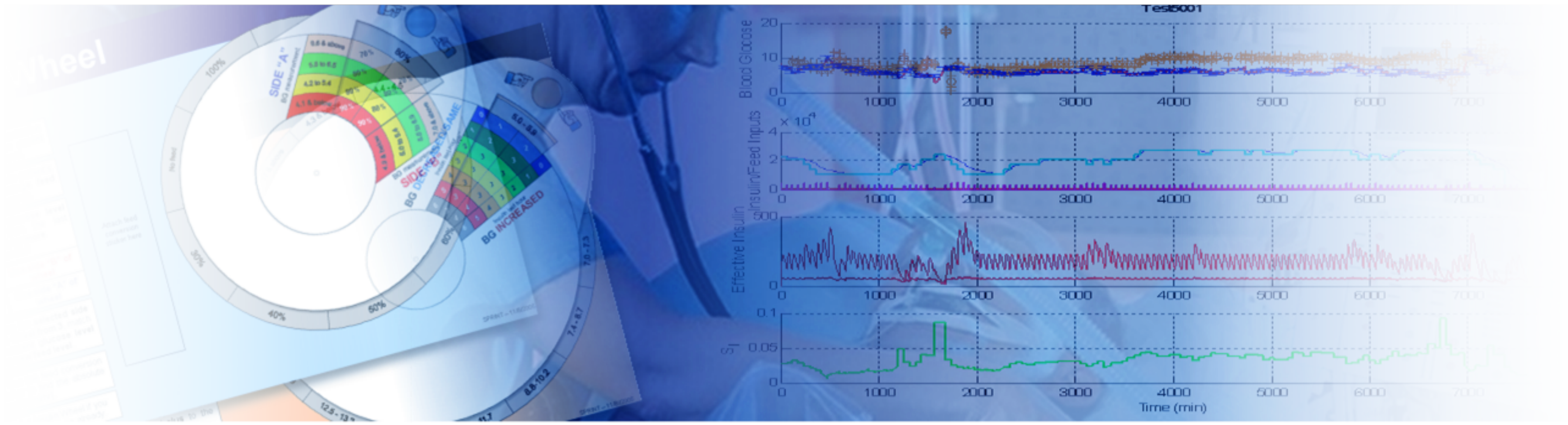
Interstitial insulin kinetic parameters for a 2-compartment insulin model with saturable clearance



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UC BIOMEDICAL ENGINEERING

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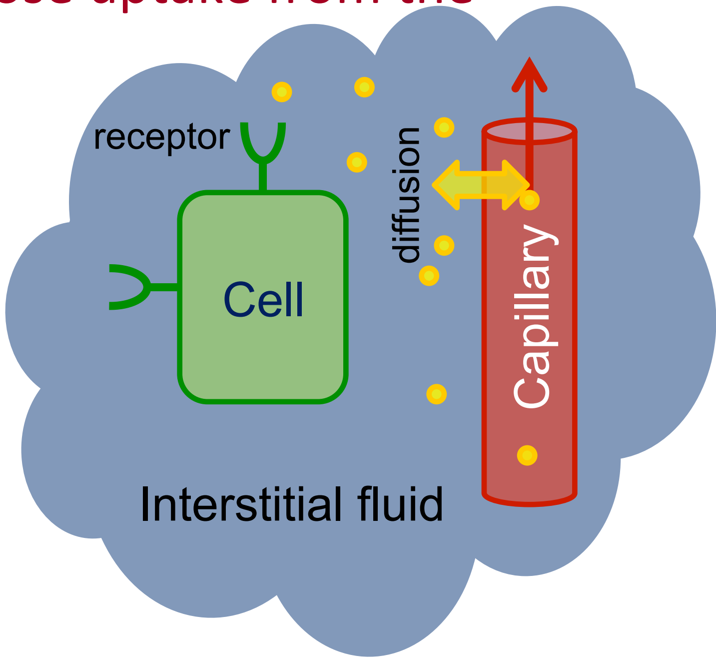
Why??

- Glucose-Insulin system models are useful and interesting!
  - Used for glycaemic control (ICU + diabetes) and diagnisis (diabetes)
- The insulin sub-model is obviously a very important part
- Physiologically, insulin mediates most glucose uptake from the interstitium
- But… Insulin is delivered to plasma
- Transport kinetics link the two

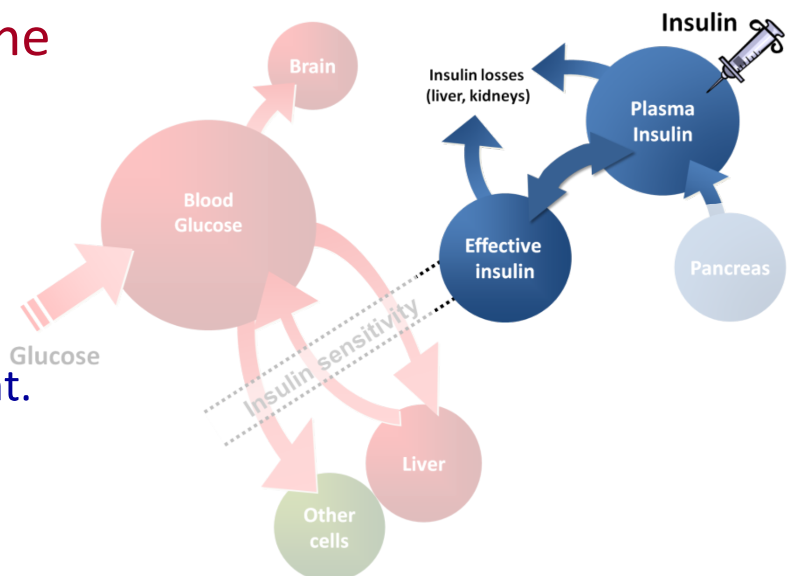


Model types

- It is common to use two insulin compartments in modelling
  - Plasma
  - Interstitum/effect compartment

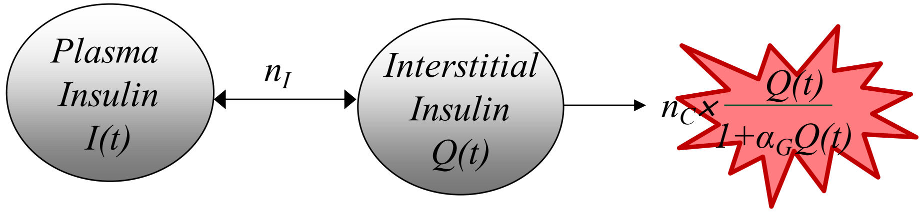
- Two compartments can adequately model the behaviour of insulin seen in experiments

- Our model aims to accurately capture the actual concentration of insulin in the interstitium.
  - Rather than using an abtract ‘insulin effect comparment’ concept.
  - Permits verfication by physical measurement.

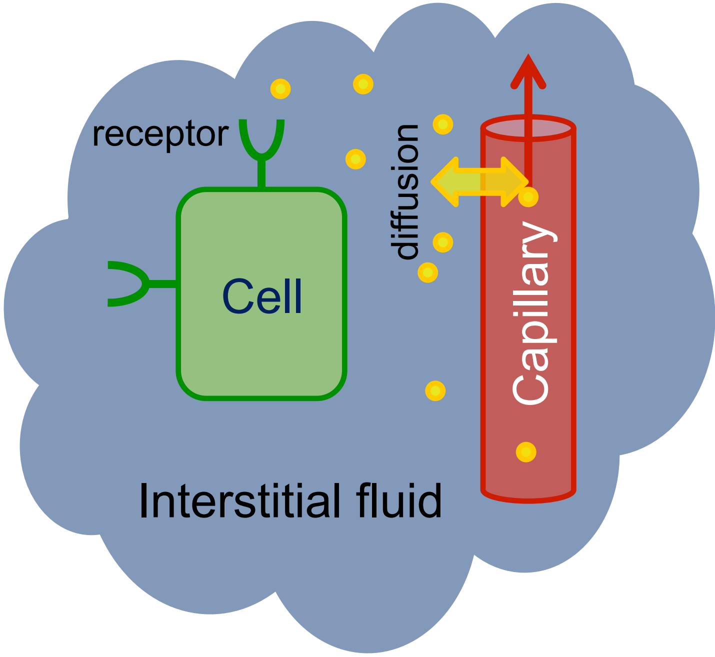


Interstitial insulin kinetics

- Interstitial insulin kinetics impact identified insulin sensitivity (SI)
  - Interstitial insulin kinetics determine how much interstitial insulin is available to mediate glucose disposal – thus, directly impacts SI
  - Previous values were taken from C-peptide kinetic data by Van Cauter et al.
  - Published data from microdialysis studies offered the opportunity to directly identify the transport parameter values

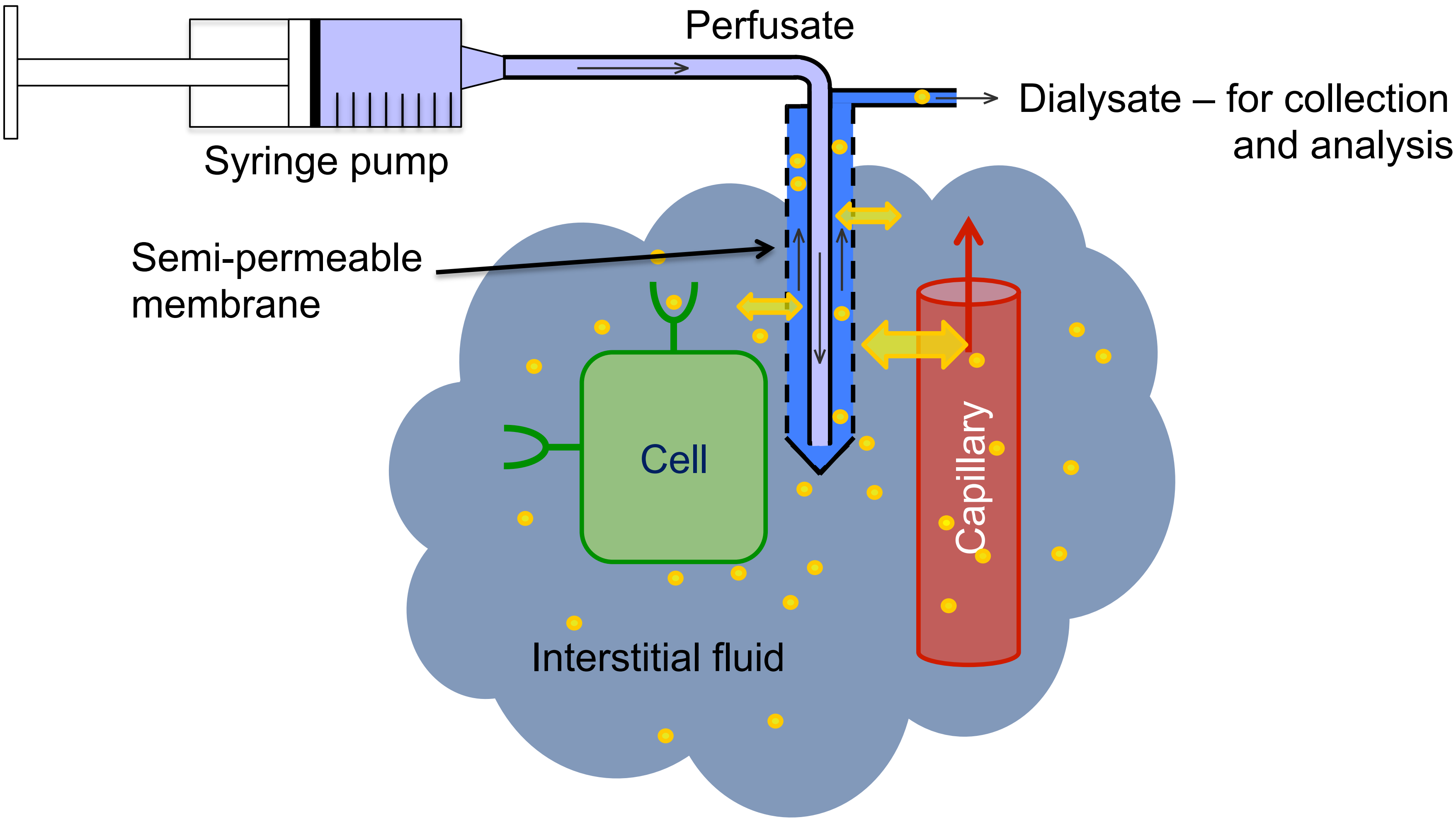


'Effective insulin' available for glucose disposal



Microdialysis

- The principle of microdialysis



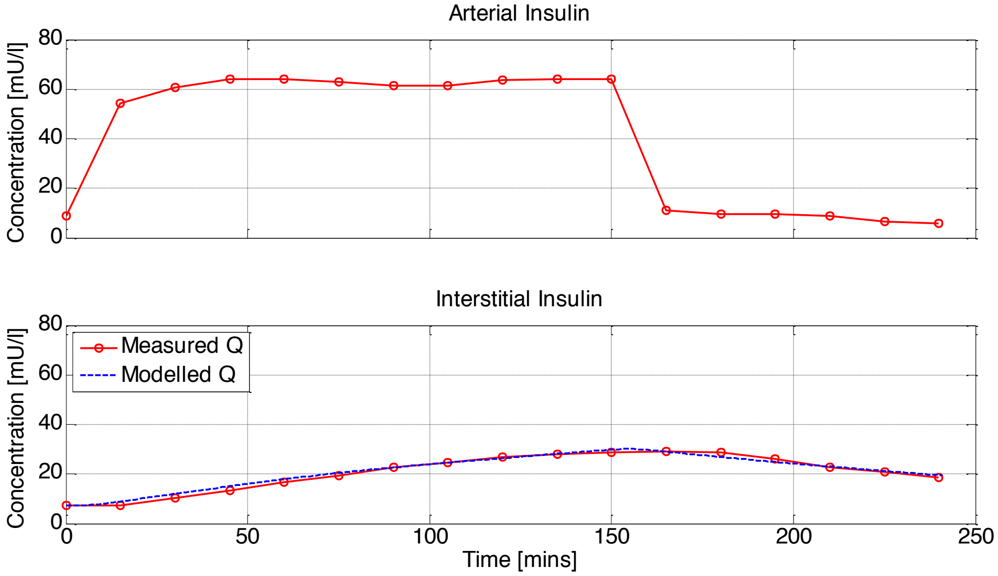
Data

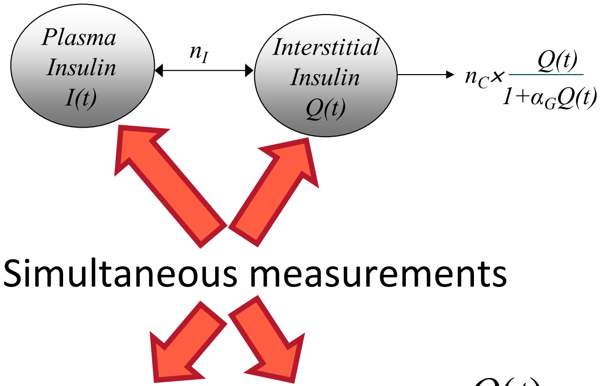
- Published studies
  - 6 published microdialysis studies
  - 12 datasets

Study	Study Method	Study Population	N	Interstitial sampling location
Jansson et al. (1993)	Euglycaemic-hyperinsulinaemic clamp	Healthy non-obese	5	Abdominal subcutaneous fat
Castillo et al. (1994)	Euglycaemic-hyperinsulinaemic clamp	Healthy: Body fat <=12%	3	Subcutaneous lymph vessel; lower leg
	Euglycaemic-hyperinsulinaemic clamp	Healthy: Body fat 13-21%	5	Subcutaneous lymph vessel; lower leg
	Euglycaemic-hyperinsulinaemic clamp	Healthy: Body fat 22-35%	3	Subcutaneous lymph vessel; lower leg
	Euglycaemic-hyperinsulinaemic clamp	Healthy: Body fat >=36%	2	Subcutaneous lymph vessel; lower leg
Sjostrand et al. (2002)	Euglycaemic-hyperinsulinaemic clamp	Healthy lean	10	Forearm muscle
	Euglycaemic-hyperinsulinaemic clamp	Healthy obese	10	Forearm muscle
Gudbjornsdottir et al. (2003)	Euglycaemic-hyperinsulinaemic clamp	Healthy lean	10	Forearm muscle
Herkner et al. (2003)	Oral glucose tolerance test	Healthy lean	8	Mid thigh muscle
	Euglycaemic-hyperinsulinaemic clamp	Healthy lean	8	Mid thigh muscle
Sjostrand et al. (2005a)	Oral glucose tolerance test	Healthy lean	10	Forearm muscle
	Oral glucose tolerance test	Healthy obese	10	Forearm muscle

Methods

- Identifying insulin kinetic parameters
  - Microdialysis studies provide simultaneous plasma (I) and interstitial (Q) insulin concentrations.
  - These data combined with the model for interstitial insulin enable n_I and n_C to be identified by minimising errors.

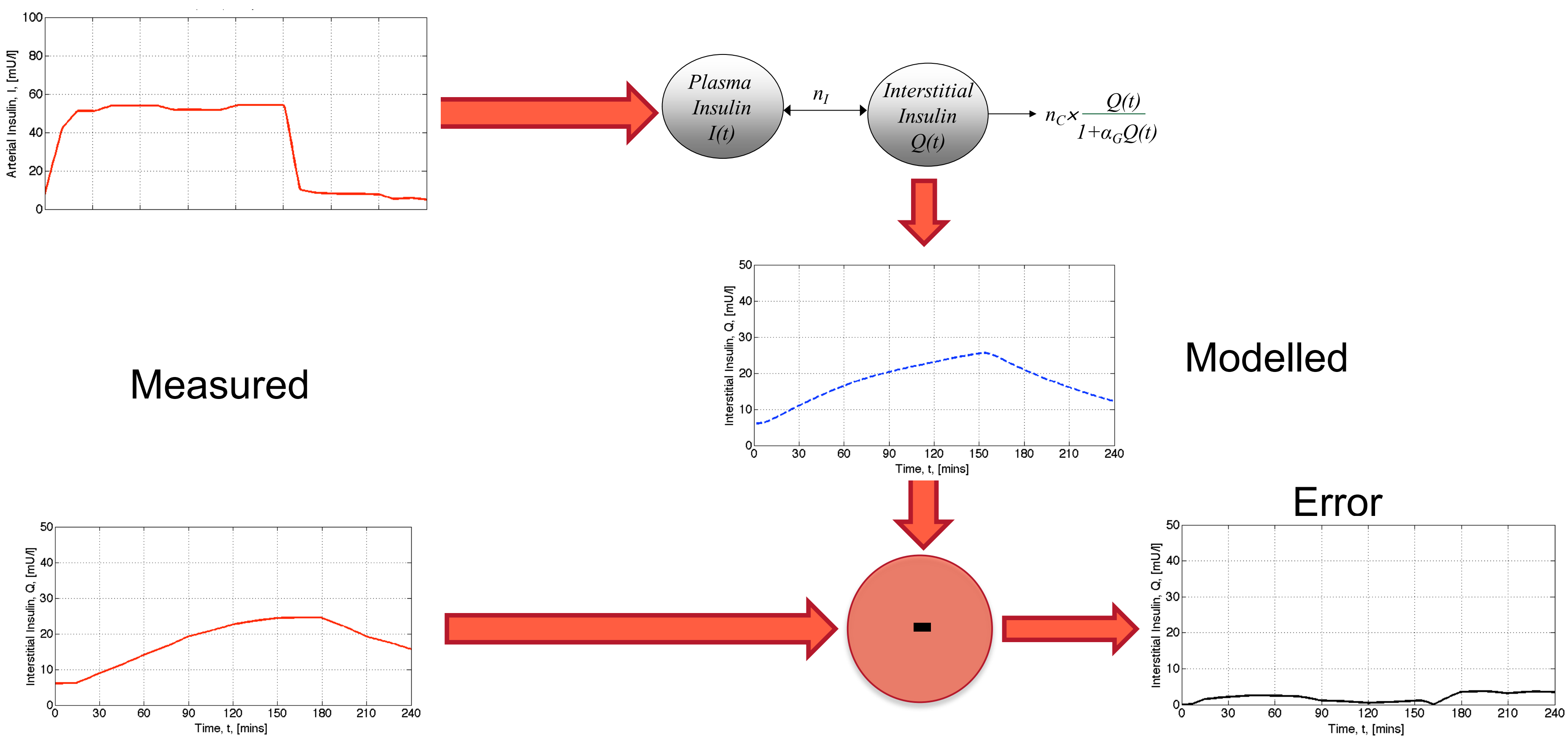




$$\dot{Q}(t) = n_I (I(t) - Q(t)) - n_C \frac{Q(t)}{1 + \alpha_G Q(t)}$$

Methods

- Identifying insulin kinetic parameters
  - Using measured plasma concentrations as the input



Identification

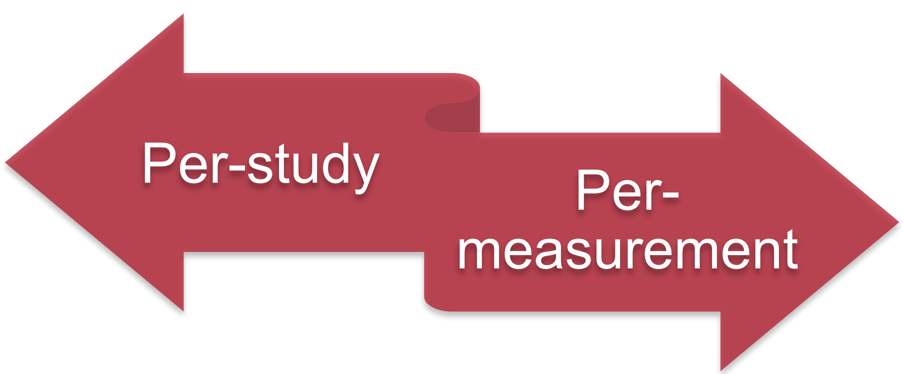
- Grid search
  - Minimise error over the parameters n_I and γ where:

$$\gamma = \frac{n_I}{n_I + n_C}$$

  - The parameter γ provides a more intuitive insight to the relative interstitial insulin concentration than n_C
    - Steady-state ratio of concentrations

- Error treatment

Each study weighted equally



Each error value weighted equally

Examples

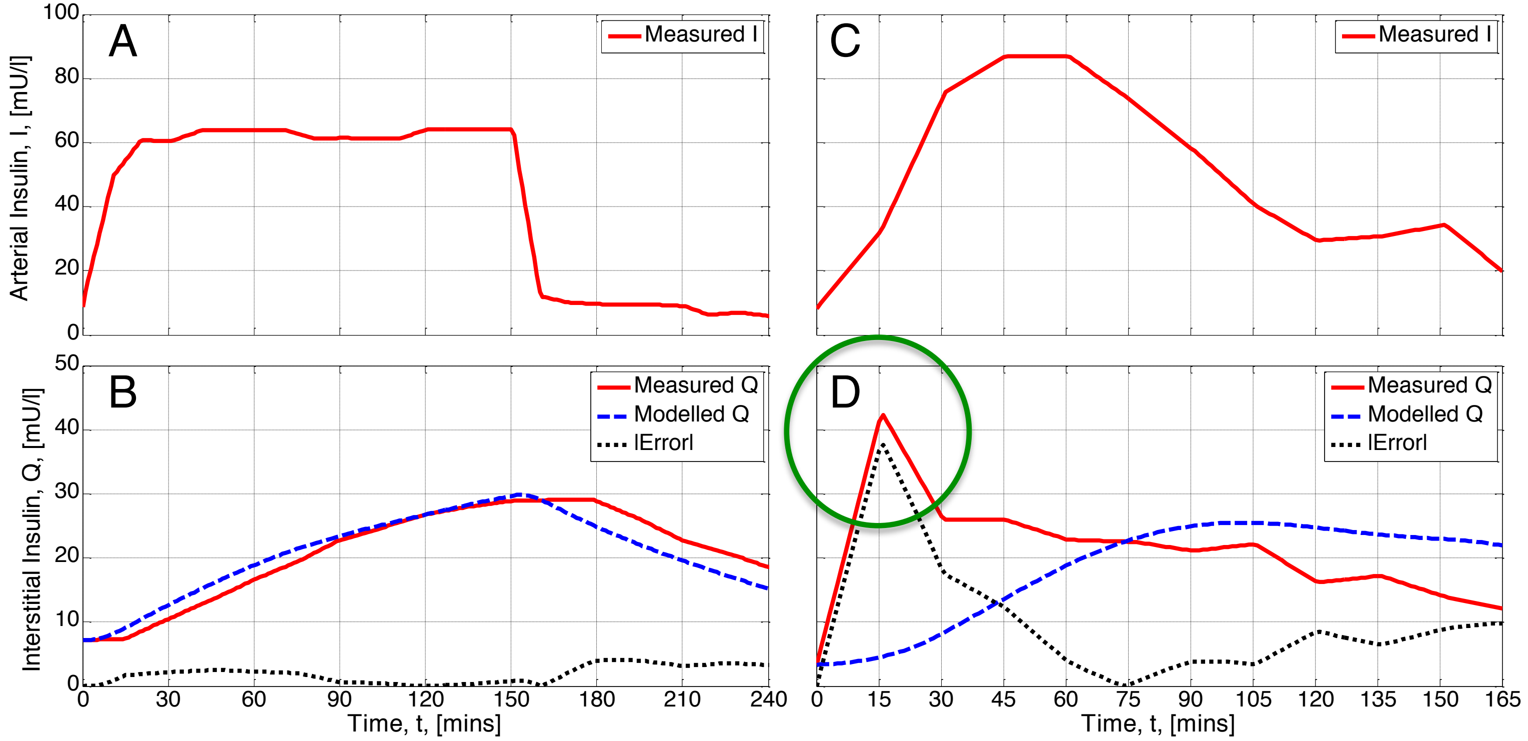
- Two very different qualities of fit

Castillo et al. (1994)
(body fat 13-21%)

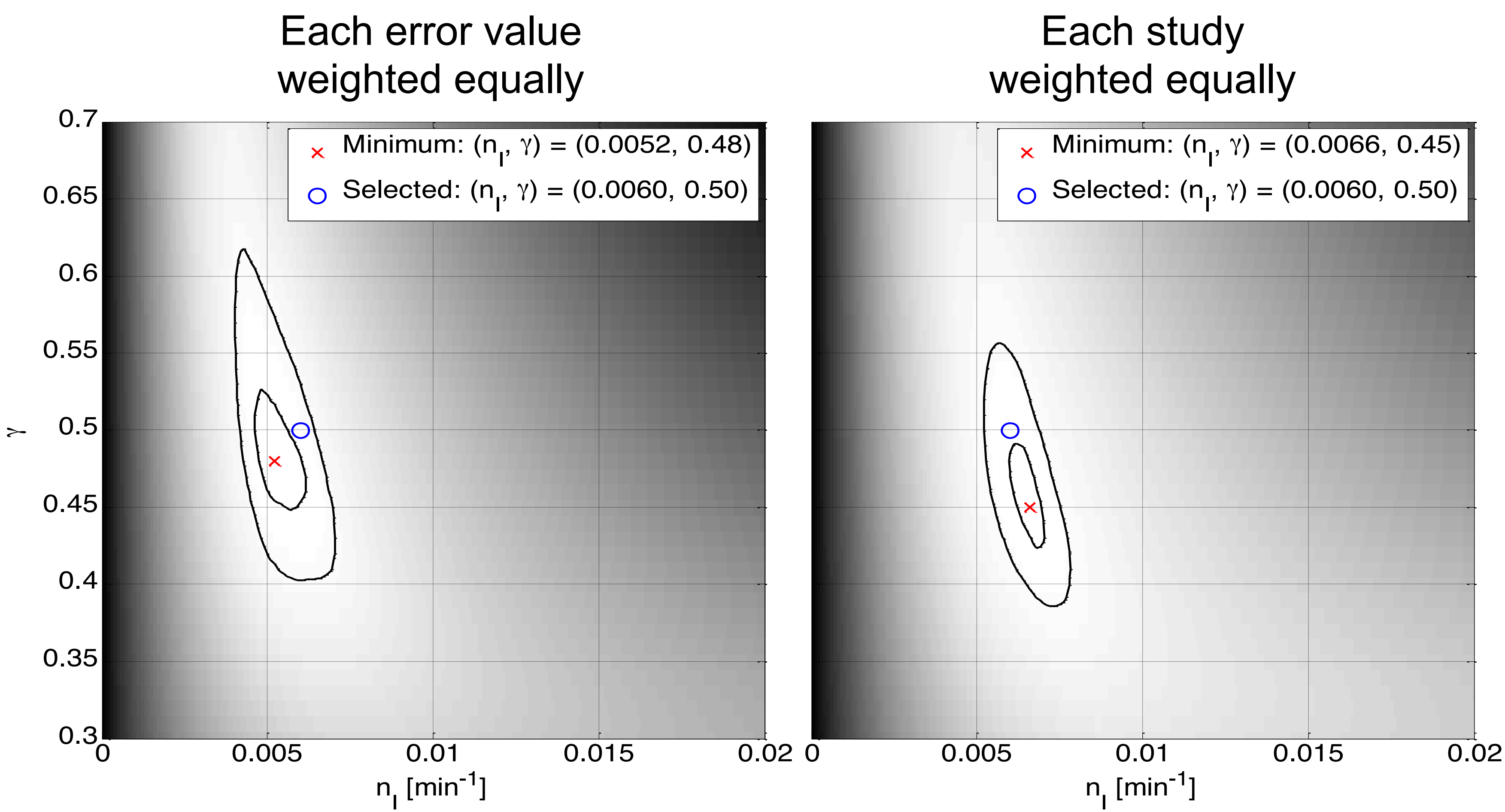
Herkner et al. (2003)
(OGTT)

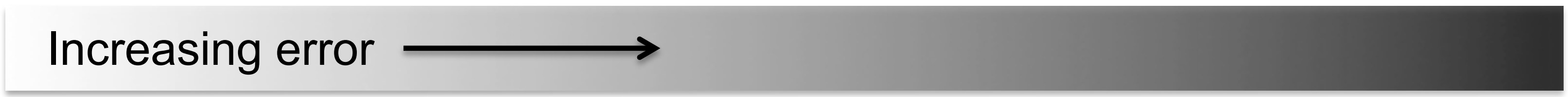
Measured plasma insulin

Measured interstitial insulin

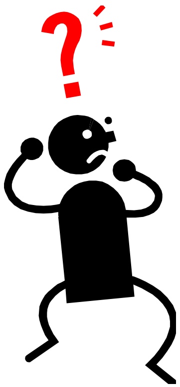


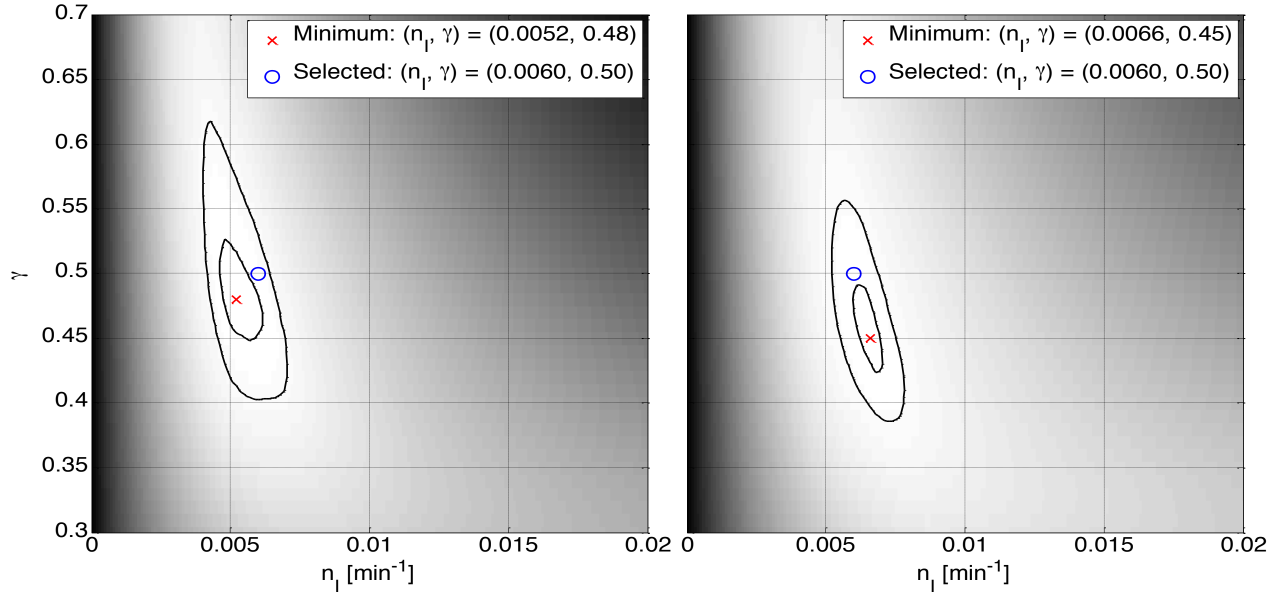
Error surfaces





Choice of values





$\gamma = 0.5$

- $n_l = n_C$
- Consistent with previous value and literature

$n_l = 0.006$ min^{-1}

- 2x previous value
- Precision indicates confidence

Within 5%

Results

- Results of the selected parameters on the individual studies
  - Considerable variation across studies, particularly for n_I
  - This might reflect:
    - Inter-patient differences
    - Poor mixing of interstital fluid
    - Difficulty of the technique
    - Lack of sensitivity

Study	Study Method	Study Population	Study optimal n_I	Study optimal γ	Study min. error	Error at selected (n_I, γ)
Jansson et al. (1993)	Clamp	Healthy non-obese	0.0054	0.30	0.142	0.233
Castillo et al. (1994)	Clamp	Healthy: Body fat <=12%	0.0031	0.53	0.103	0.305
	Clamp	Healthy: Body fat 13-21%	0.0048	0.62	0.038	0.090
	Clamp	Healthy: Body fat 22-35%	0.0041	0.61	0.029	0.101
	Clamp	Healthy: Body fat >=36%	0.0040	0.44	0.044	0.204
Sjostrand et al. (2002)	Clamp	Healthy lean	0.0128	0.48	0.060	0.191
	Clamp	Healthy obese	0.0054	0.70	0.057	0.072
Gudbjornsdottir et al. (2003)	Clamp	Healthy lean	0.0061	0.67	0.143	0.180
Herkner et al. (2003)	~~OGTT~~	~~Healthy lean~~	~~0.0116~~	~~0.31~~	~~0.300~~	~~0.458~~
	Clamp	Healthy lean	0	0	0.137	1.546
Sjostrand et al. (2005a)	OGTT	Healthy lean	0.0600	0.57	0.101	0.610
	OGTT	Healthy obese	0.0400	0.46	0.058	0.516

Comparison of results

- Comparison to literature
  - Limited direct comparisons as few models use physiological compartment

Study	n_I	γ	$t_{½}$
This study	0.006 min^{-1}	0.5	58 min
Lin et al. (2010)	0.003 min^{-1}	0.5	116 min
Lotz et al. (2008)	0.0486 min^{-1}	0.6	7 min

$$t_{1/2} = \frac{\ln(2)}{n_I + n_C}$$

  - Lin et al. → long half-life due to insulin pooling and delayed utilisation
  - Lotz et al. → Parameters based on C-peptide from van Cauter et al.

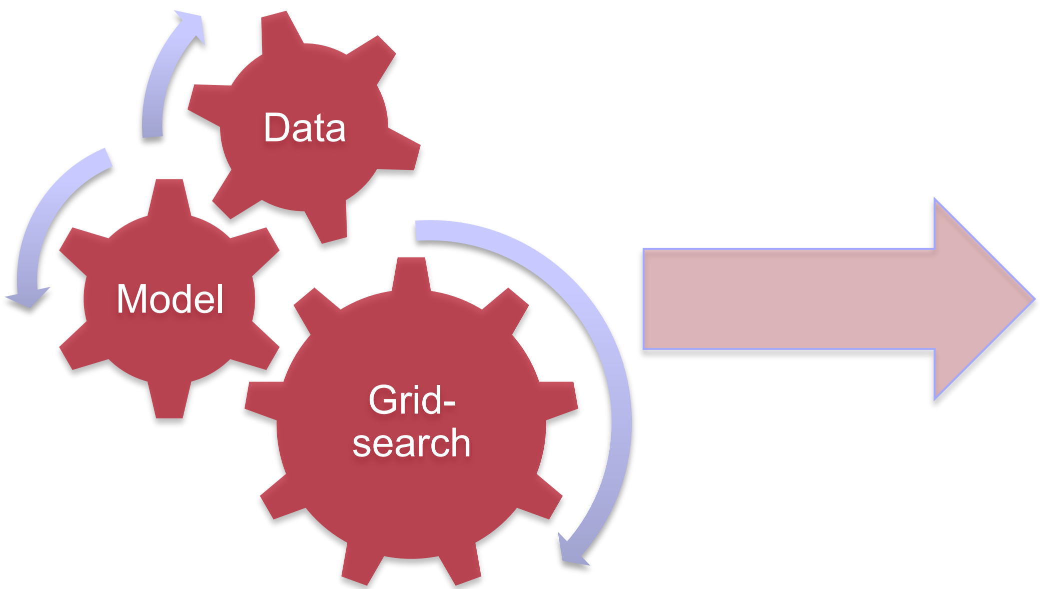
  - $t_{½}$ in the range 25-130 mins
    - Mari & Valerio 1997
    - Natali 2000
    - Turnheim & Waldhausl 1998

Summary

- Insulin transport kinetics directly impacts SI

  → model applications

- Used data from 6 published microdialysis studies to refine interstitial insulin kinetic parameters



$\gamma = 0.5$

$n_I = 0.006\ \mathrm{min}^{-1}$

- Questions?