Quantification of convection-enhanced drug delivery in an in vitro brain model

Final Report

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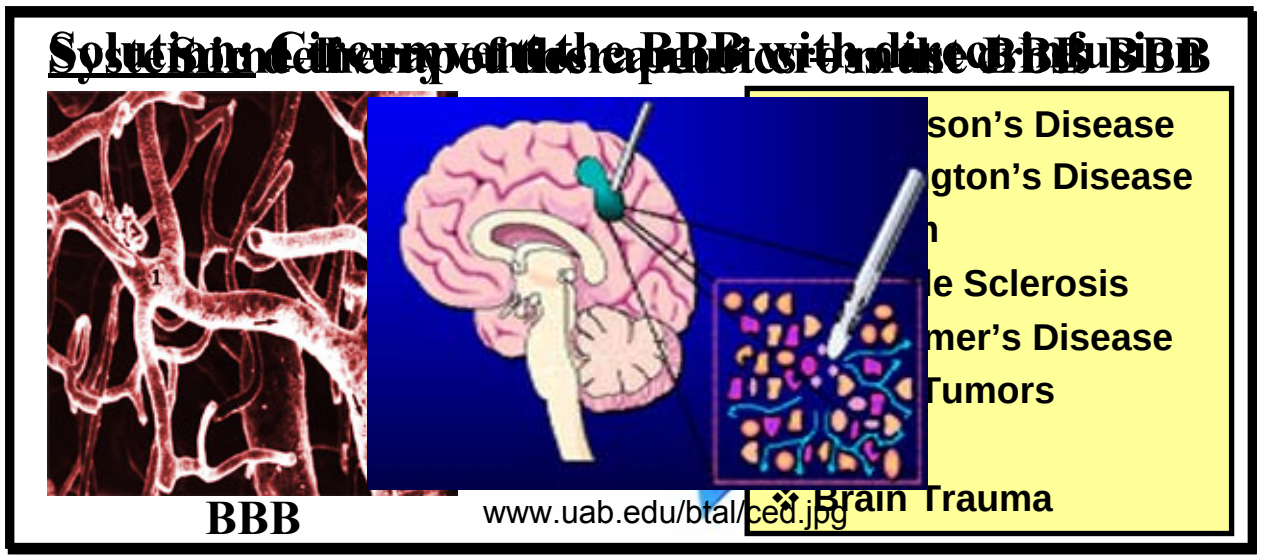
Motivation for systematic design of drug delivery

- **80 million people afflicted with neurodegenerative diseases of the central nervous system (CNS)**



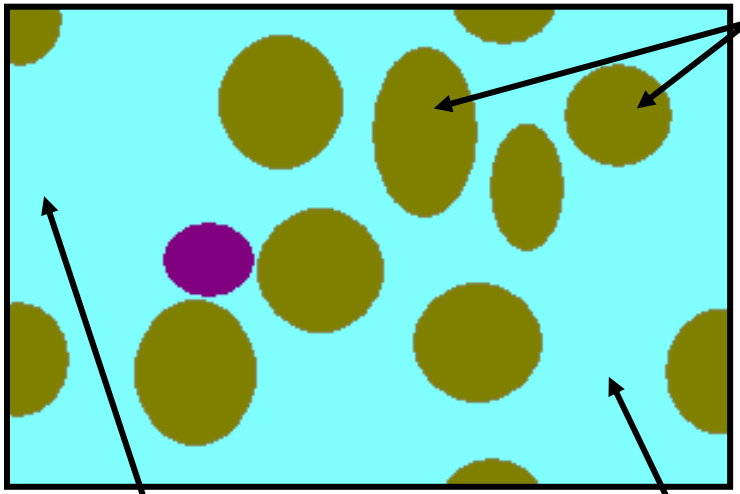
- **Necessary to accurately quantify regional drug distributions**

- **From first principles, provide qualitative and quantitative predictions of achievable treatment volume for clinical use**

Why study convection-enhanced delivery?

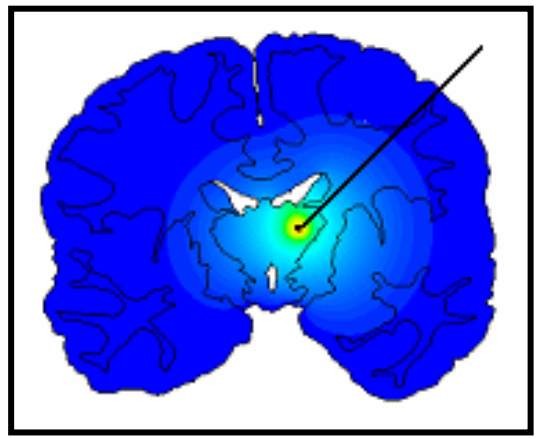
Diffusion only

Solid nerve fibers



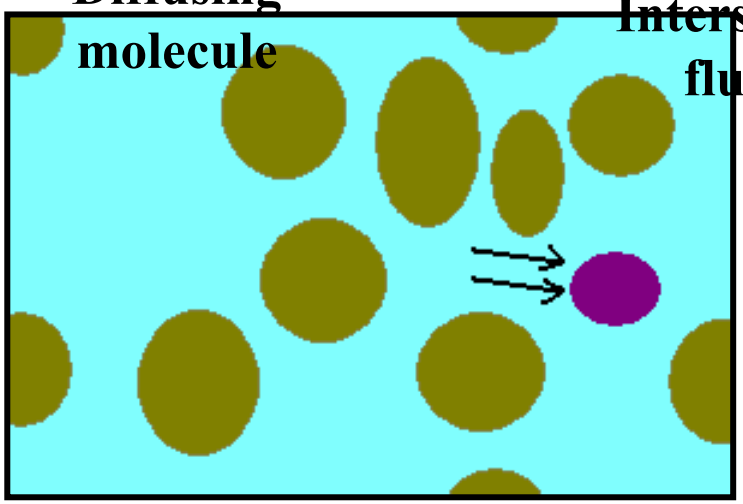
Diffusing molecule

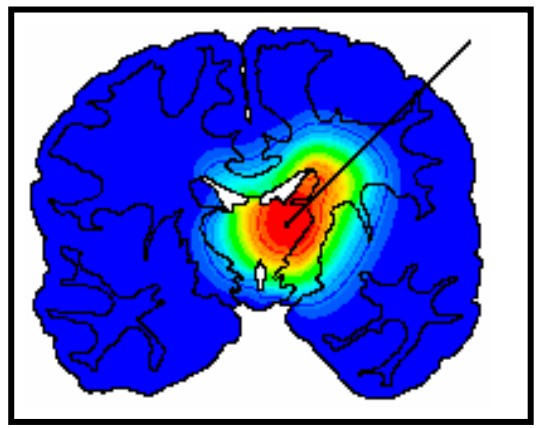
Interstitial fluid



Simulation: Diffusion

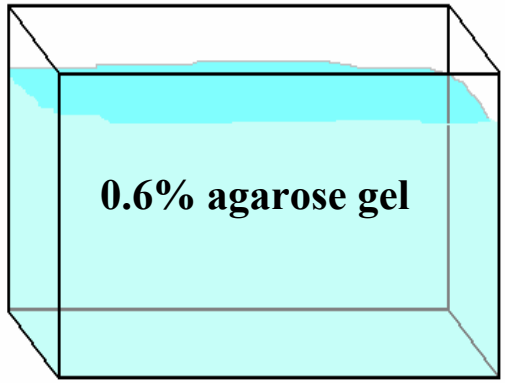
Convection-enhanced





Simulation: Convection-enhanced

In vitro gel model



0.6% agarose gel as surrogate brain tissue (Z. Chen et al., 2004)

Comparison of properties: brain and agarose gel

	Brain	**Agarose Gel**
Material type	Poroelastic	Poroelastic
Homogeneity	Largely inhomogeneous	Homogeneous*
Isotropy	Anisotropic	Isotropic*
Availability	Limited supply	Unlimited supply
Optical properties	Opaque	Transparent
Properties in general	Vary from brain to brain	Highly reproducible

Methods and materials

Catheter diameter: 0.16 – 0.41 ID

Infusion flow rate: 0.5 – 5.0 µl/min

Infusion volume: 30 µl

Temperature: Room (23˚ C)

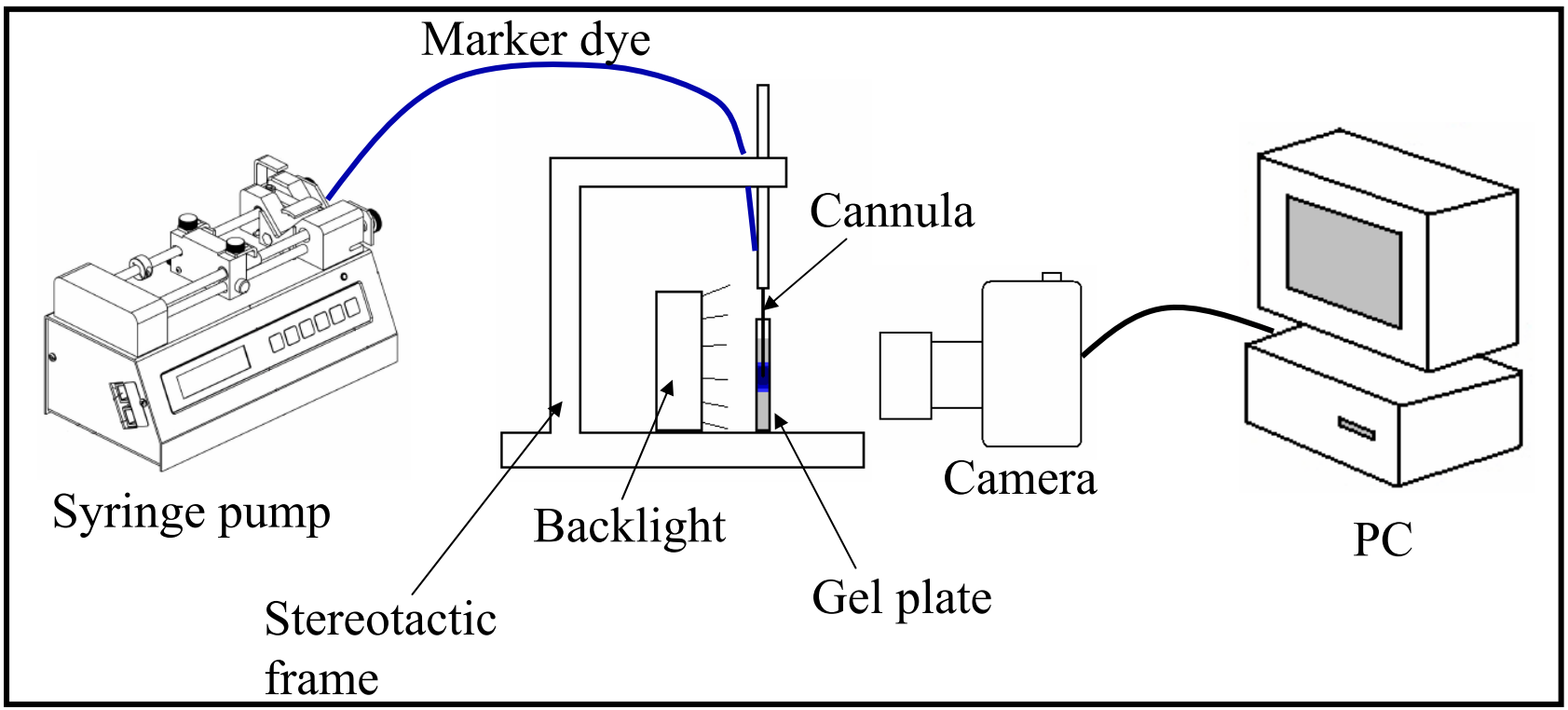
Gel porosity: > 0.99

Dye: Trypan blue

Molecular weight: 961 Da

Dye: Bromophenol blue

Molecular weight: 669 Da



Quantification of transport processes in porous media

Conversion of pixel intensity to dye concentration

- **Assume exponential attenuation of light as it passes through the semi-transparent dye (the Beer-Lambert Law)**

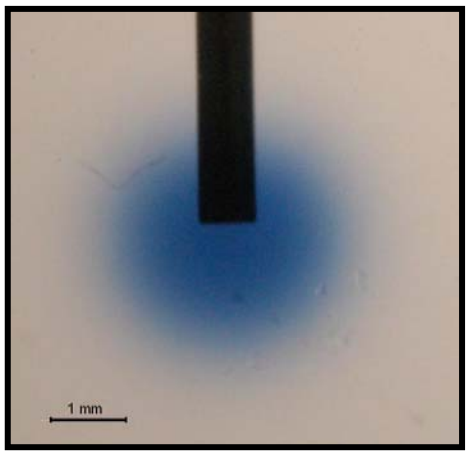
$$C = -K \ln(I/I_o)$$

dye concentration — C

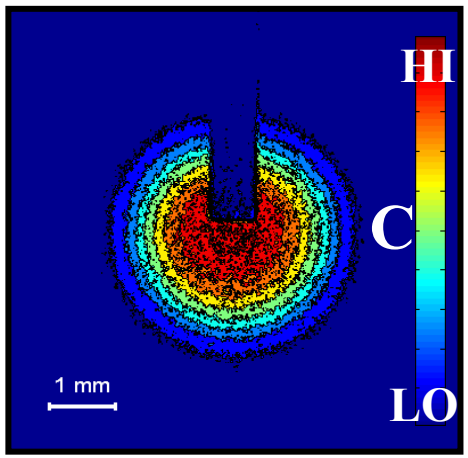
constant — K

measured light intensity (pixel intensity) — I

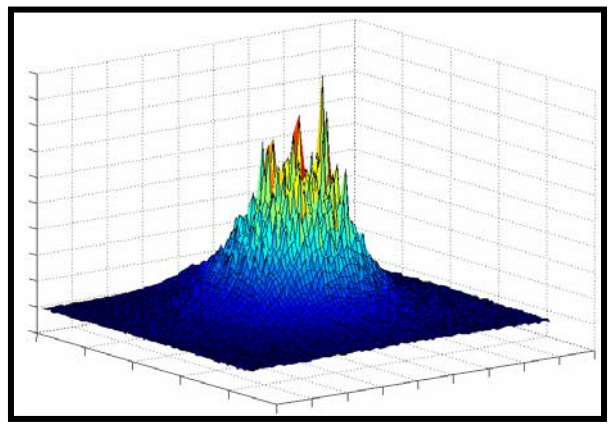
original light intensity — I_o



Digital photo

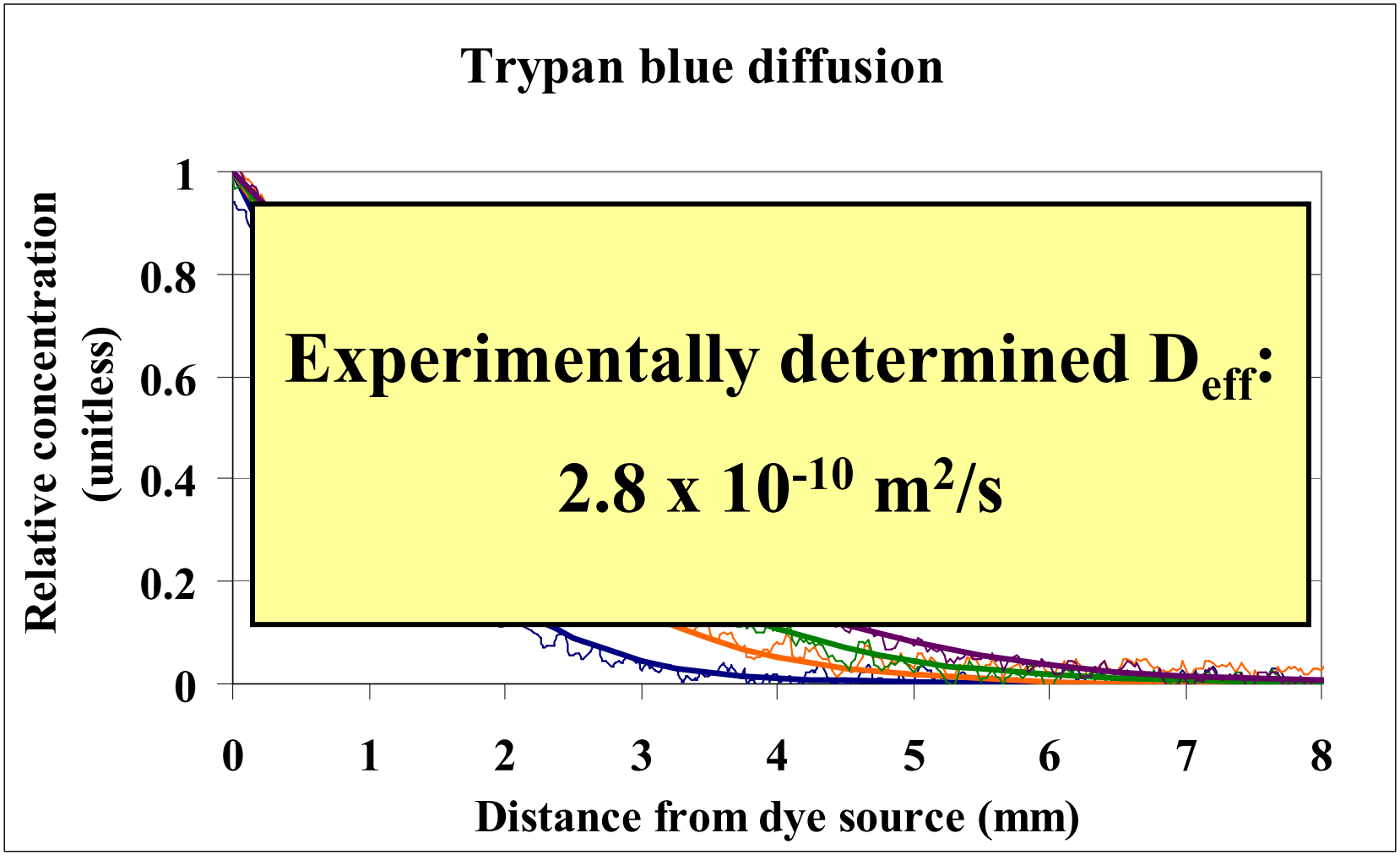


Concentration contours

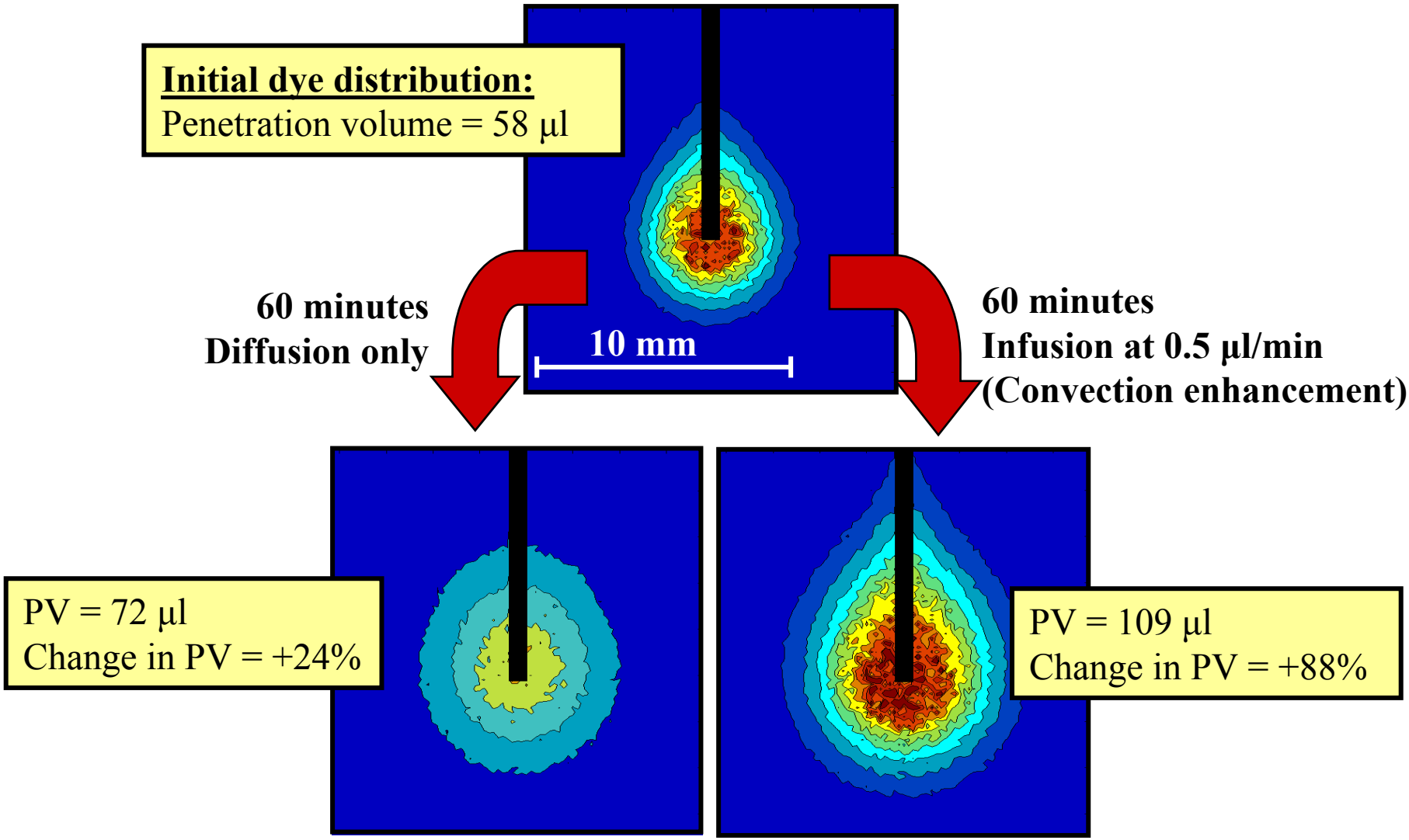


Concentration surface plot

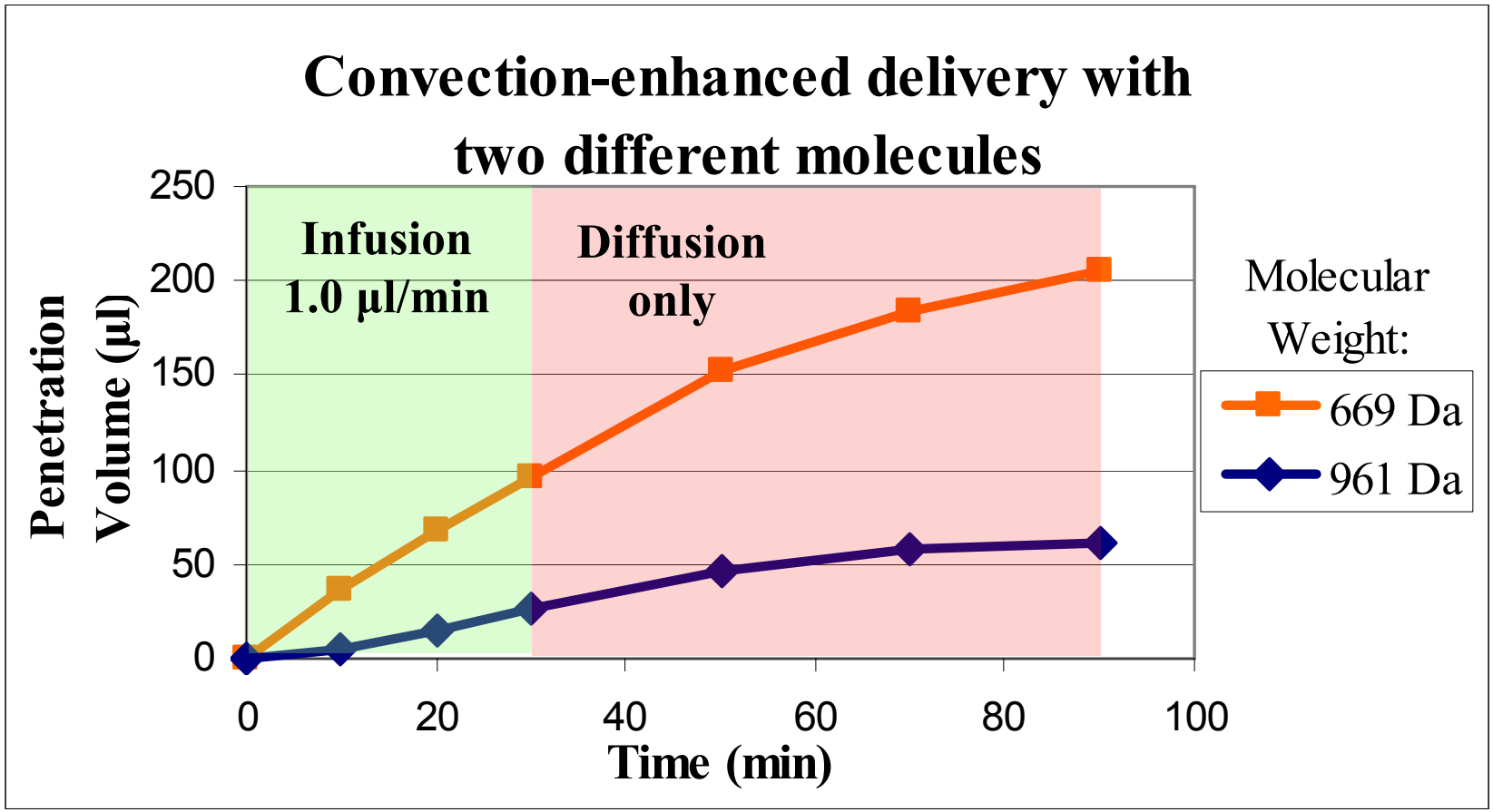
Diffusion in porous media



Convection increases the penetration volume

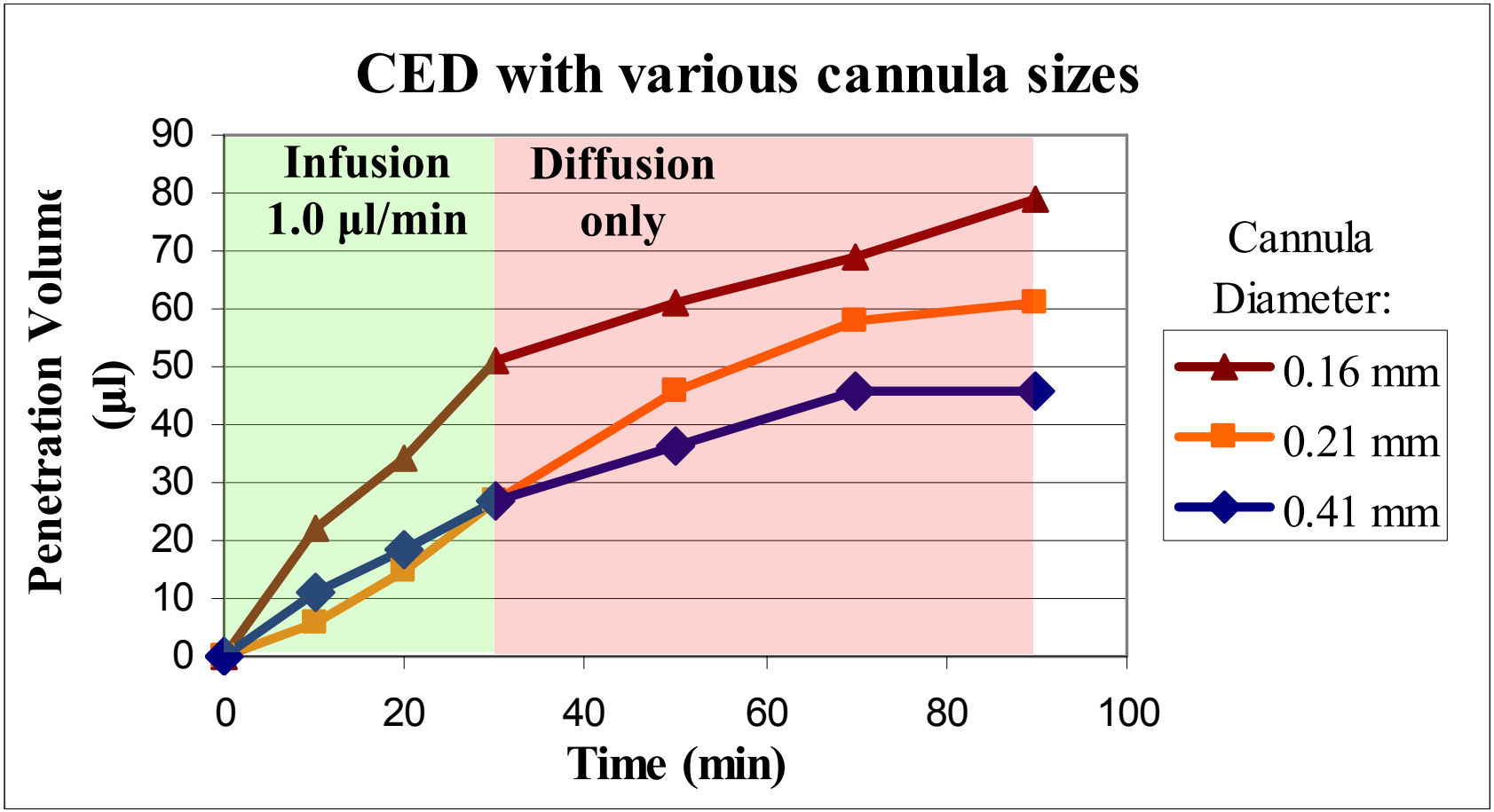


Effect of molecule size on penetration volume



Smaller molecules travel away from the infusion site faster than do larger molecules, resulting in larger treatment volumes.

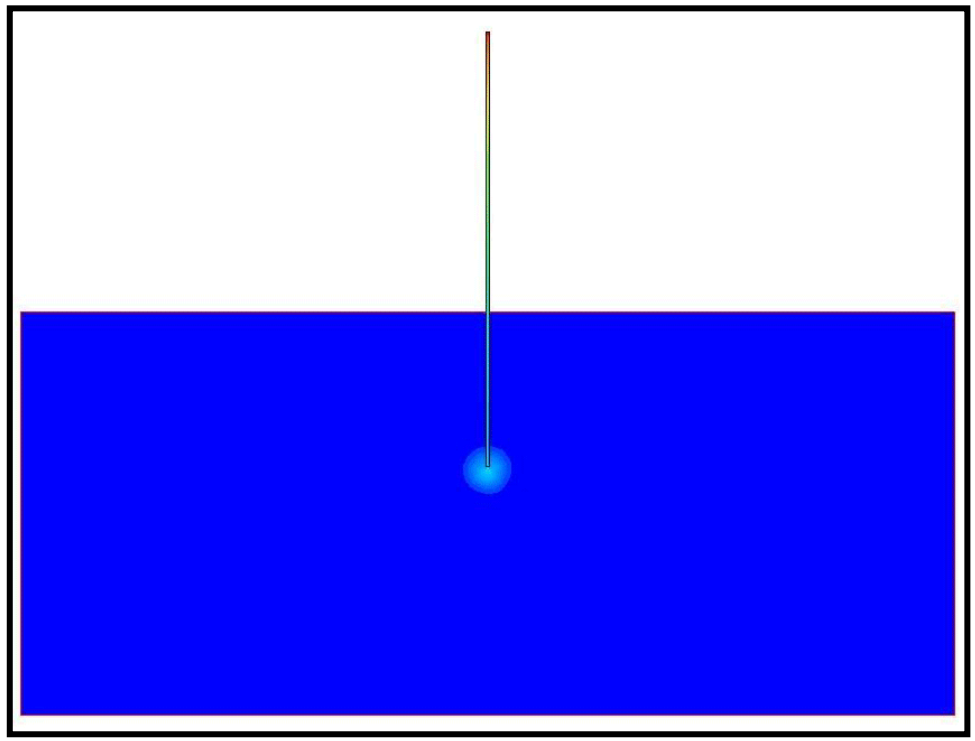
Effect of cannula diameter on penetration volume



A very narrow cannula causes the inflow velocity to be high, possibly resulting in larger treatment volumes during infusion.

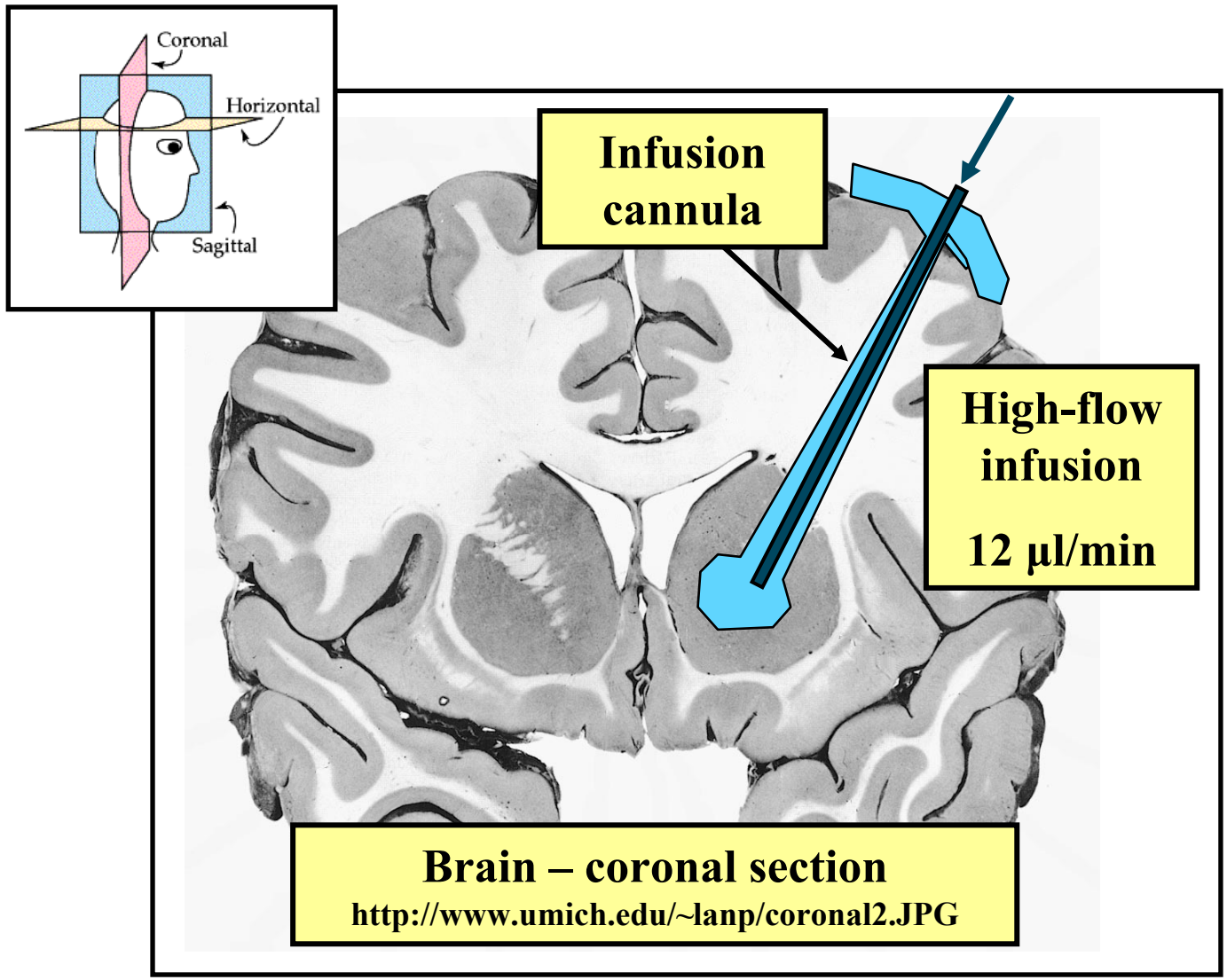
Prediction of drug distribution using simulations

Experimental observation

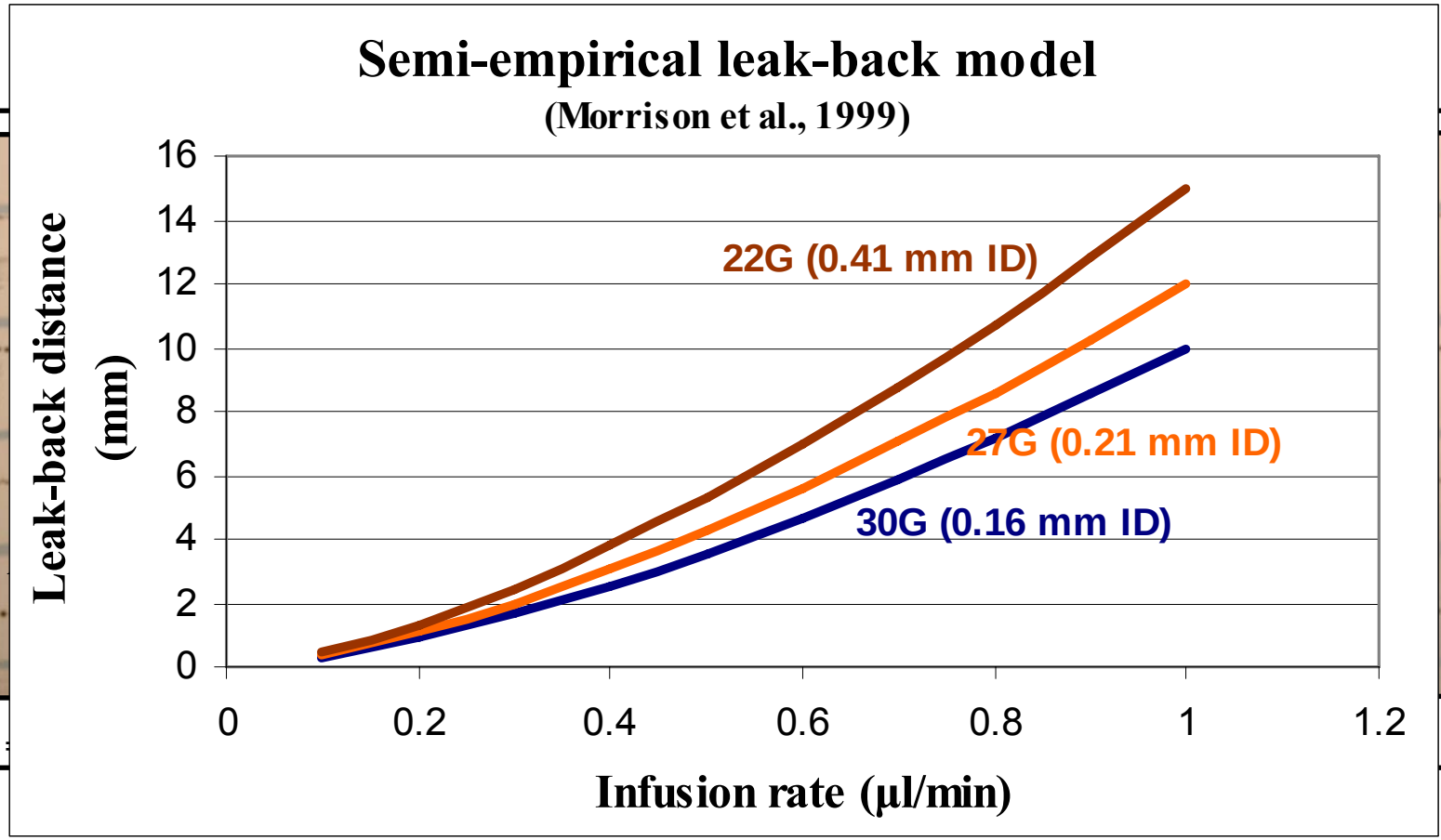


Numerical simulation

Existence of leak-back phenomenon with convection



Experimental observation of leakback



Conclusions

- **We used an in vitro system to investigate convection-enhanced delivery.**

- **Optical methods were used to quantify distribution of blue dye within transparent agarose gel.**
  - Diffusive effects were small, though not negligible, compared to convective effects.
  - Smaller infusate molecules spread away from the infusion site more rapidly than larger infusate molecules.
  - Narrower infusion cannulas cause the infusion velocity to be higher, which may result in larger treatment volumes.

- **Using radiography or magnetic resonance techniques, analogous methods could be used to quantify the distribution of marker molecules in real brain tissue.**

Future directions

- **Quantification of leakback**
- **Convection-enhanced delivery in anisotropic gels (diffusion is not the same in all directions)**
- **Prediction of dye or drug distribution given a set of infusion parameters**
- **Convection-enhanced delivery in real brain tissue**

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