



*GlucoWatch Biographer  
by Cygnus*

## Alternative sampling methods in TDM: Transdermal Reverse Iontophoresis in TDM

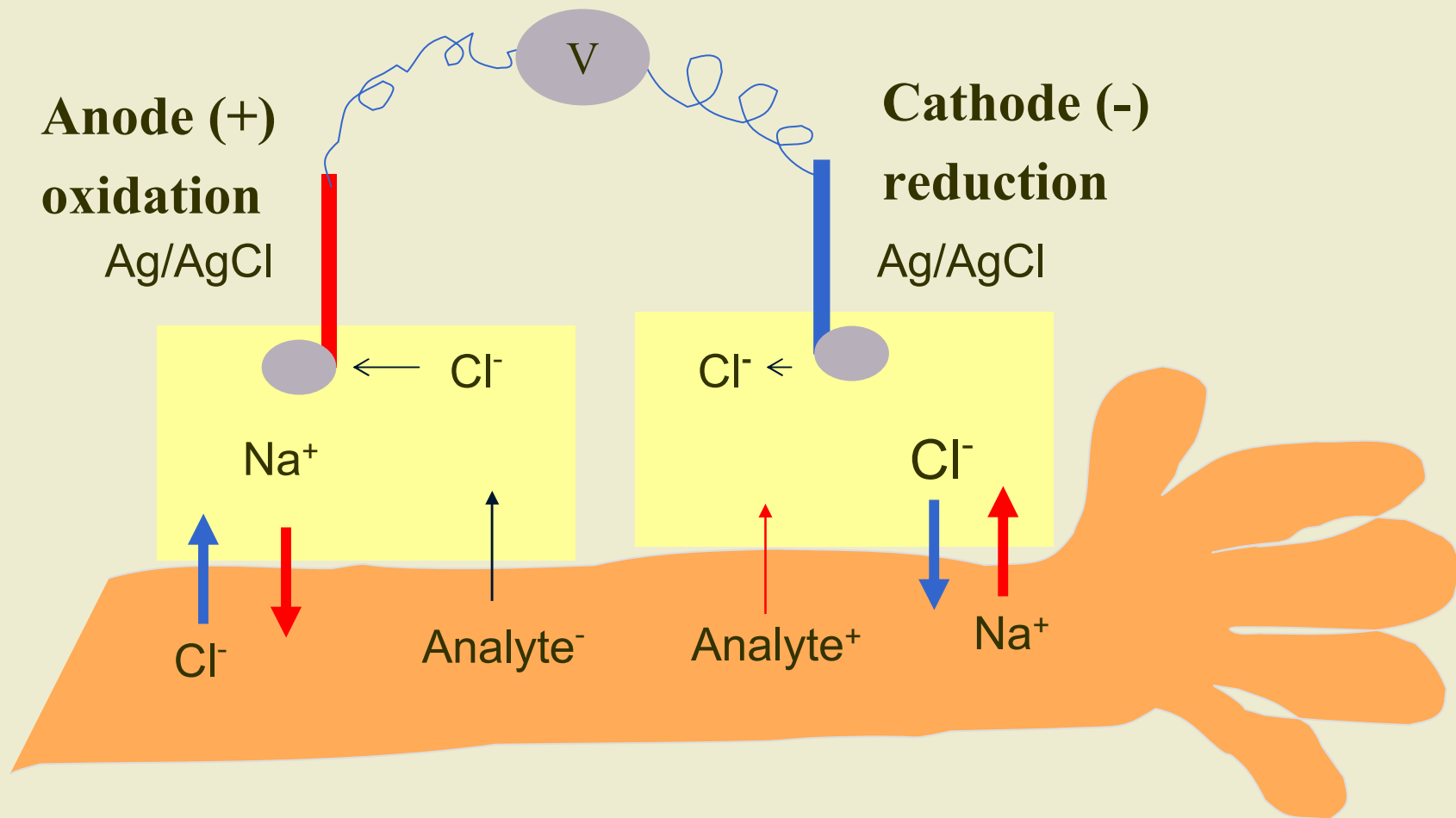
**M. Begoña Delgado-Charro, PhD**

**[B.Delgado-Charro@bath.ac.uk](mailto:B.Delgado-Charro@bath.ac.uk)**

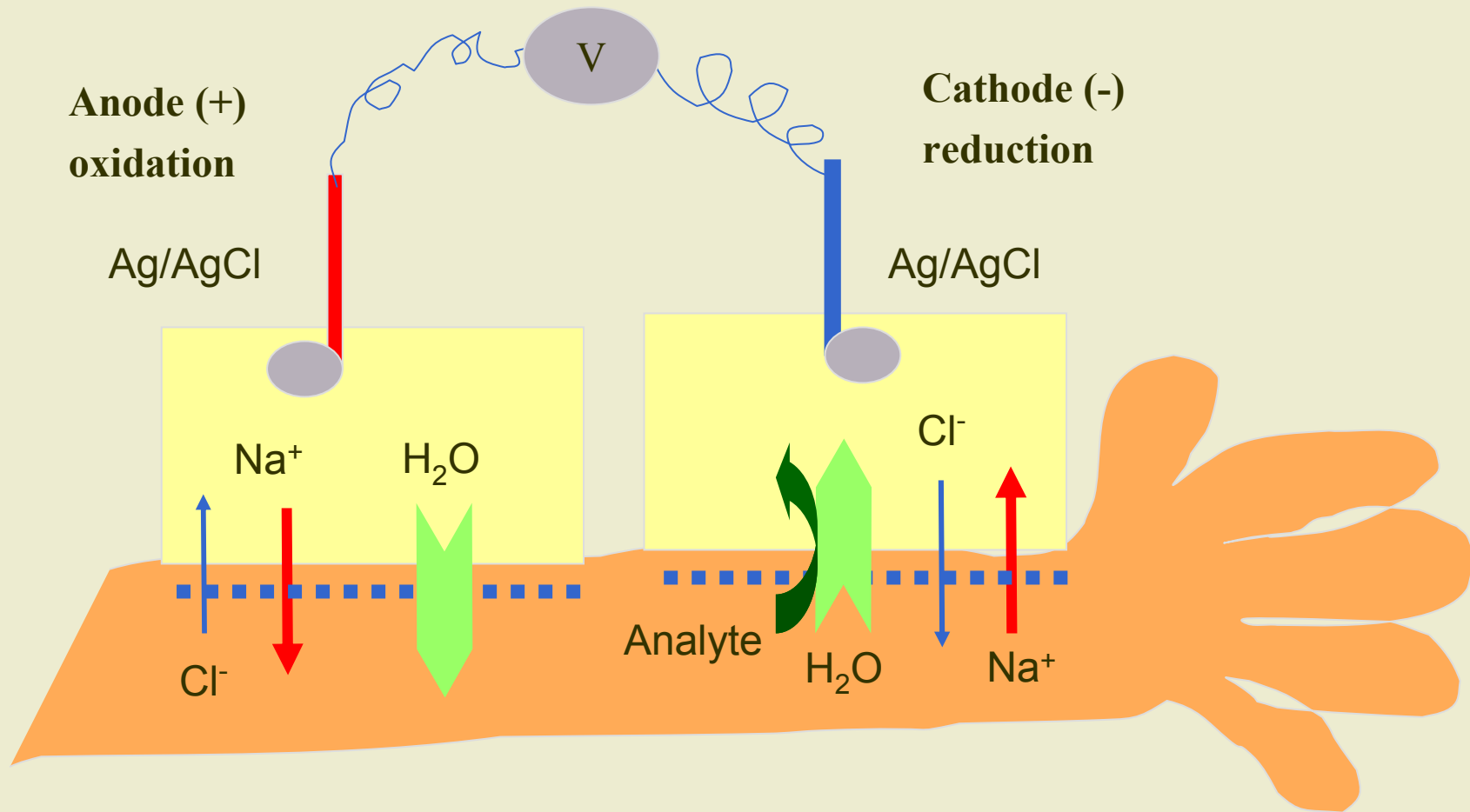


# Electromigration: Transport numbers

$$J_i = \frac{t_i \cdot I}{F \cdot z_i} \approx K \cdot C_{\text{analyte}} \quad \sum_i t_i = 1 \quad t_a = \frac{Z_a \cdot U_a \cdot C_a}{\sum Z_i \cdot U_i \cdot C_i}$$



# Convective flow & Electroosmosis

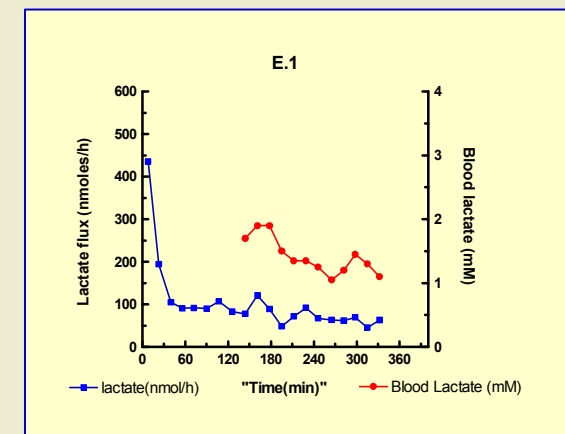
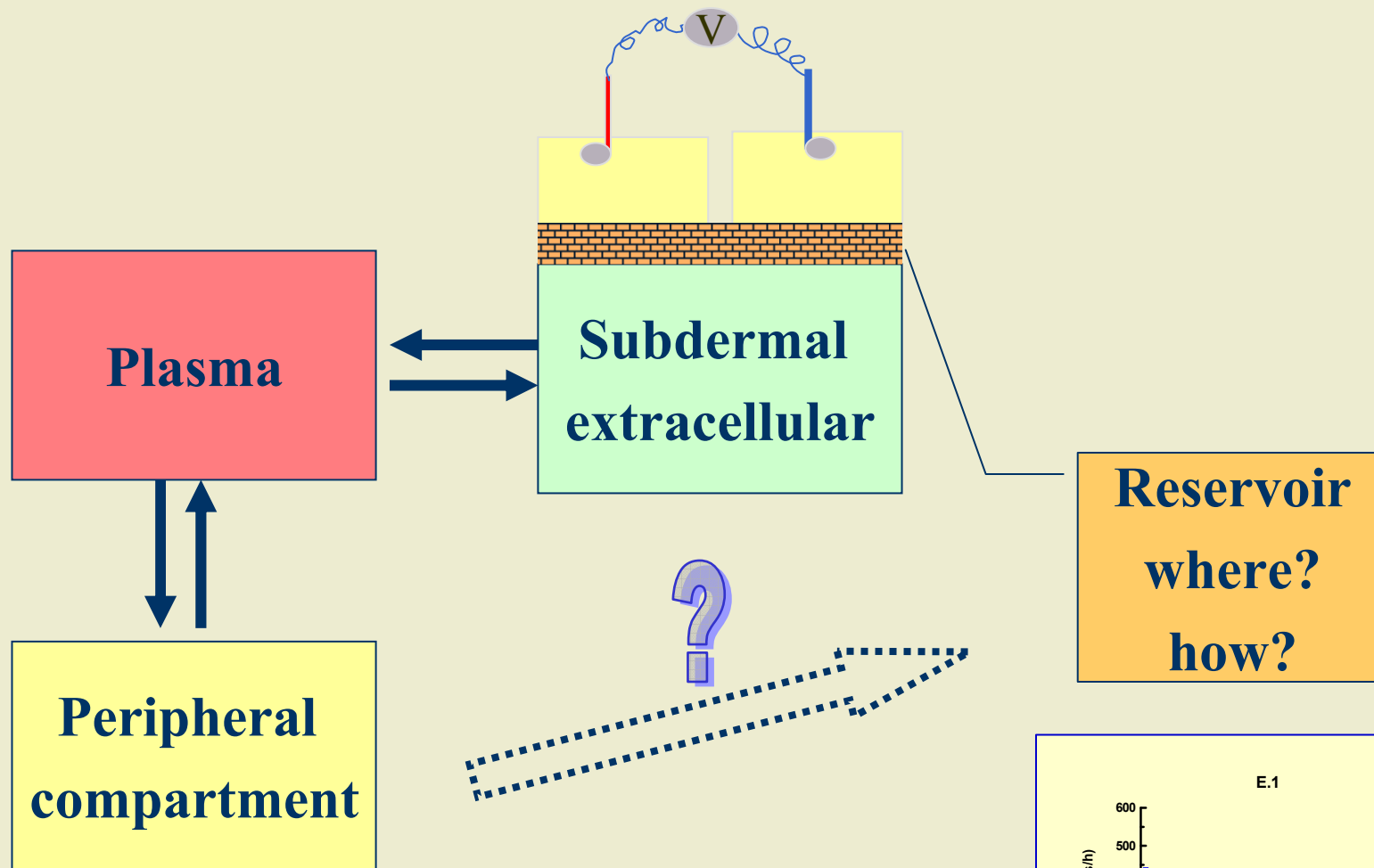


$$J_{E.O.} = J_{solv} \cdot C_a$$

# What we know about extraction fluxes...

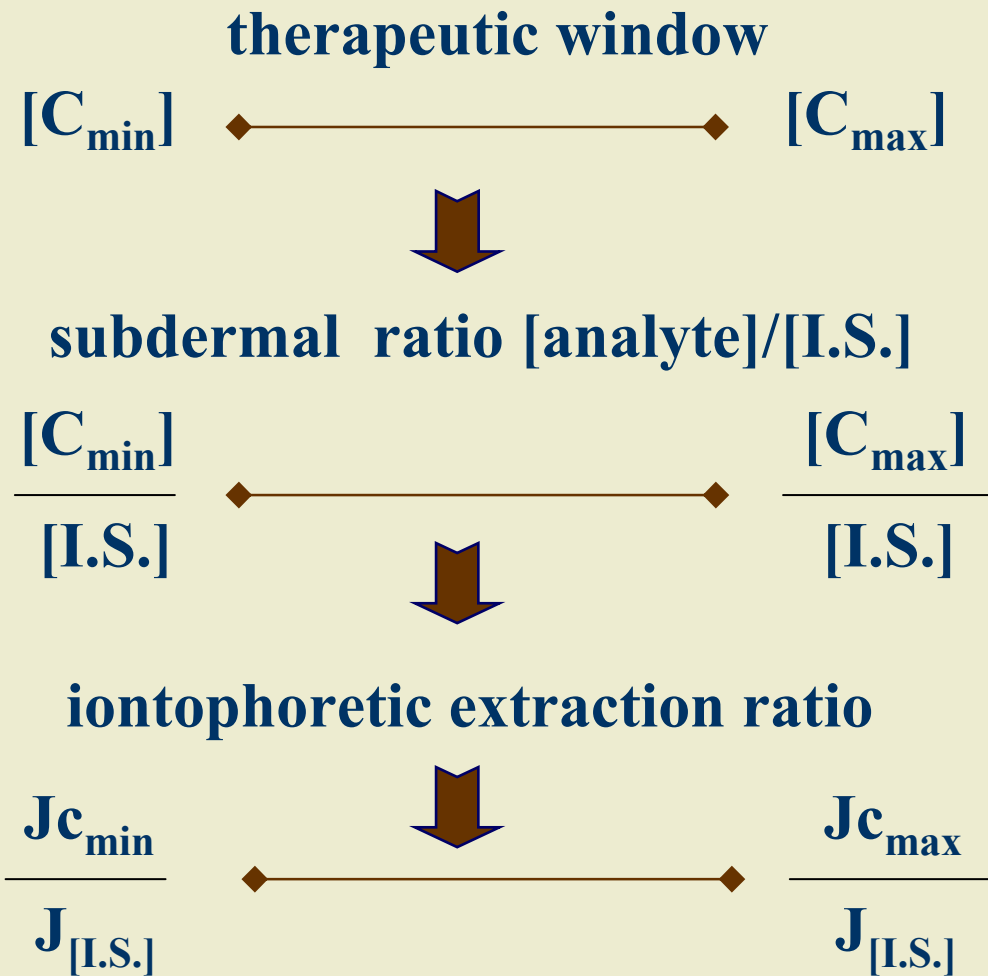
1. Electromigration and electroosmosis based extraction fluxes.
2. Extraction is not specific + Dilution = Analytical challenge.
3. Fluxes of extraction proportional to subdermal concentration.
  - 👉 Flux =  $\gamma \cdot C_{\text{analyte, subdermal}}$   
but  $\gamma$  requires some time to become “constant”
  - 👉 *in vivo* variability of  $\gamma$  is analyte dependent: large and small
  - 👉 Need for calibration – internal standard
4. Fluxes of extraction report on free drug concentration.
5. Initial fluxes sometimes confounded by the so-called “skin reservoir”.
  - 👉 Skin-reservoir: historical / skin health
  - 👉 Real time: depending on equilibrium kinetics
6. And:

# Reverse Iontophoresis does NOT sample in blood



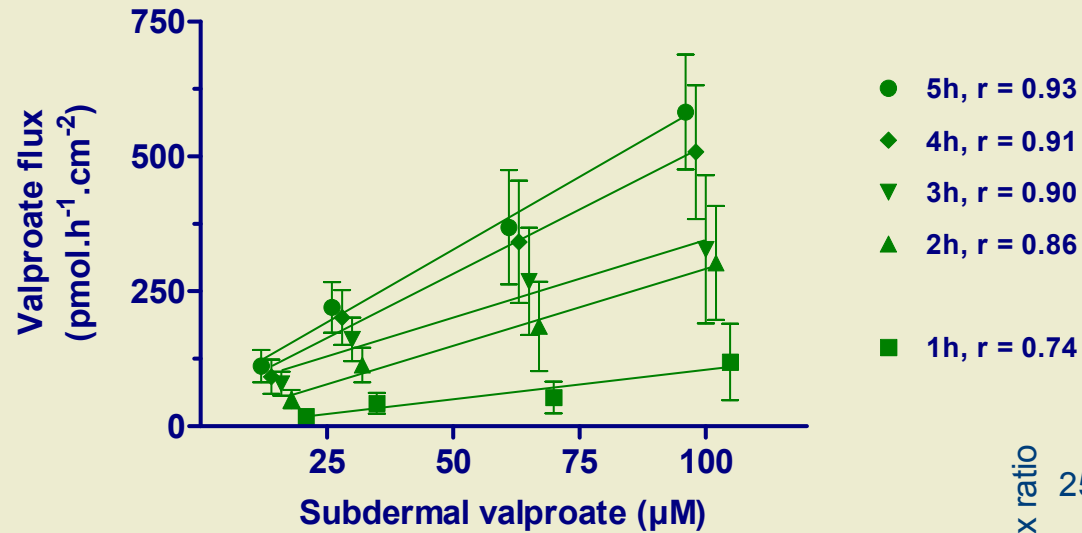
*S. Nixon. J.Pharm.Sci.2007*

# Internal standard:



$$\frac{J_{analyte}}{J_{I.S.}} = K \cdot \frac{[analyte]}{[I.S.]}$$

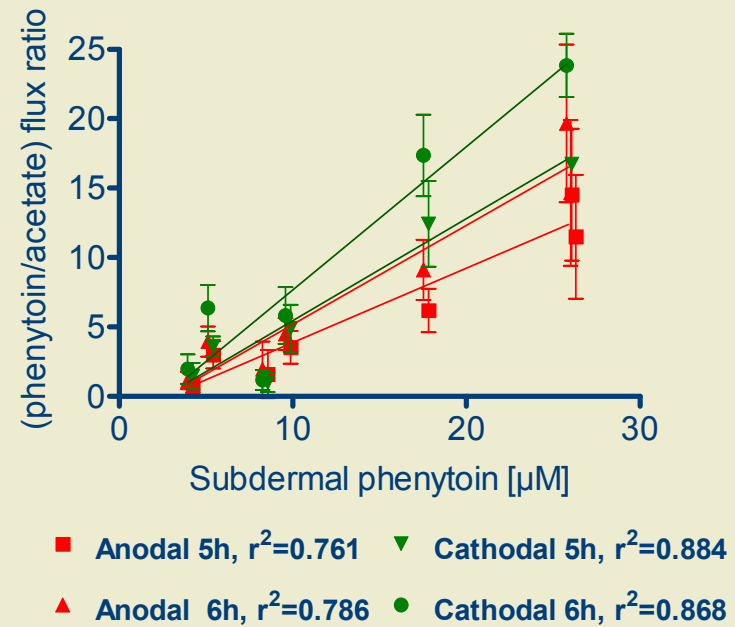
# Concentration-dependent fluxes



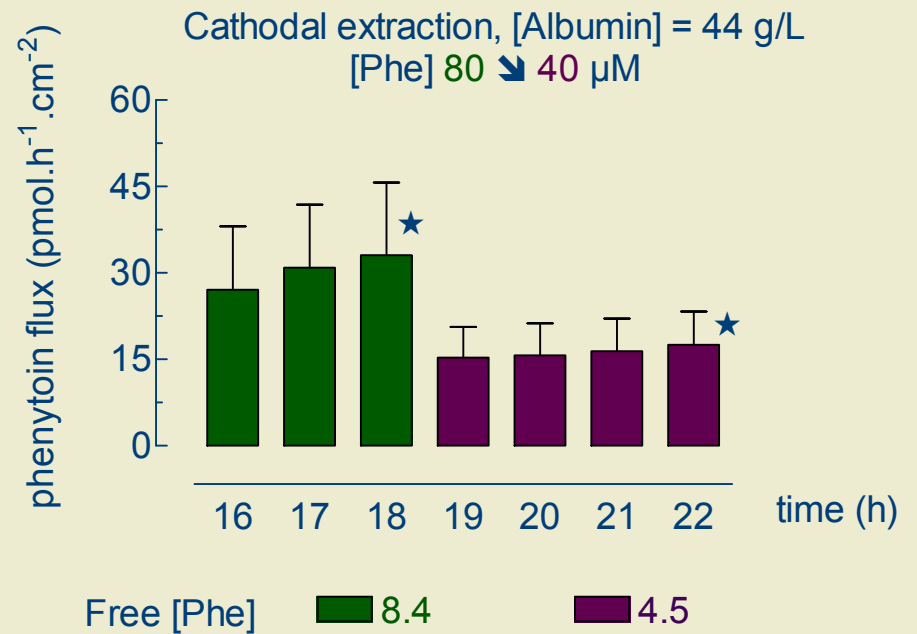
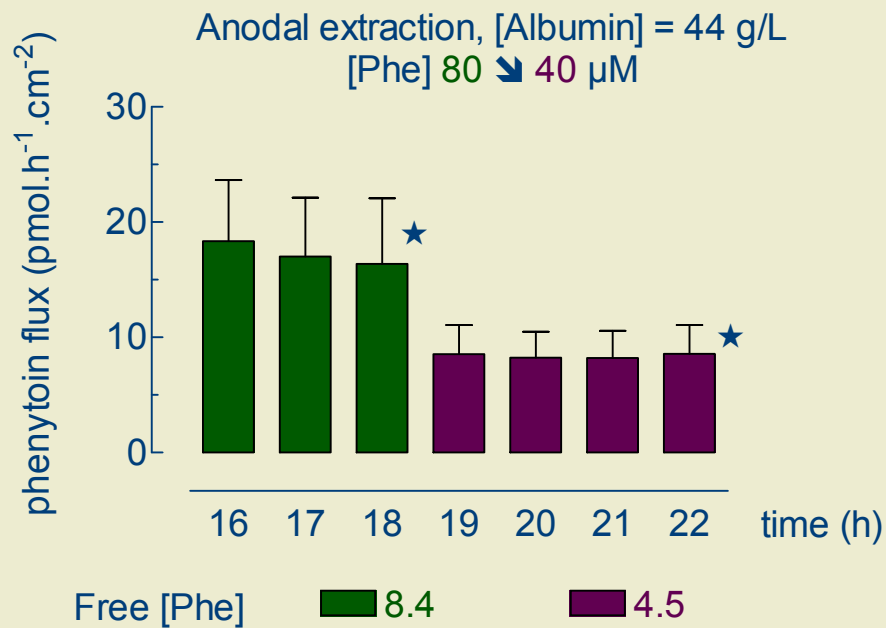
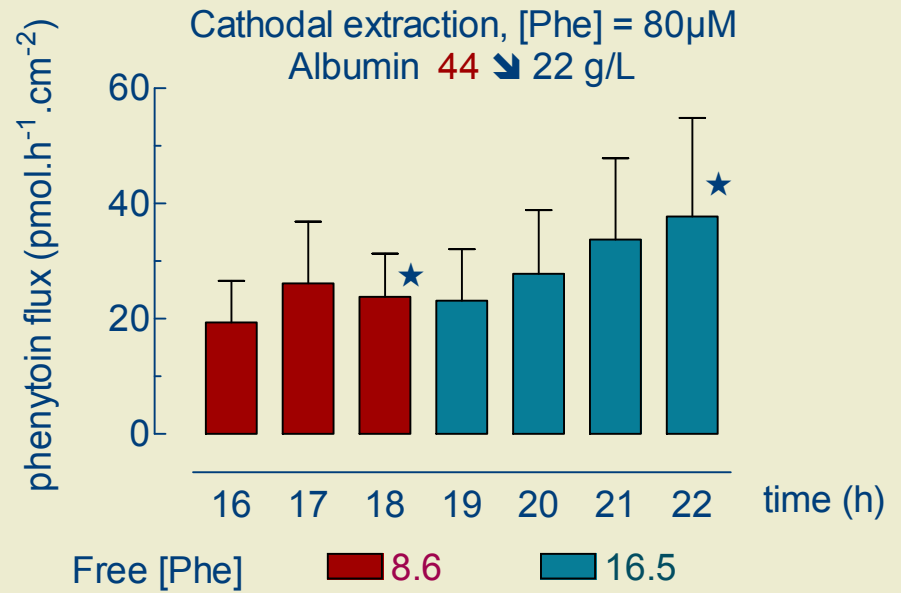
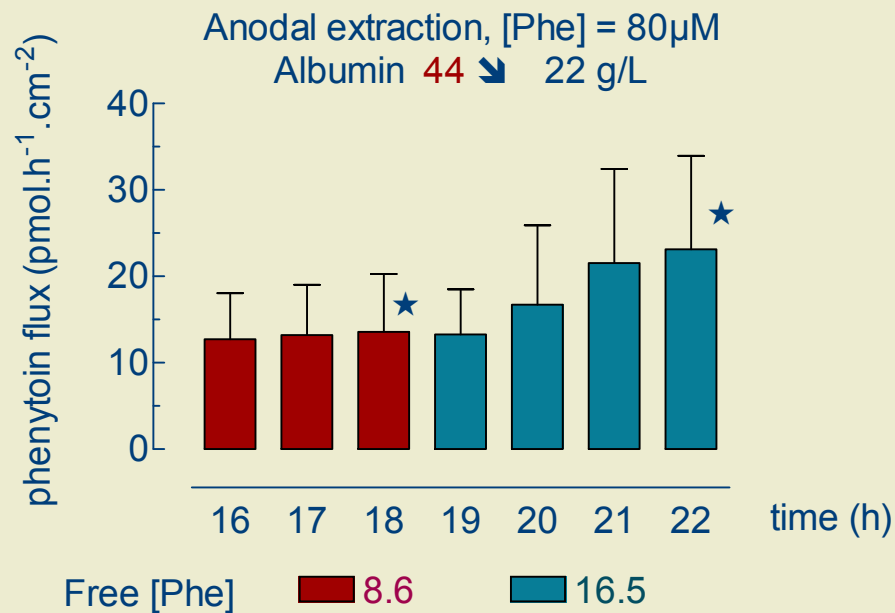
*Pharm. Res., 2003.*

$$J_i = \frac{t_i \cdot I}{F \cdot z_i} = \gamma \cdot C_{analyte}$$

$$J_i = J_{solvent} \cdot C_{analyte} = \gamma \cdot C_{analyte}$$



*Eur. J. Pharm. Sci. 2004*



# In vivo: TDM of Lithium



**Cathode:** His 10 mM (pH=7.65)  
Ag/AgCl; area 2 cm<sup>2</sup>

**Anode:** Patch Iogel

**Iontophoresis: 4 x 30 minutes; 0.8 mA**

**Blood sample at 1.5 h**

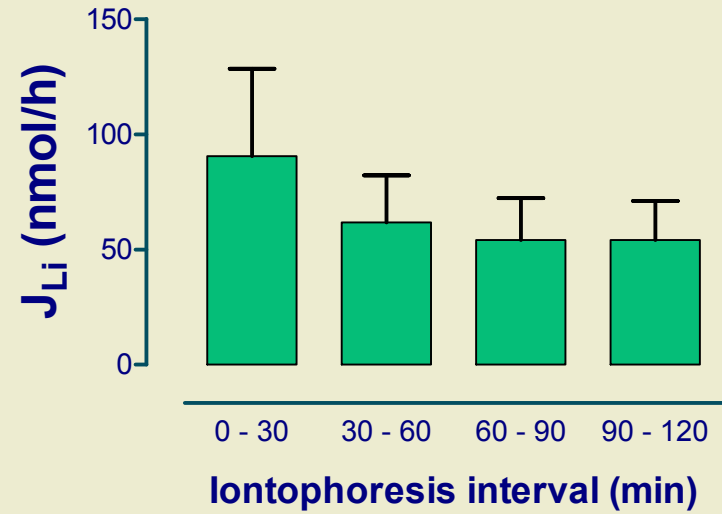
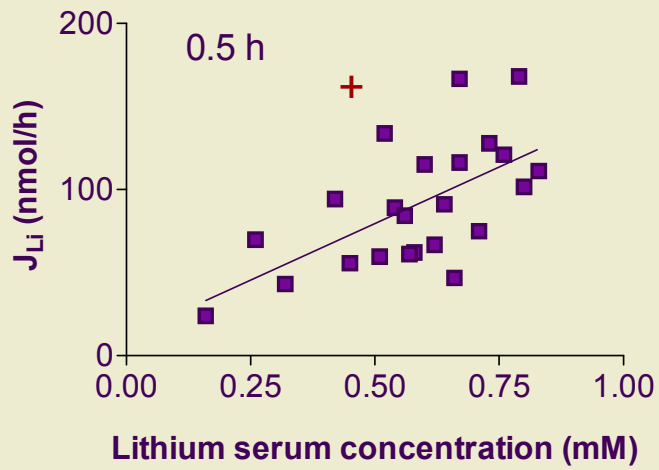
**22 patients (8 female, 14 male);  
22-59 years**

**“Ionto” samples**

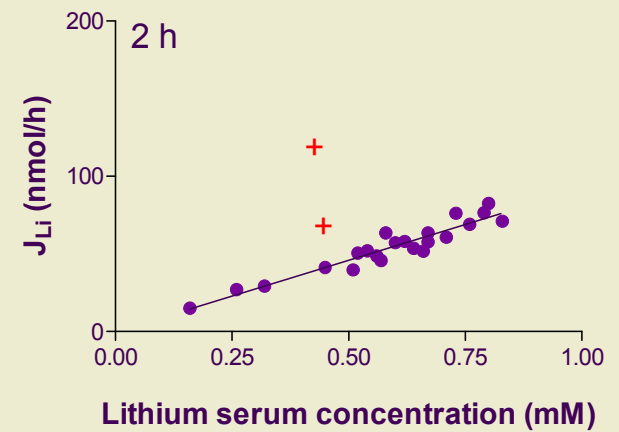
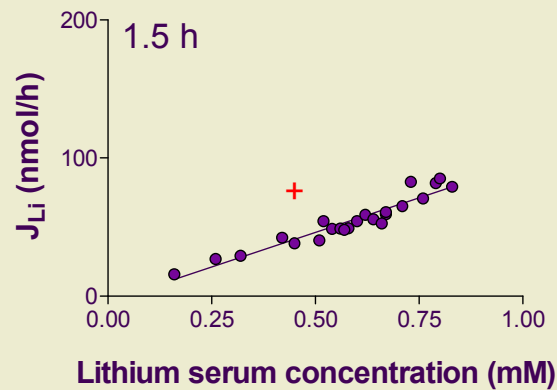
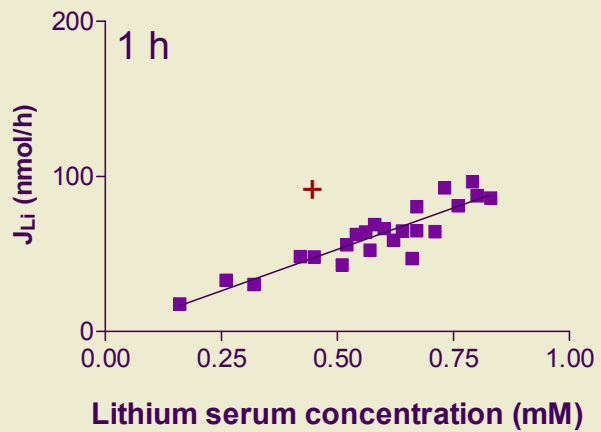


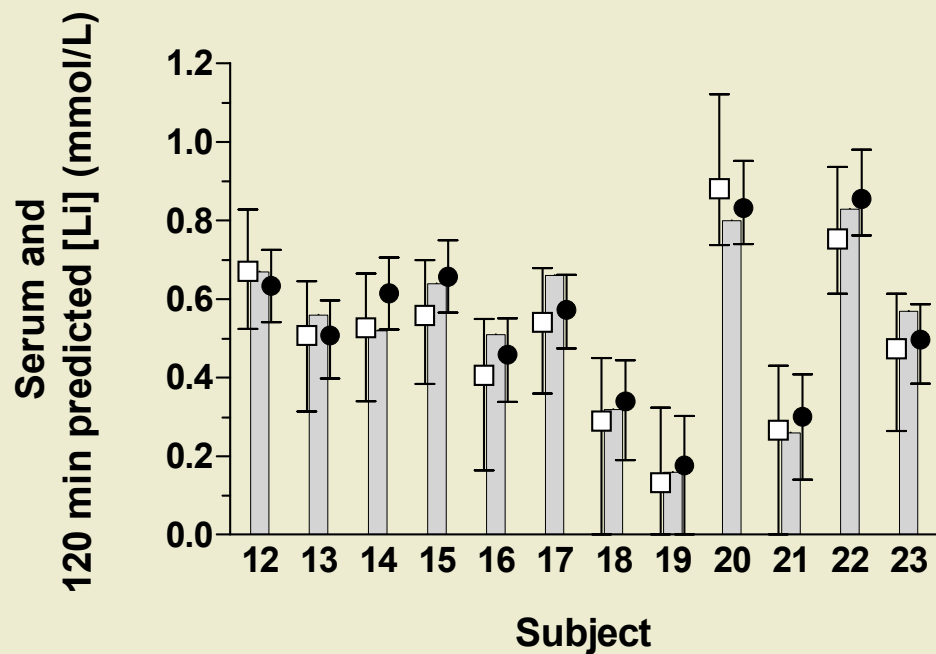
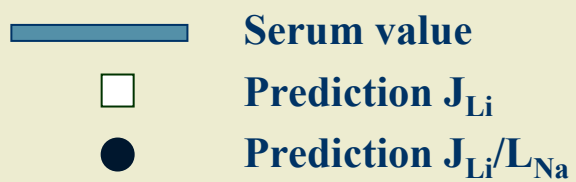
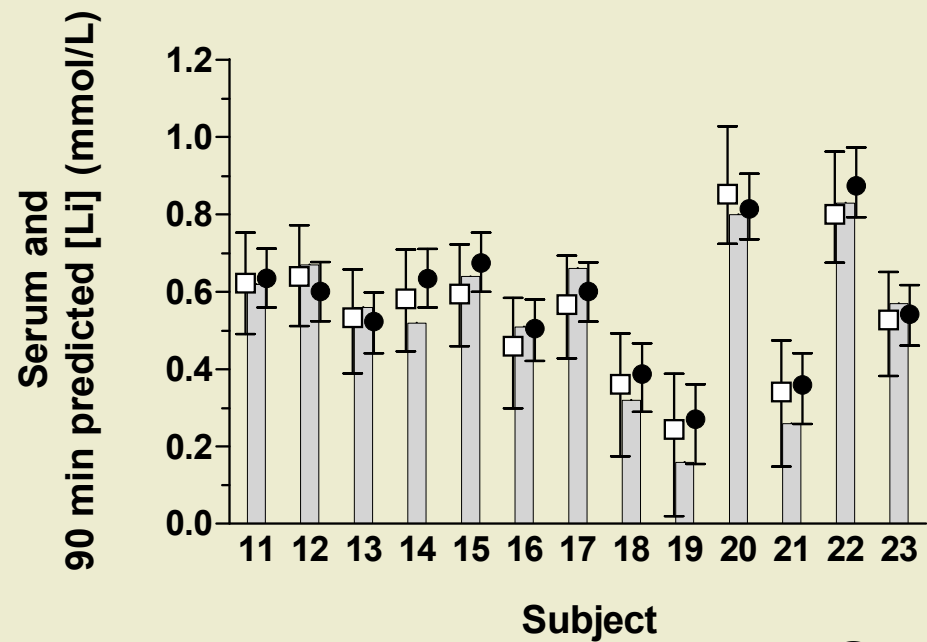
**Blood sample**

B. Leboulanger et al, Clin. Chem. 2004



$$J_{Li} = \gamma \cdot C_{Li}$$



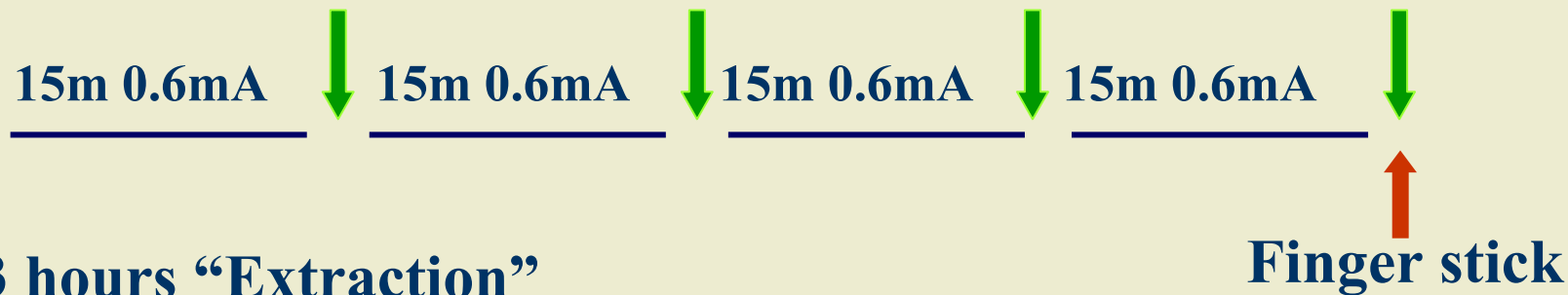


# Glucose, *in vivo*

- 12 healthy volunteers
- Blood sugar measured with a conventional glucose monitor

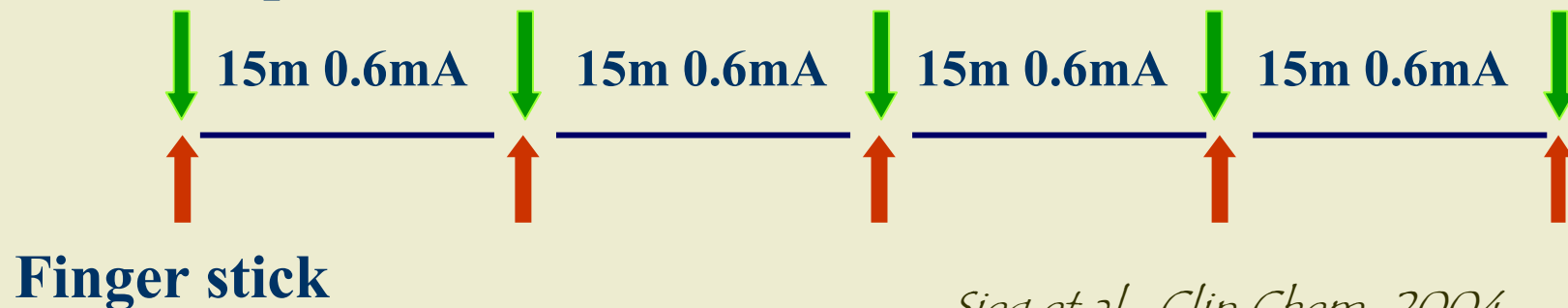
## I. 2 hours “Warm-up step”

Ionto sample

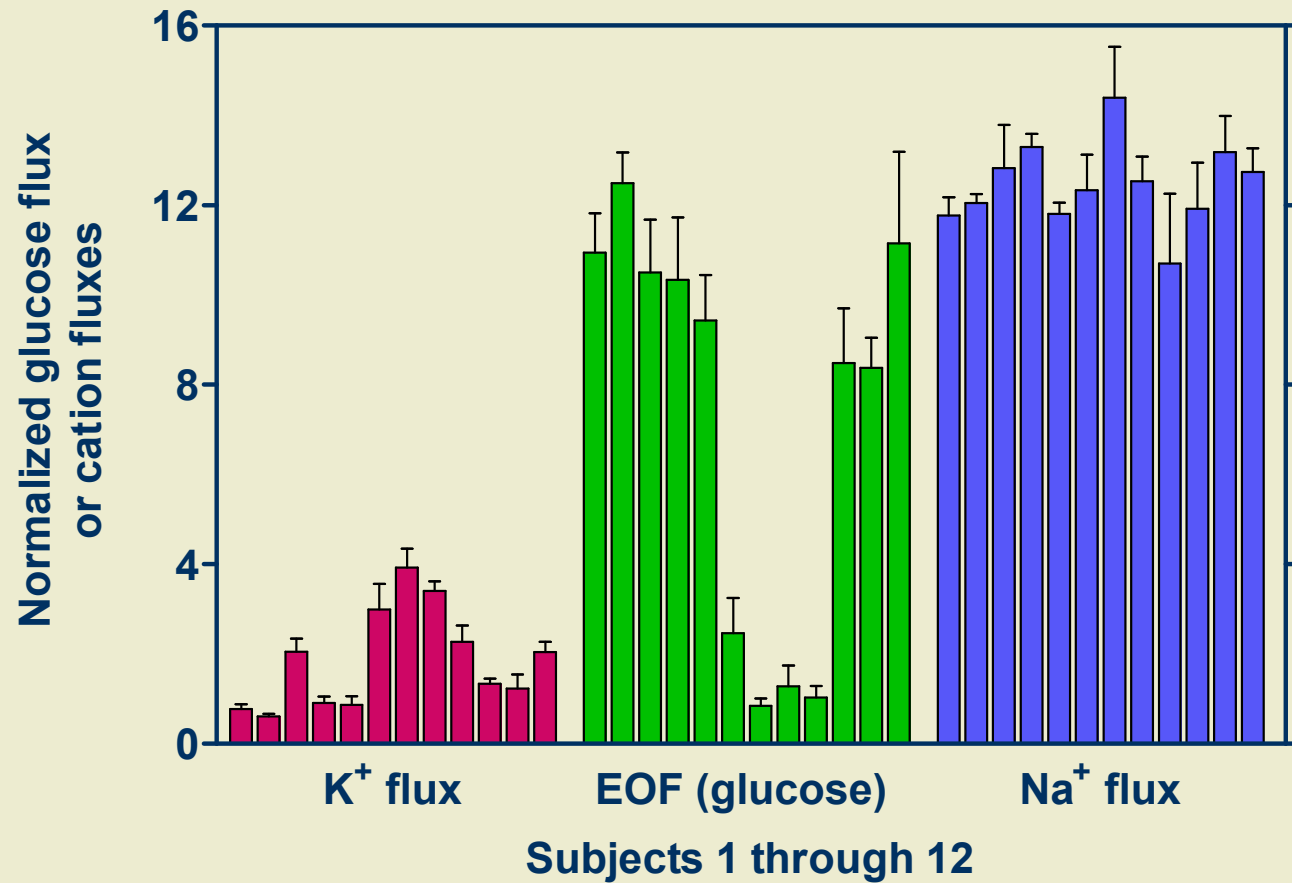


## II. 3 hours “Extraction”

Ionto sample



# Inter-subject variability



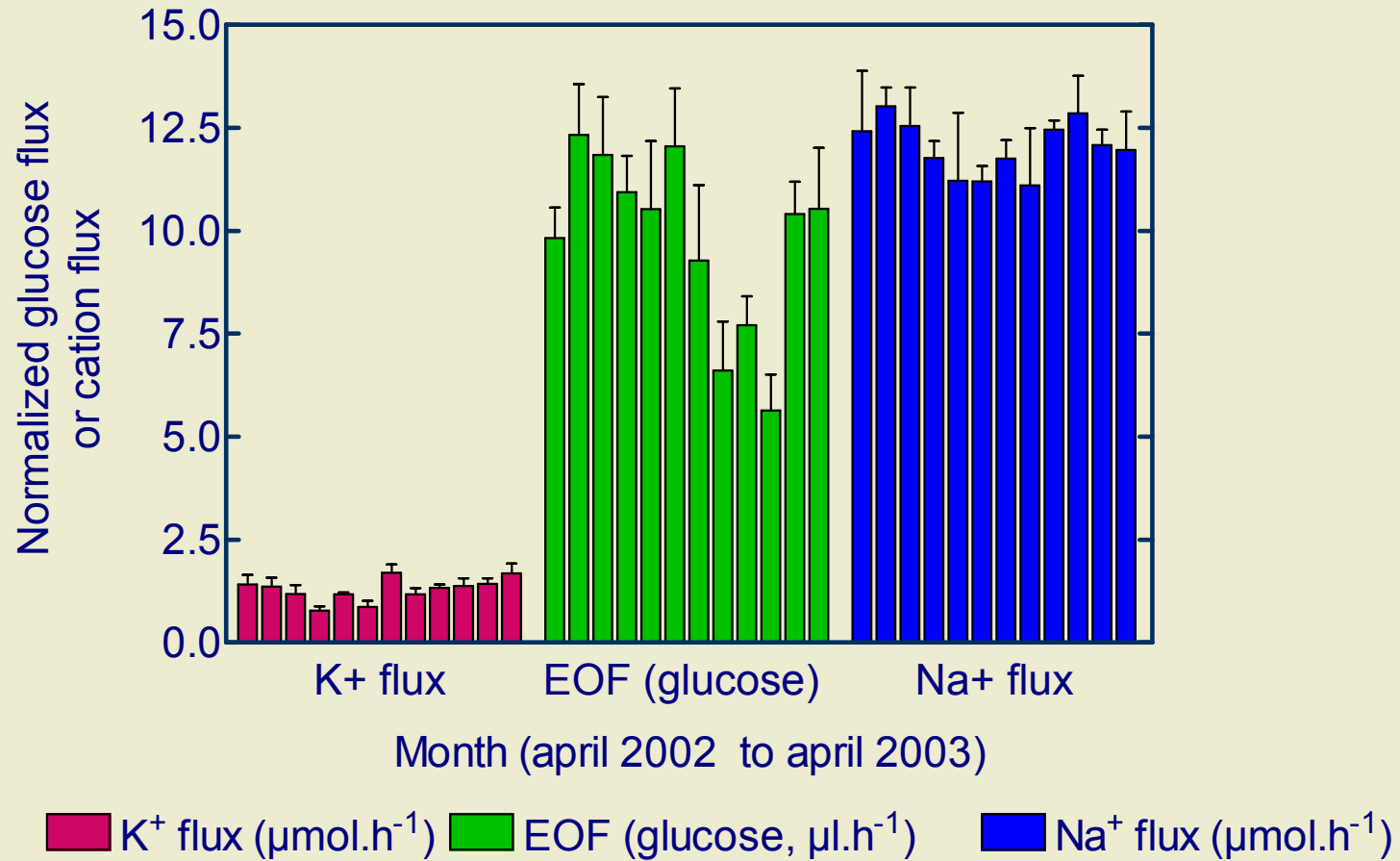
■ K<sup>+</sup> flux (μmol·h<sup>-1</sup>)

■ EOF (glucose) (μl·h<sup>-1</sup>)

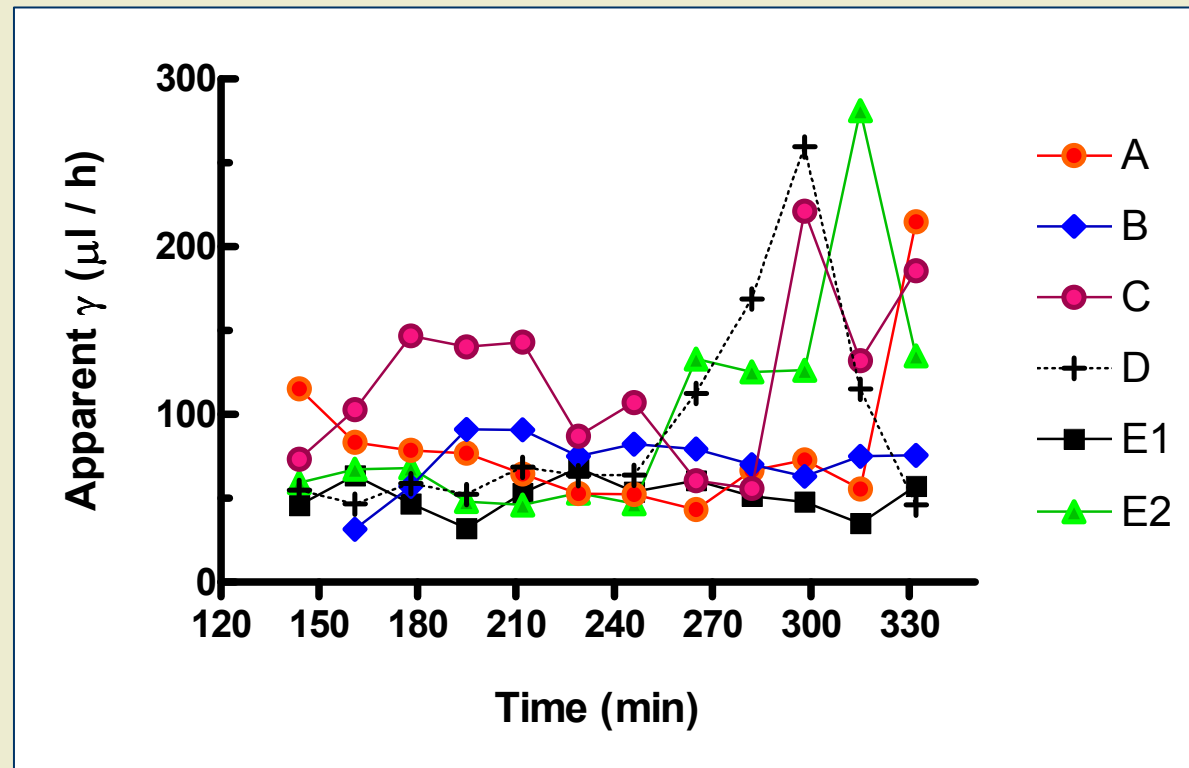
■ Na<sup>+</sup> flux (μmol·h<sup>-1</sup>)

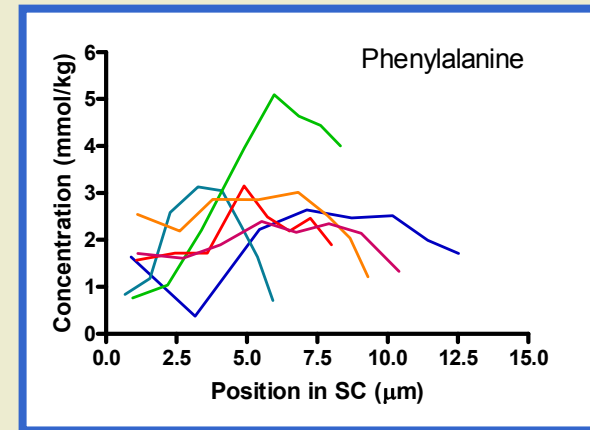
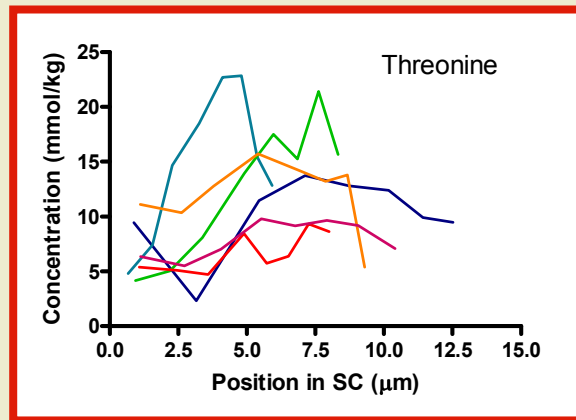
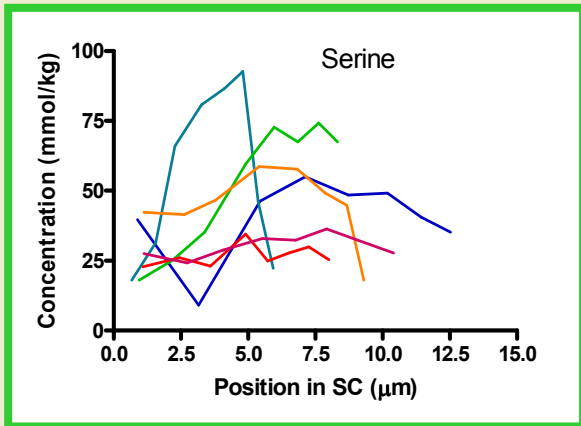
# Intra-subject variability

Subject 1



# Lactate: Intravariability or local release?



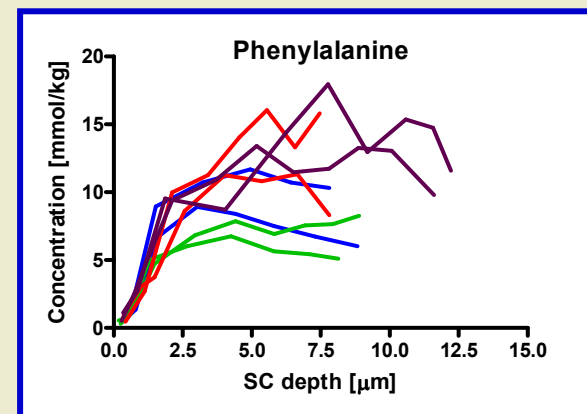
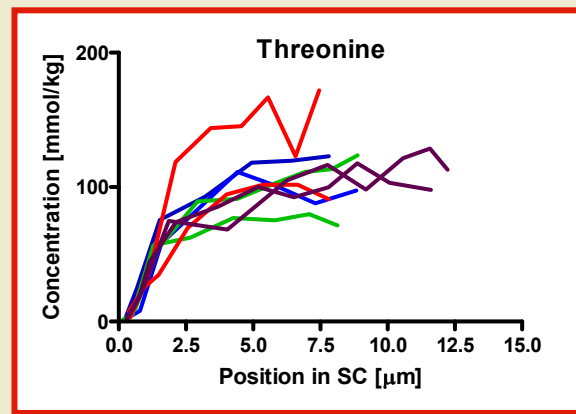
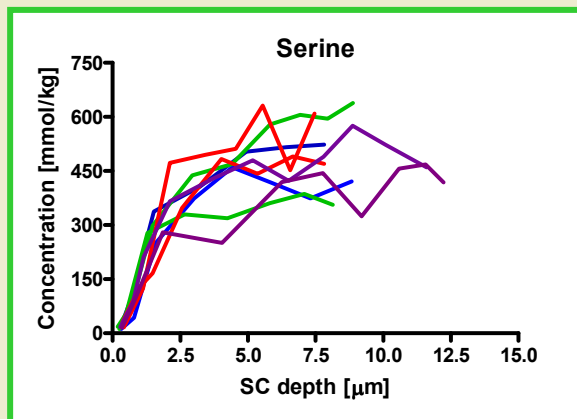


Group 1: Ser, Gly, Ala, His (40-23 mmol/kg)

Group 2: Thr, Pro, Leu (10-7 mmol/kg)

Group 3: Val, Ile, Tyr, Phe, Asn, Trp (3.5-0.6 mmol/kg)

**Pig Skin**



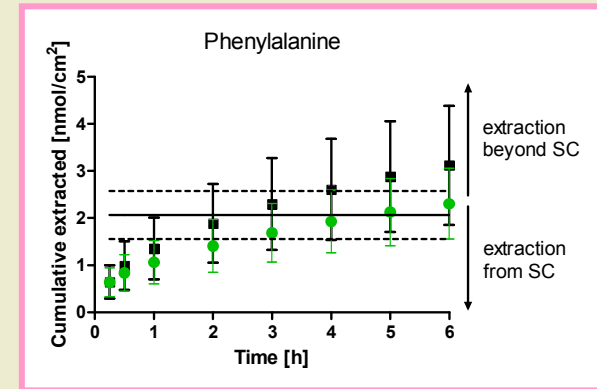
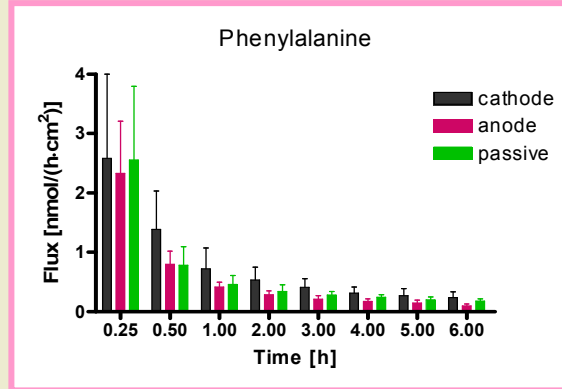
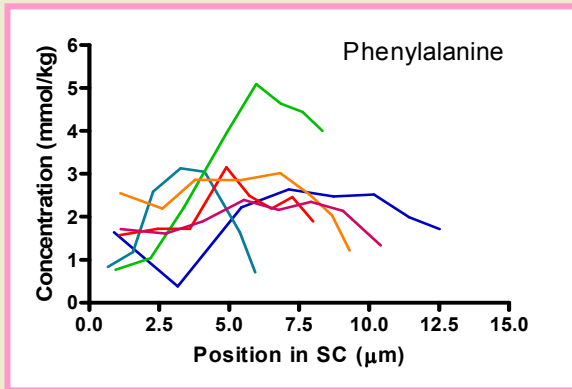
Group 1: Ser, Gly, Ala, His (370-101 mmol/kg)

Group 2: Thr, Pro, Val, Tyr, Leu (84 – 20 mmol/kg)

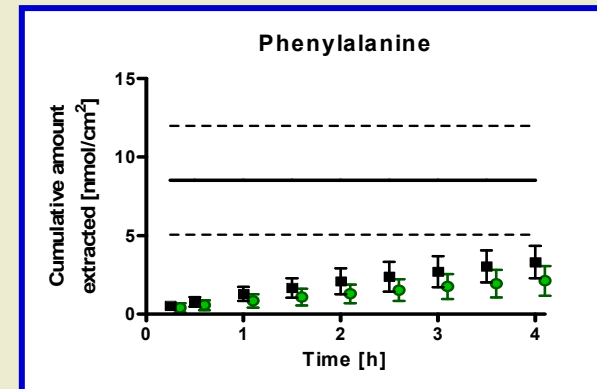
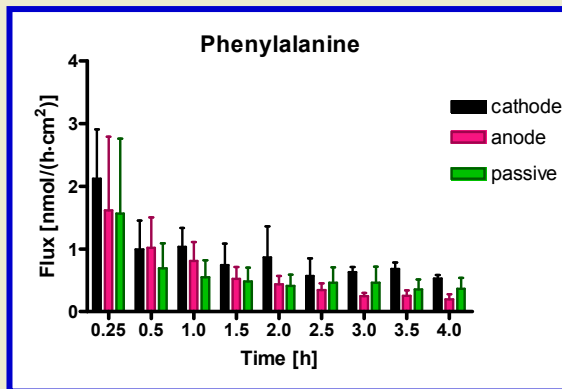
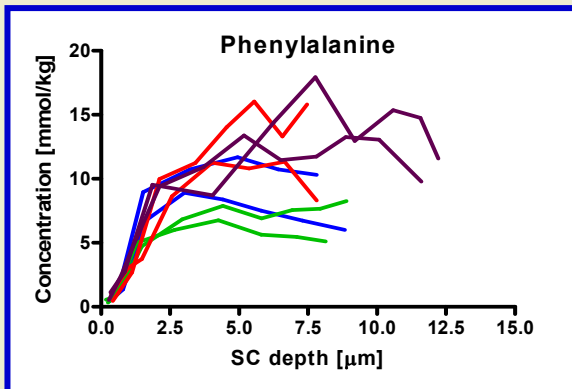
Group 3: Asn, Ile, Trp, Phe (14-8.5 mmol/kg)

**Humans**

## Pig Skin



## Humans



● Passive diffusion

■ Cathodal extraction

■ Anodal extraction

CAN WE DO PK?

$$J_{Li} = \gamma \cdot C_{Li}$$

$$J_{Li}/J_{I.S.} = R_{I.S.} = \gamma^{\#} \cdot C_{Li}$$

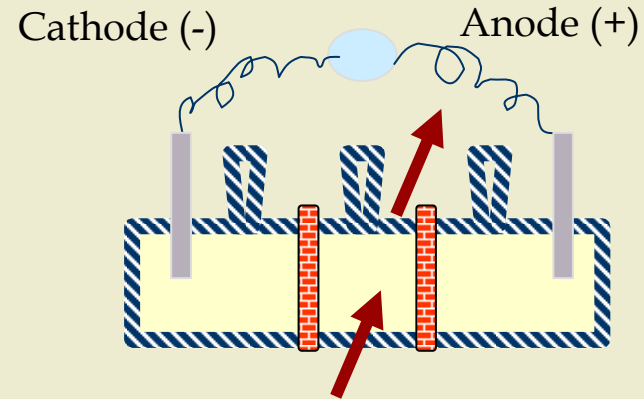
+

$$C_t = C_0 \cdot e^{-K_e \cdot t}$$

↓ ?

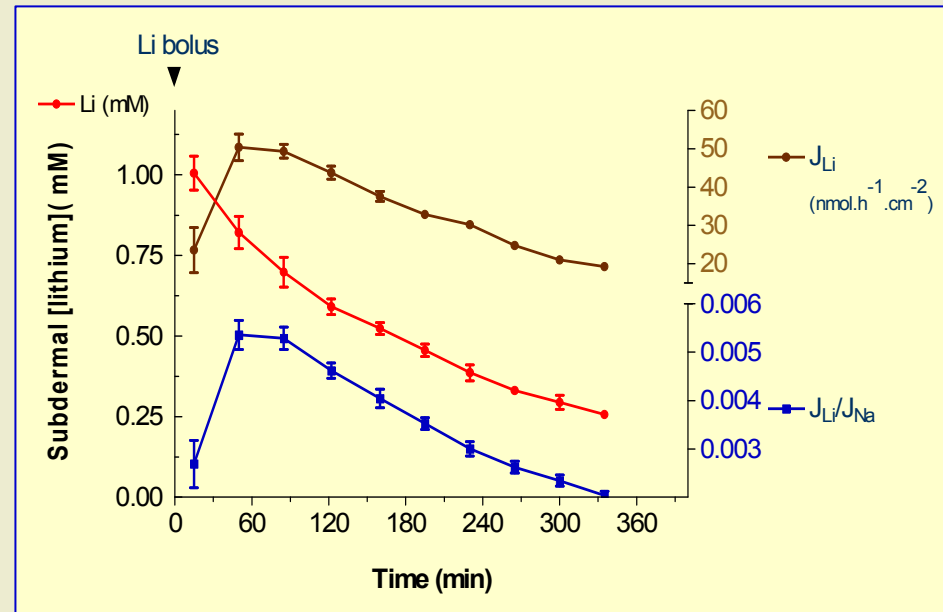
$$J_{Li} = \gamma \cdot C_0 \cdot e^{-K_e \cdot t}$$

$$R_{I.S.} = \gamma^{\#} \cdot C_0 \cdot e^{-K_e \cdot t}$$



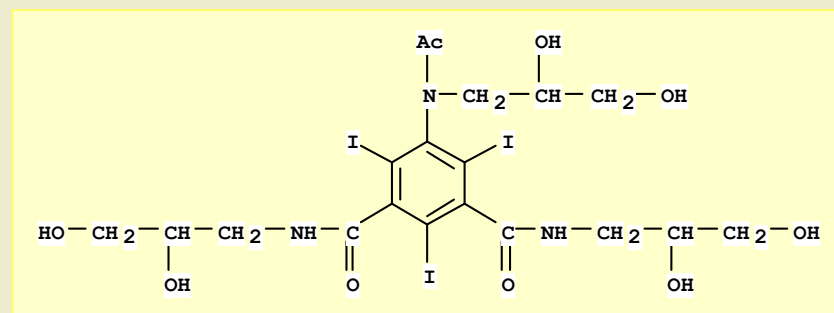
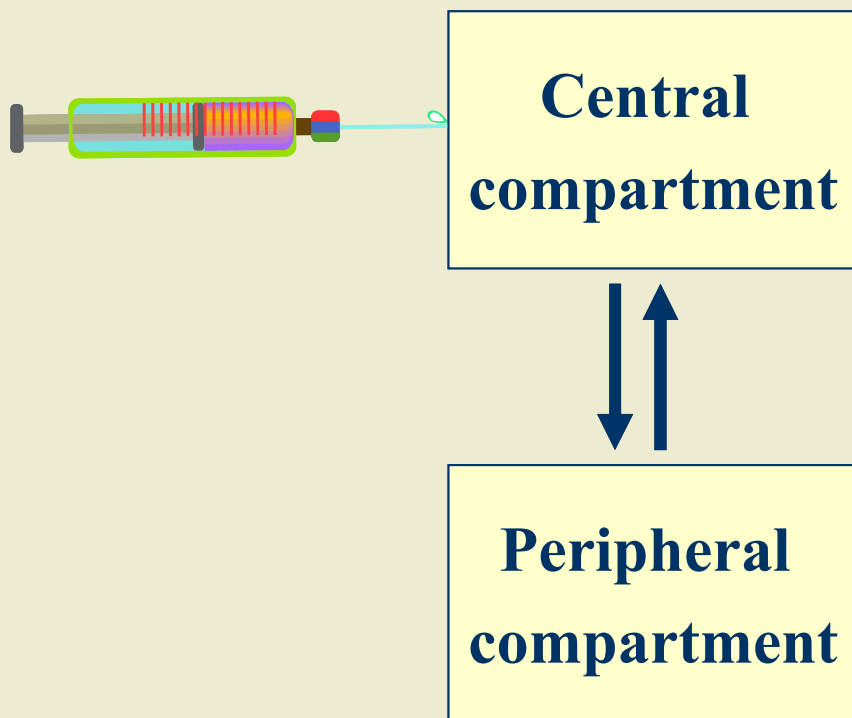
### Lithium: « In Vitro Bolus »

K<sup>+</sup> (internal standard at 4 mM), Na<sup>+</sup> (internal standard at 120 mM)



# GFR & Iohexol:

(see A. Djabri abstract for Reverse Iontophoresis results)

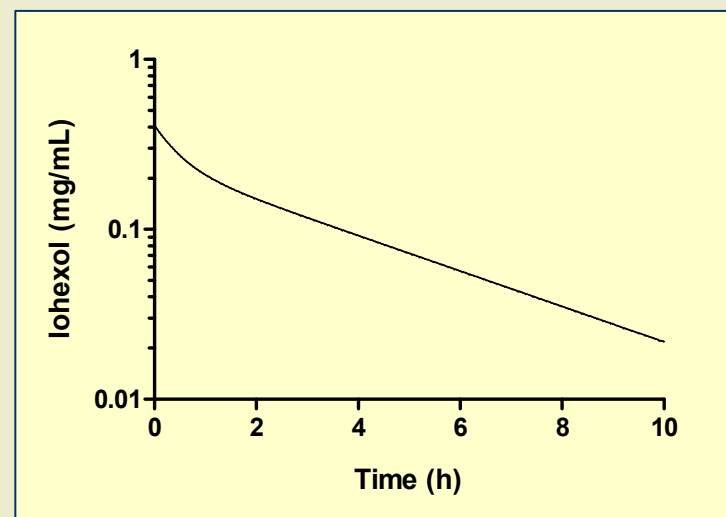


MW = 821, log P = -3 to -4

$$C_{iohexol} = 0.24e^{-0.24 \cdot t} + 0.17e^{-2.1 \cdot t}$$

C (mg/mL);  $\alpha$  and  $\beta$  ( $\text{h}^{-1}$ ), Mean Dose = 3.2 g

Schwartz et al. *Kidney International*, 2006



# Conclusions

- Dual information.
  - Clear potential for non-invasive TDM and PK.
  - Tool to “explore the skin”.
- Type of information obtained determined by:
  - Mechanism of extraction: ER vs EO
  - [Skin]

## More about:

- ☒ Better understanding of
  - kinetics, equilibrium subdermal-plasma
  - causes of variability - calibration
- ☒ What is the “skin” reservoir? Where is it?
- ☒ Development of models combining pharmacokinetics with extraction kinetics.
- ☒ What to do with all this information?