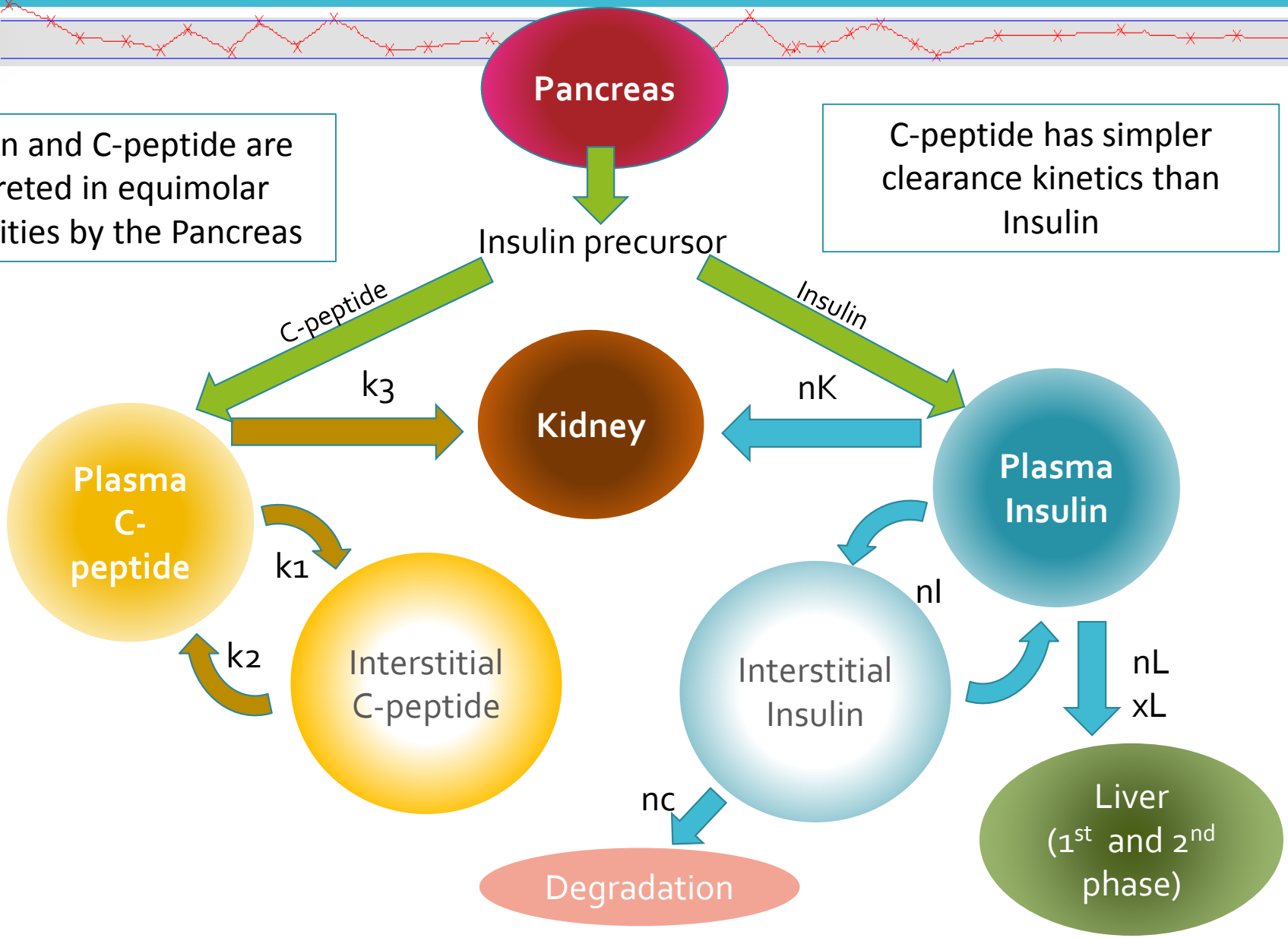
Insulin kinetics are not that simple, even when simplified.....



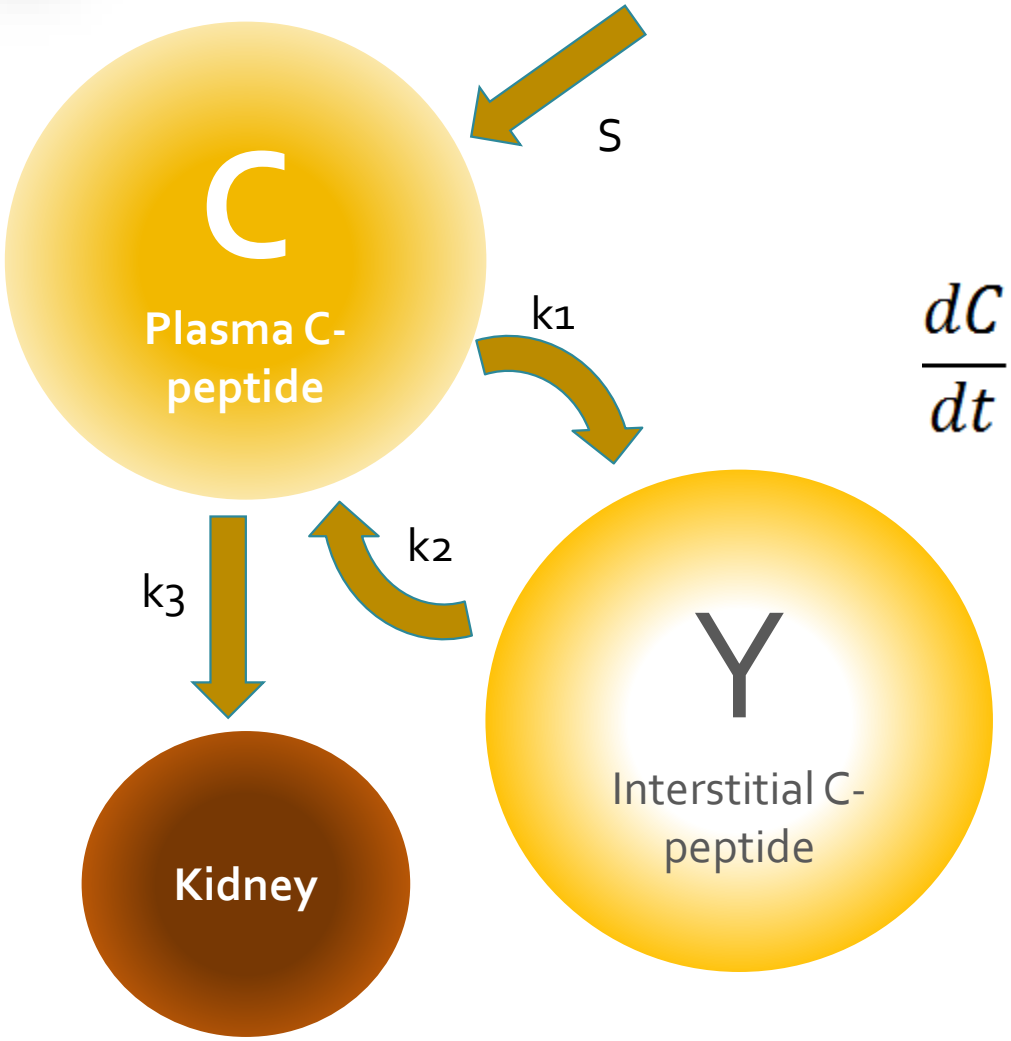
Why plasma C-Peptide?

Insulin and C-peptide are secreted in equimolar quantities by the Pancreas

C-peptide has simpler clearance kinetics than Insulin



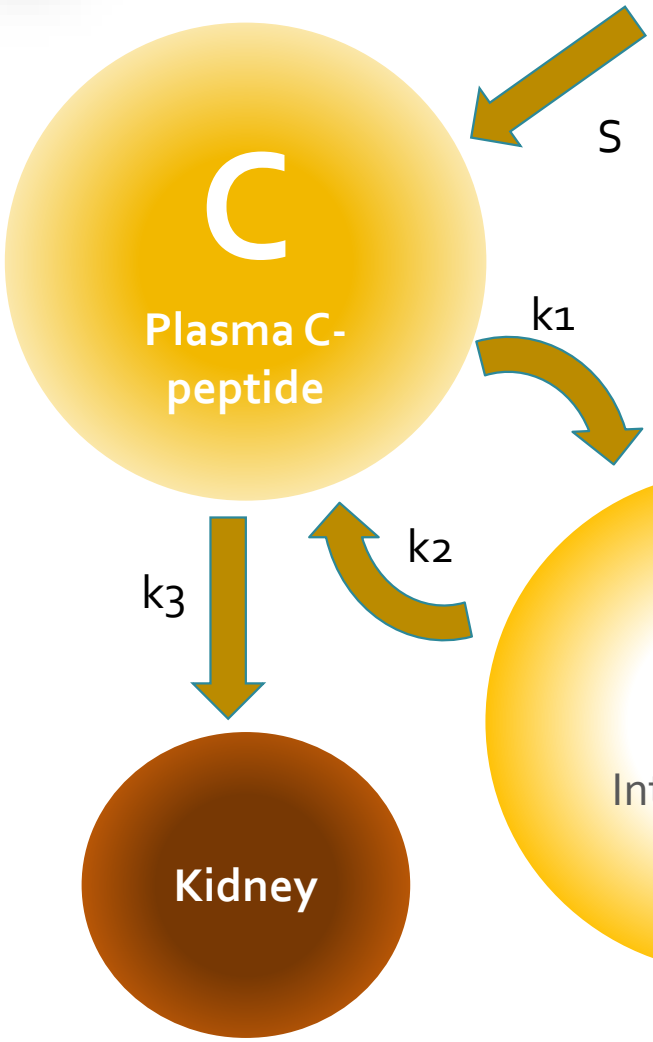
Van Cauter model of C-peptide



$$\frac{dC}{dt} = S - (k_1 + k_3)C + k_2 Y$$

$$\frac{dY}{dt} = k_1 C - k_2 Y$$

Van Cauter model of C-peptide



Low blood volume of extremely premature infants restricts sampling.

→ Assume steady state at time of sampling:

$$0 = S - (k_1 + k_3)C + k_2Y$$

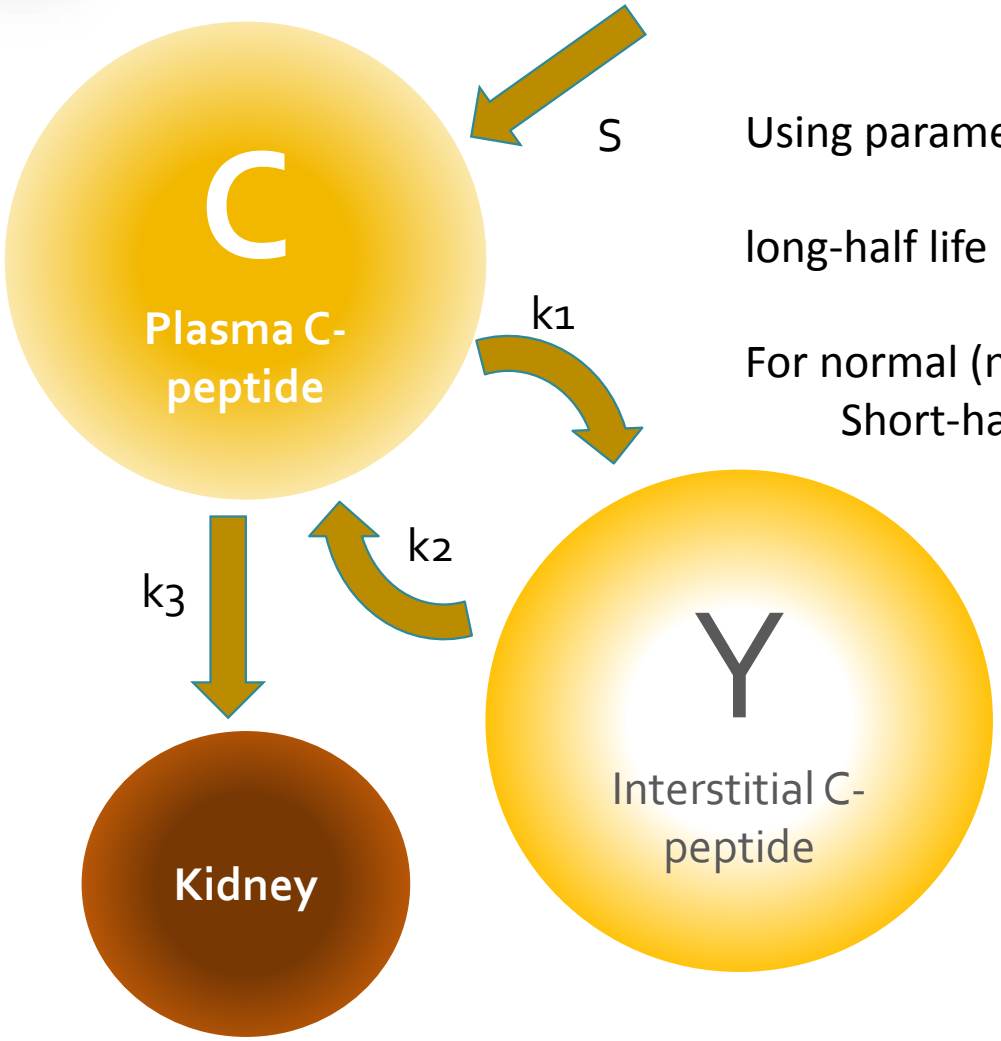
$$0 = k_1C - k_2Y$$

$$k_1C = k_2Y$$

$$S = k_3C$$

Can use this equation to estimate insulin secretion given a C-peptide concentration

Van Cauter model of C-peptide



Using parameters methods from Van Cauter et al:

long-half life (min) = 0.14 Age (years) + 29.2.
= 29.2 min

For normal (non-diabetic) subjects:

Short-half life = 4.95 min

F = 0.96

Given: a = log(2)/(short half-life)

b = log(2)/(long half-life)

And $k_2 = F\,(b - a) + a$

$$k_3 = \frac{a\,b}{k_2}$$

k_3=0.064 min^{-1}

Results

Blood samples:

•Intermittent samples from some of the infants in the HINT study (*Alsweiler et al, 2012*)

$$S = k_3 C$$

Looking for trends between insulin secretion and:

•Age (Gestational, postnatal)
•Weight
•Feed types or regimes
•Therapy usage (steroid/insulin)

The HINT cohort

	Whole cohort	Blood samples
Number of Patients		
Total	88	41
Control group	45	21
TGC group	43	20
Male n (%)	42 (48%)	20(49%)
Number of samples	-	54
Birth weight, g	**793 [691-901]**	**839 [735-1000]**
Gestational age, wks	**26 [25–27]**	**27 [26- 29]**
Post natal age, days		
At Enrolment	4 [3-7]	3.5 [3-6.5]
At time of Sample	N/A	9.5 [4 -17]
Day of Randomisation	N/A	7 [0 – 14]
Ethnicity		
Asian	10	9 (22%)
Caucasian	12	11 (27%)
Maori	15	17 (41%)
Pacific Island	6	4 (10%)

Sample selection:

- Gestational age < 31 weeks
- C-peptide concentration determined using immunomentric assays.

Results: Gender is significant

	All Samples		
	Male	Female	P
n	25	29	-
n (DOR=0)	11	13	
Weight [g]	930 [755-1041]	815 [702-975]	0.15
GA [wks]	26 [25 – 27]	26 [25 – 26.3]	0.60
PNA	9 [3.8-16.5]	11 [4.8-17]	0.71
BG [mmol/L]	6.9 [5.5-10.2]	7.6 [4.9-10.8]	0.77
Plasma Insulin [mU/L]	14 [6.8 – 26]	16 [8.9 – 7]	0.52
Insulin Secretion [mU/L/kg/min]	4.7 [2.1-8.3]	11.7 [5.3 – 18.7]	**0.003**
Average Total Dextrose Intake [mg/kg/min]	9.4 [7.7-11.1]	9.3 [7.8 – 11.8]	0.79
PN glucose [g/day]	5.0 [0-8.8]	3.6 [0-8.4]	0.29
EN lactose [g/day]	2.6 [0.7-11.9]	6.5 [0.5-19.6]	0.74
Protein Intake that day [g/kg]	3.1 [2.5-3.9]	2.8 [2.6-3.8]	0.39
Number receiving insulin	10	4	
Insulin at sample [U/kg/hr]	0.00 [0.00-0.05]	0.00 [0.00-0.00]	0.06
Total Insulin that day [U/kg]	0.00 [0.18-0.64]	0.00 [0.00-0.48]	0.10

Insulin secretion differs significantly between the sexes in very preterm infants

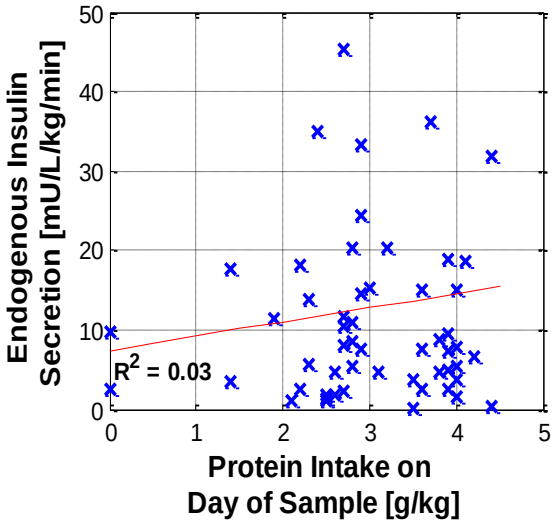
Results: factors that were not significant

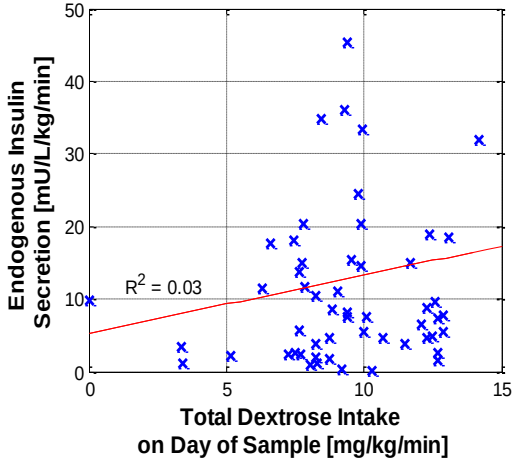
Insulin secretion was NOT significantly dependant on:

- Birth weight
- Gestational age
- Post natal age (when corrected for blood glucose)
- Protein intake
- Dextrose intake and method (IV/enteral)
- Steroid use

While generally insulin secretion did seem to be lower in the presence of exogenous insulin infusion, this was not statistically significant, and secretion fell well within the variability of insulin secretion values in infants not receiving insulin.

Insulin secretion in the very premature infant seems to be immature, and very patient specific.



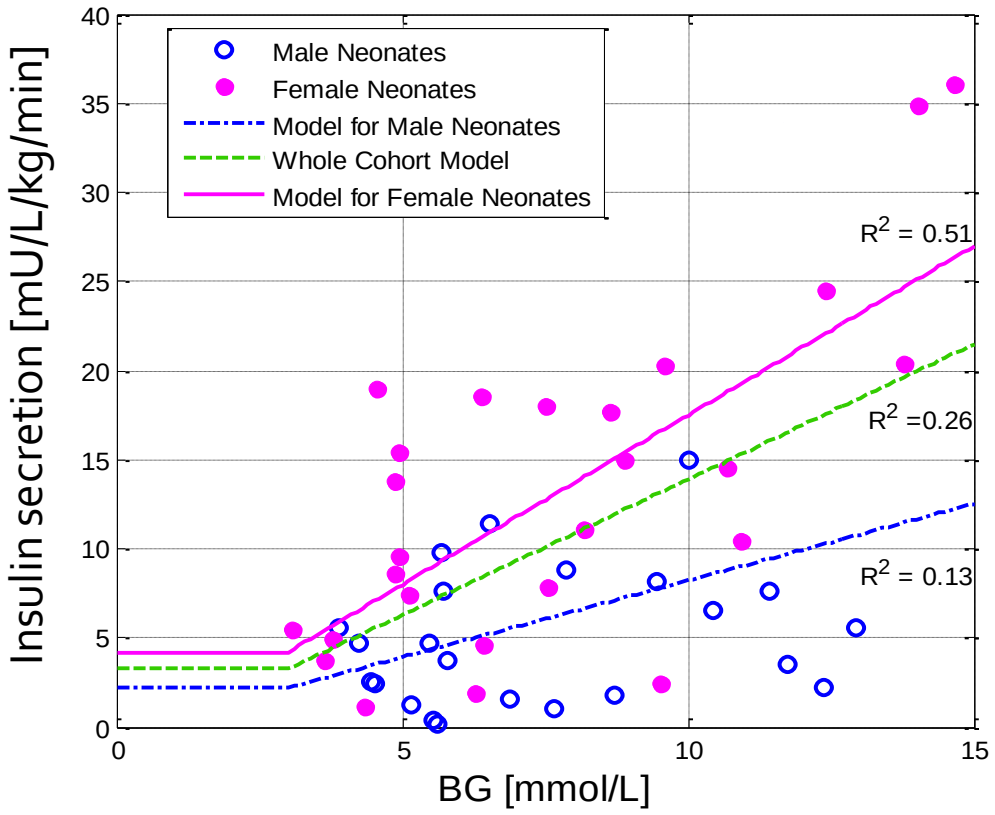


Results: Gender is still significant

	No Exogenous Insulin only		
	Male	Female	P
n	15	25	-
n (DOR=0)	8	11	
Weight [g]	930 [730–1044]	845[725–991]	0.49
GA [wks]	26 [25 – 27]	26 [25.3 – 27]	0.51
PNA	6 [3-17]	11 [4.8-17]	0.38
BG [mmol/L]	8.0 [5.6-11.6]	7.6 [4.9-10.8]	0.79
Plasma Insulin [mU/L]	10.4 [3.5 – 30.8]	14.3 [8.9 – 27.1]	0.34
Insulin Secretion [mU/L/kg/min]	5.6 [2.5-11.1]	13.8 [7.7 – 18.7]	**0.03**
Average Total Dextrose Intake [mg/kg/min]	9.2 [6.6-10.1]	9.4 [8.1–11.9]	0.36
PN glucose [g/day]	7.9 [3.7-9.9]	3.6 [0-9.0]	0.11
EN lactose [g/day]	1.5 [0.5-8.2]	6.5 [0.5-15.2]	0.24
Protein Intake that day [g/kg]	2.9 [2.3-3.8]	2.9 [2.7-3.8]	0.92
Number receiving insulin	-	-	-
Insulin at sample [U/kg/hr]	-	-	-
Total Insulin that day [U/kg]	0.00 [0.00-0.27]	0.00 [0.00-0.09]	0.40

This difference holds if only infants who did not receive insulin are considered

Results: An insulin secretion model



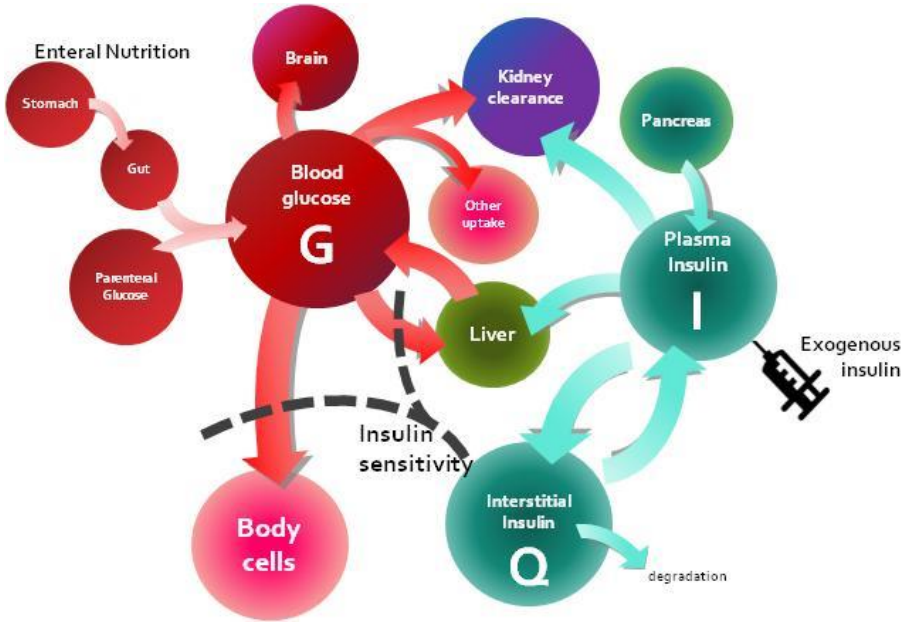
Girls vs. Boys

- Insulin secretion higher in girls across the range of blood glucose values

→ **Models generated for insulin secretion in male and female very premature infants**

Plugging insulin secretion into the NICING model

Neonatal Intensive Care Insulin-Nutrition-Glucose model



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

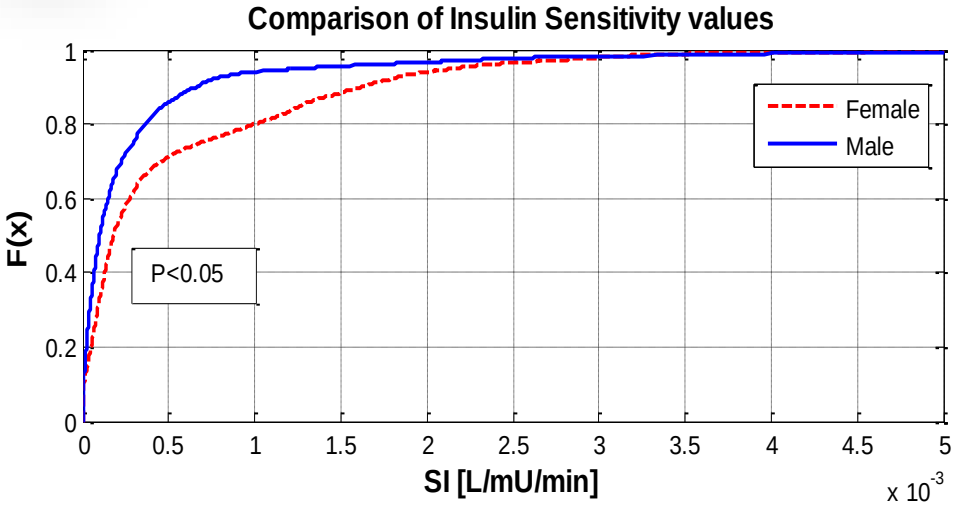
$$\dot{I} = -\frac{n_L I(t)}{1 + \alpha_I I(t)} - n_K I(t) - n_I\big(I(t) - Q(t)\big) + \frac{u_{ex}(t)}{V_{I,frac} * m_{body}} + (1 - x_L) u_{en}$$

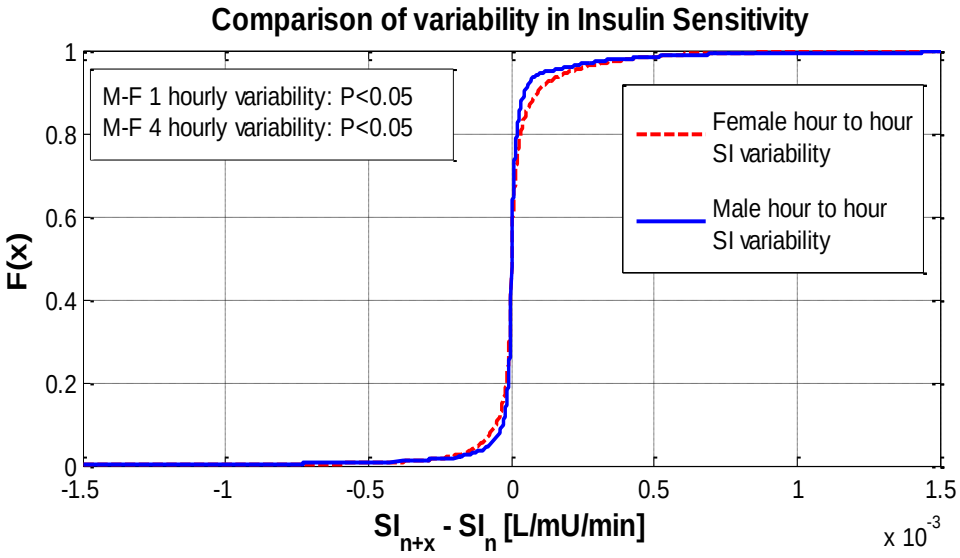
$$\dot{Q} = n_I\big(I(t) - Q(t)\big) - n_C \frac{Q(t)}{1 + \alpha_G Q(t)}$$

S

Using the NICING model fit to clinical data (BG, nutrition, insulin treatment records) we can work out the **insulin sensitivity (SI)** of a patient over time

Insulin Sensitivity in very premature infants





If we fit the NICING model to clinical data (>12hrs of BG, insulin, nutrition records) we get Insulin Sensitivity (SI) traces for each patient. These were compared across all patients.

Girls vs. Boys

- Insulin sensitivity **higher** in female very preterm infants
- Similar clinical characteristics between the groups

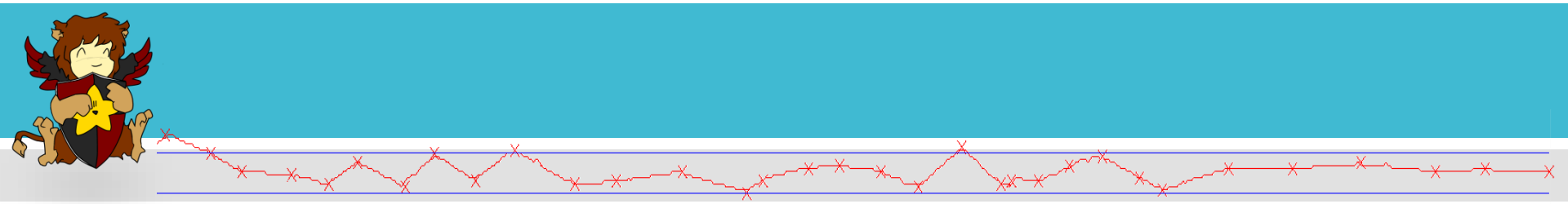
Are girls and boys really that different?

Glycaemic differences between the sexes are observed in infancy and later life

- Male preterm infants are generally sicker
- Higher plasma insulin concentrations are observed in term female babies (*Ibanez, 2008*)
- Women have higher insulin sensitivity(*Sung, 2013, Mathai, 2012)*
- post-pubertal, pre-menopausal women are less likely to develop diabetes (*Liu, 2010)*
- Oestrogen protect beta-cells in the pancreas of mice (*Le May, 2006*)
- Oestrogen replacement therapy reduces the incidence of Type 2 Diabetes in post-menopausal women (*Margolis, 2004*, *Kanaya, 2003*)

So it is good to be a girl...?

- Up until menopause... After that women have a higher likelihood of developing diabetes than men. (*Liu, 2010)*



Limitations?

•Higher C-peptide concentration could results from lower glomerular filtration rate (GFR). GFR was not available, but has not been observed to be different in preterm infants previously (*Rodin 2009)*

•Use of C-peptide parameters extrapolated from adult data-based equations: Changing k3 would only scale the magnitude of insulin secretion, but not affect any trends in results, and differences between cohorts.

•Assumption of steady state: reasonable in very preterm infants, so long as samples are not taken around the time of an IV infusion change, or a large feed.

Conclusions

→ Gender affects insulin-glucose metabolism at an early age

→ Models have been generated and incorporated into the STAR-GRYPHON protocol

→ Variability in insulin secretion was best captured though models of:

- Insulin secretion as a function of blood glucose
- Differing models for male and female premature infants

Acknowledgements

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The UC BioEng Crew

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Any Questions?