Towards More Inclusive Mathematical Models for Microdialysis, 4th Int'l Symposium on Microdialysis in Drug R & D, Vienna, June 2004

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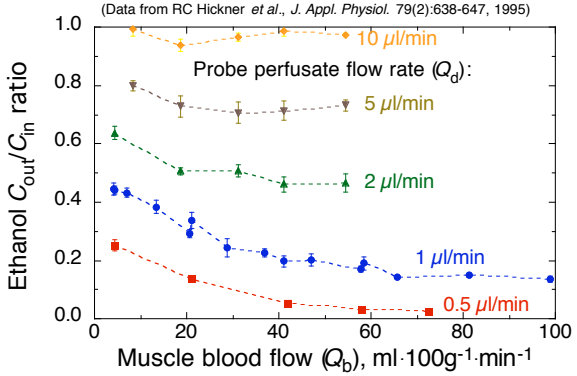
1. Including generalized analyte diffusion through tissue

- Previous *in vivo* microdialysis models assume that analyte movement through tissue occurs by diffusion through the extracellular space (ECS) characterized by an ECS volume fraction, ϕ_e, and diffusion coefficient, D_e.
- However, transcellular or other diffusional pathways can make significant contributions for some analytes, such as small lipophilic solutes.
- To allow for alternative pathways the models can be recast in terms of the tissue-volume based diffusion coefficient, D_t.

Example: ethanol loss from perfusate to tissue is related to blood flow in isolated perfused cat muscle

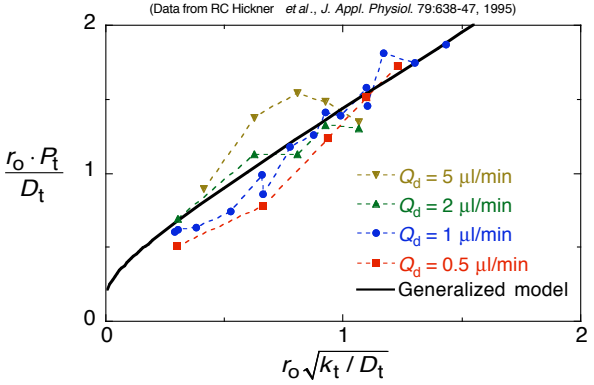
(Data from RC Hickner *et al.*, *J. Appl. Physiol.* 79(2):638-647, 1995)



Rate of ethanol loss from tissue to blood is expressed through tissue-volume based rate constant, $k_t = \rho \cdot \Phi_b \cdot Q_b$, in which ρ = tissue density and Φ_b = blood-to-ECS partition coefficient. D_t, k_t and the probe radius, r_o, determine the tissue permeability, P_t, which is the ease with which the analyte (ethanol) penetrates the tissue from the probe.

Model yields fit to ethanol data for D_t/D_d=0.27, whereas $D_t/D_d \sim \phi_e/\lambda^2 \sim 0.05$ for analytes confined to ECS in muscle

(Data from RC Hickner *et al.*, *J. Appl. Physiol.* 79:638-47, 1995)



2. Including ultrafiltration through probe membrane

- Some perfusate will be driven across all microdialysis membrane depending upon the pressure drop across the membrane and the membrane fluid permeability.
- Ultrafiltration might either confound interpretation of microdialysis sampling data or be exploited for enhancing local delivery of therapeutic agents.

New parameters required to incorporate ultrafiltration

For differing perfusate $\left(Q_d^{in}\right)$ and dialysate $\left(Q_d^{out}\right)$ flow rates:

Fluid: ultrafiltration fraction, $f_Q = 1 - \dfrac{Q_d^{out}}{Q_d^{in}}$

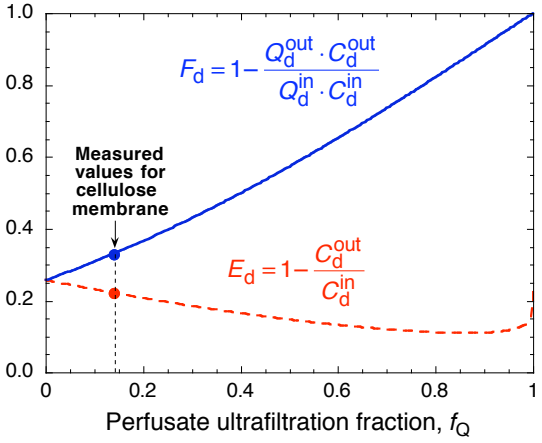
Analyte: flow-based delivery fraction,

$$F_d = 1 - \frac{Q_d^{out} \cdot C_d^{out}}{Q_d^{in} \cdot C_d^{in}}$$

in addition to analyte concentration-based extraction fraction,

$$E_d = 1 - \frac{C_d^{out}}{C_d^{in}}$$

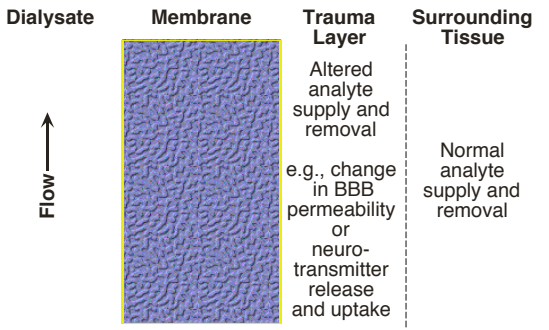
Example: 3-mm probe in rat striatum perfused with ethanol



- Model predicts outward ultrafiltration augments delivery fraction, but diminishes extraction fraction.
- High ultrafiltration fractions for enhanced delivery are possible with longer, more fluid permeable membranes or perforated catheters.
- Delivery by ultrafiltration is particularly attractive for agents with low diffusion coefficients

3. Including effects of probe implantation trauma

- Among the numerous effects of probe insertion trauma are altered local rates of analyte extracellular supply and removal.
- Consequences for microdialysis measurements have been simulated by incorporating a layer of damaged tissue surrounding the probe.



Example

- Groothuis *et al.* observed persistent enhanced influx from blood to brain tissue surrounding chronic non-perfused probes.
- Tissue autoradiography was used to measure influx during 15-min interval following i.v administration of radiolabeled solute at various times (up to 28 days) after probe insertion.
- Altered BBB permeability appeared to be spatially distributed over millimeter distances from probe.
- Microdialysis model provides alternative interpretation for the observed spatial pattern: solute enters tissue in thin trauma layer and diffuses through ECS into surrounding normal tissue.