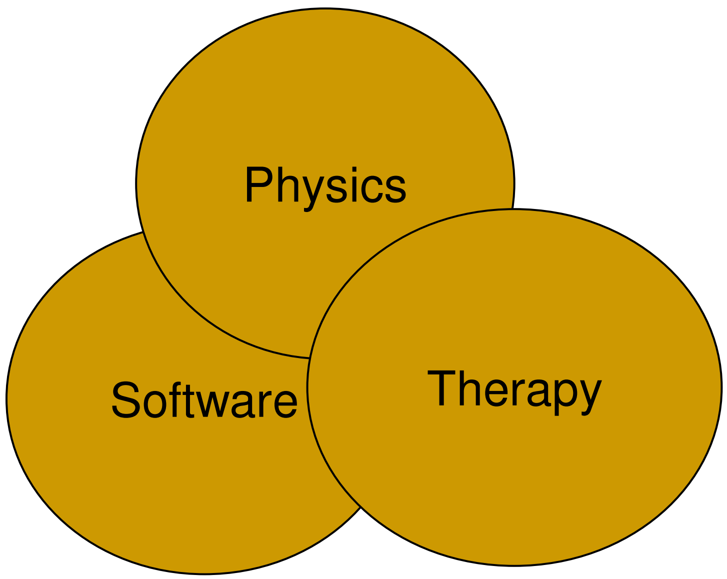
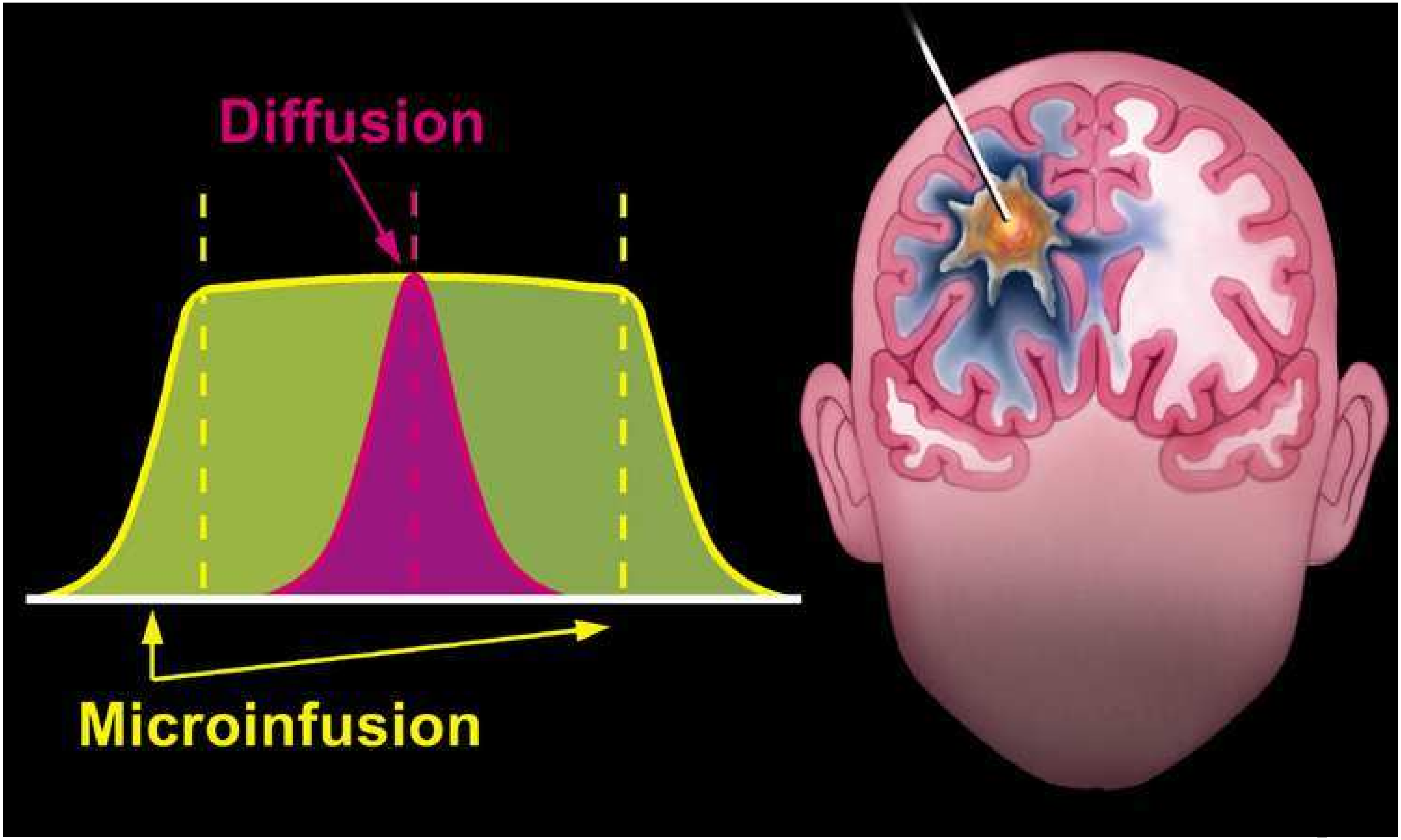
Aristotelian physics and brain disease



Raghu Raghavan

October 19, 2007

Pressure-driven intraparenchymal infusion



Problems with delivery of CNS therapies

“Universe of discourse”: Therapies that have difficulty crossing the blood-brain barrier (BBB)

- Direct (intraparenchymal) delivery

  Problem: Coverage of target

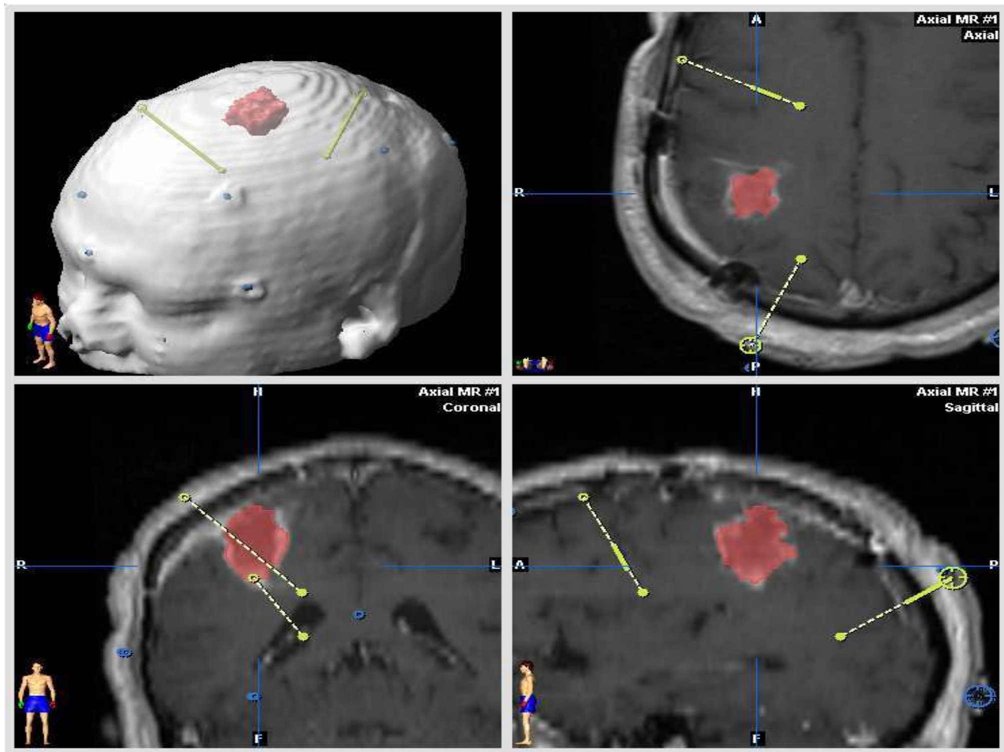
- Local placement of therapy

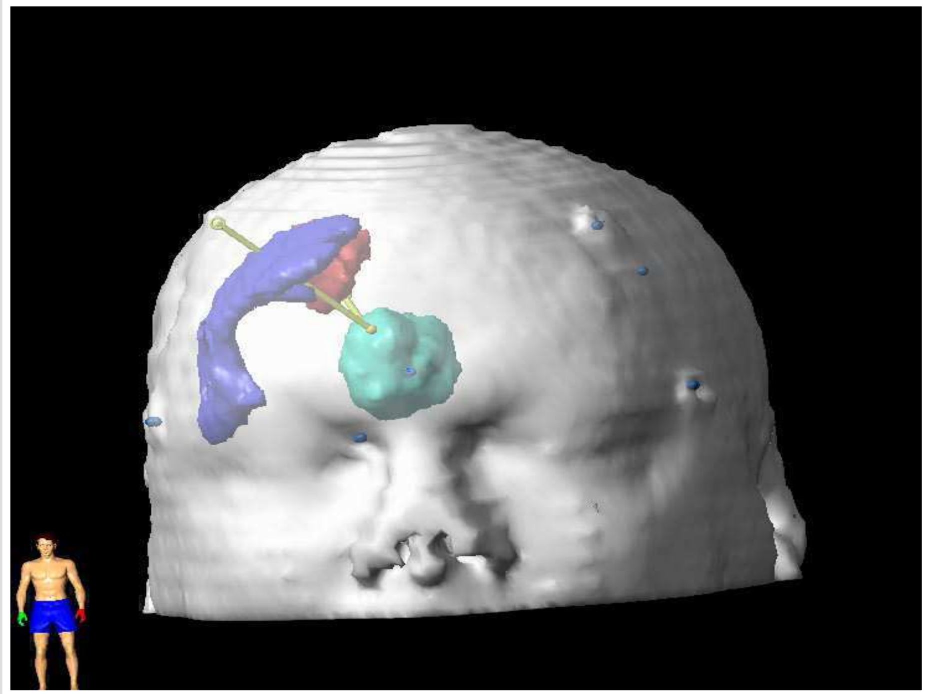
  Problem: Dose calculations and drug transport

- Systemic delivery

  Problem: Interstitial distribution of drug *vs* systemic toxicity

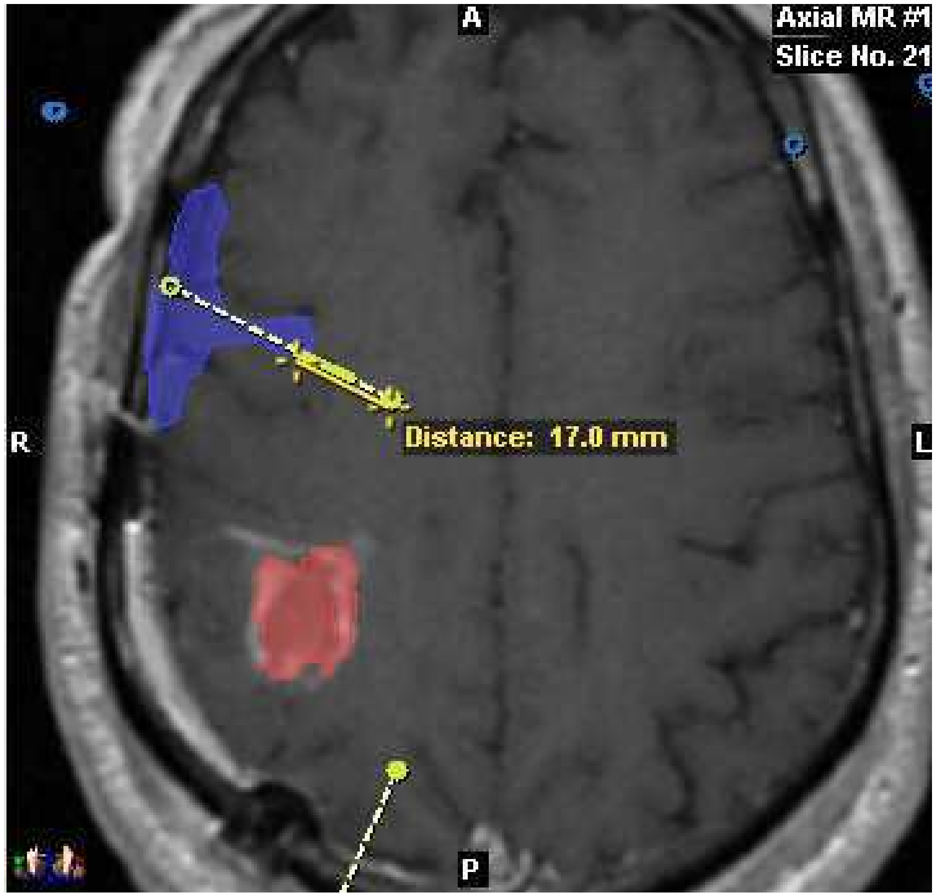
Intraparenchymal delivery: device and placement matter

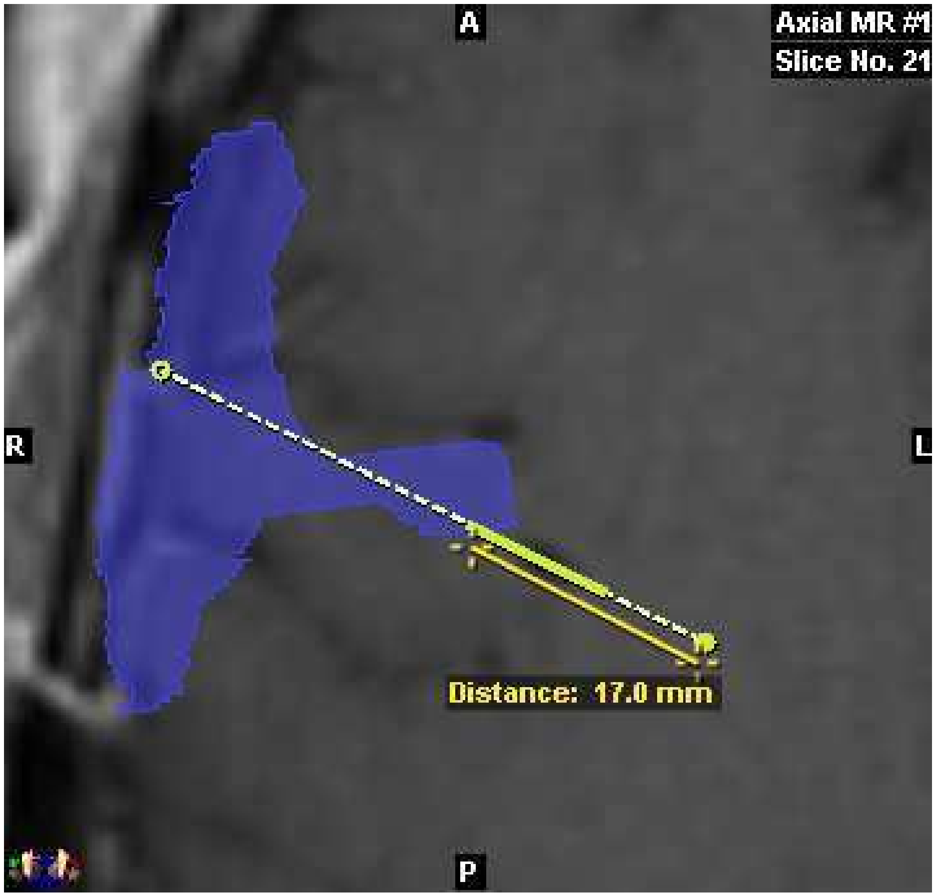




BrainLAB iPlanFlow™


5-06-99 THU
11:52:49 AM


A
Axial MR #1
Slice No. 21
R
L
Distance: 17.0 mm
P


A
Axial MR #1
Slice No. 21
R
L
Distance: 17.0 mm
P

Local placement

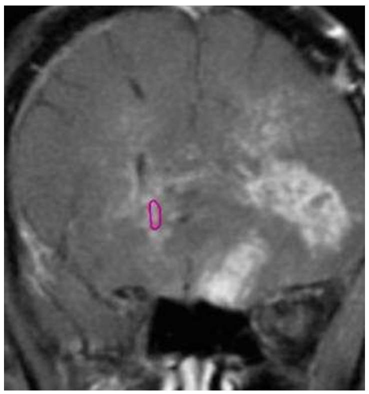
Gliadel Wafer label extension rejected due to unproven clinical benefits

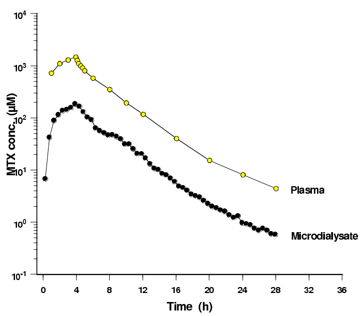
What is the right dose?

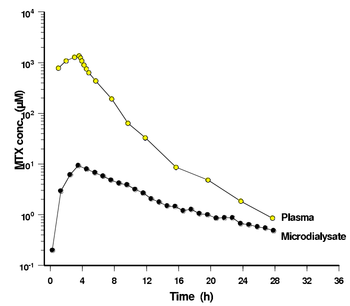
Dose often calculated from systemic pharmacokinetics and totally inadequate for local placement

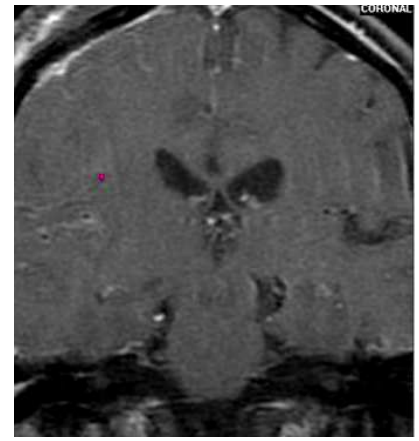
When the wafer faces the resection cavity where will the drug go?

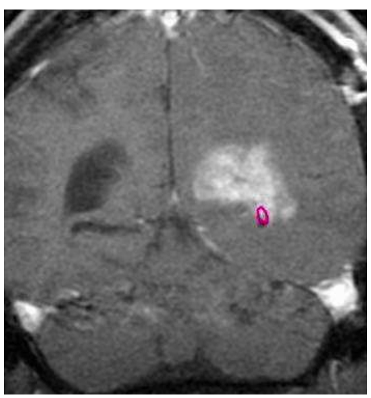
Systemic delivery: surgeon's selection of (equal) residual tumor show very different dose characteristics

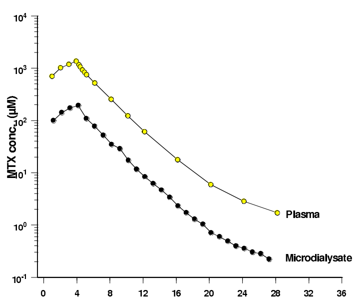


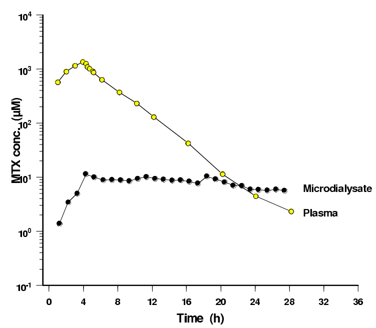


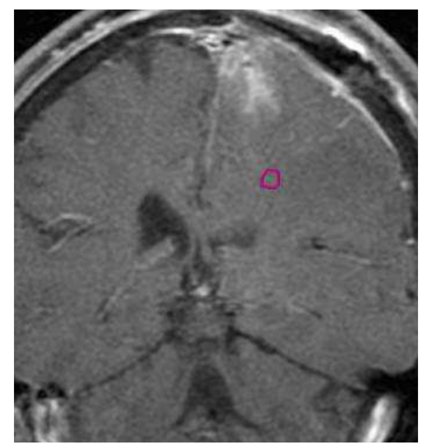












Human trials

"Each new agent should be introduced into human efficacy trials in a manner that *optimizes its chances of success*"

- Suitable patients
- Suitable adjuvant trials (may affect dose!)
- Assessment of efficacy
- Delivery to target

Amgen Trials of Intraputamenal GDNF

"Point source concentration of GDNF may explain failure of phase II clinical trial"

Salvatore et. al., *Experimental Neurology,* 2006

"… patients who experienced large drug losses across gray tissue boundaries due to variation in catheter placement."

Convective delivery of glial cell line-derived neurotrophic factor in the human putamen, Morrison et. al., *Journal of Neurosurgery,* 2007

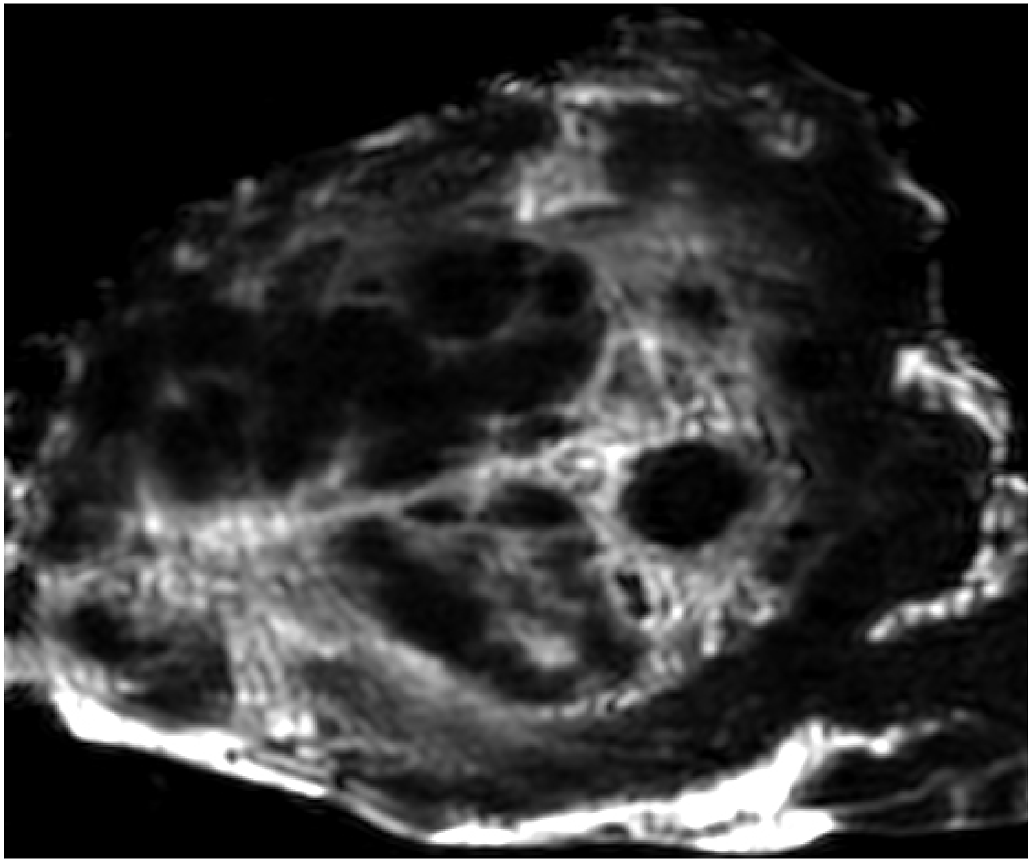
MRI and histology of ex vivo Protox injection studies of human prostates

Observations of four procedures at
Scott & White Memorial Hospital, Temple, Texas

Study conducted by:

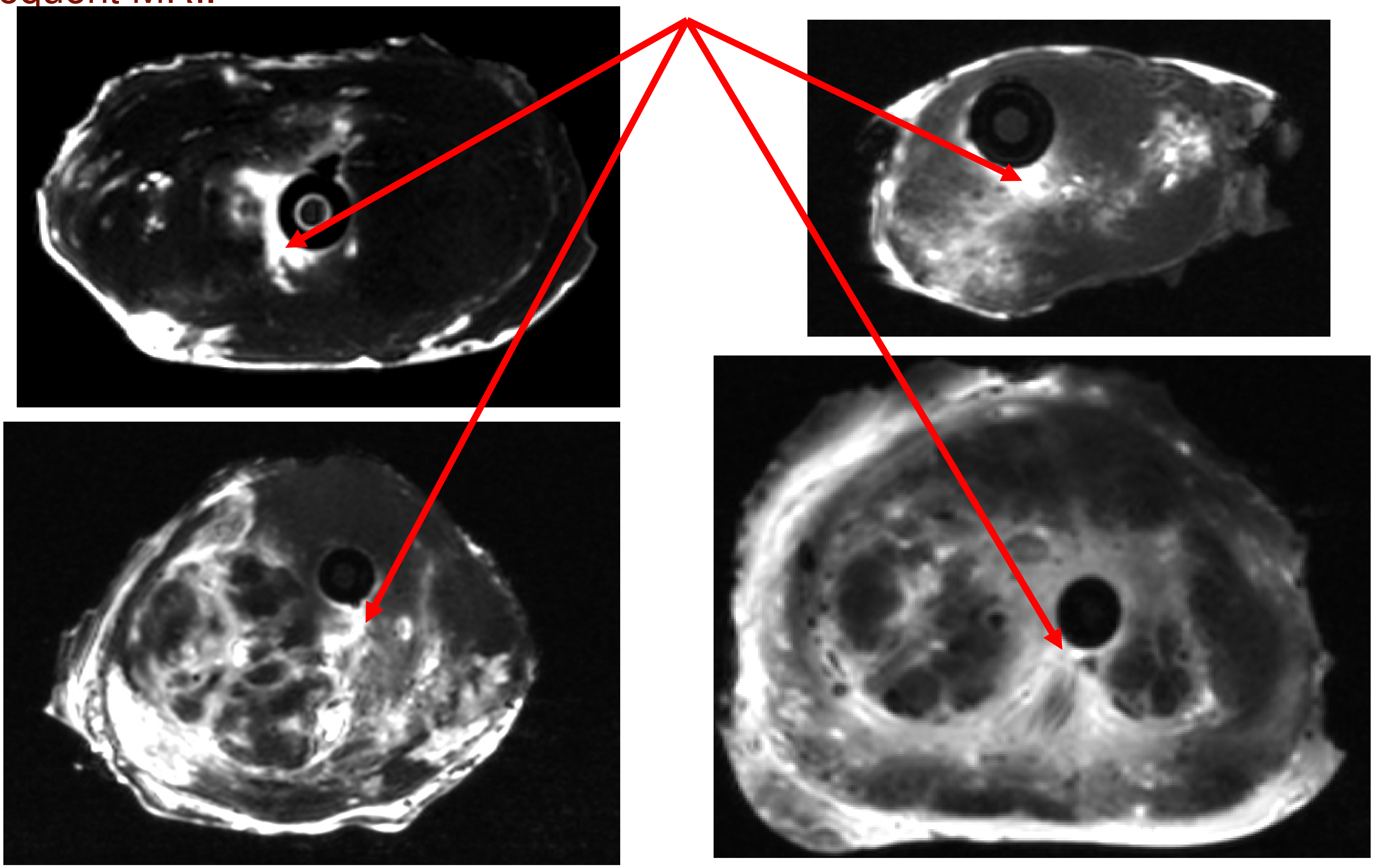
Thomas Kuehl, Arthur Boyer, John Milleman, and Scott Coffield

Contrast, as an indicator of delivery of agent to tissues, is not uniformly distributed.

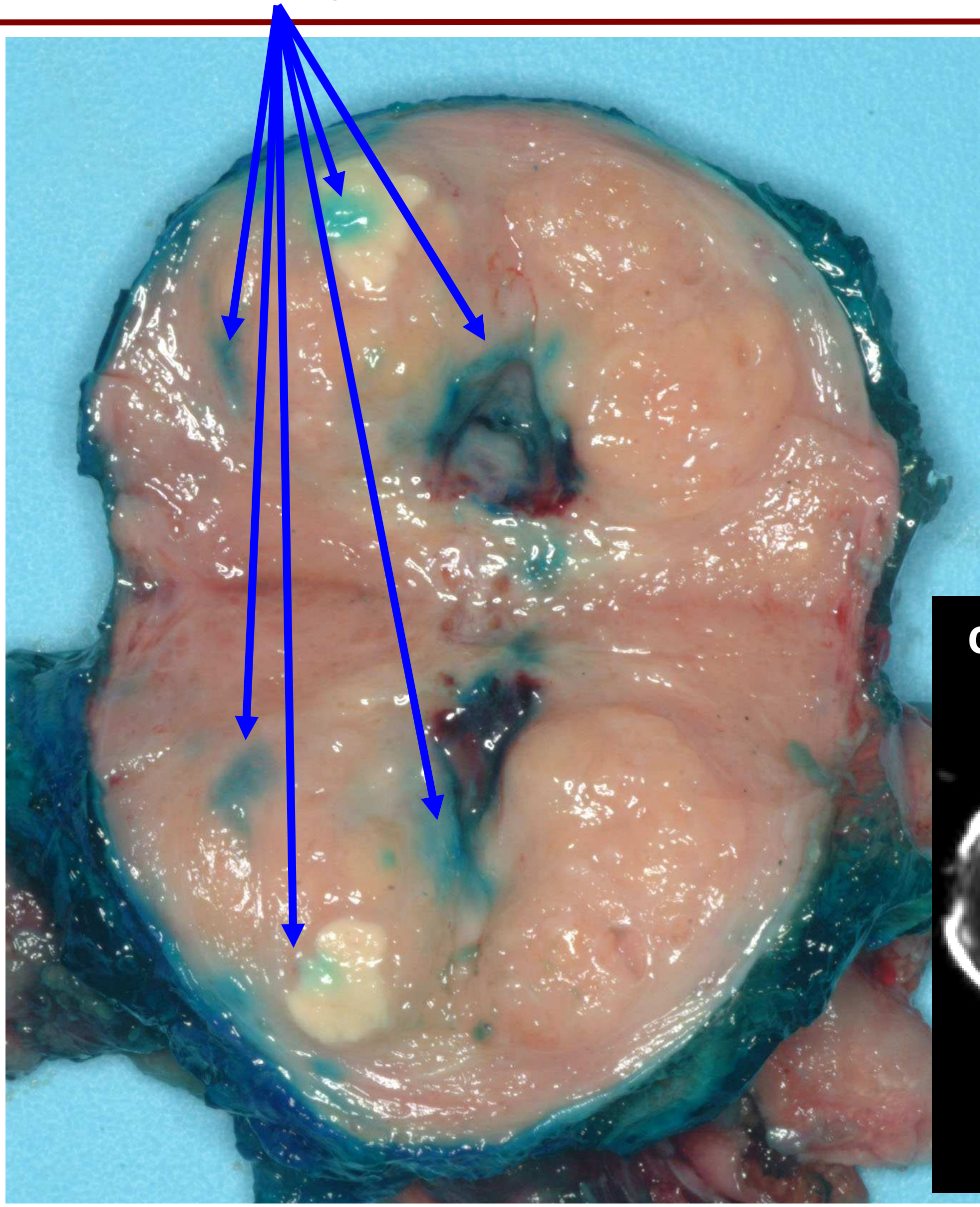


Histopathology shows that prostate is not a uniform tissue in older patients with cancer and BPH.
MRI with contrast also shows the distribution is not uniform.

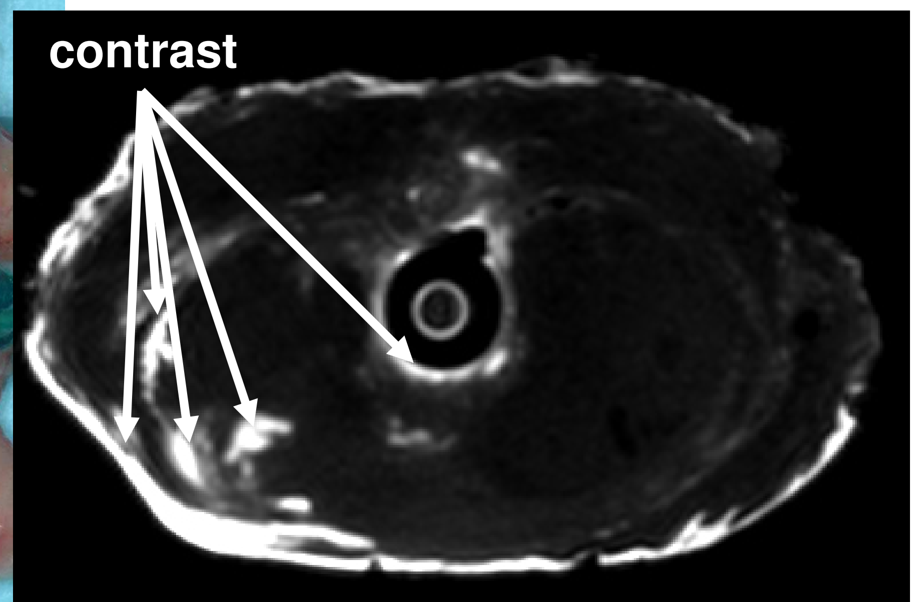
Injection solution moves from injection site to urethra during US directed administration in all 4 samples. Visible as contrast next to urethral catheter in subsequent MRI.



Blue dye



MR contrast & blue dye demonstrate variability in distribution in prostate #3 with material concentrated around capsule, urethra, and a few injection sites



Simplest equation for drug transport

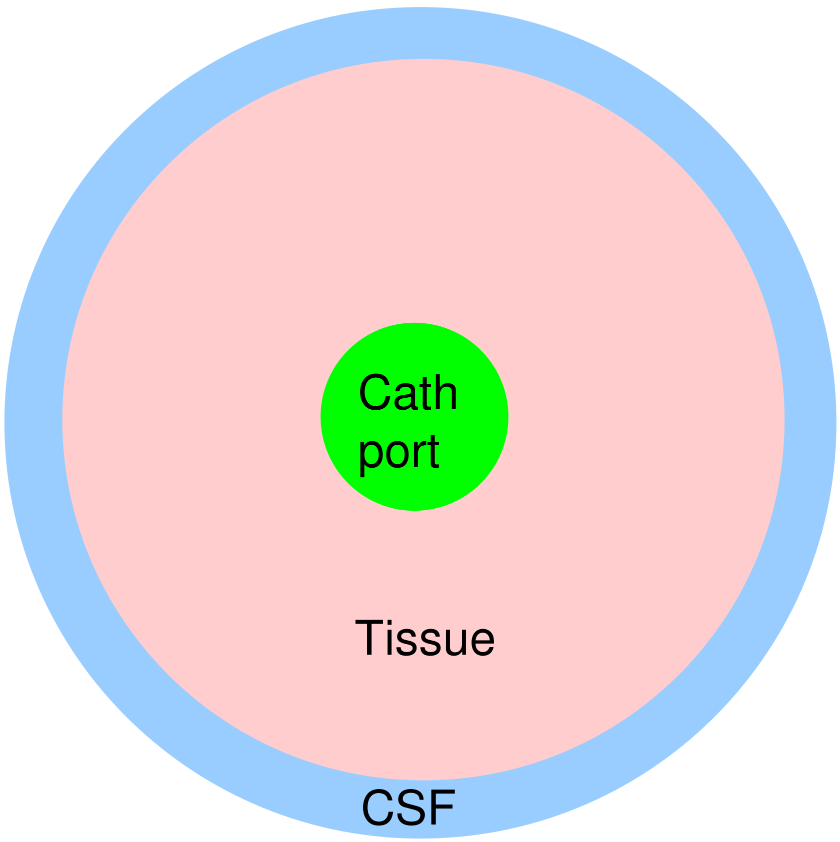
$$\partial c / \partial t = \nabla\nabla : (Dc) - \nabla \bullet (vc) + 1/\phi \, [F_{capillary} - R_{bind} (c, b)]$$

- **Where the drug ends up depends on:**

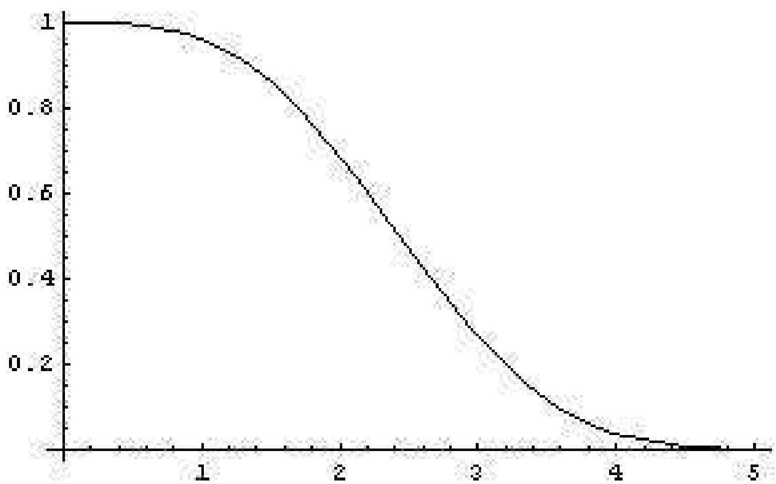
Convection by fluid
Drainage from tissue into capillaries
Diffusion &
Binding

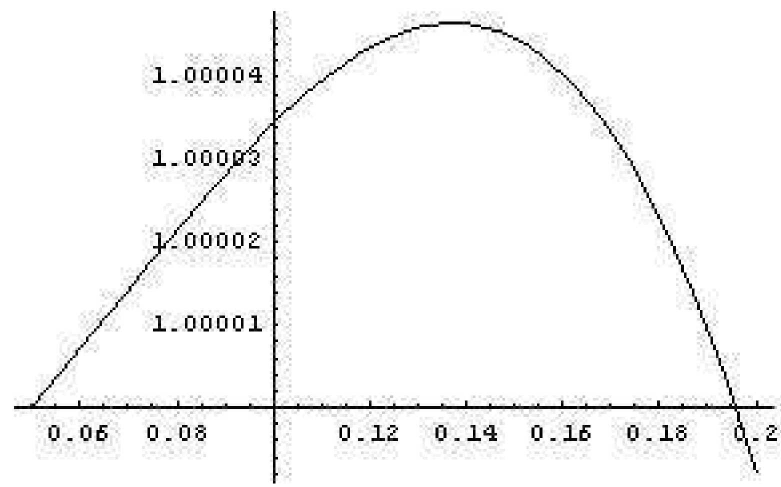
plus **initial-boundary values**

Simple Infusion Model



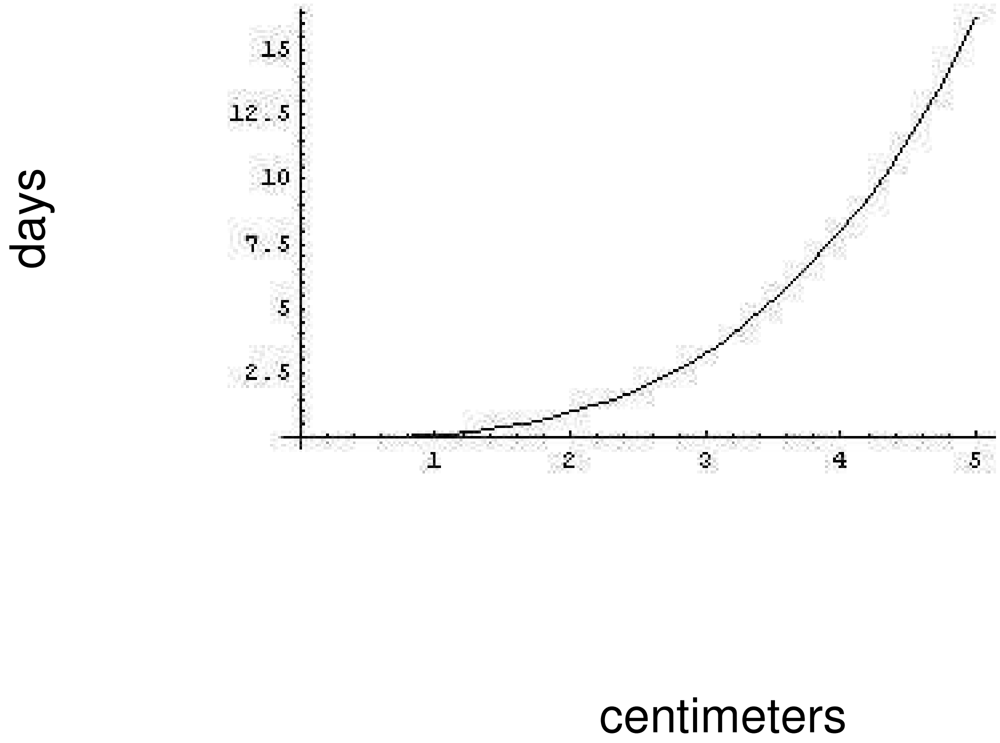
Drug concentration reaches steady state even in absence of leakage into subdural and other spaces





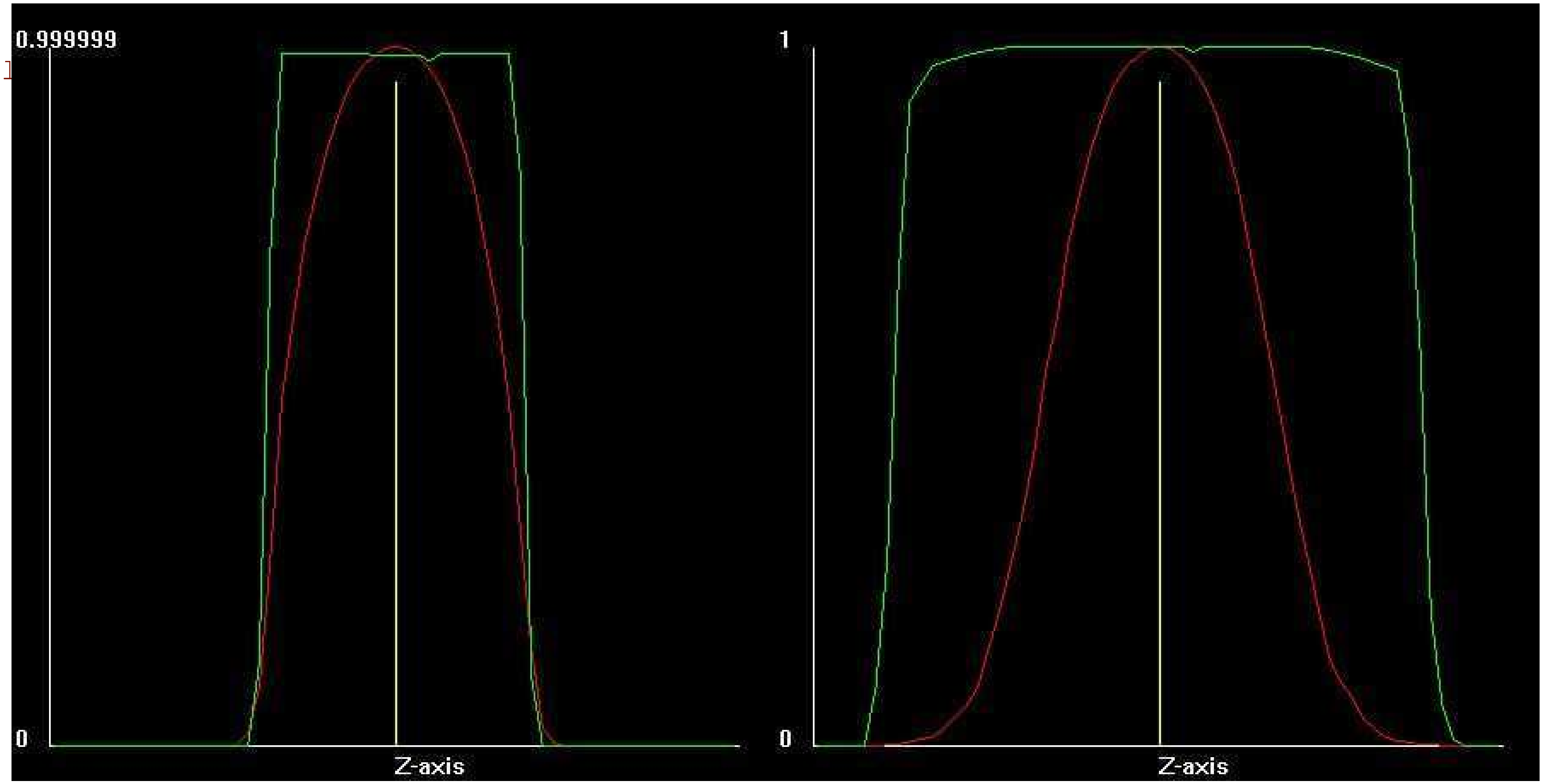
Steady state conc. Conc. near tip
vs radial distance (spherical source)

Reach of convected drug from spherical source



Distribution of molecules according to size

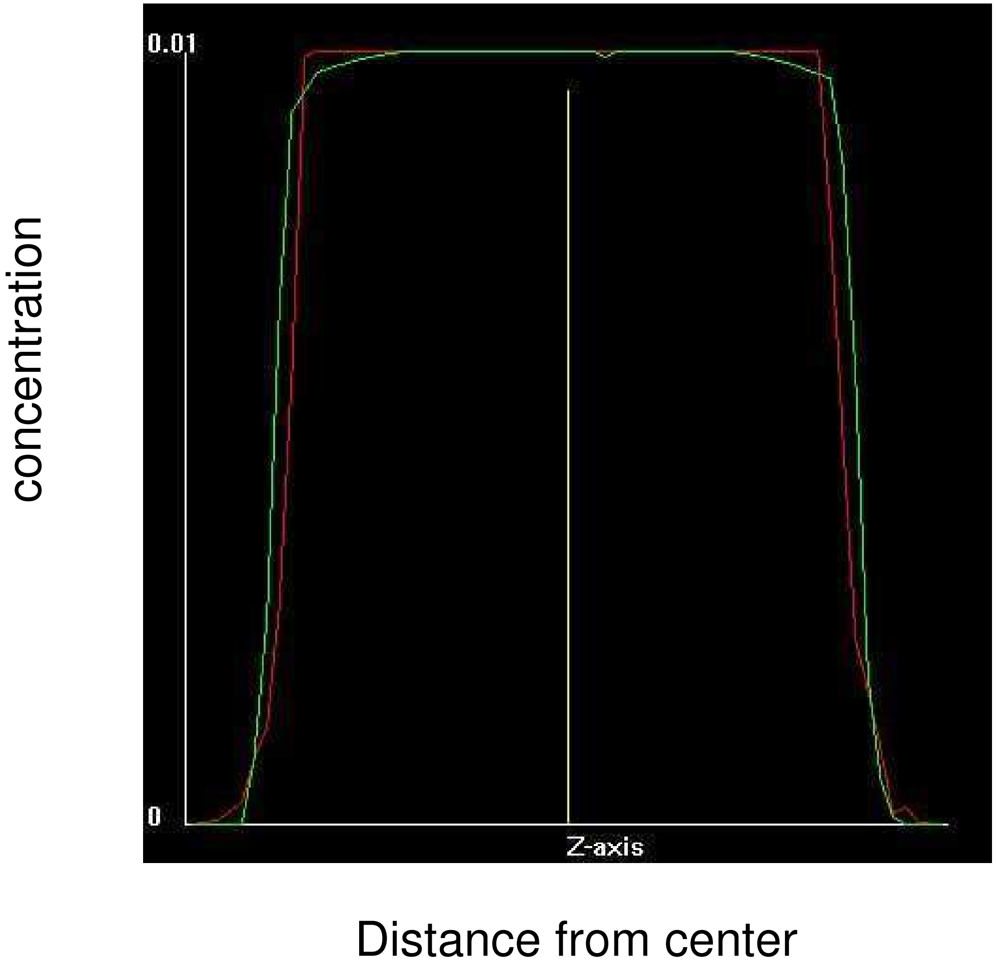
concentration



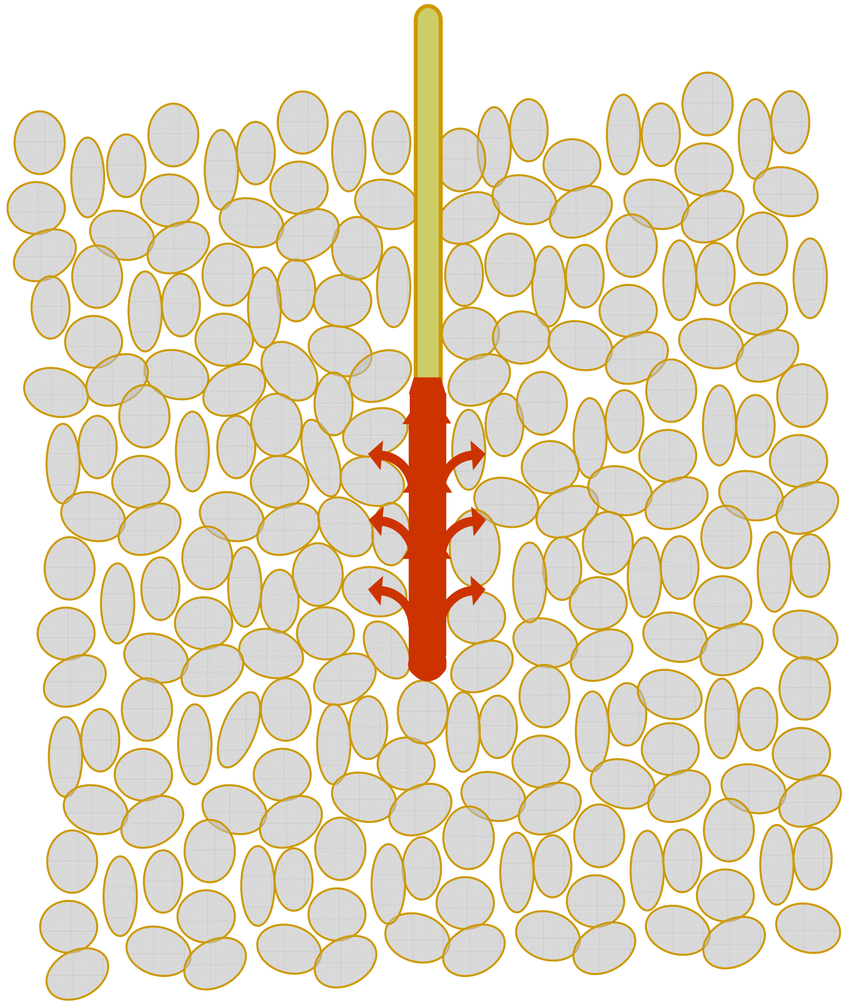
6 hours X-axis = Distance 48 hours

Small vs large molecule

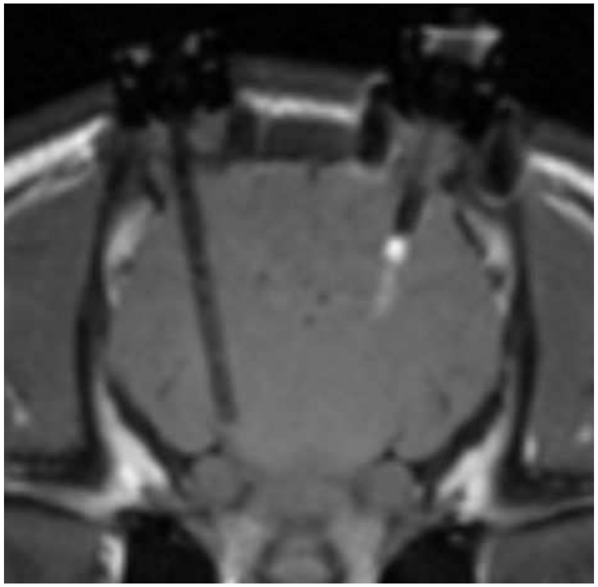
Re-scale intensity level of small molecule: the fronts match – implications for surrogate tracers



Backflow as a boundary condition



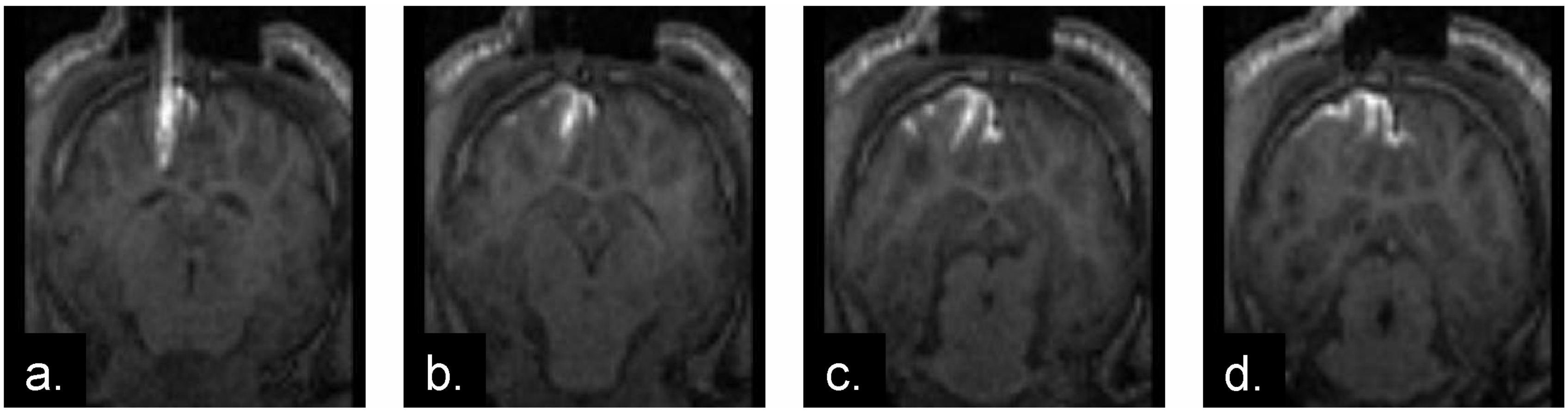
Gd-saline infusion, 6 min



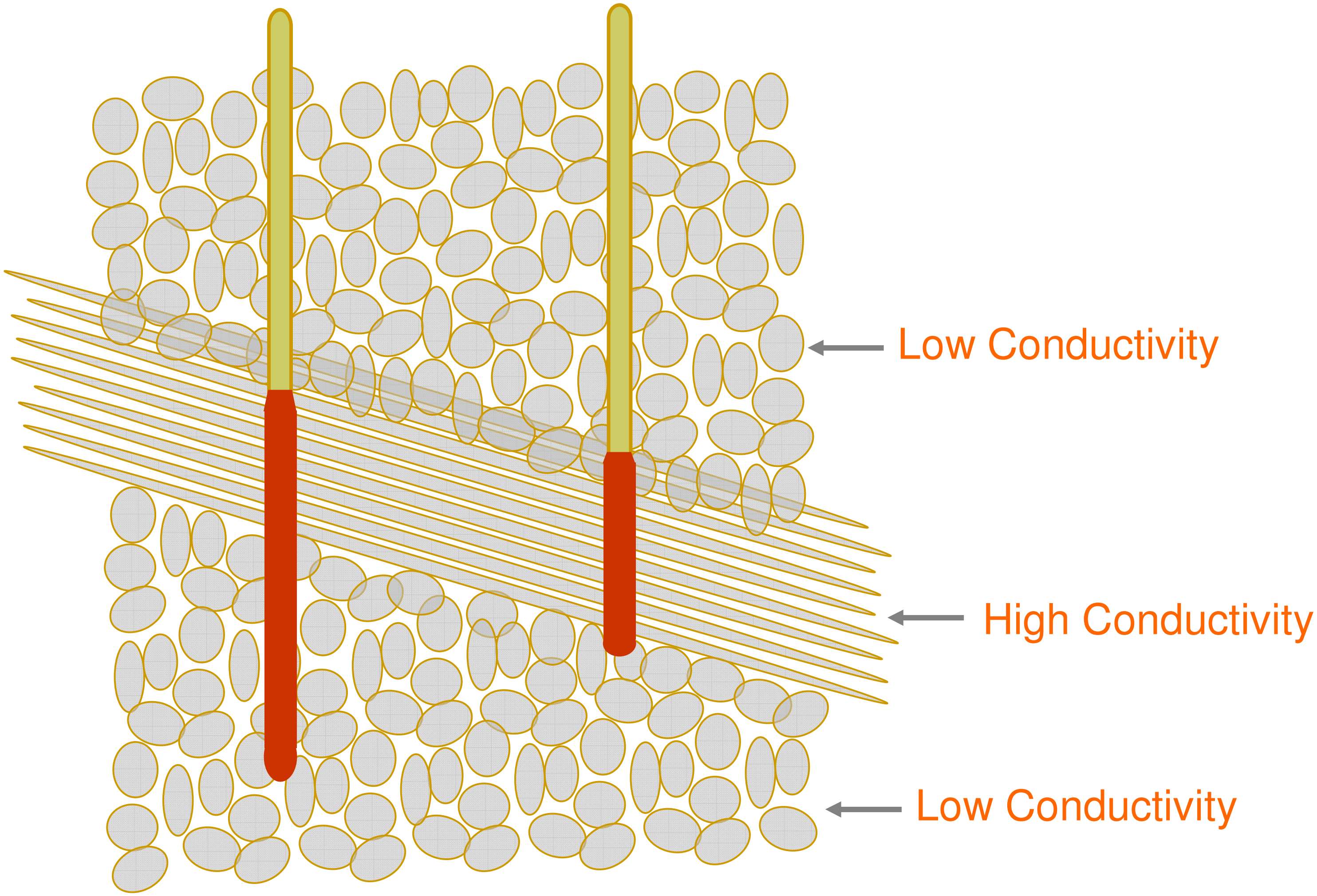
Moseley, Stanford University, 2000

Outflow from catheter is not from the port but from an extended region of several centimeters

Backflow to cortical surface



Backflow through inhomogeneous tissue

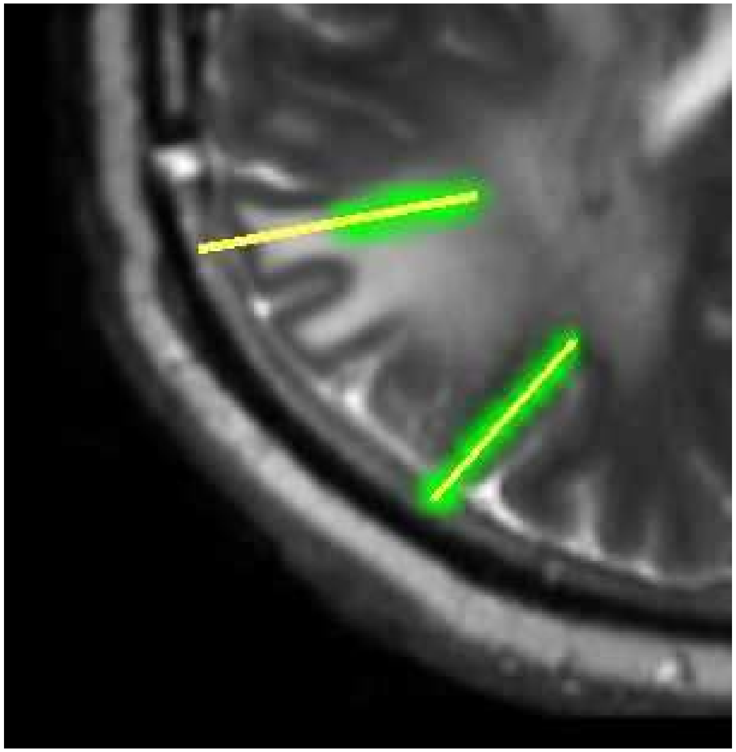


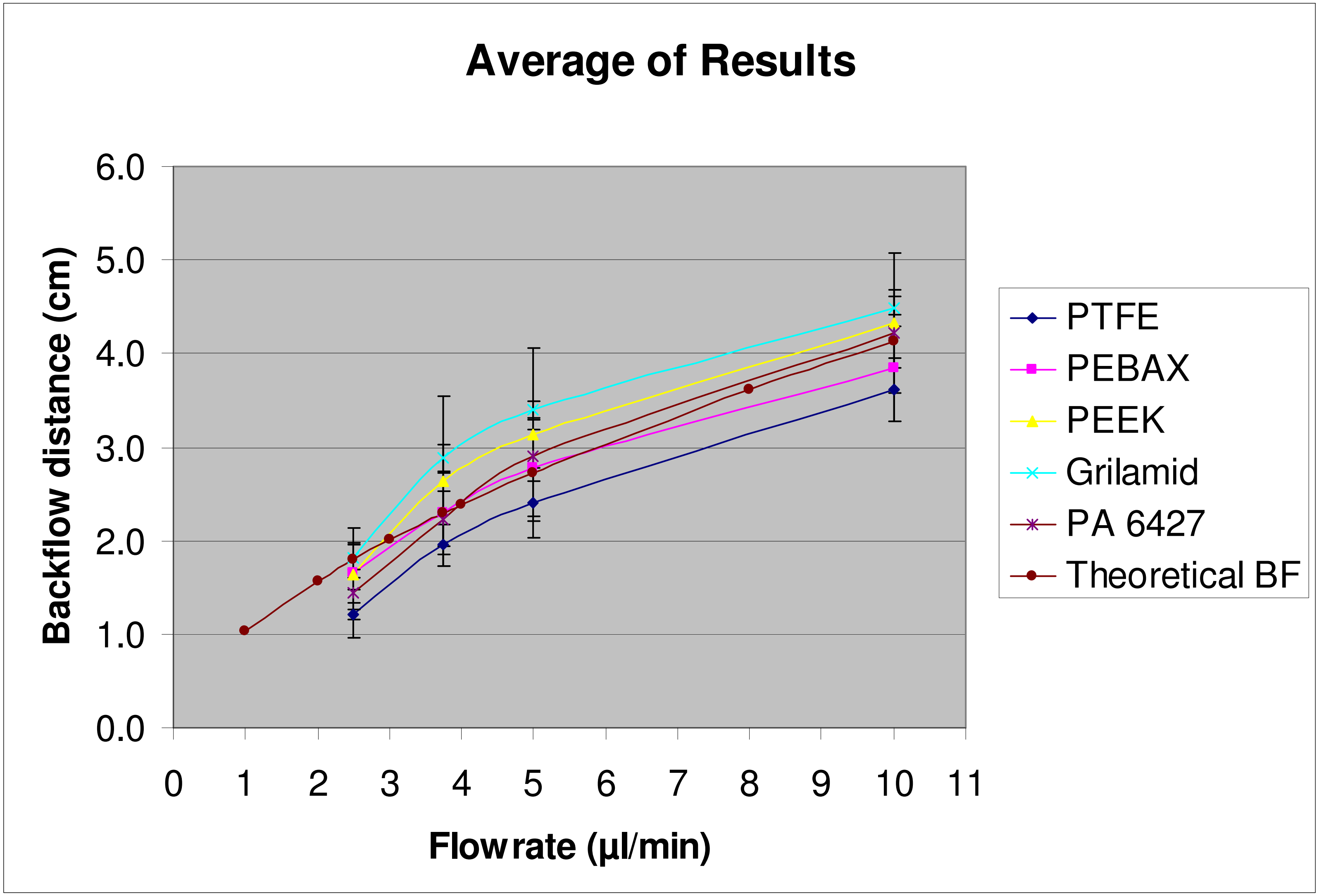
Tissue conductivity barriers will be barriers to backflow

SWITCH TO TEX SLIDES

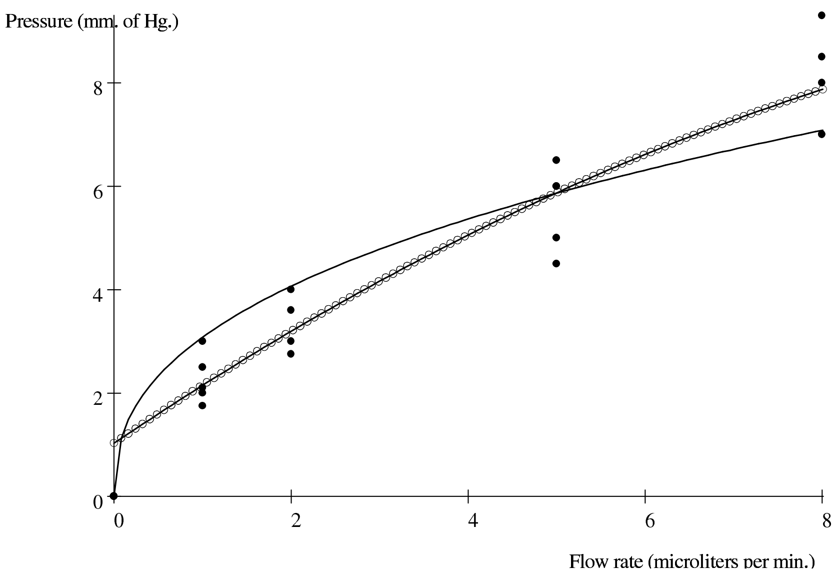
Simulated backflow through inhomogeneous tissue

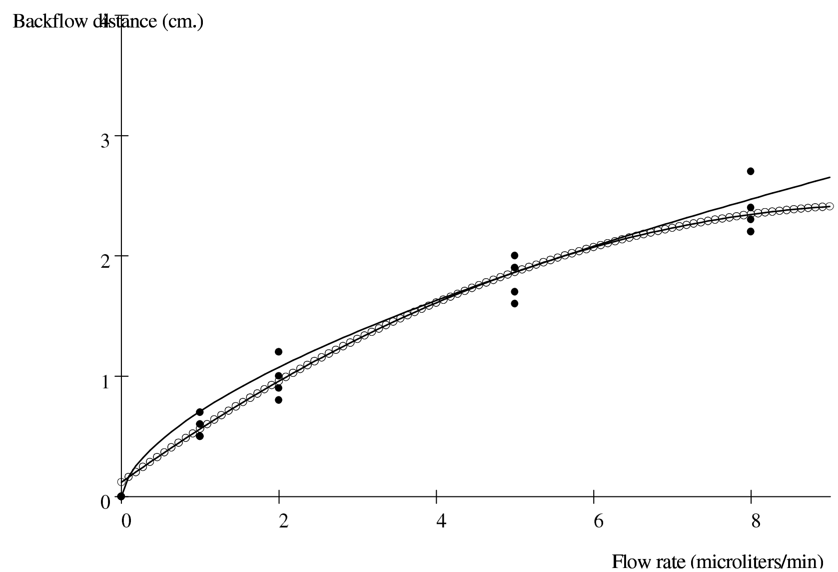
Backflow distance goes down as hydraulic conductivity goes up




Average of Results
6.0
5.0
4.0
3.0
2.0
1.0
0.0
Backflow distance (cm)
0
1
2
3
4
5
6
7
8
9
10
11
Flowrate (µl/min)
PTFE
PEBAX
PEEK
Grilamid
PA 6427
Theoretical BF

Experimental tests at Virginia Commonwealth University under NIH grant.

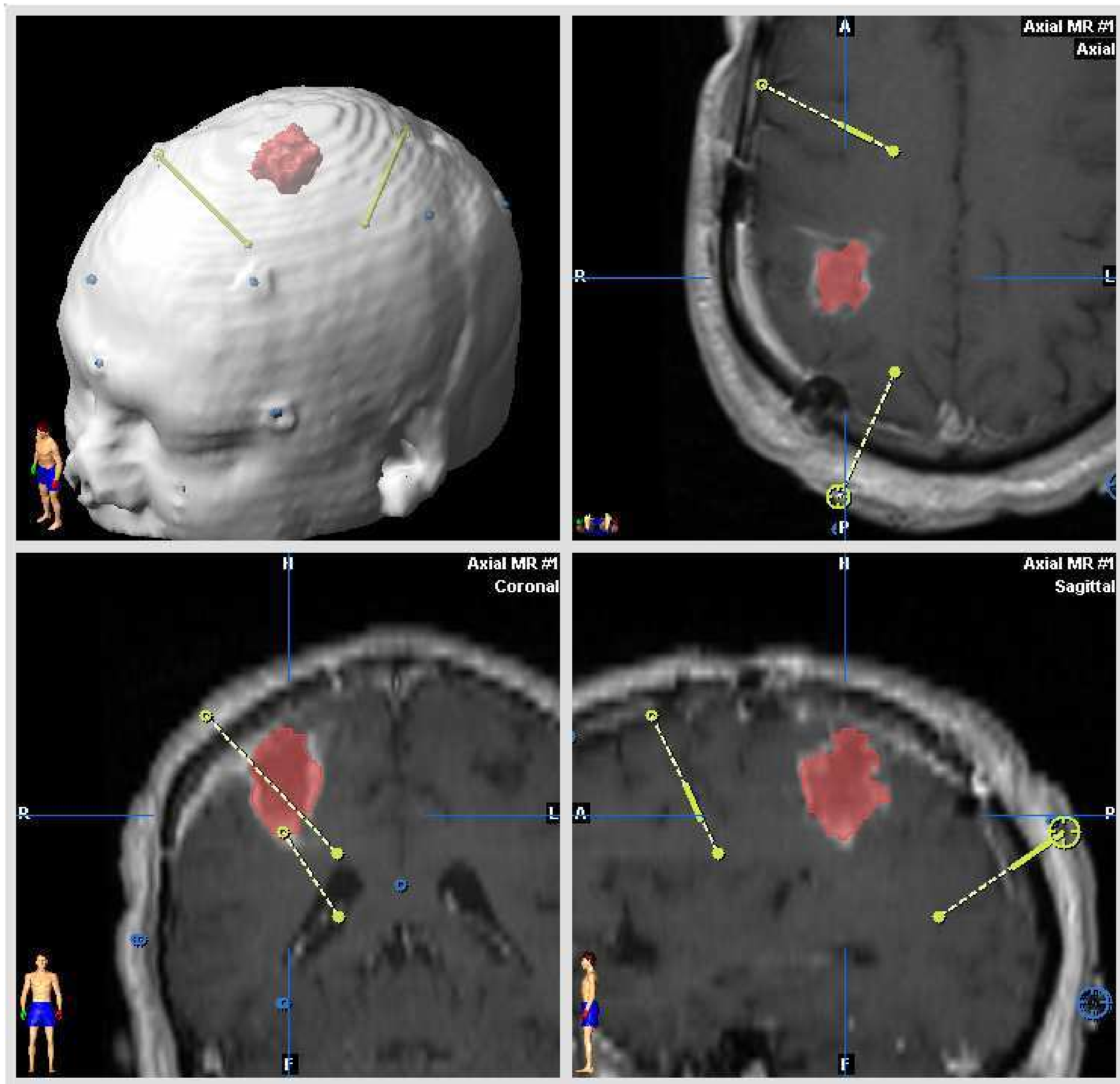




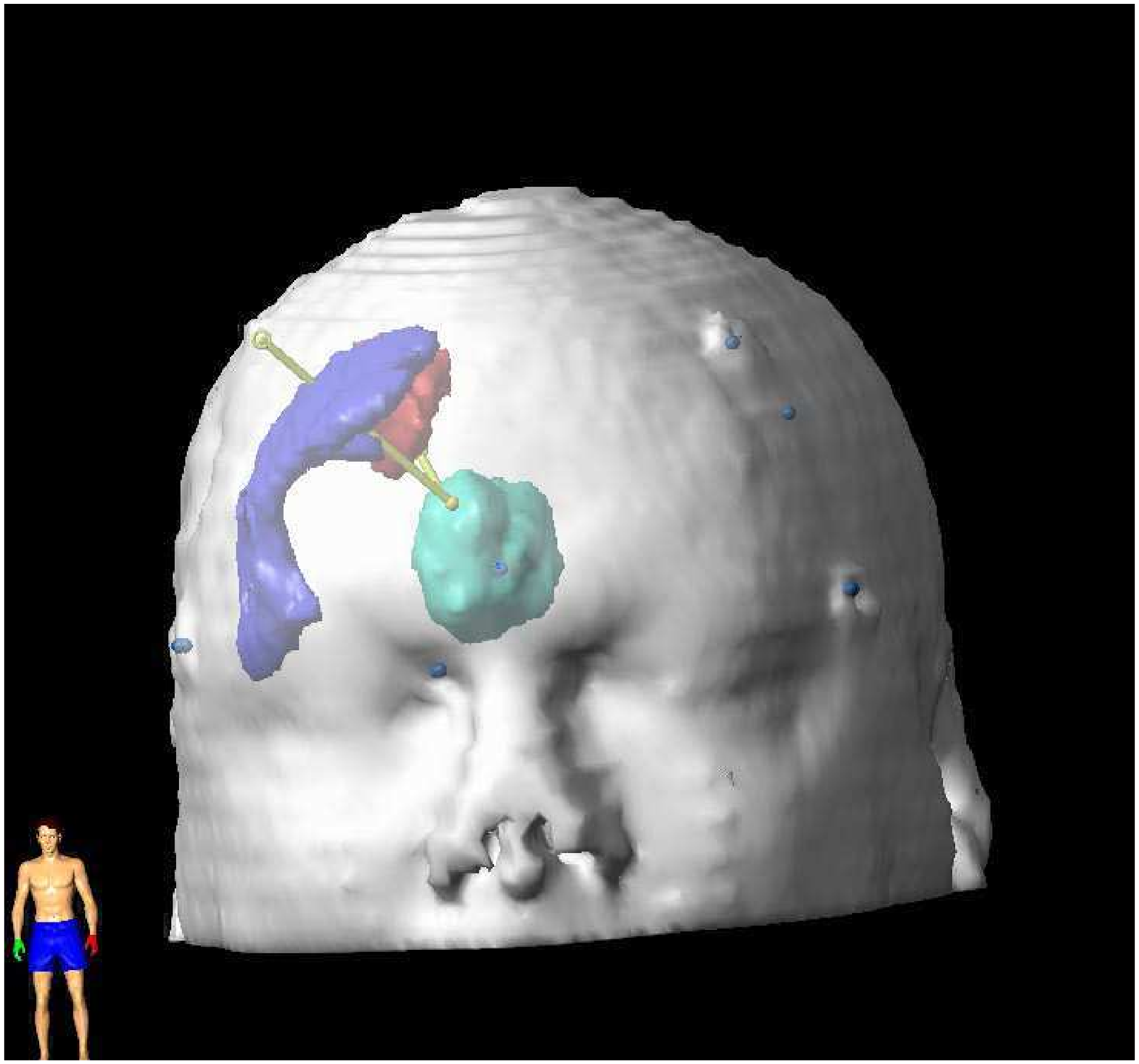
PRESSURE BACKFLOW LENGTH

vs Flow rate

Tumor location and catheter placement



Infusion and Tumor Location



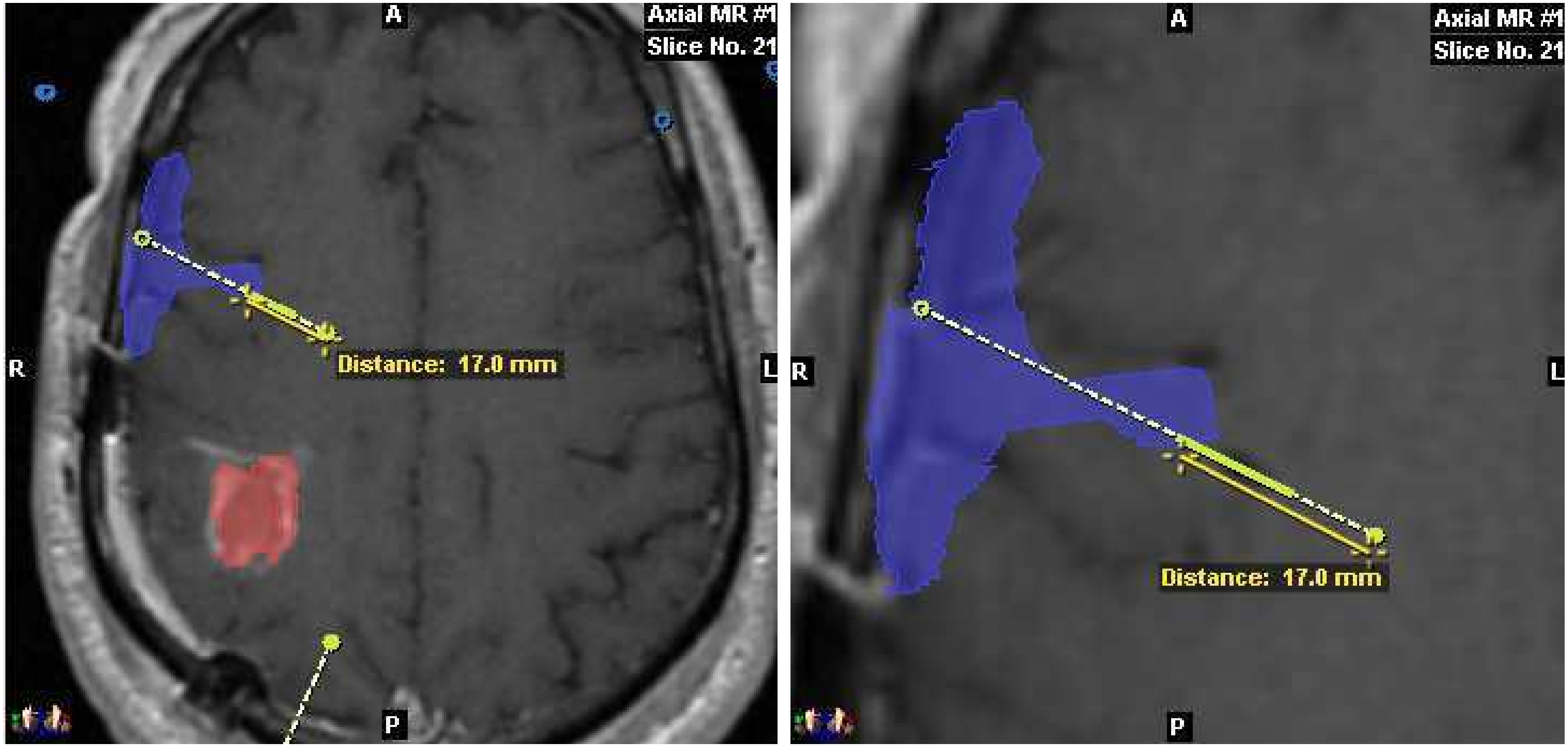
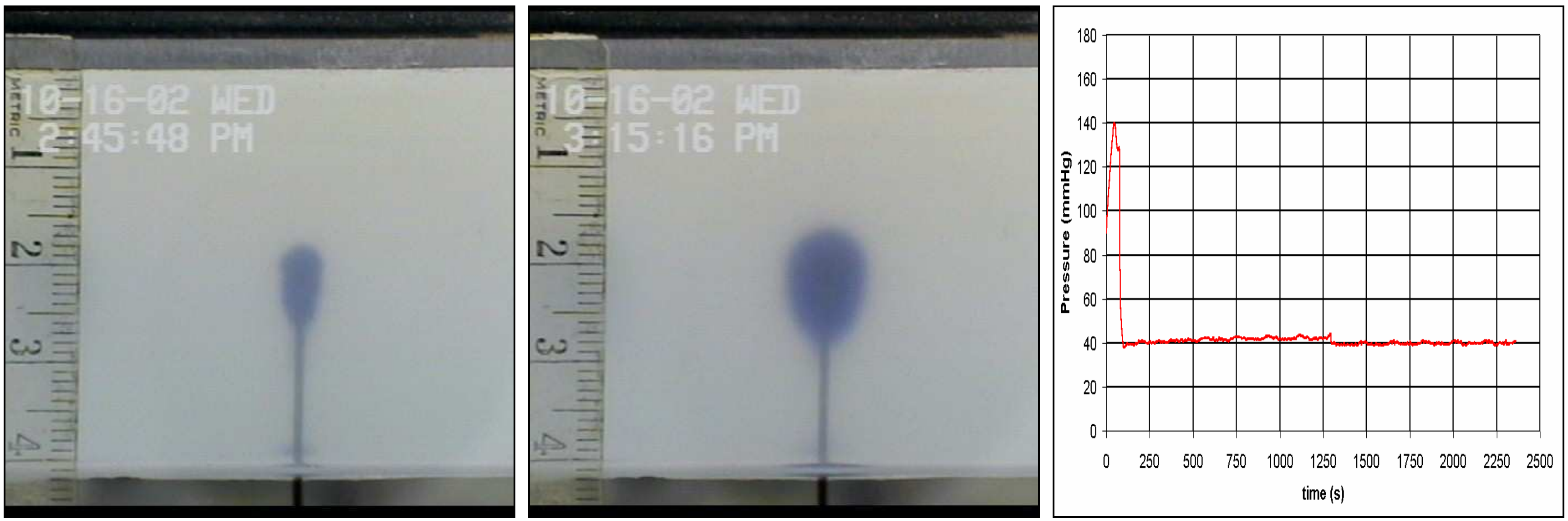
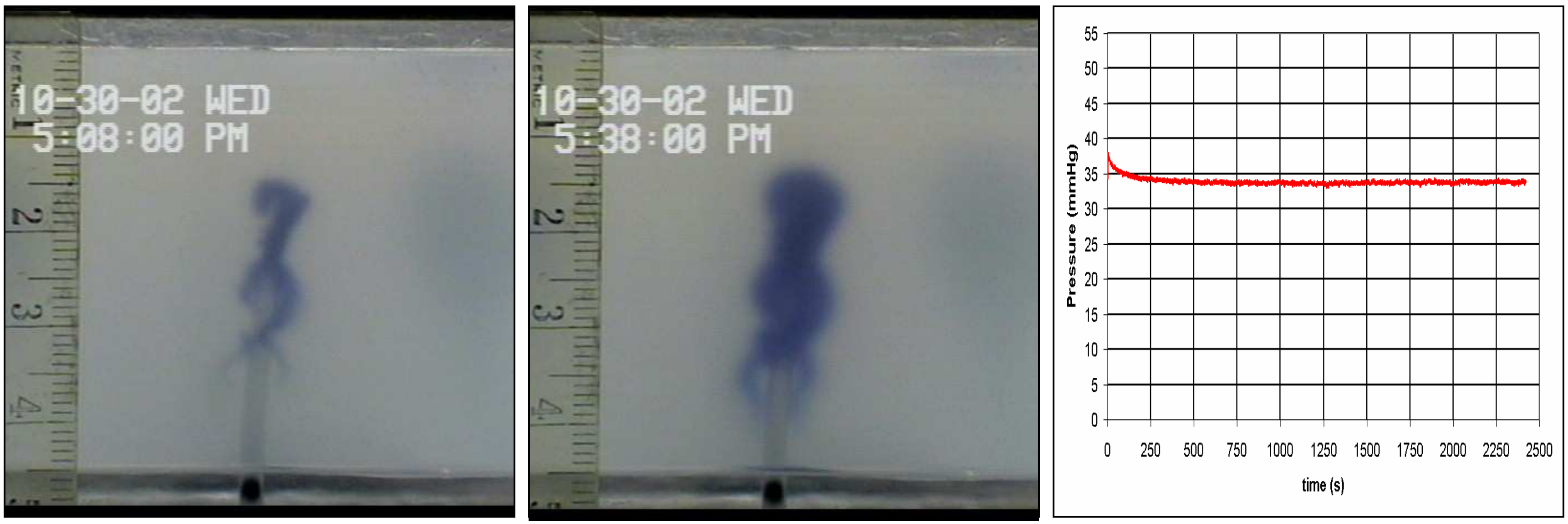

A
Axial MR #1
Slice No. 21
R
L
Distance: 17.0 mm
P
A
Axial MR #1
Slice No. 21
R
L
Distance: 17.0 mm
P

Figure 12



a. b. c.

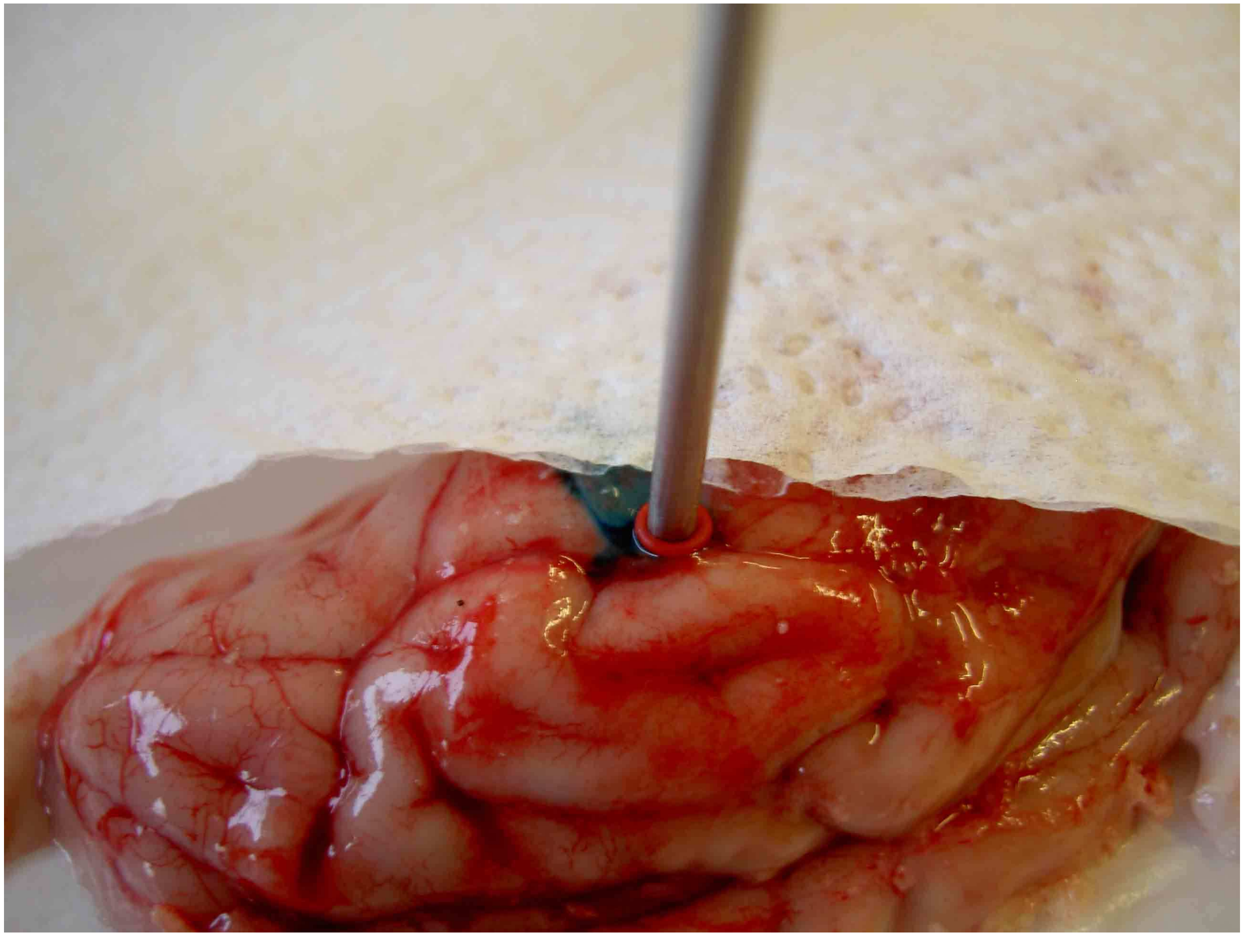
Figure 13



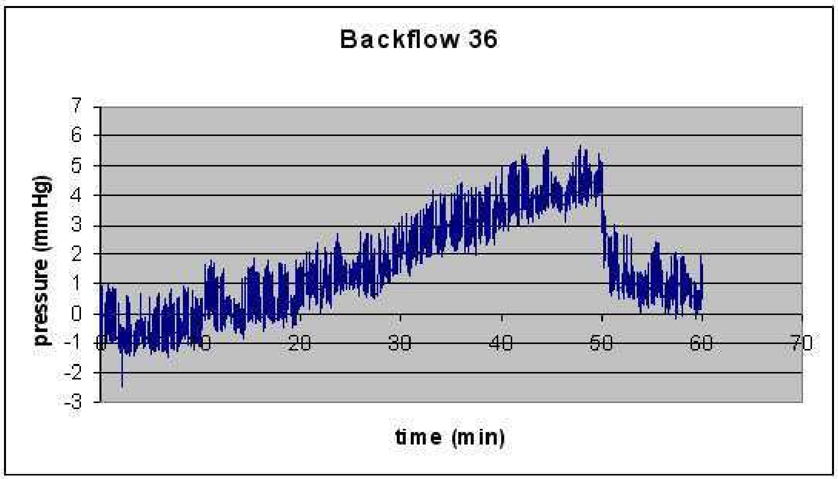
a. b. c.

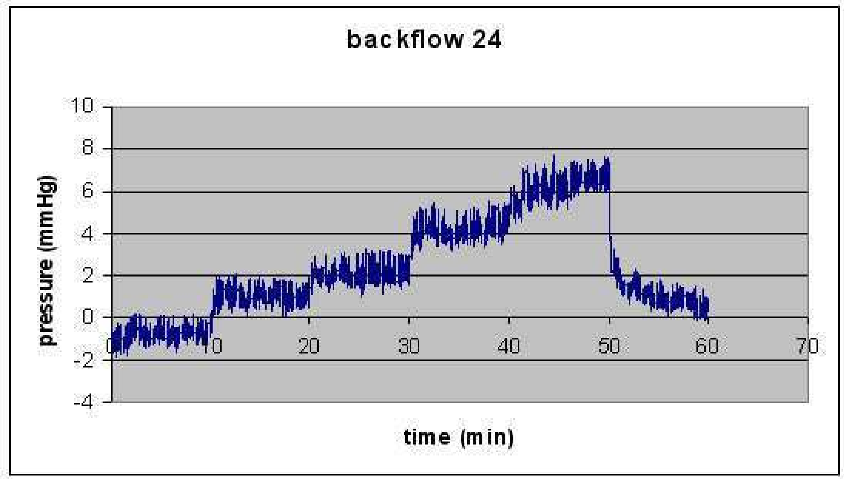
Current catheters won’t work for cortical delivery

Designs that confine infusion to layers

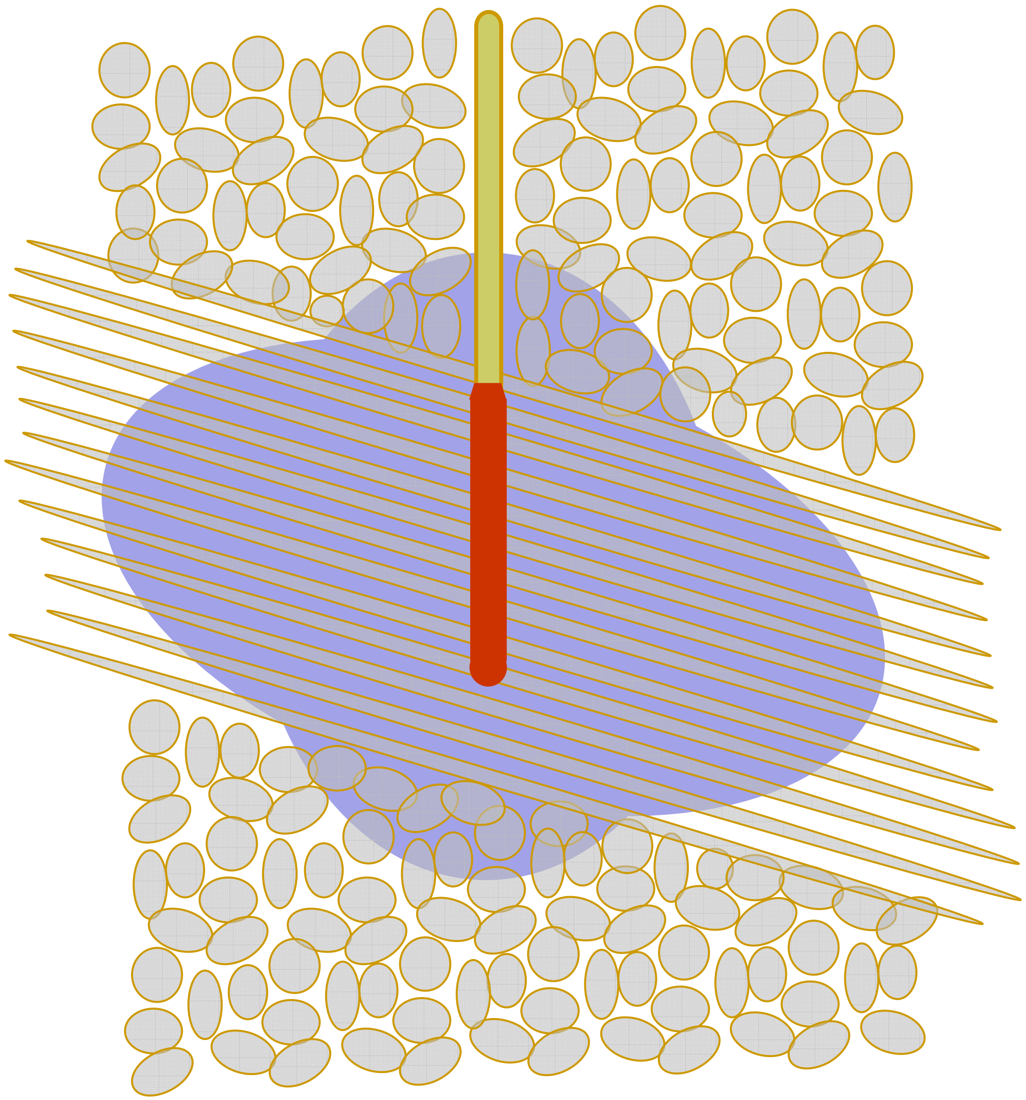


The theory of backflow is a *steady state* theory but there is significant non-equilibriation

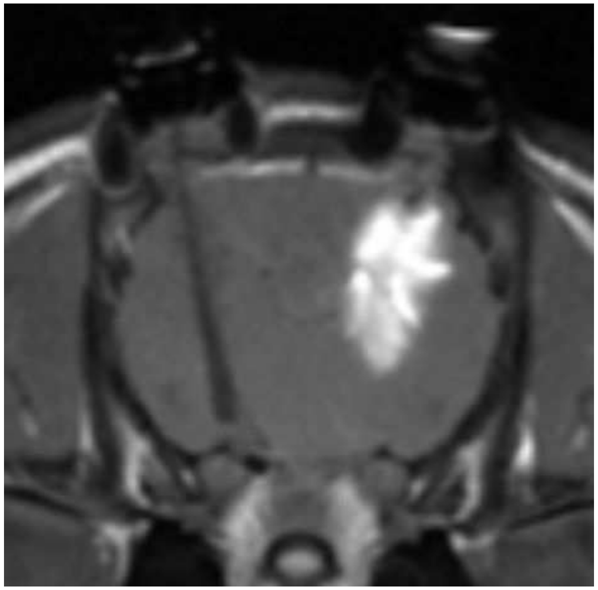




Convection



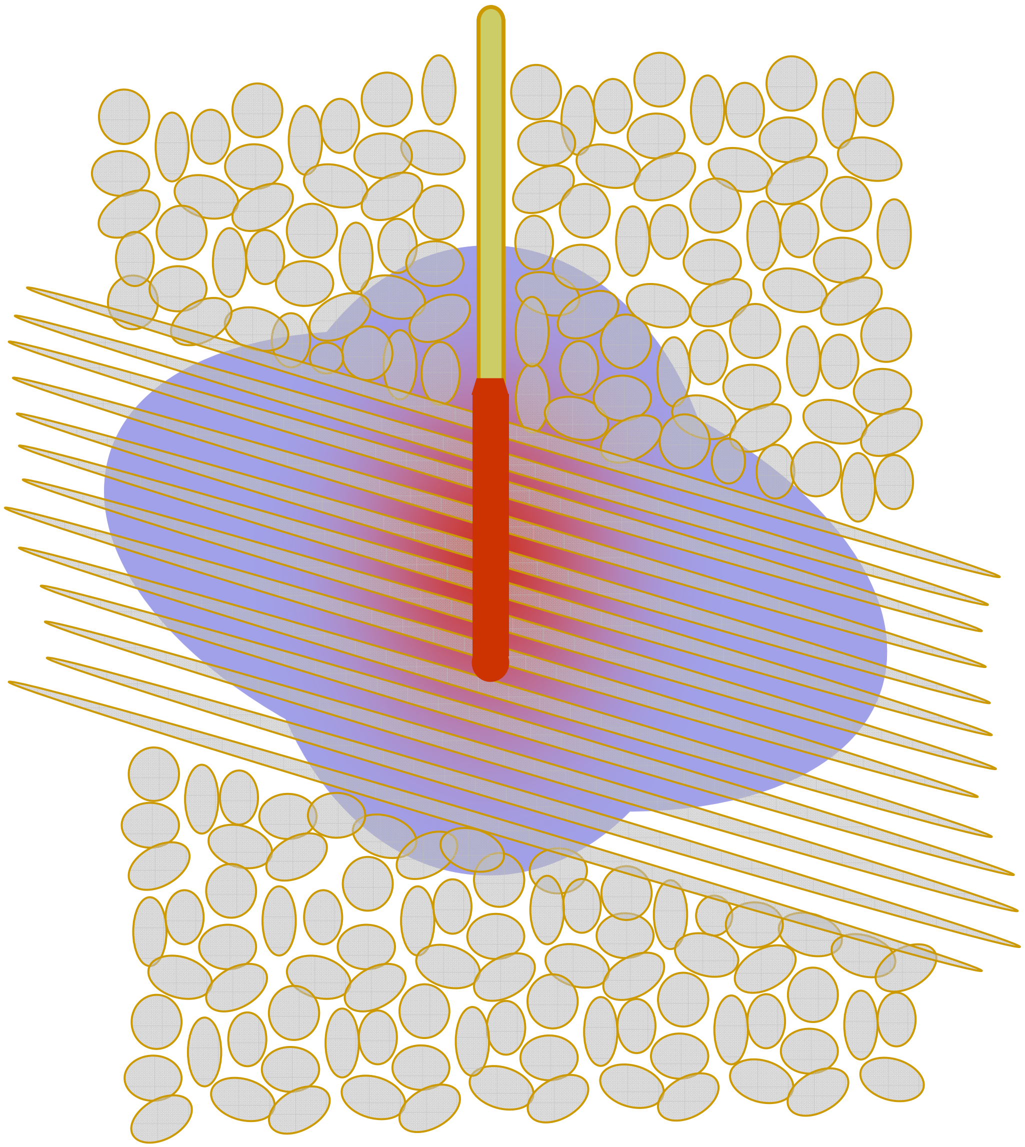
Gd-saline infusion, 100 min



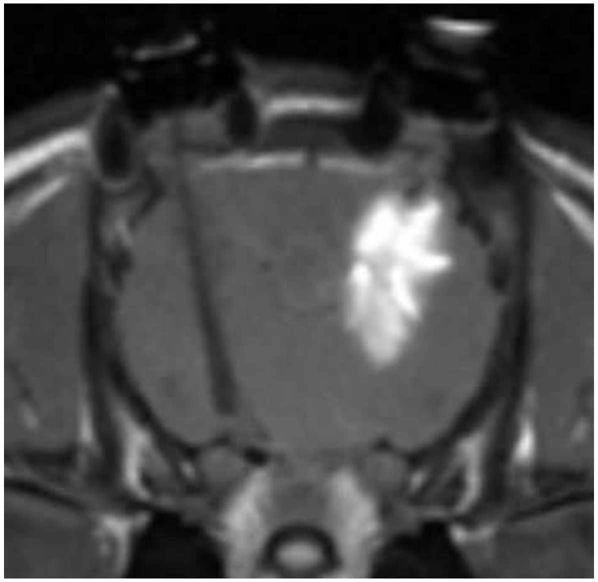
Moseley, Stanford University, 2000

Convection of fluid spreads from the backflow region

Convection



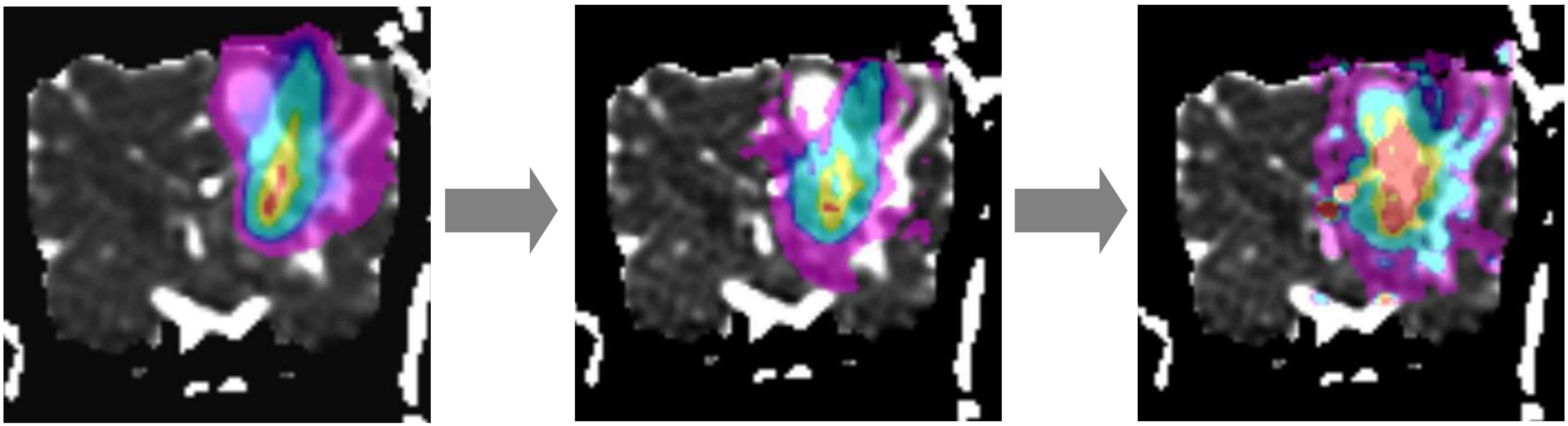
Gd-saline infusion, 100 min



Moseley, Stanford University, 2000

Deceleration due to capillary removal leads to increased drug concentration

Pressure and Velocity: D‘Arcy‘s law says interstitial fluid velocity is a linear map of pressure gradient



Pressure | Grad(P) | | Fluid Velocity |

Fields estimated from simulation and displayed over Trace(HC).

D‘Arcy‘s law is a steady state theory
(*e.g.* no time dependence of pressure)

Where the drug goes in a specific subject requires specific inputs

Process	Parameters
Catheter insertion	Tissue damage, coring, …
Backflow	Input flowrate Tissue properties near catheter
Fluid flow in tissue	Hydraulic conductivity (HC) Efflux Interstitial pressure variations
Agent transport	Diffusion Efflux
Agent binding	Adsorption Pharmacokinetics Receptor densities

The inputs needed can be gotten from imaging plus mathematics

Example: getting one physical property from another more directly obtained from imaging

$$p = \frac{p_e}{G_e} + \frac{p_i}{G_i} + \int_0^\infty dx \frac{g(x)}{\frac{1}{p_i} + \frac{x}{p_e}}$$

The *p*'s depend on the physical property, not on geometry

The *G*, *g*'s depend on the geometry *only*

Extracellular Conductivity:

- **Different physical response functions face the same geometry of cellular organization.**
- **Use a measurable response function (*e.g.* water diffusion) to disentangle geometry from physics.**

Experimental tests at Virginia Commonwealth University under NIH grant.

Properties from Diffusion Tensor Imaging

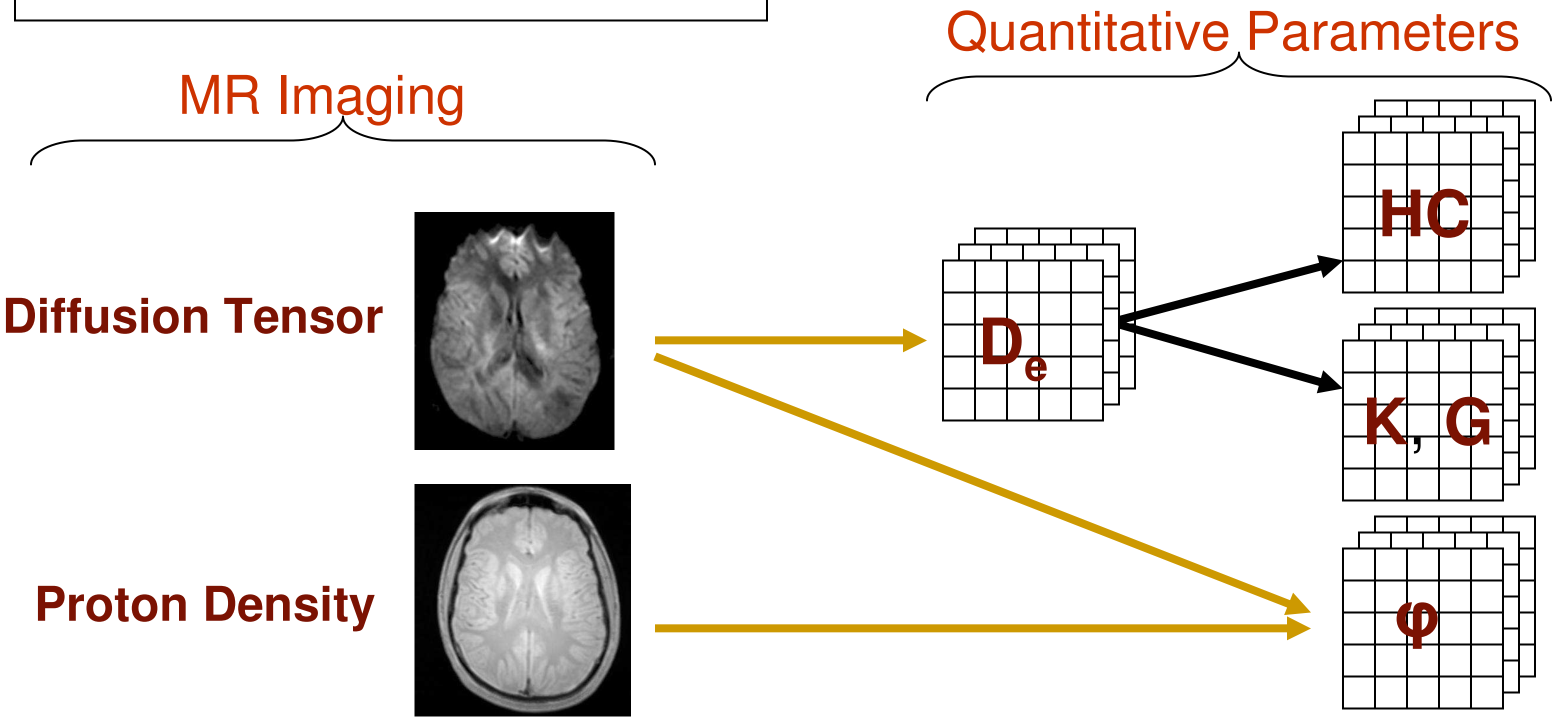
Property	Uses
Hydraulic conductivity	CED prediction for drug delivery Intrinsic pathways for disease progression
Shear modulus	Backflow for catheter placement/design Disease monitoring/diagnosis
Bulk modulus	Physiological consequences of edema

Other applications of DTI

Property	Uses
Thermal conductivity	Prediction of heat dissipation in tissue for removing unwanted side effects or for heat therapy
Electrical conductivity	Deep brain stimulator placement/design for Parkinson's Trans-cranial magnetic stimulation
Molecular diffusivity	Long-term particle distribution

Some CED Simulation Data Requirements

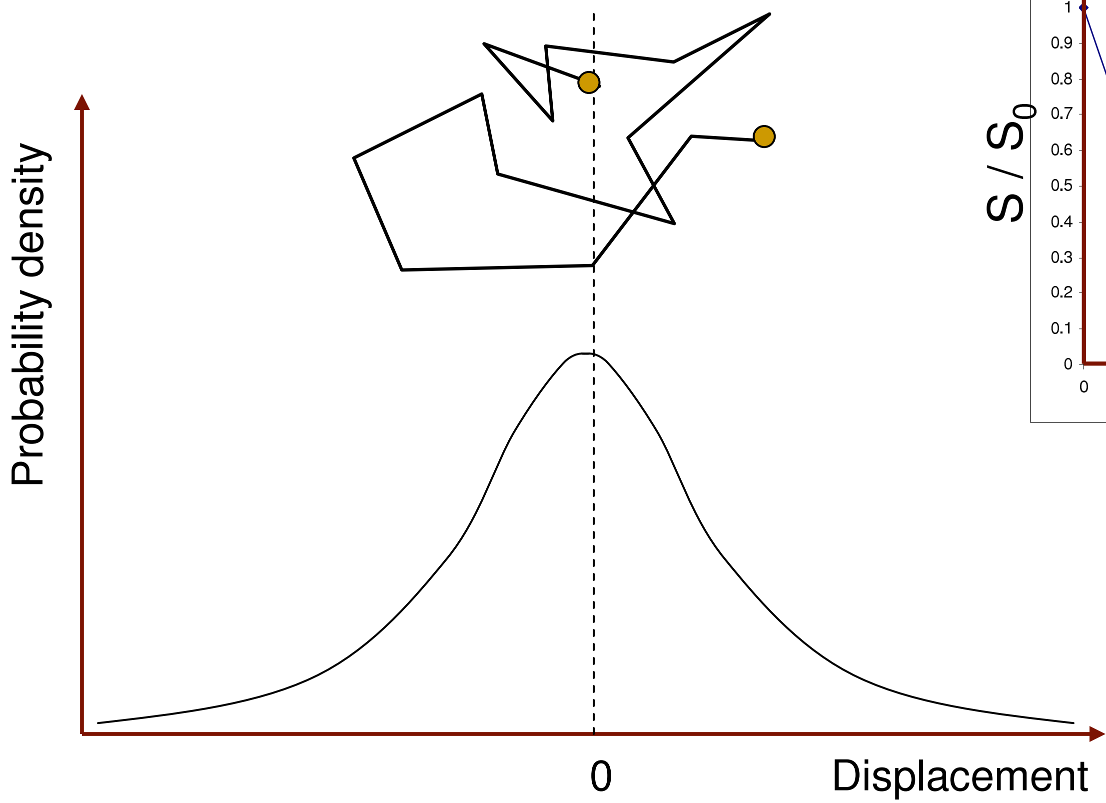
- Hydraulic Conductivity, **HC**
- Elastic moduli, **K**,**G**
- Pore Fraction, **φ**
- Extracellular Diffusion, **De**

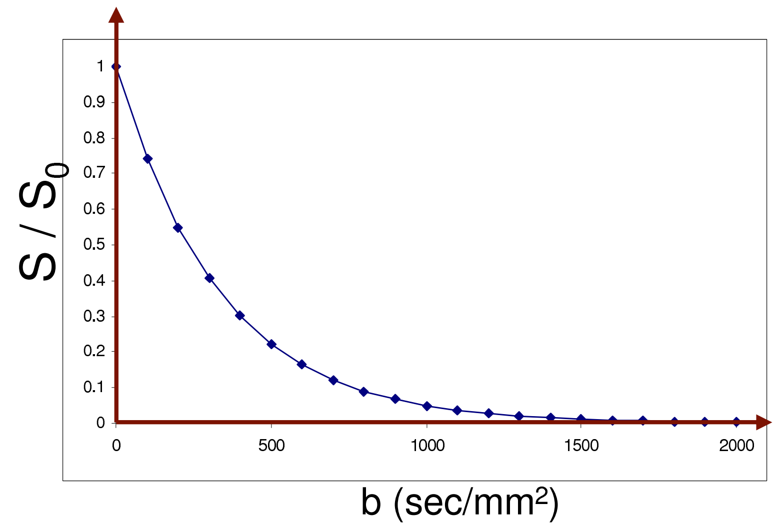


Gaussian Diffusion

Measured in MRI with DWI/DTI

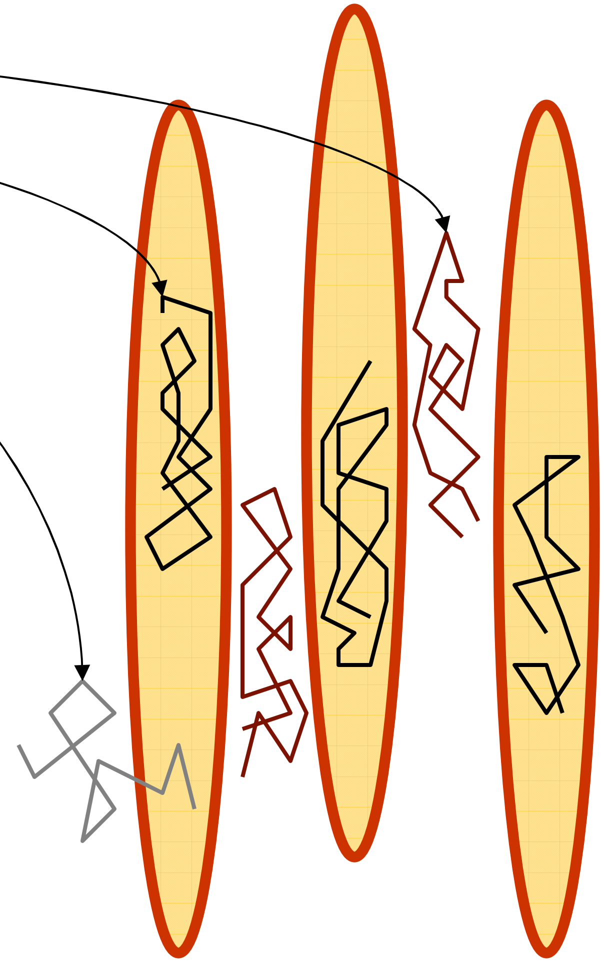
$$\frac{S}{S_0} = e^{-b*ADC}$$



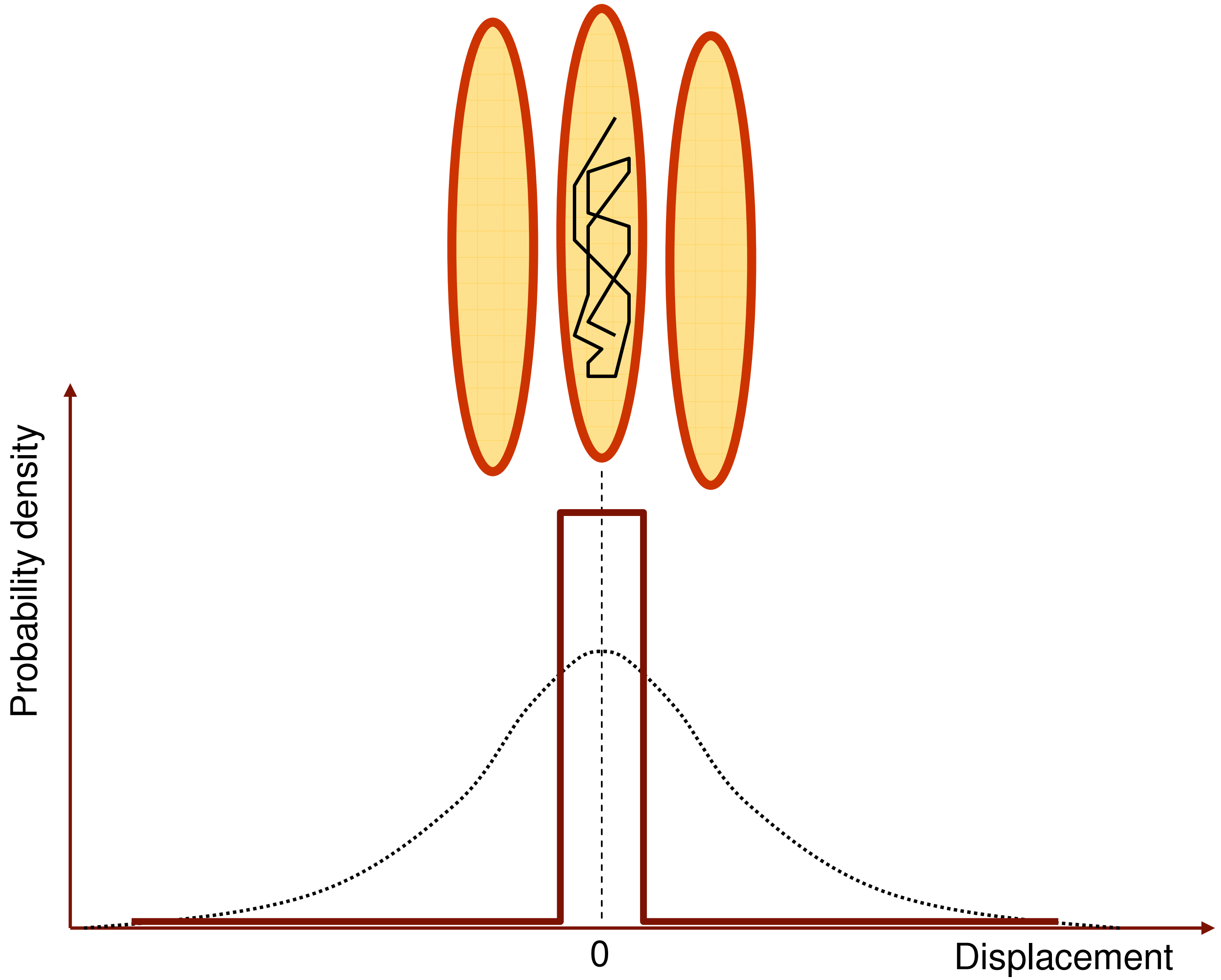


Diffusion in white matter

- Extracellular
- Intracellular
- ~~Exchange~~



Restricted Diffusion



Two-compartment model

- Extracellular
- Intracellular

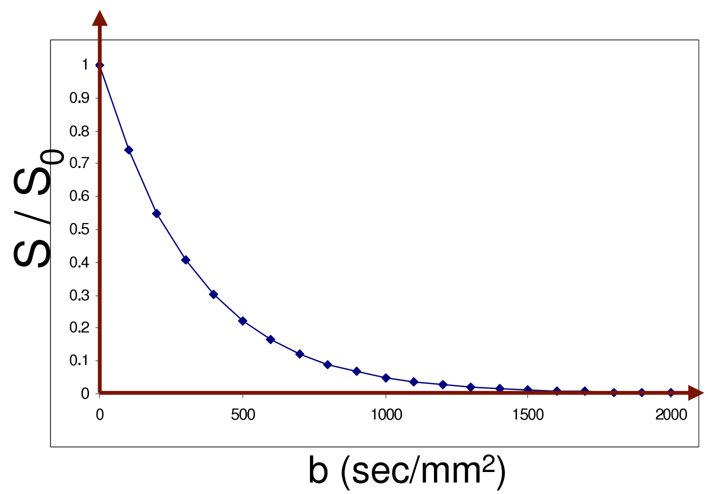
$$\frac{S}{S_0} = w_e S_e + (1 - w_e) S_i$$

$$S_e = e^{-b \cdot D_e}$$

?

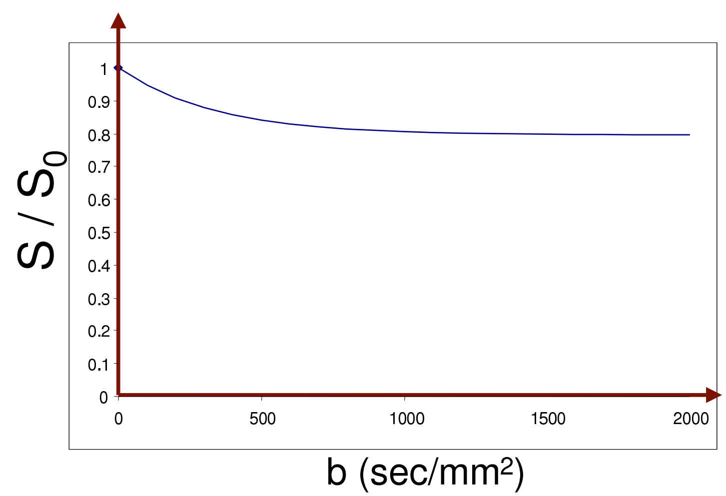
Extracellular water:

Gaussian diffusion

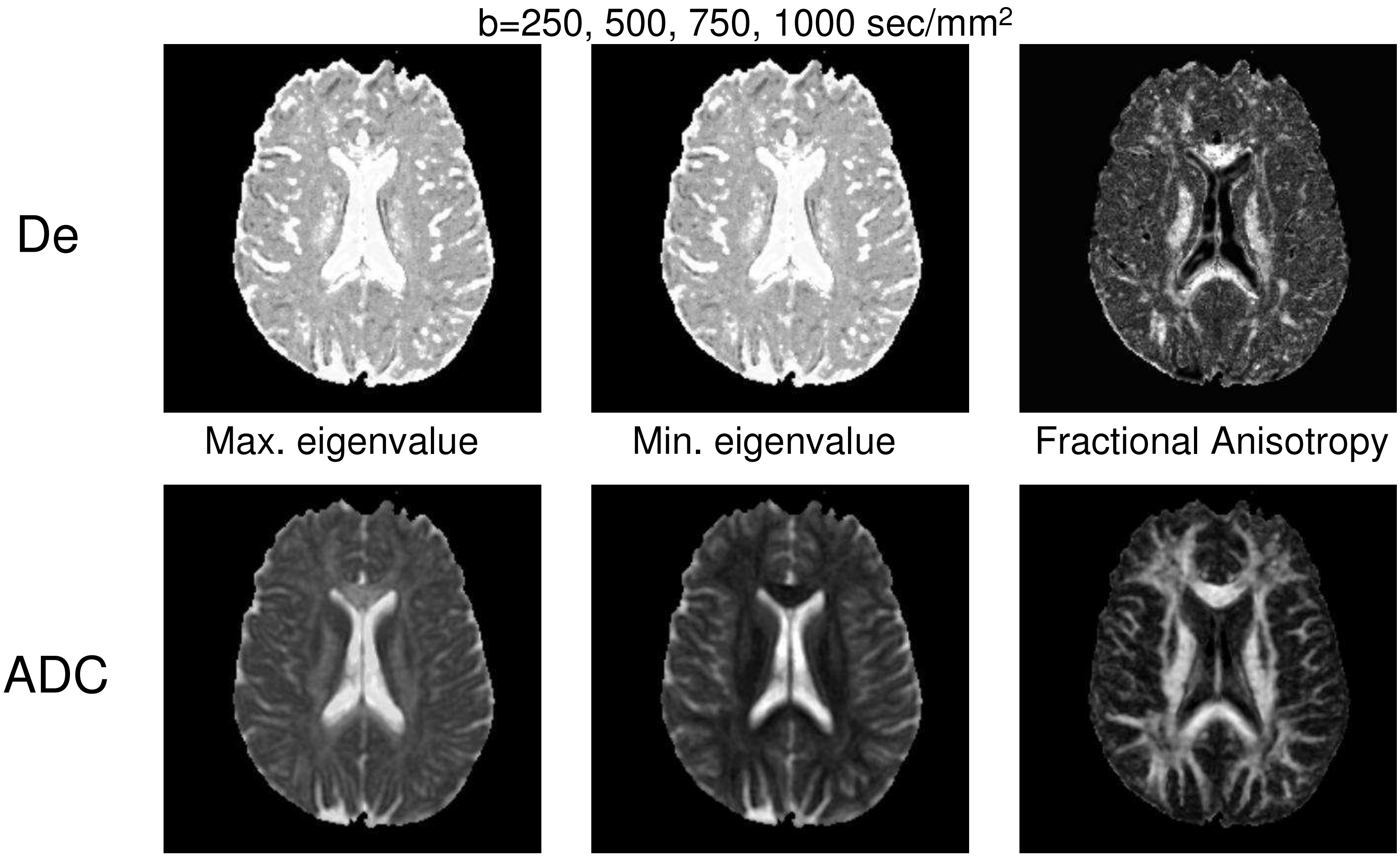


Intracellular water:

Restricted diffusion

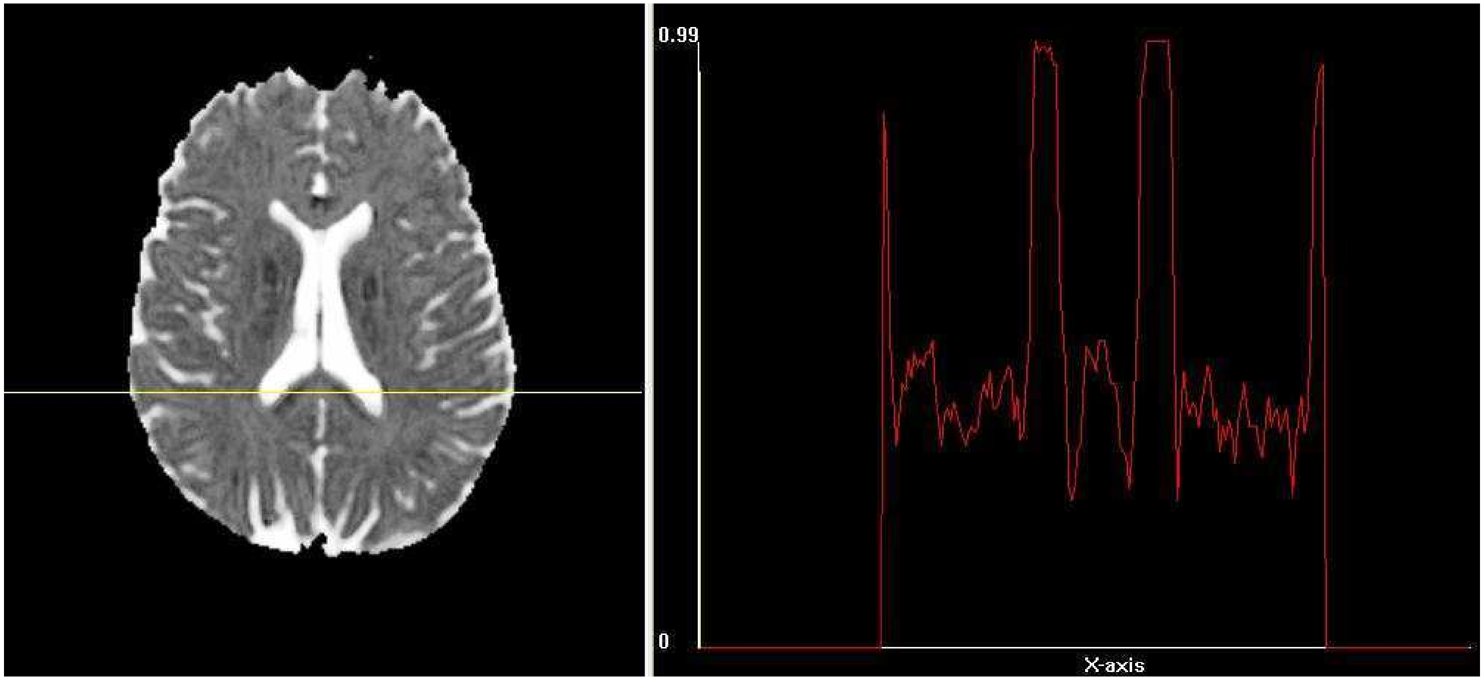


Extracellular diffusion tensor



MR imaging courtesy of Dr. Panos Fatouros, Virginia Commonwealth University

Extracellular water fraction, We

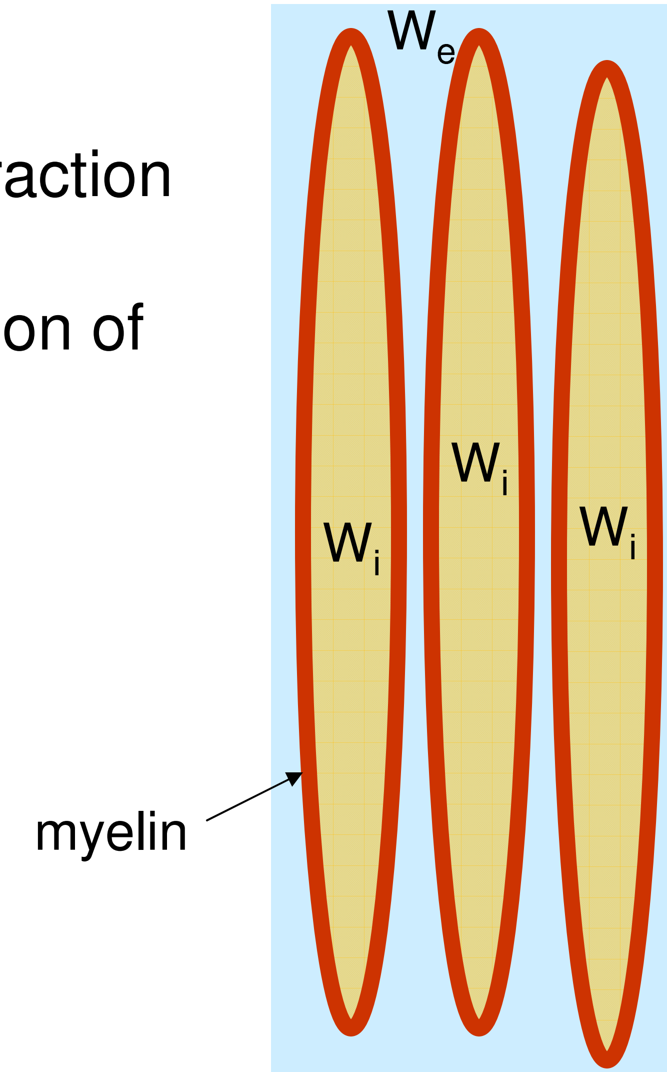


Obtaining pore fraction from We

Water fraction ≠ Volume (pore) fraction

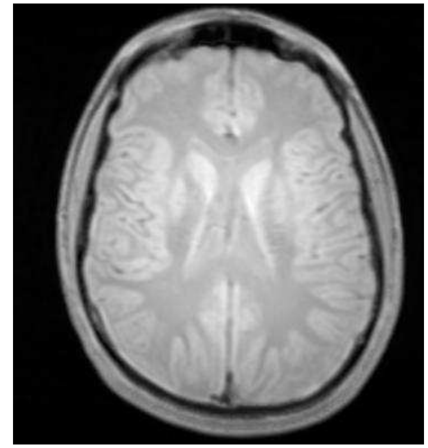
W_e should be scaled by the fraction of the volume containing water:

$$\varphi = \frac{\rho}{\rho_0} W_e$$

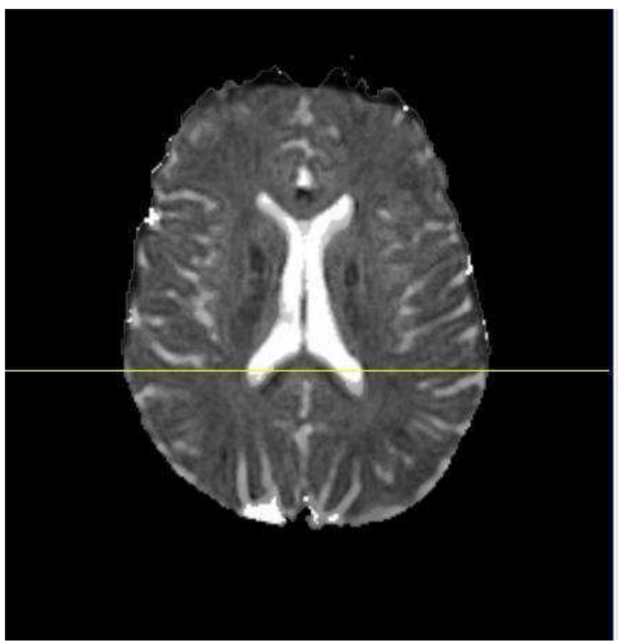


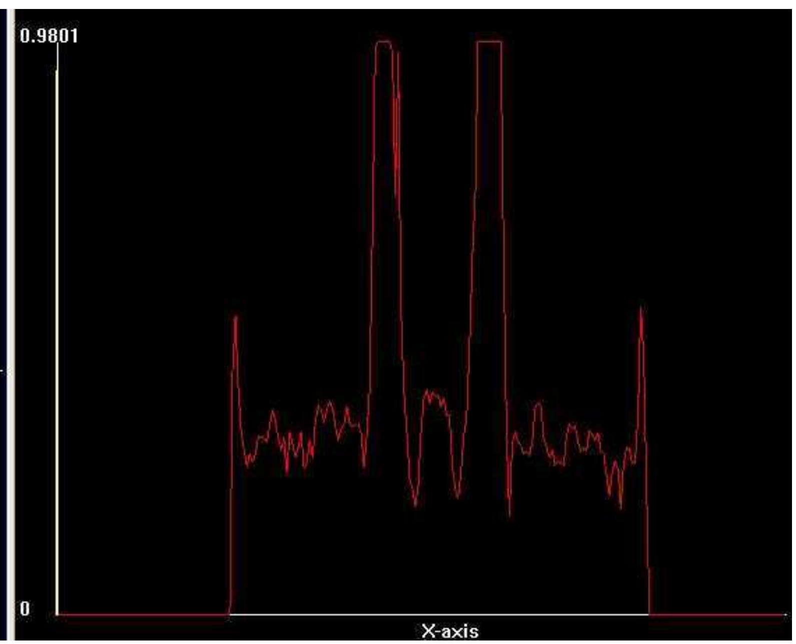
Pore fraction map

We x ρ/ρ_0



$= \varphi$

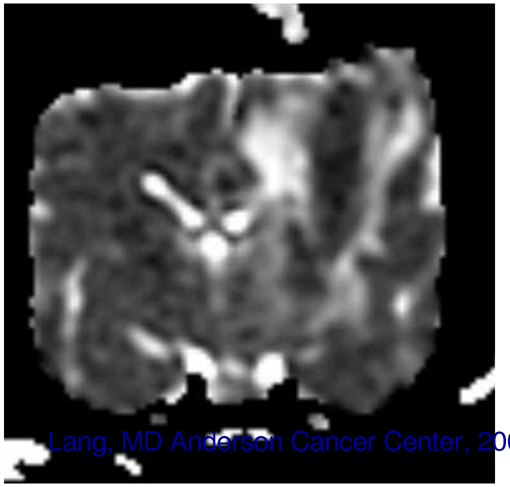




Hydraulic Conductivity

Diffusivity | Estimated Hydraulic Conductivity

Trace:

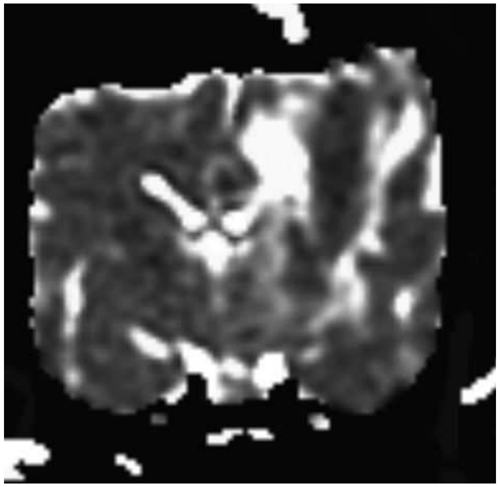


Lang, MD Anderson Cancer Center, 2004

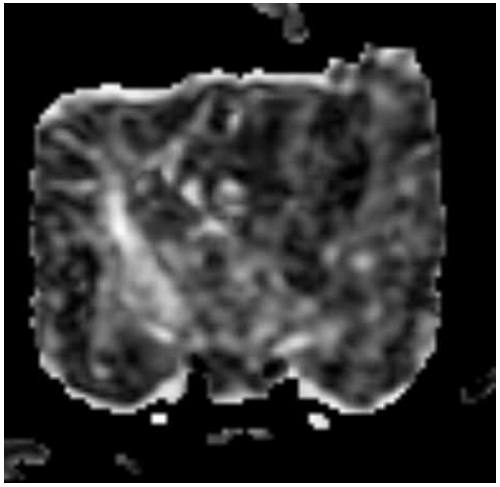
Tissue hydraulic conductivity is both:

inhomogeneous

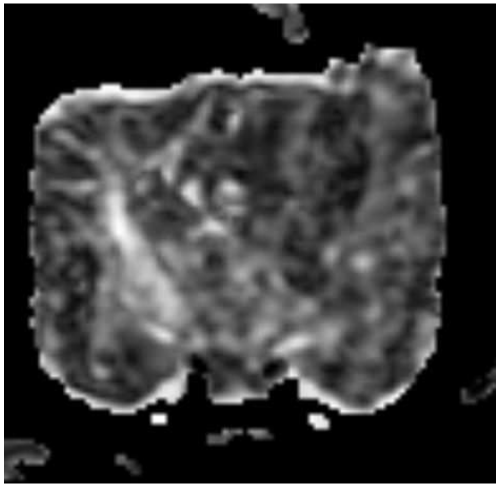
and



Fractional Anisotropy:



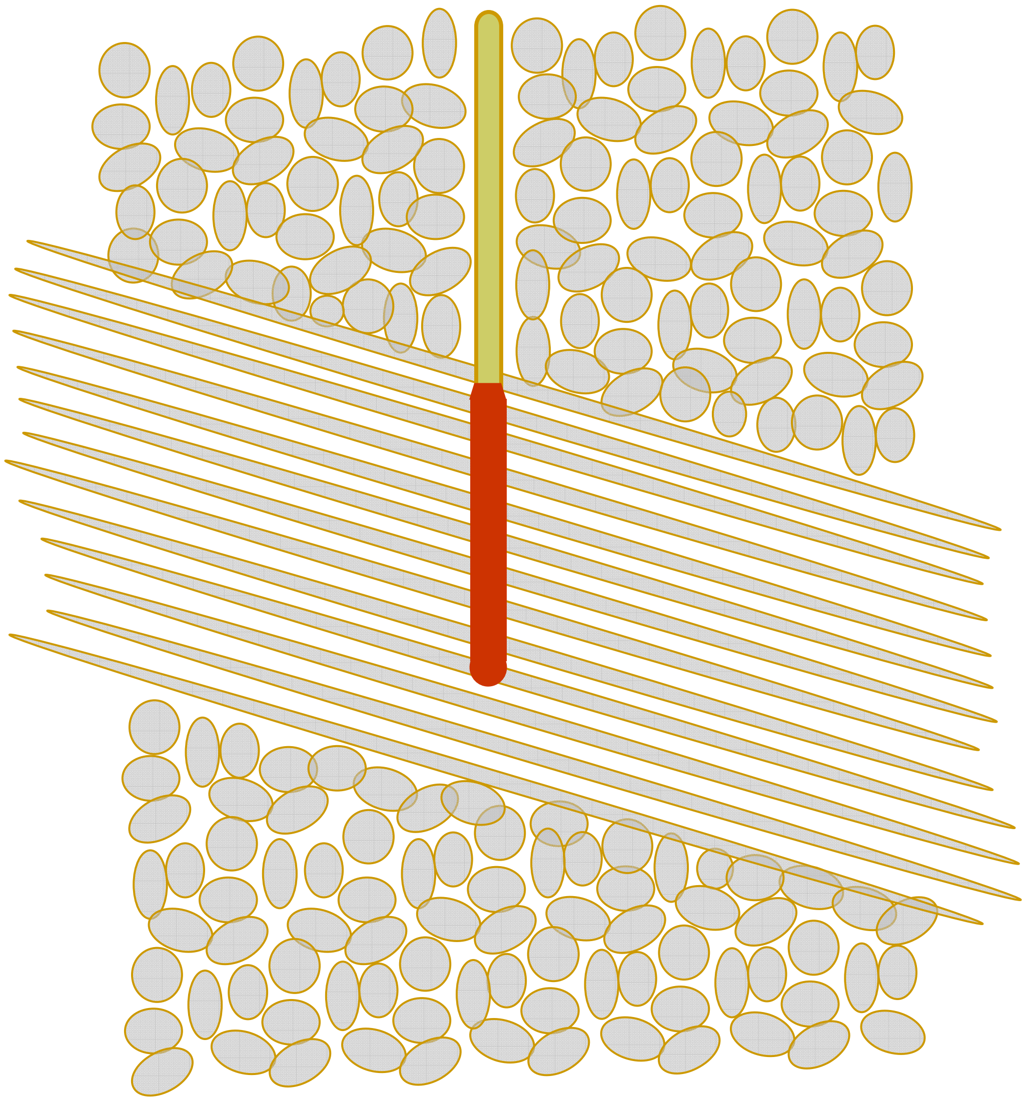
anisotropic



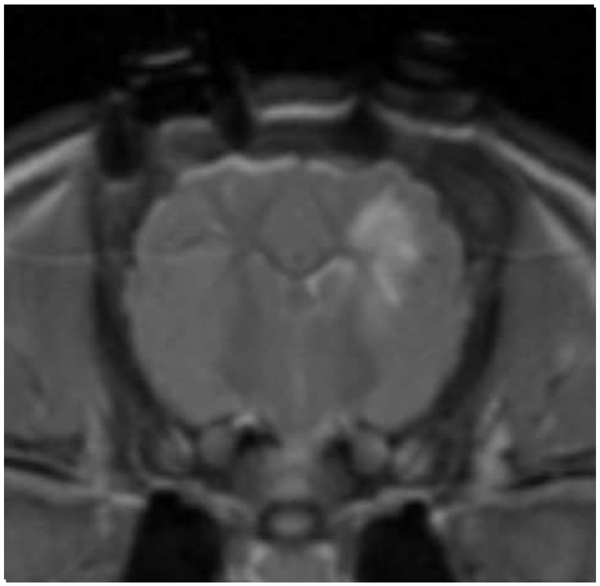
Where the drug goes in a specific subject requires specific inputs

Process	Parameters
Catheter insertion	Tissue damage, coring, …
Backflow	Input flowrate Tissue properties near catheter
Fluid flow in tissue	Hydraulic conductivity (HC) Efflux Interstitial pressure variations
Agent transport	Diffusion Efflux
Agent binding	Adsorption Pharmacokinetics Receptor densities

Elastic (reversible) deformation



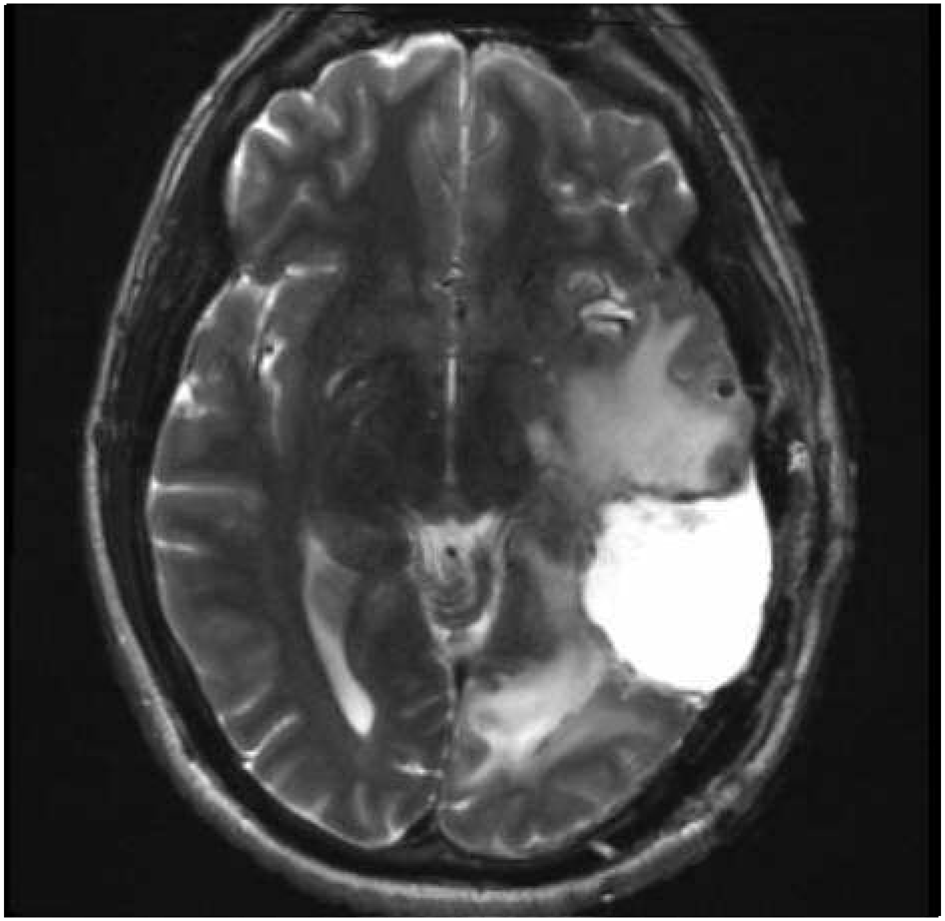
Proton Density, 100 min



Moseley, Stanford University, 2000

Infusion-induced edema is significant, just as tumor-induced edema

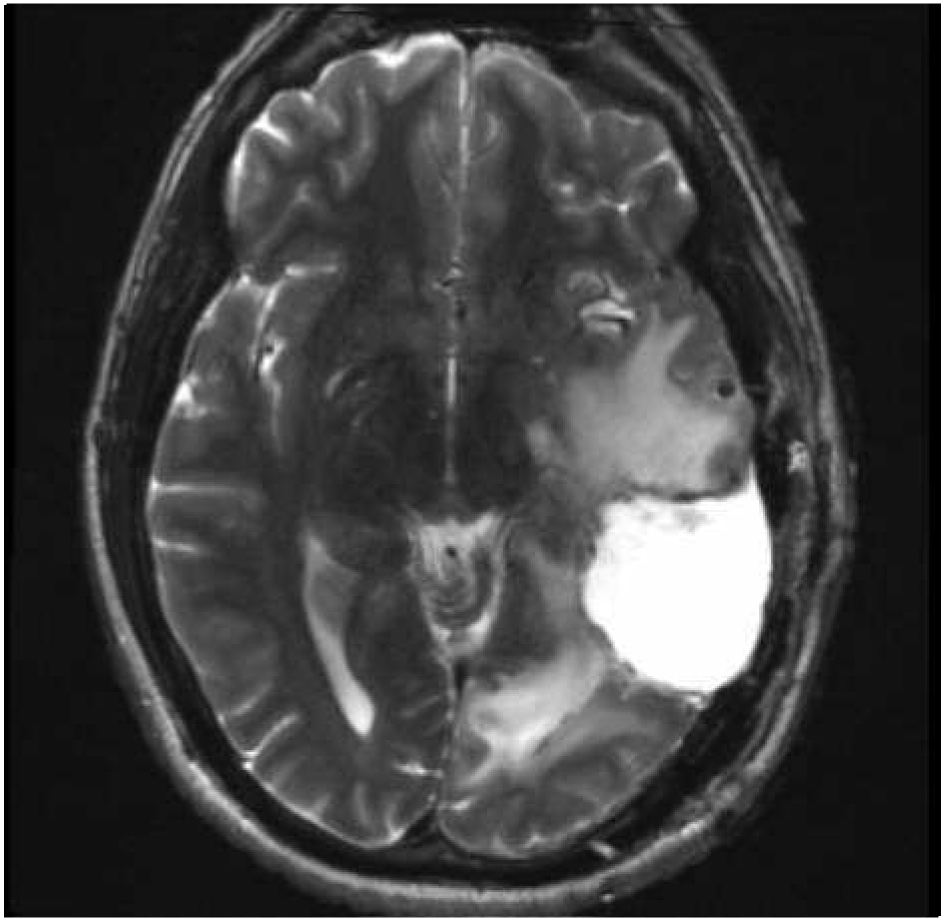
Elastic Deformation



Sampson, Duke University, 2004

Under infusion- or tumor-induced edema, dramatic increases in conductivity in white matter occur

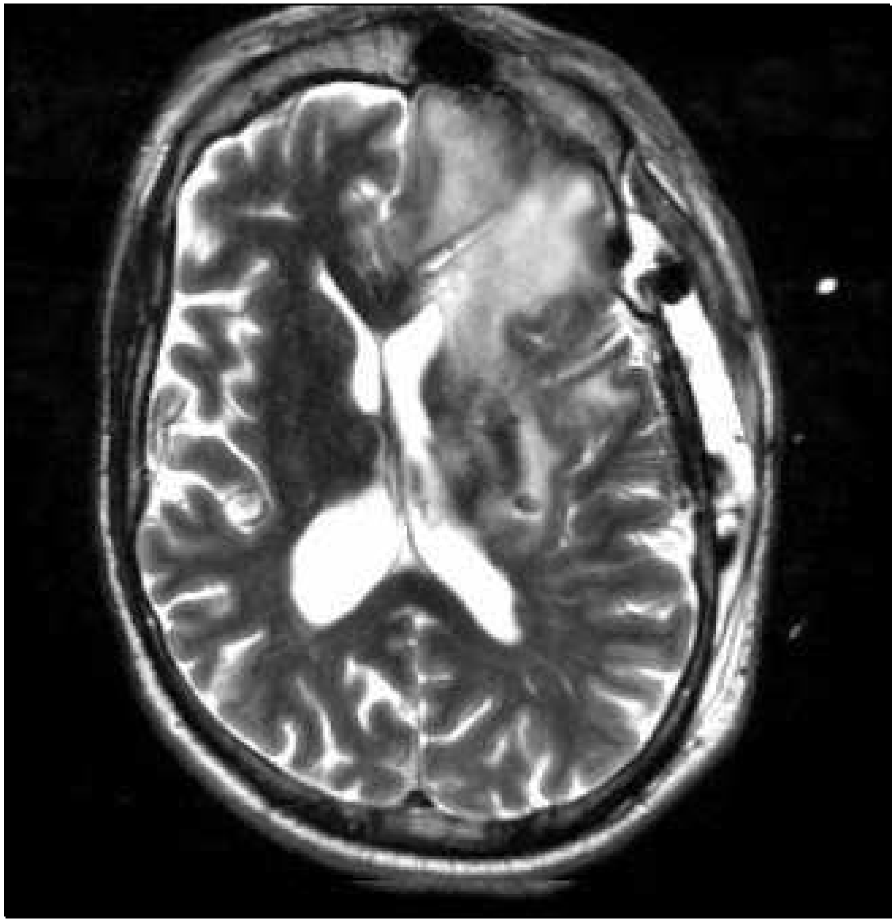
Elastic Deformation



Sampson, Duke University, 2004

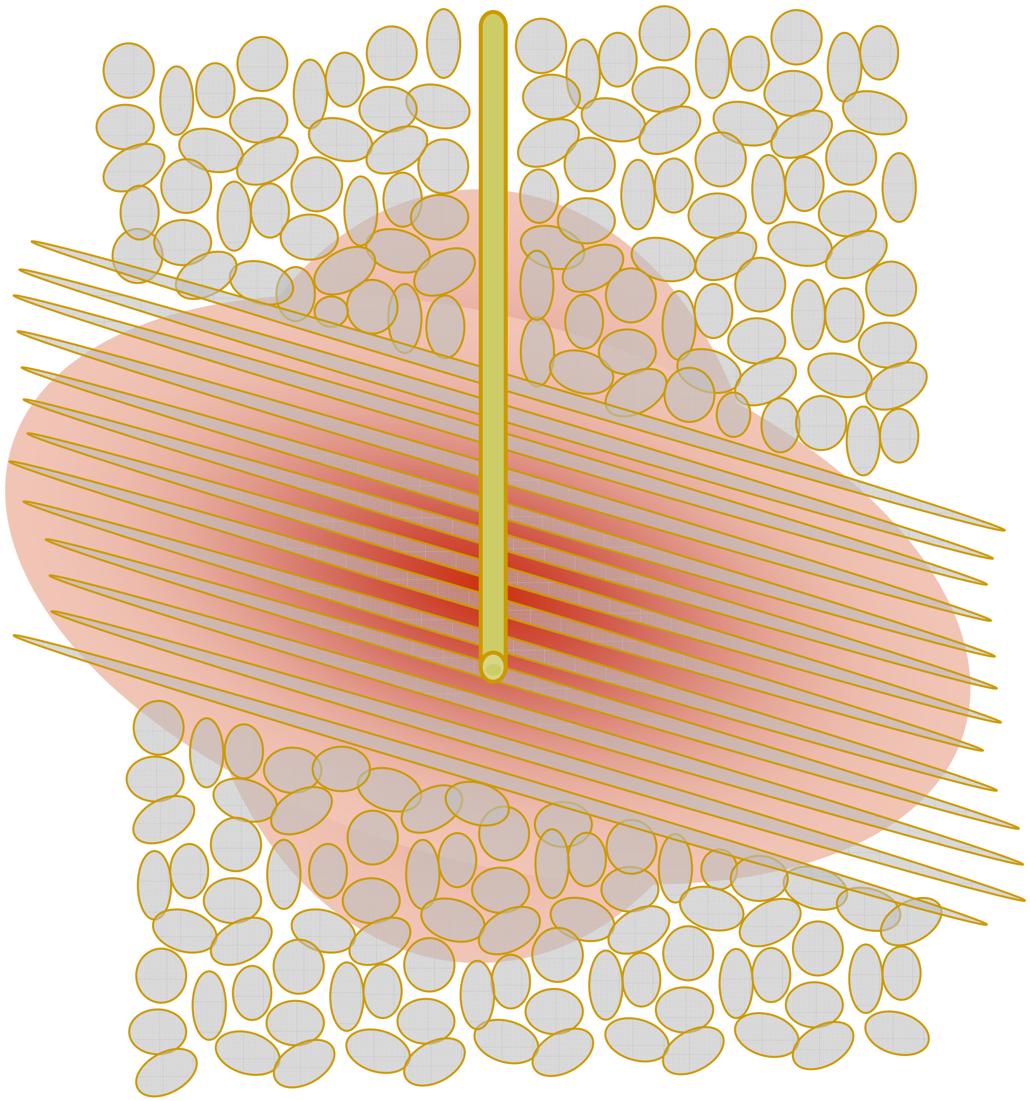
Under infusion- or tumor-induced edema, dramatic increases in conductivity in white matter occur

Elastic Deformation

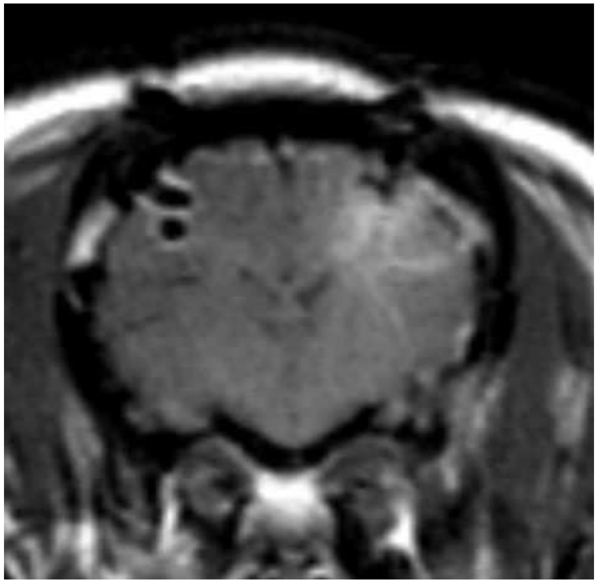


Sampson, Duke University, 2003

Diffusion



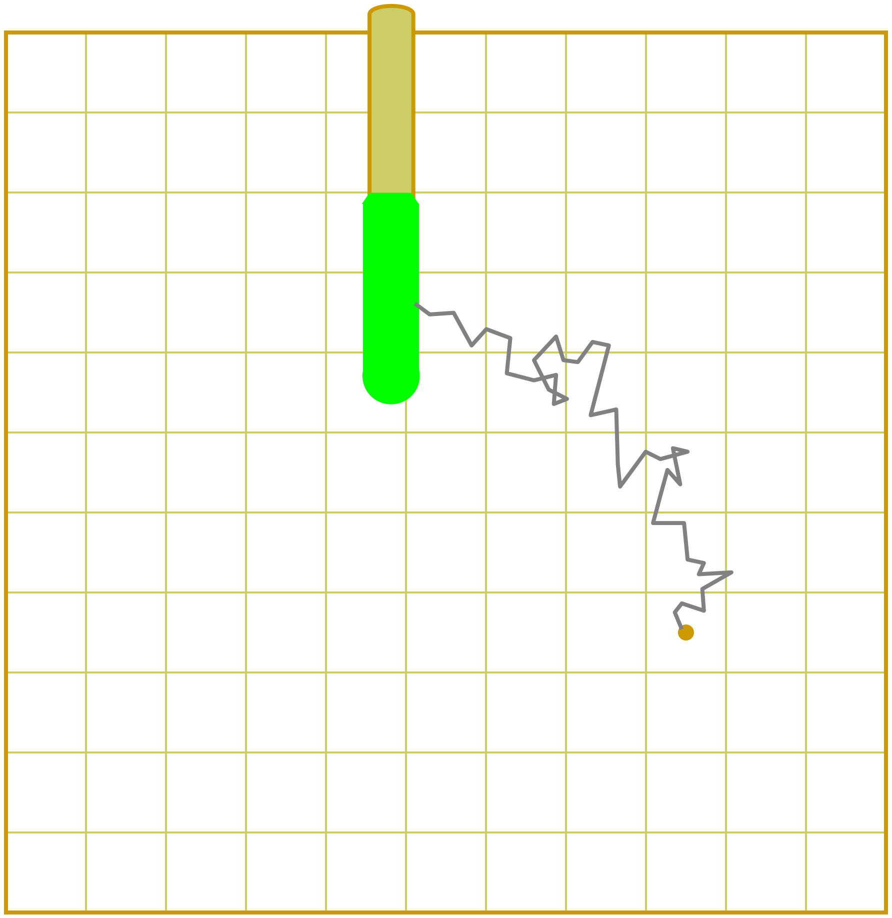
19 hours post infusion



Moseley, Stanford University, 2000

Diffusion allows slow spread of drug molecules not metabolized or degraded

Particle simulation step



One step, from location *x*:

1. Convection:

   $v(x) * \Delta t$

2. Hydrodynamic Dispersion:

   g * HD * sqrt(2Δt), Rotate

3. Diffusion:

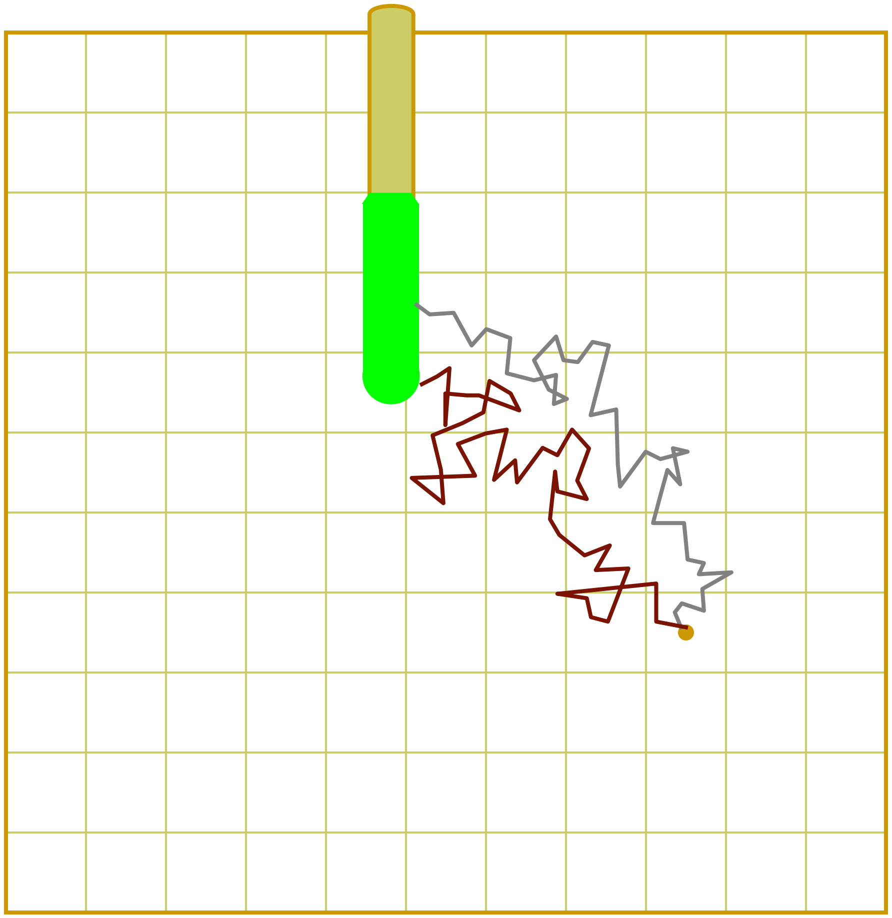
   g * D(x) * sqrt(2 Δt), Rotate

4. Accumulate Degradation

   $-\alpha(x) * \Delta t$

e

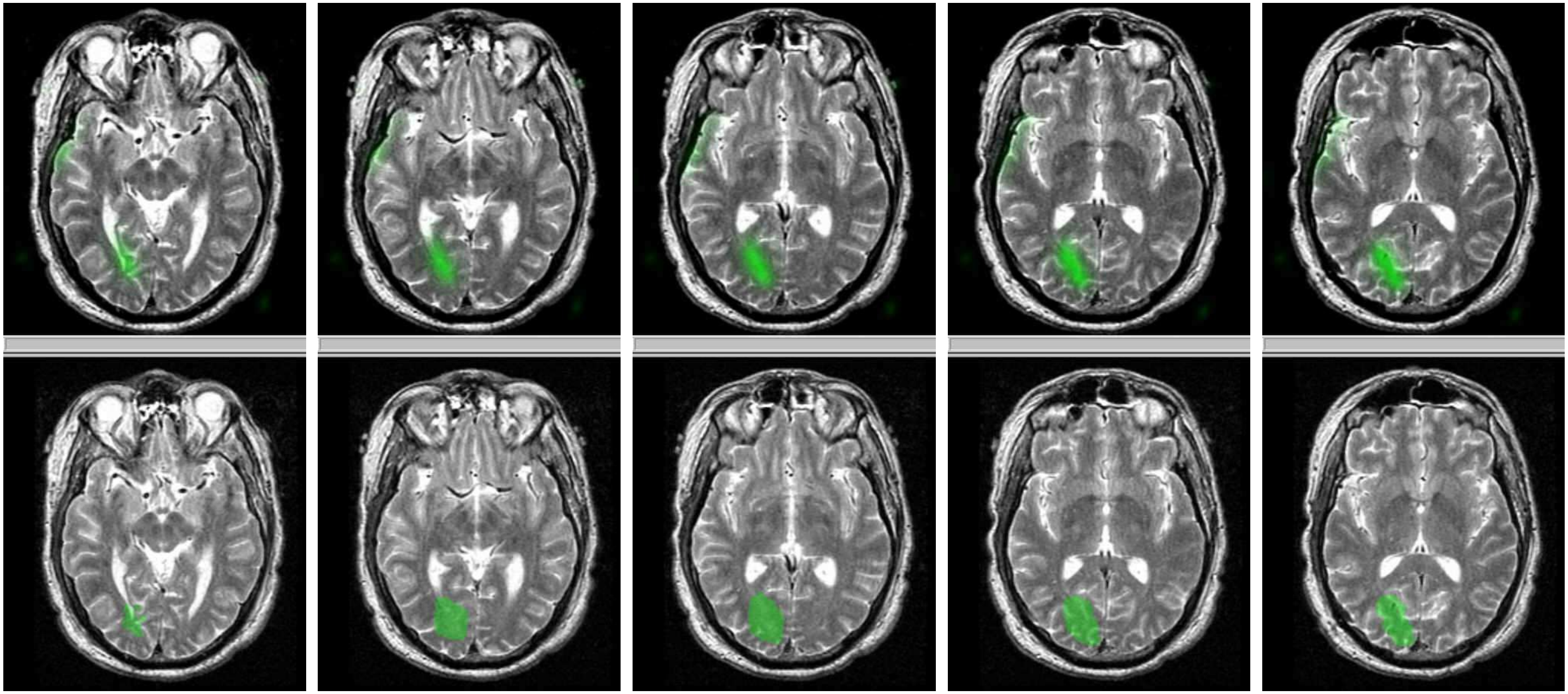
Particle simulation path



Repeat with n particles from *x*:

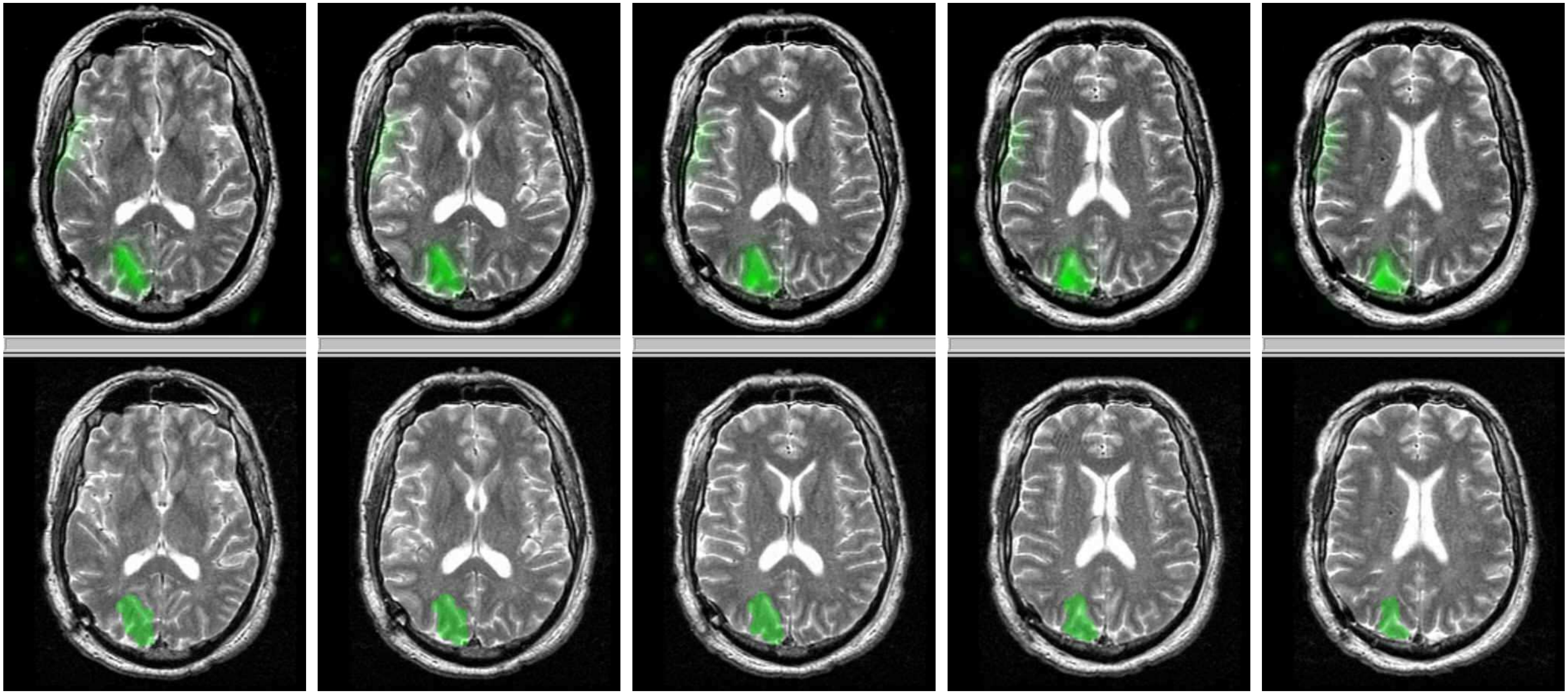
1. Run up to (t / dt) steps.
2. Check for collision with boundary.
   - Sample value from boundary
   - Scale by degradation
3. Average into bin at *x*.

Labelled albumin (1)



Upper row: SPECT measurements
Lower row: Simulation results

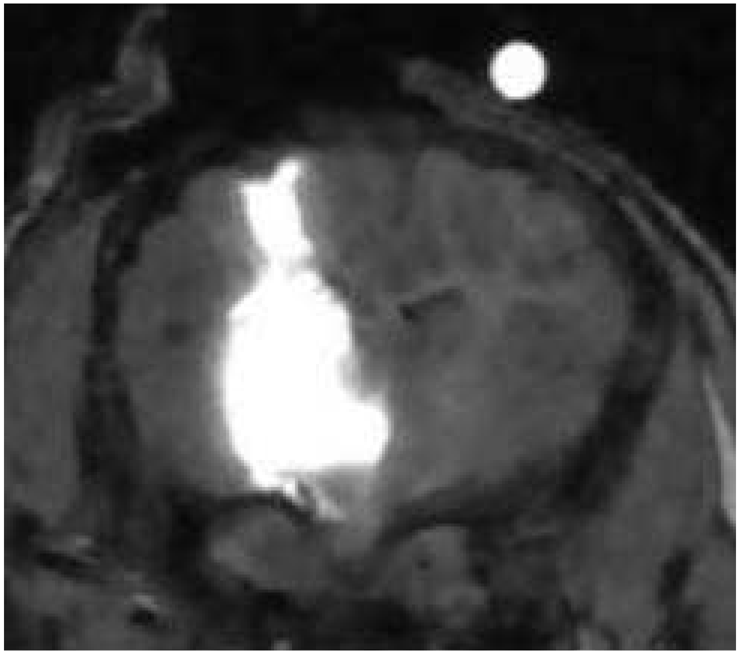
Labelled albumin (2)

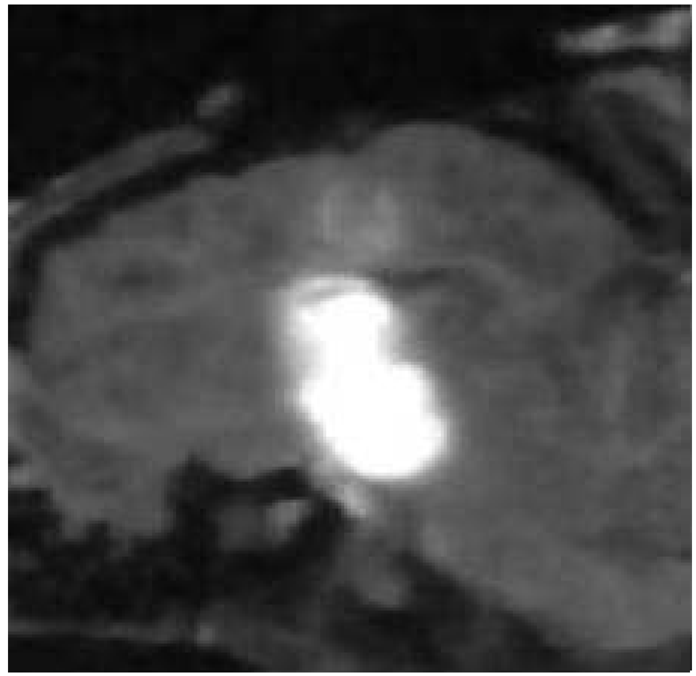


Upper row: SPECT measurements
Lower row: Simulation results

Infusion Progression

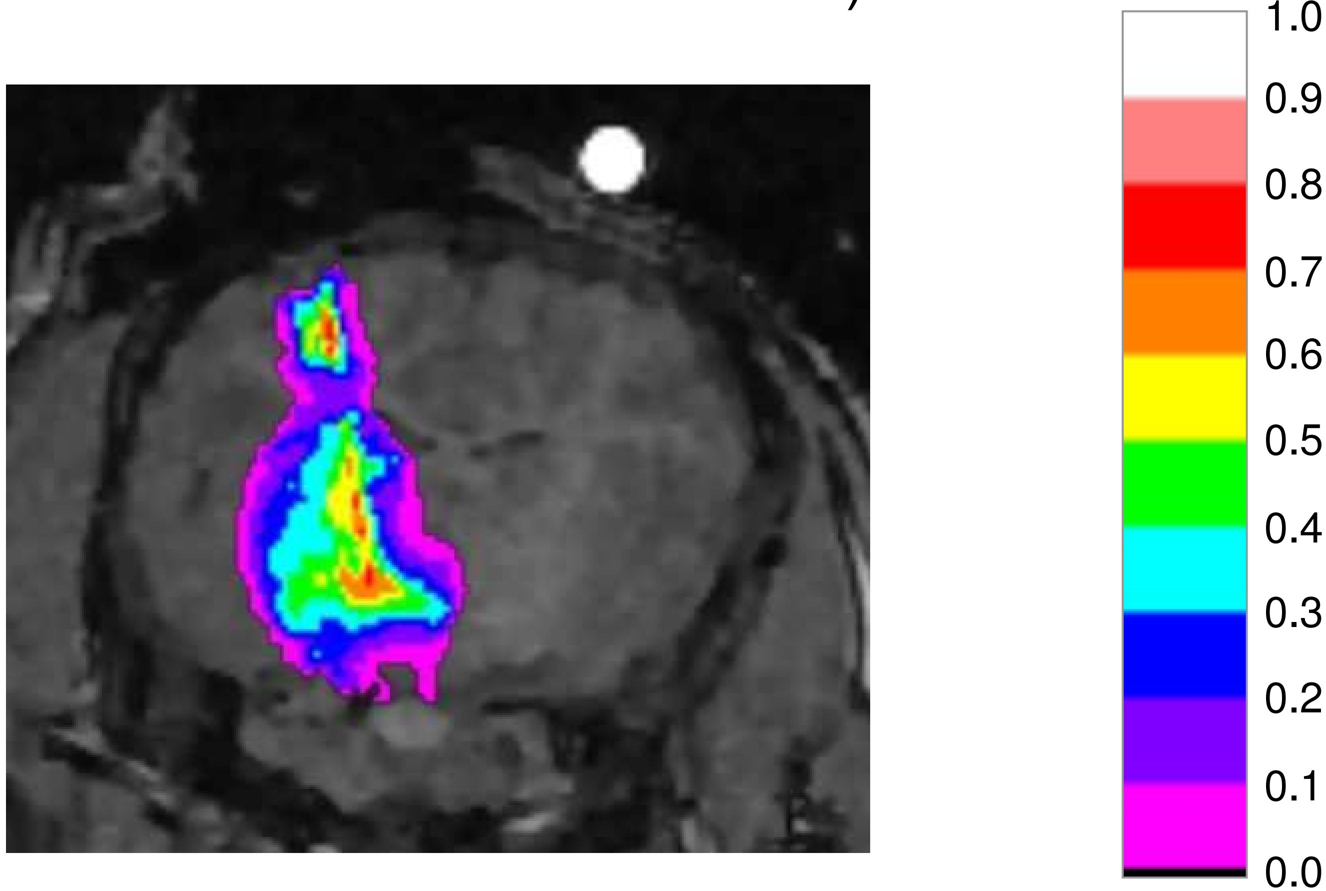
12ul 65ul 102ul 192ul 267ul 337ul 647ul 752ul 917ul





P08 Measured Concentration

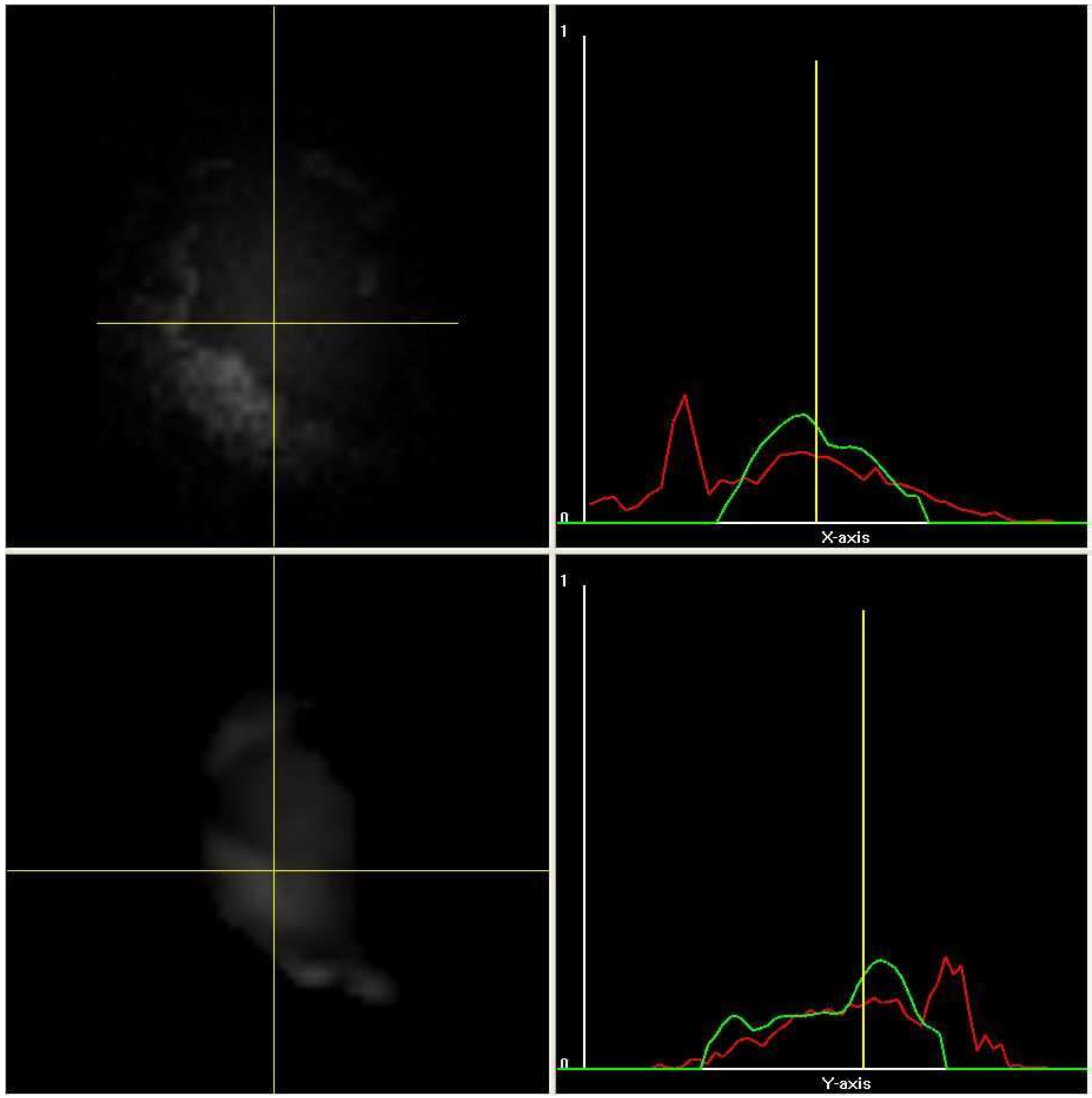
(as a fraction of infused concentration)



Simulation vs. Measured Concentration:
Measured Pore Fraction, Isotropic Diffusion/HC Model

Simulated:

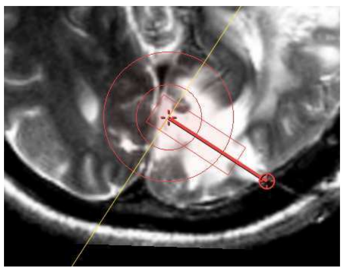
Measured:

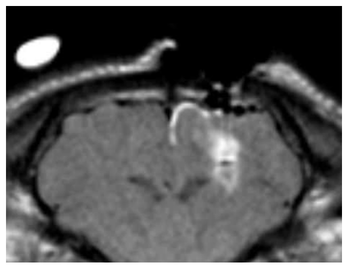


Red: Sim.
Green: Meas.

Goal : patient-specific simulation of CED

CED is patient specific

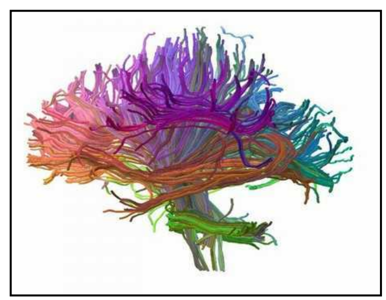


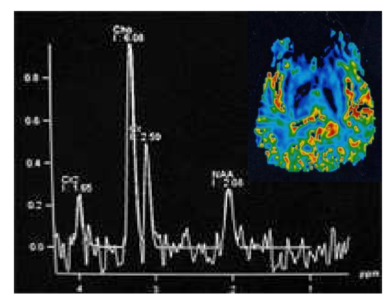


mathematical models, *e.g.*

$$\partial c / \partial t = \nabla\nabla : (Dc) - \nabla \bullet (vc) + \frac{1}{\phi} \left[F_{capillary} - R_{bind}(c, b) \right]$$

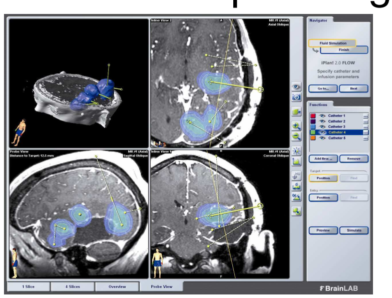
require patient-specific information

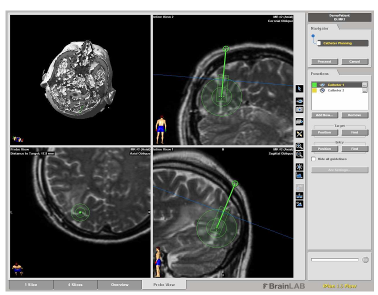




To predict for an individual

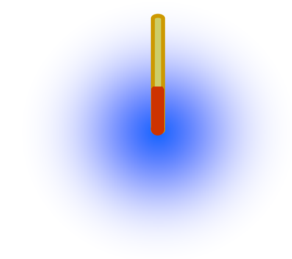
Software for planning CED





Symbol	Meaning	How obtained
φ	connected extracellular fluid volume fraction	Proton density imaging
$\mathbf{v}$	fluid velocity field relative to tissue	Solved *via* D'Arcy's law
q	rate of production of interstitial fluid	DCE
K	hydraulic permeability	DTI
p	hydrostatic pressure relative to a resting pressure in tissue	Solved for
c	concentration of serum protein in interstitium	Solved for
Π	osmotic pressure of serum protein in interstitium	constitutive relation to *c*
D	extracellular diffusion tensor of serum protein in interstitium	DTI
k_d	degradation and loss of serum protein from interstitium	Assumed/estimated
R	reflection coefficient for serum protein from capillary walls	DCE
$\frac{PS}{V}$	Permeability-area product per unit tissue volume for serum protein	DCE
$\frac{L_p S}{V}$	Capillary hydraulic conductivity per unit tissue volume	DCE
B	Coefficient of *expansion* of extracellular volume	DTI

Summary

Influx &	Transport &	Efflux	Distribution
Determined by	Determined by	Determined by	
Flow rate **Duration**	**Convection** **Diffusion** **Conductivity pathways** **Surfaces / sulci**	**Binding** **Capillary permeability**	

Endogenous flow:

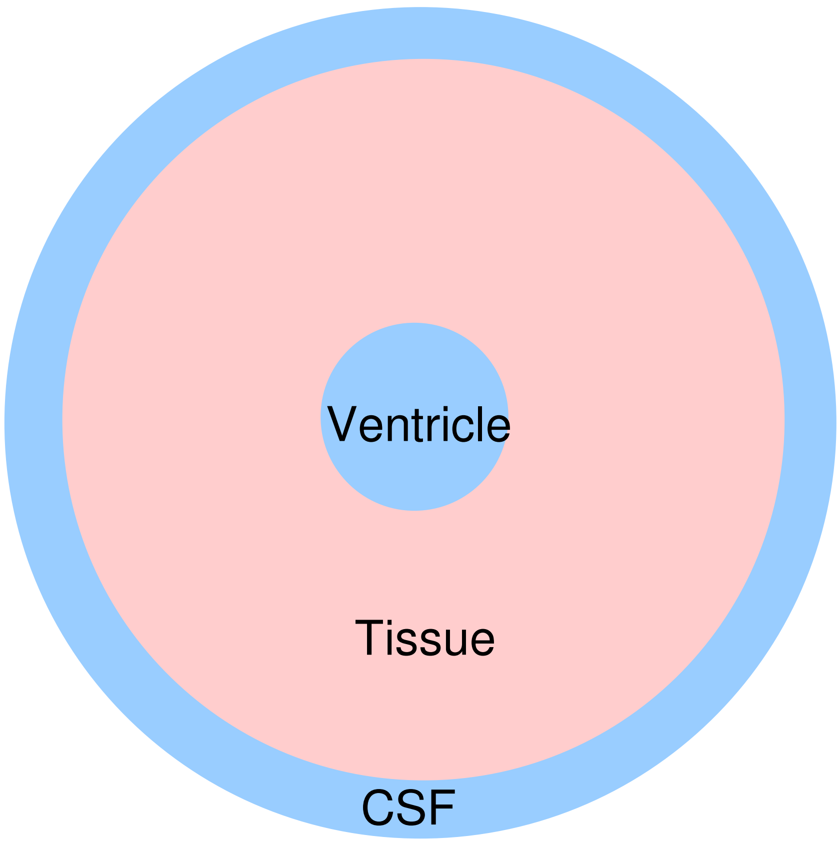
Endogenous flow even in absence damage/disease

ISF (interstitial fluid) circulation is substantial (~ 20% of flow from ventricles)

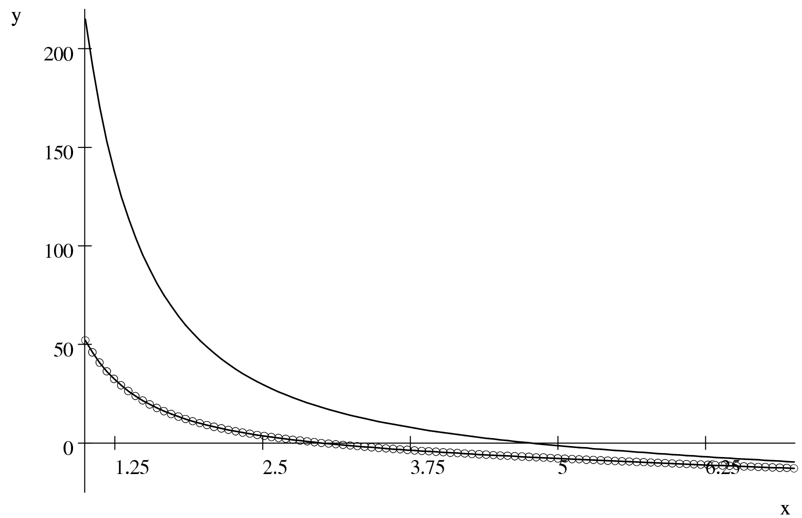
Results in pressure gradients in resting tissue

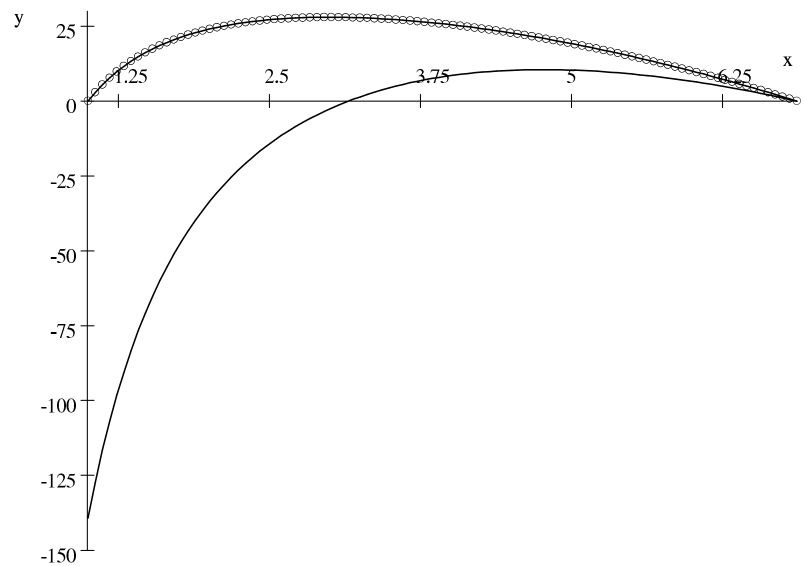
- Significant enhancements in edema

Simple Endogenous flow Model



Interstitial flow in spherical model

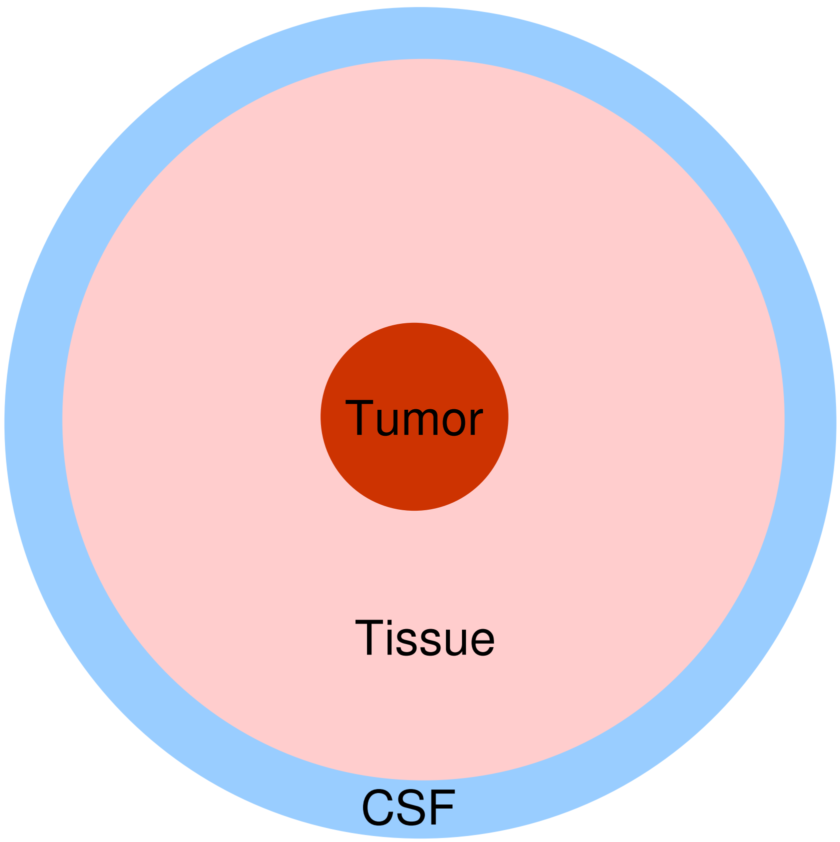




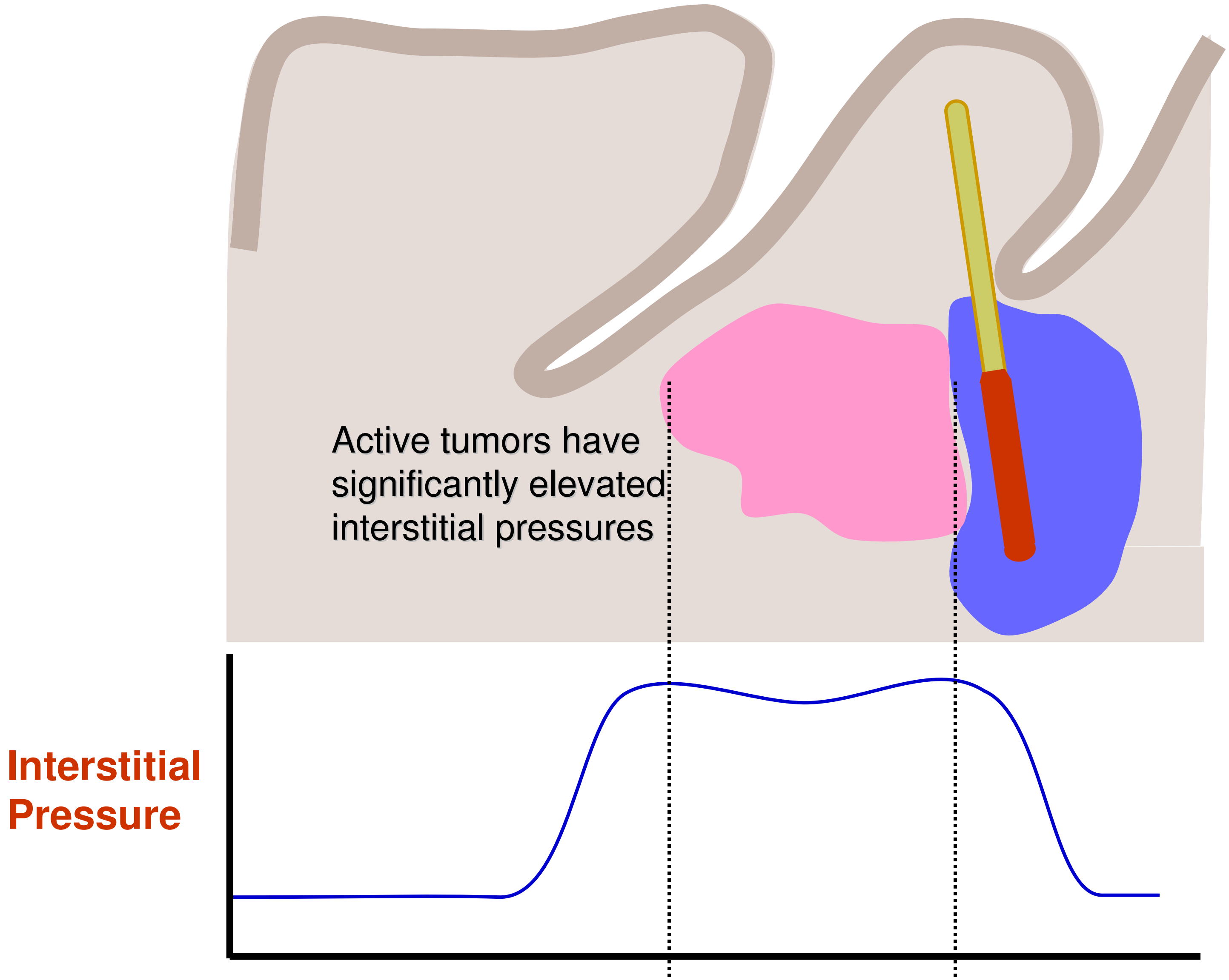
FLOW VELOCITY PRESSURE

vs radial distance

Simple Tumor Model (with no necrotic core)

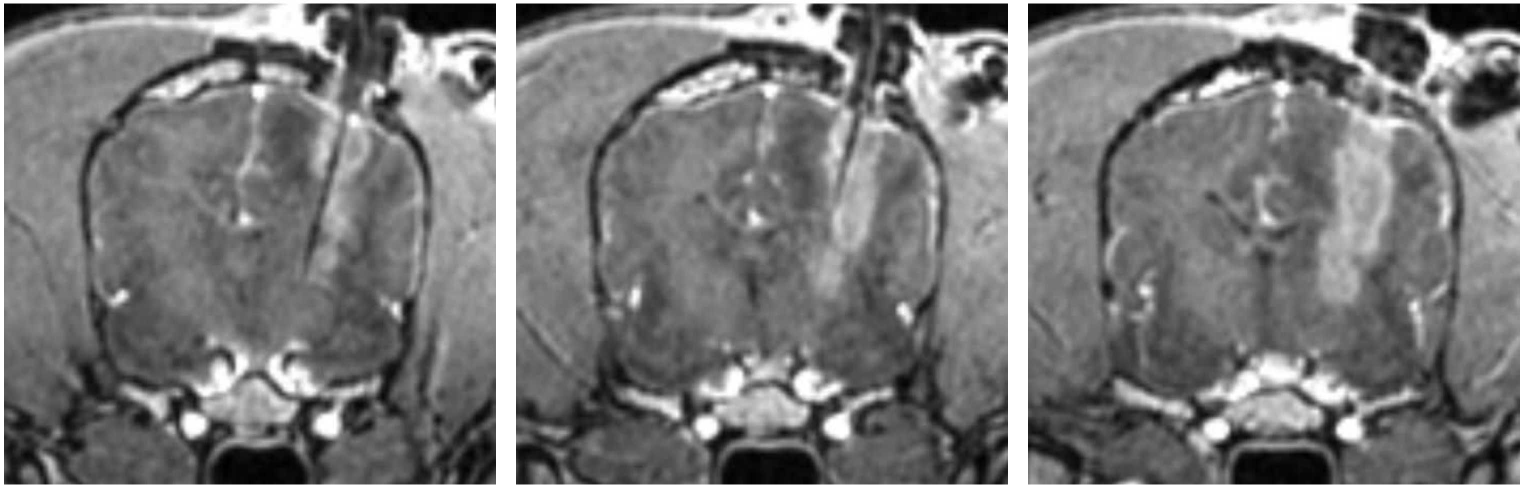


Elevated tumor pressure is barrier to delivery



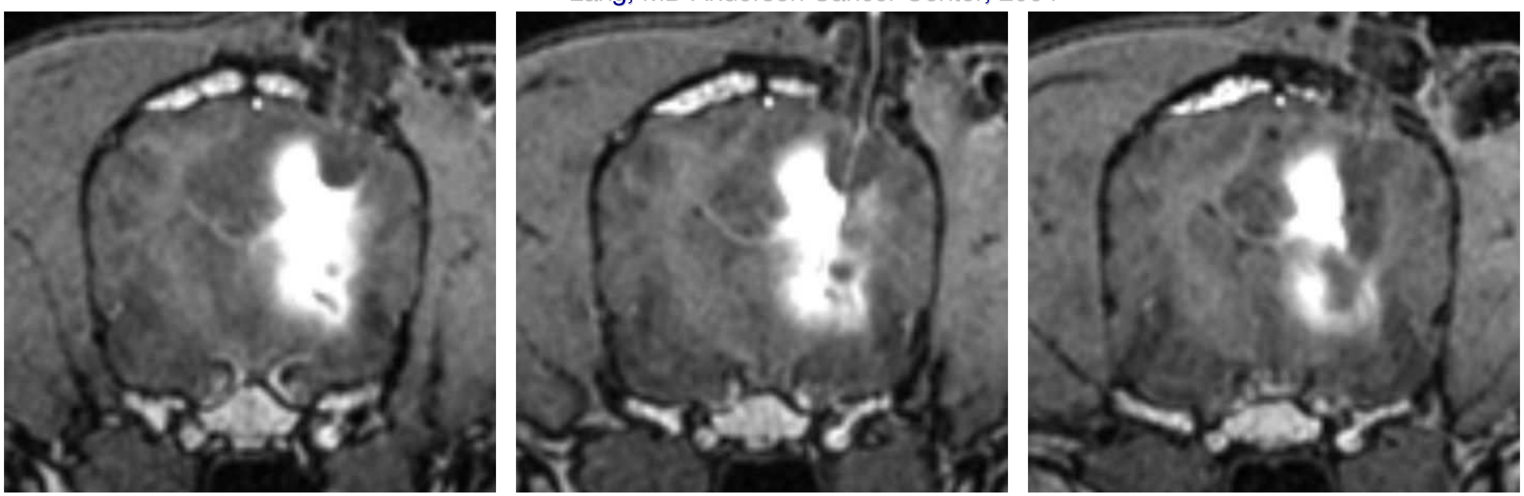
Tumor Infusion, catheter near enhancing rim

T1 + Contrast

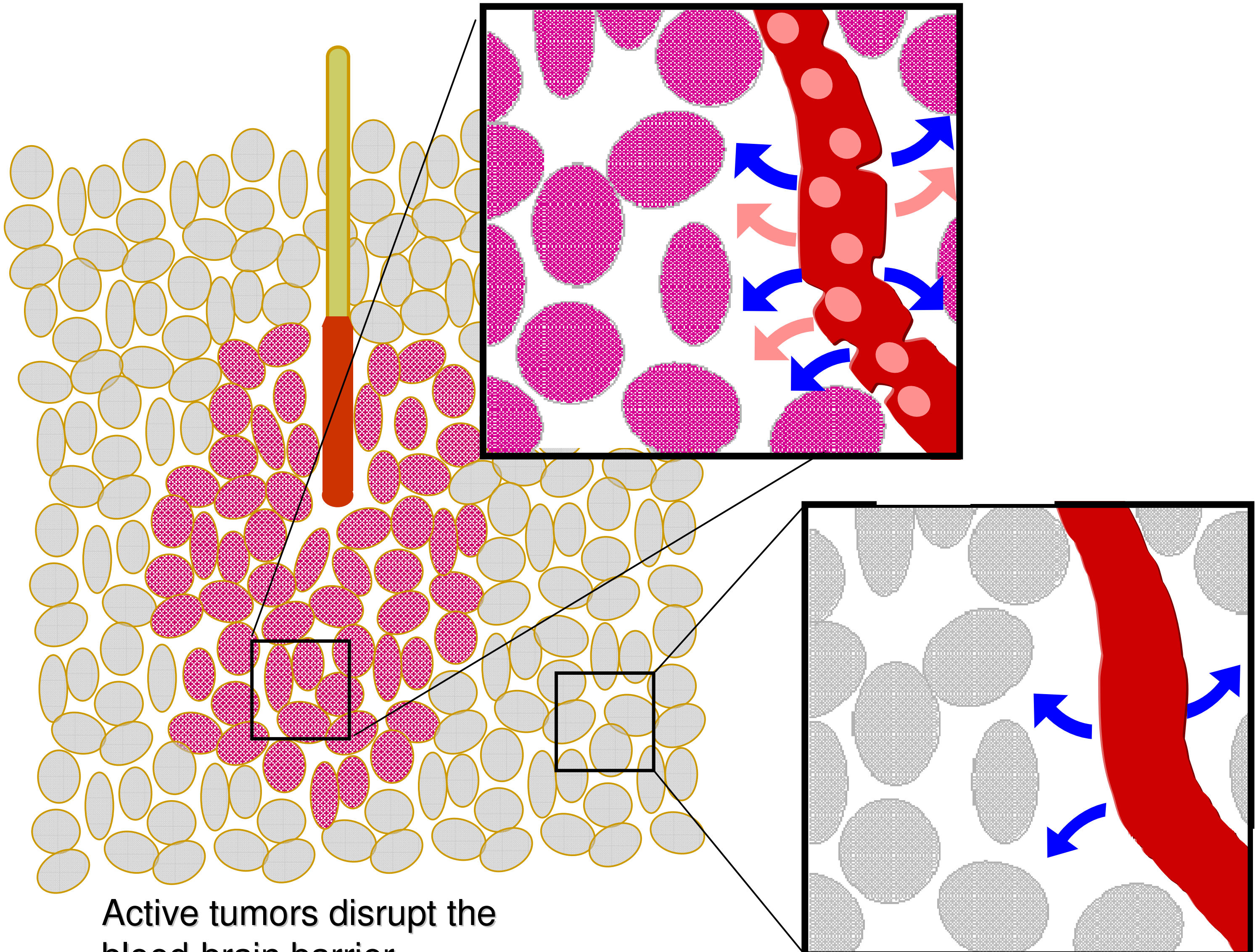


Lang, MD Anderson Cancer Center, 2004

T1, Gd Infusion



BBB disruption is a cause for edema

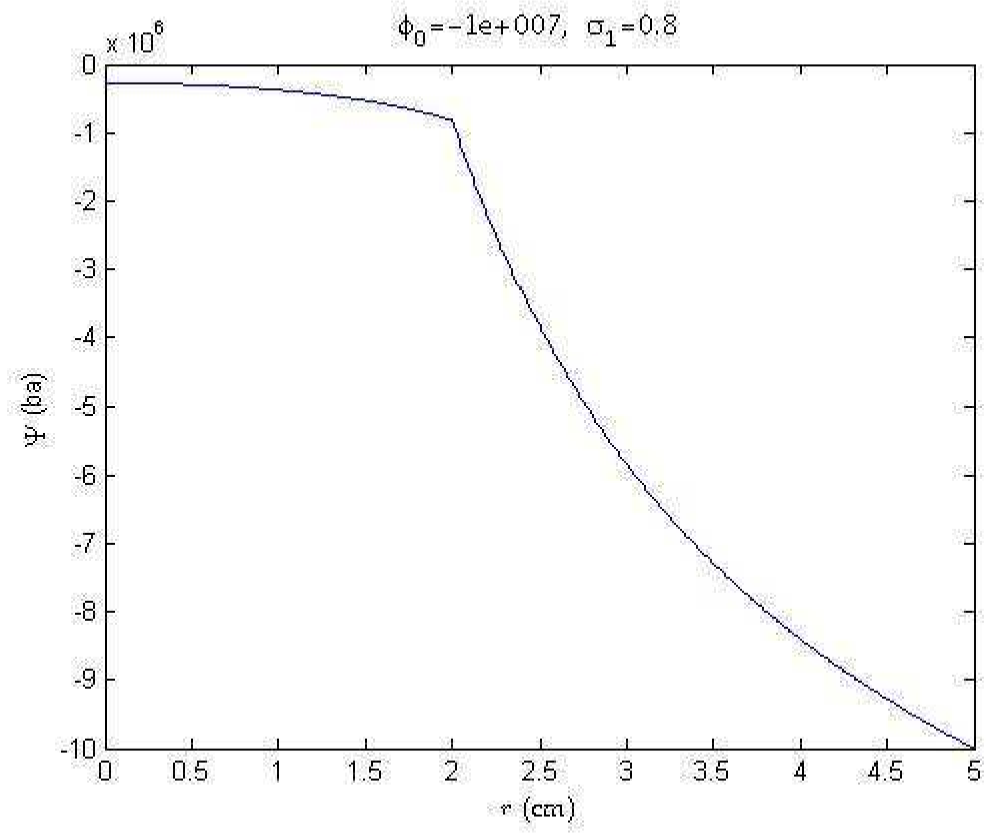


Active tumors disrupt the blood-brain barrier

A more refined point of view

- Disrupted BBB causes edema and spilling of serum proteins into interstitium
- Endogenous flow will carry proteins into tissue
- Osmotic pressure of proteins will alter pressure outside tumor
- Coupled nonlinear differential equations for hydrostatic & osmotic pressures

Spherical tumor model



Effective interstital pressure

Distance from center

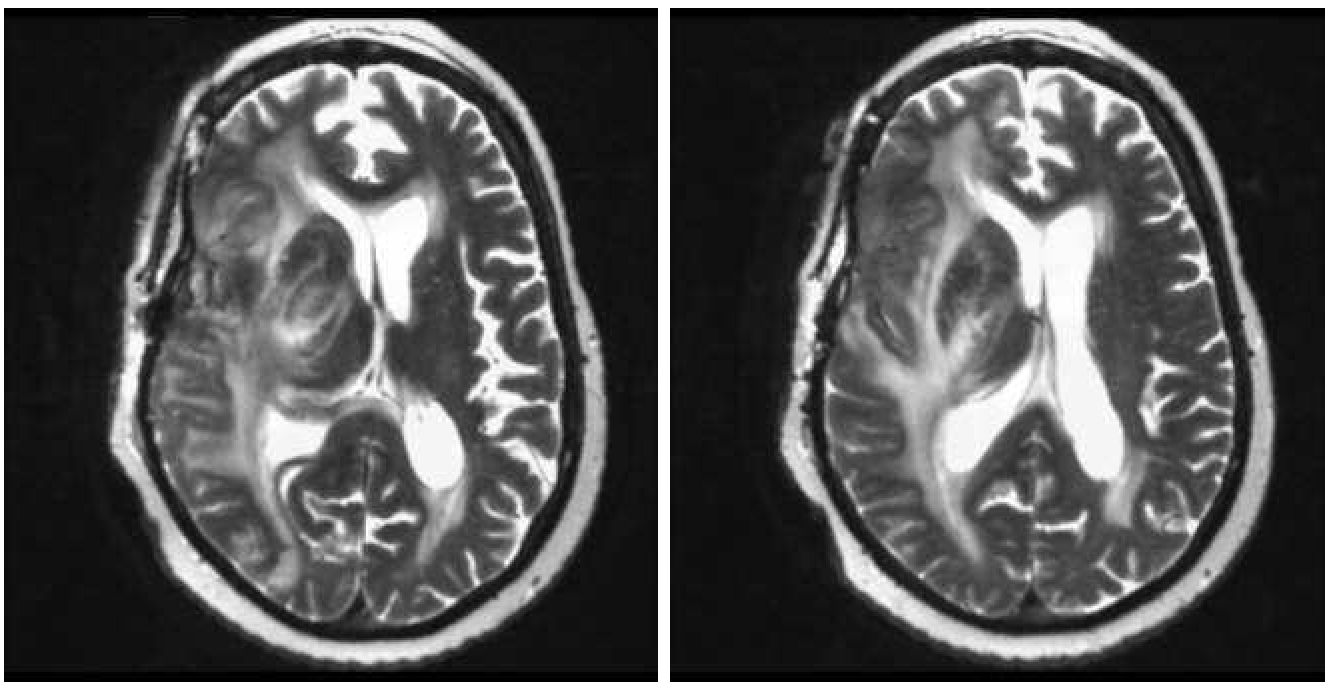
Cancer: active tumor targets for infusions

Active tumors present a variety of additional barriers to drug delivery

- high interstitial tumor pressure
- decreased vascular surface area, heterogeneous distribution
- increased intra-capillary distance
- peritumoral edema, disrupted BBB

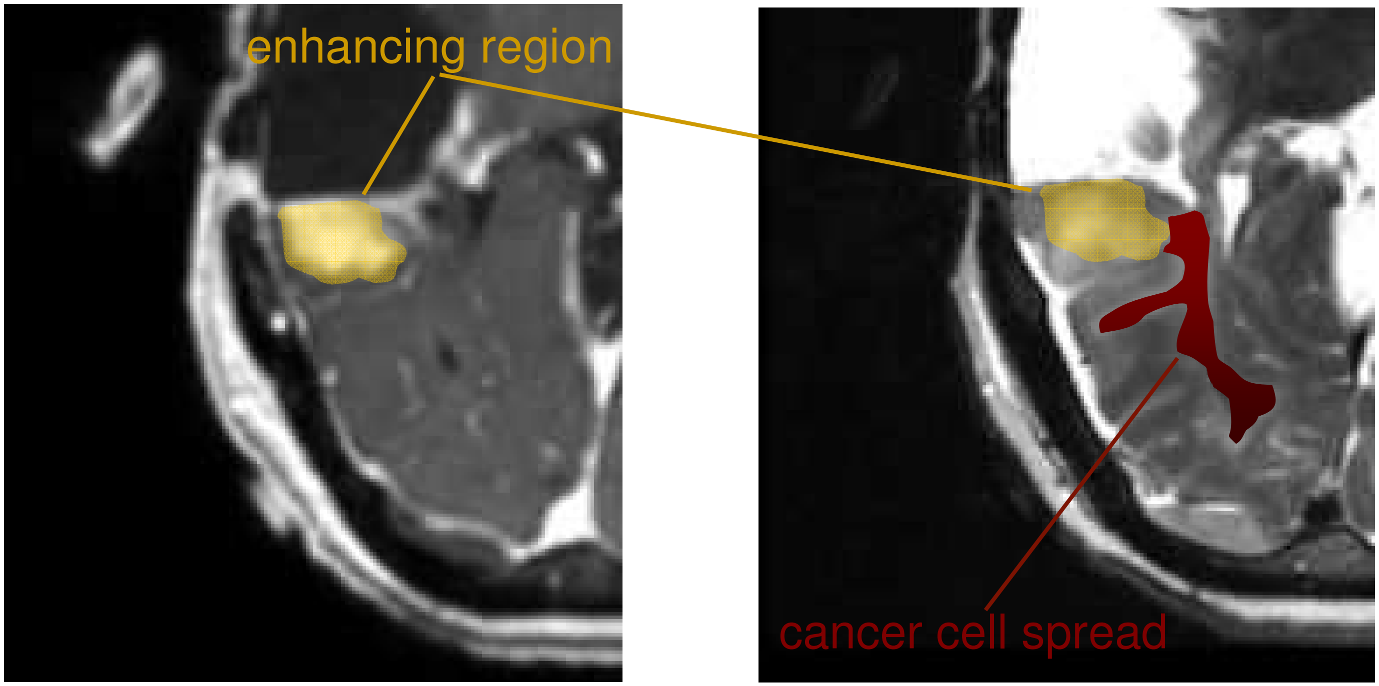
Cancer: predicting disease progression for better intervention

Significant edema, and white matter pathways offer enhanced route for dissemination of primary cancer



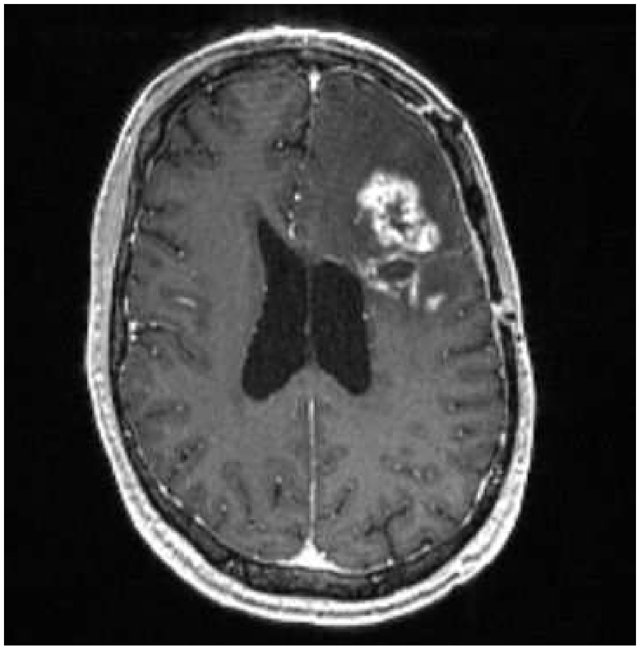
Understanding cancer cell dissemination can integrate therapies

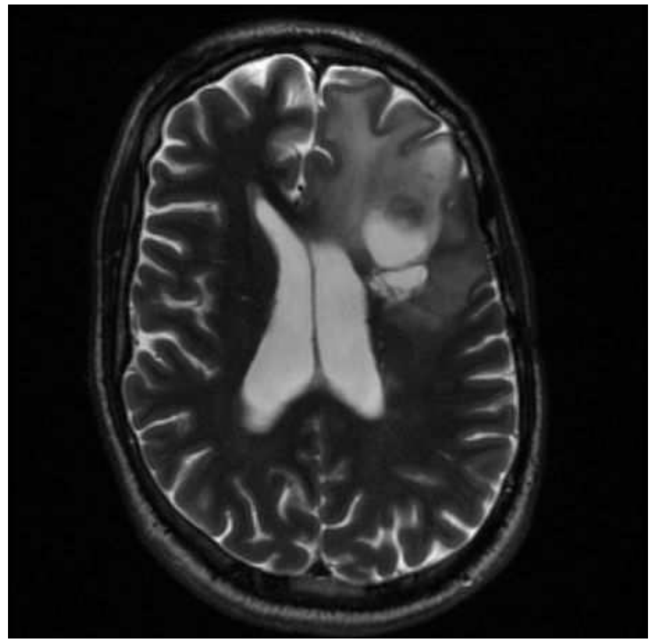
- expand radiosugical target area
- combine radiosurgery and targeted drug delivery

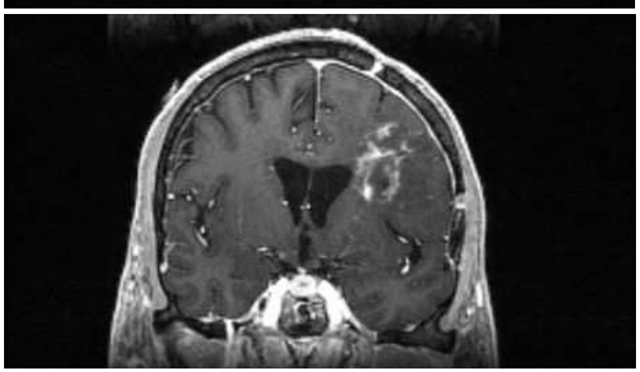


T1-contrast image   T2-weighted image

Neural stem cells seem to be migrating from sub-ependymal zone







Stem cells may also be key in causing cancer!

Neurodegenerative diseases

One problem: insoluble protein aggregates (plaque)

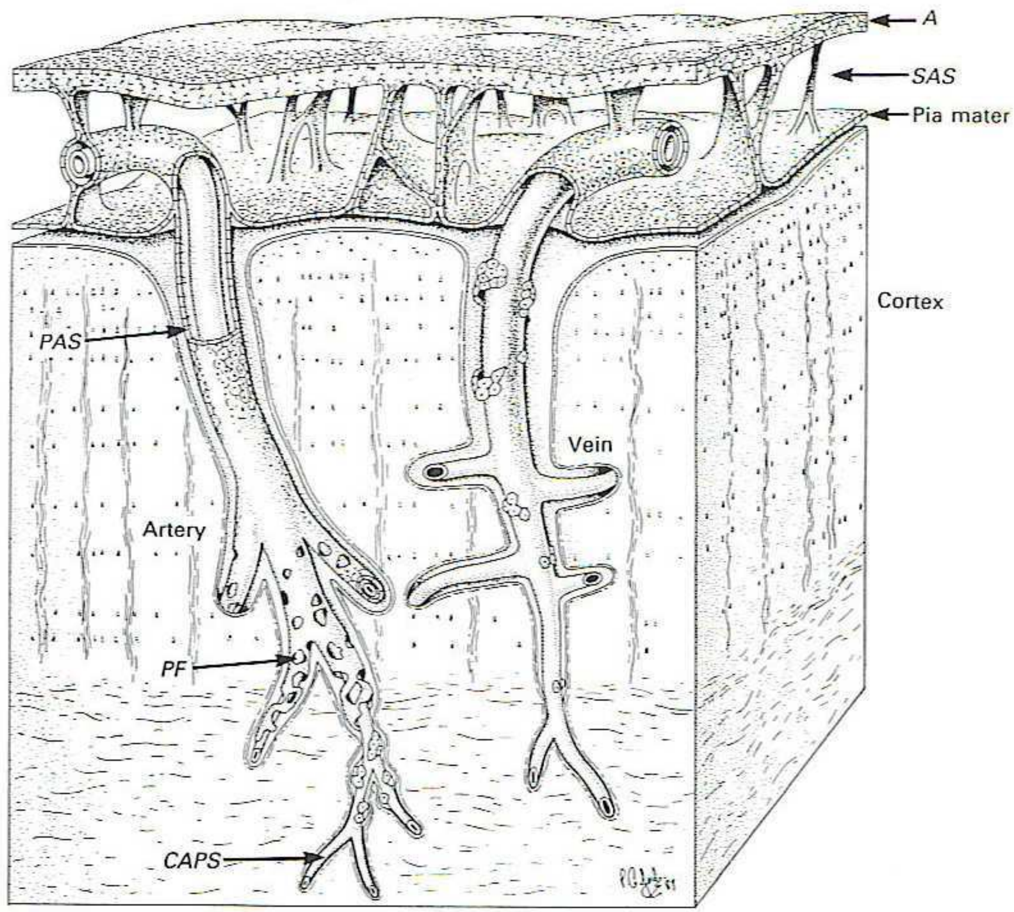
Pathways for dissemination are confined to cortex (thin sheet not volume)

Plaque dissolving therapies must also be confined to cortical sheets

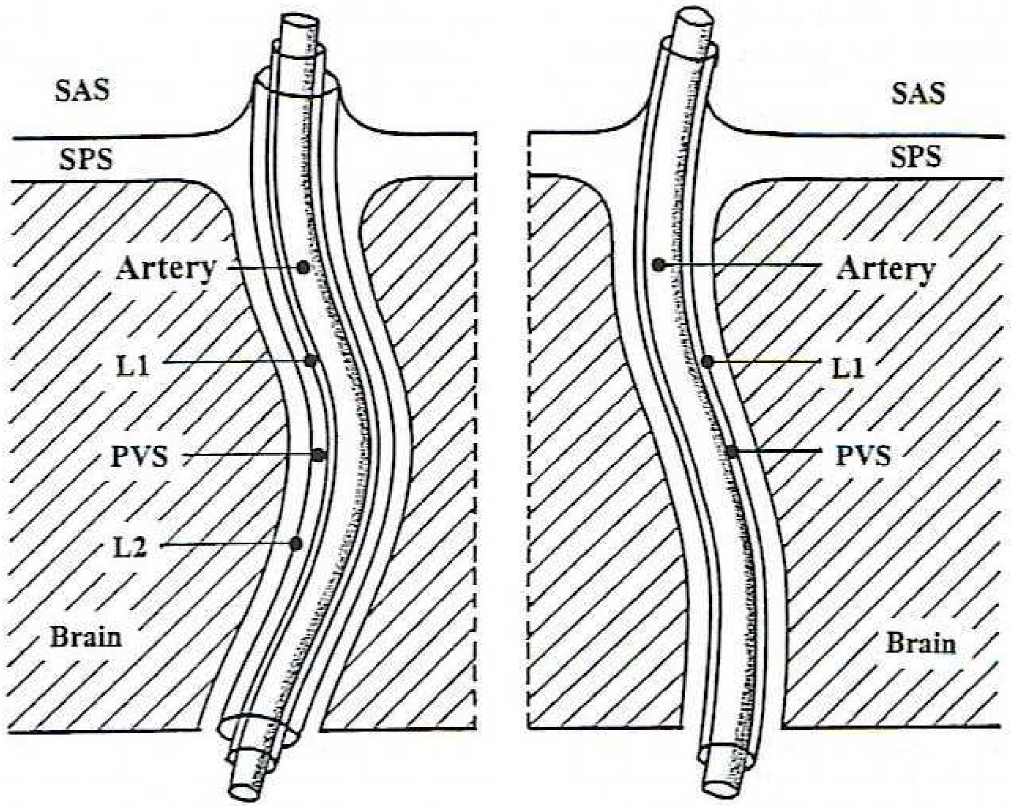
Other deep brain infusions can be currently supported

Plaque deposition regions are periarterial spaces

120 E. T. ZHANG, C. B. E. INMAN AND R. O. WELLER

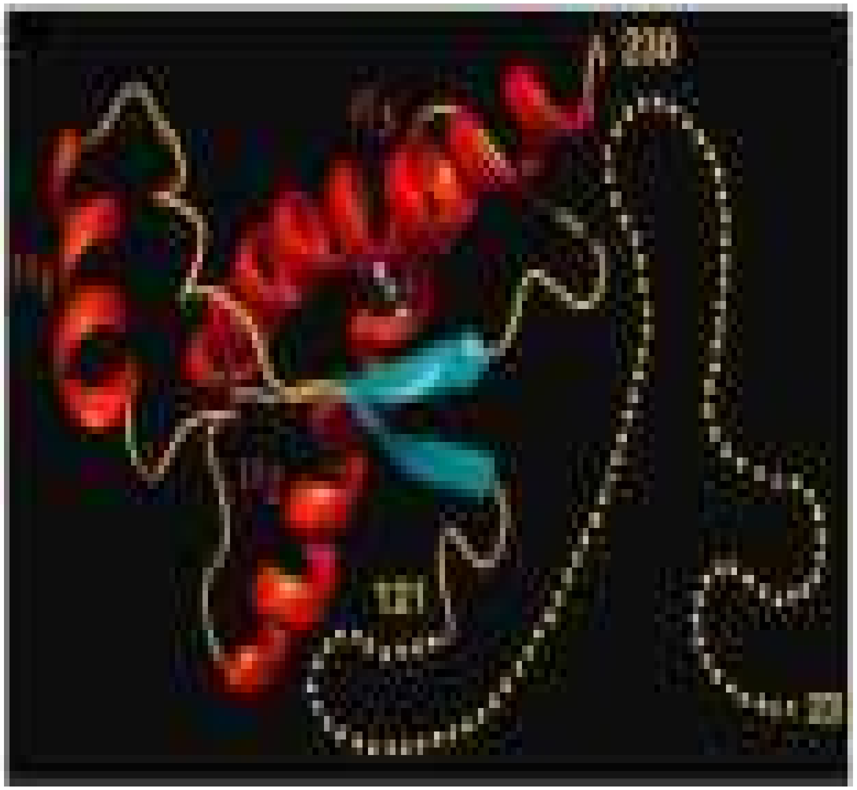


Basal ganglial spaces not involved

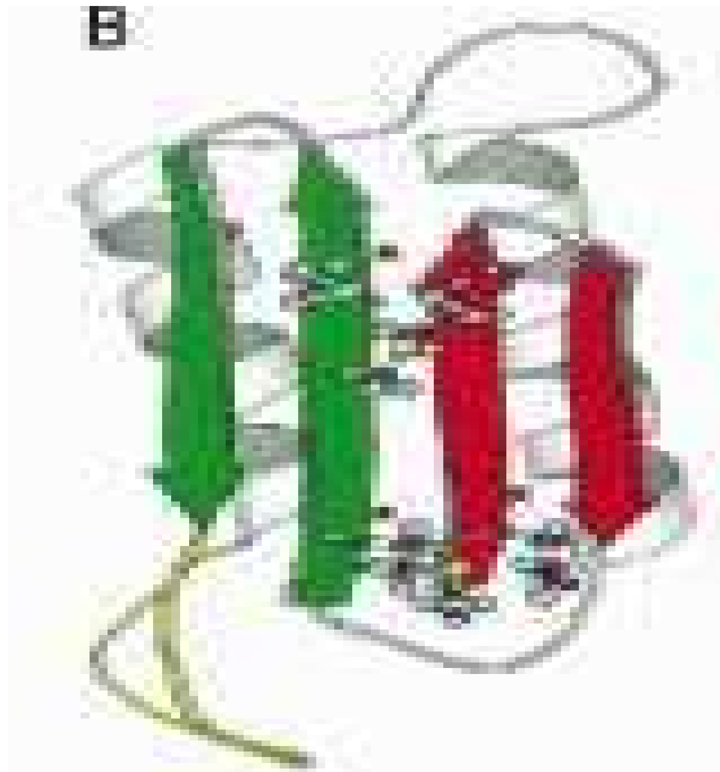


(a) Artery in Basal Ganglia (b) Artery in Cerebral Cortex

Digression: Infectious proteins

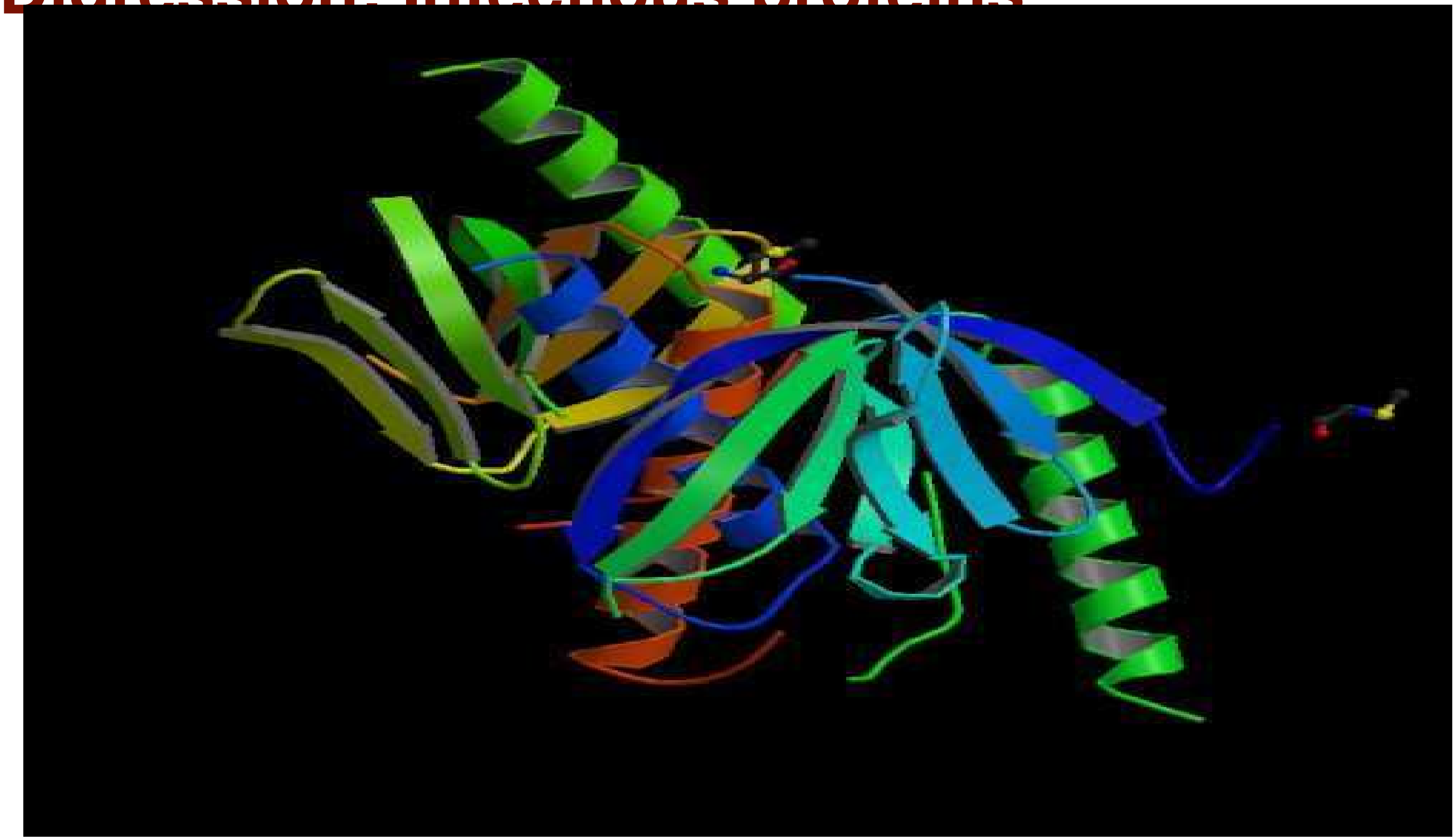


Prion: Normal



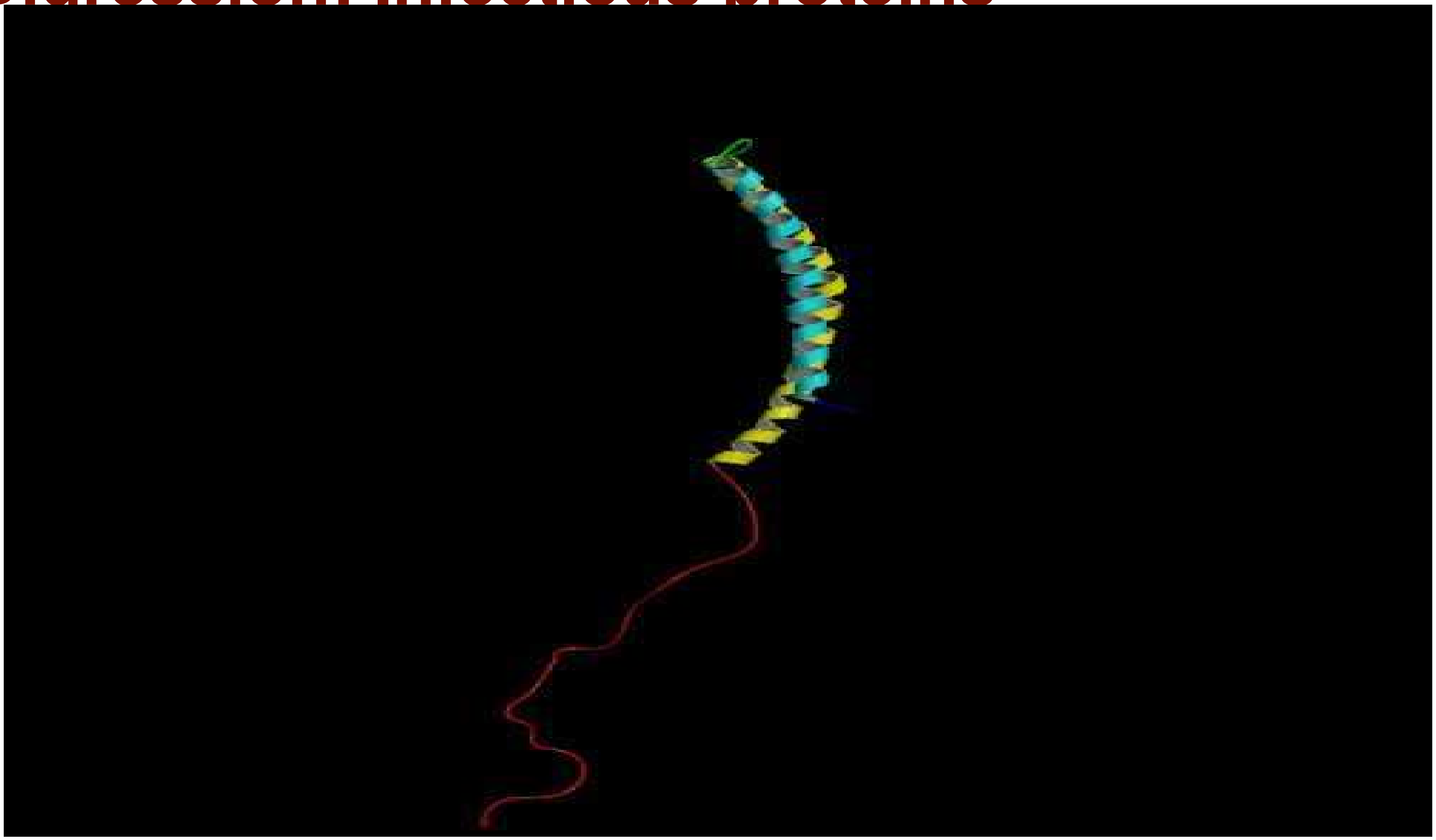
Prion: Mutated

Digression: Infectious proteins



Alzheimer's

Digression: Infectious proteins



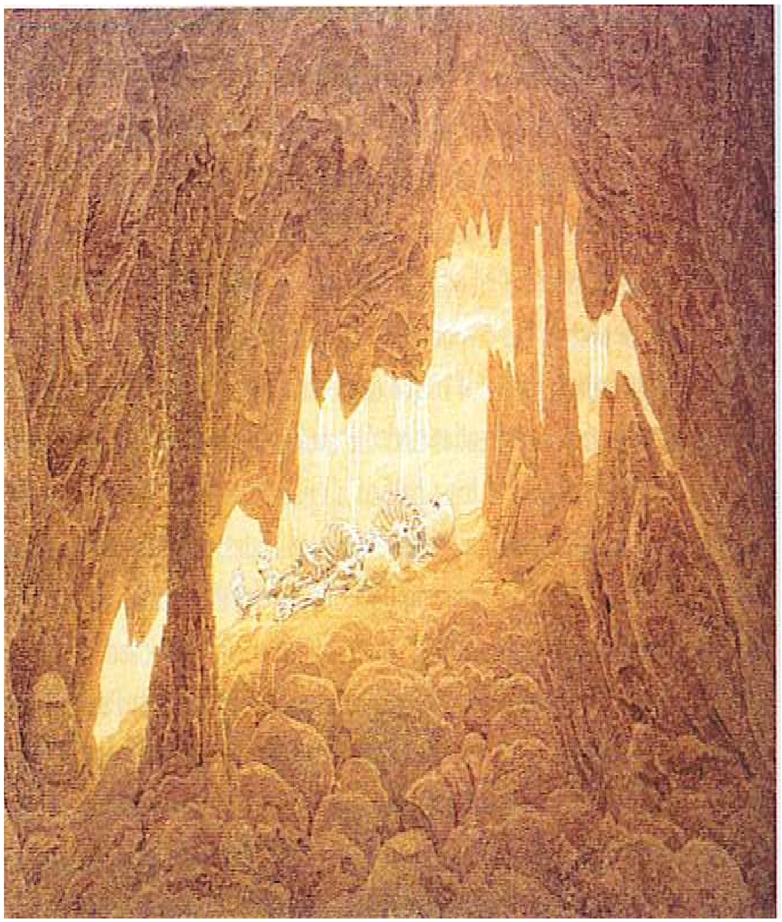
Parkinson's

When all else fails

If you must get brain disease

Be an artist!

Caspar David Friedrich stroke 1830's



Before

After

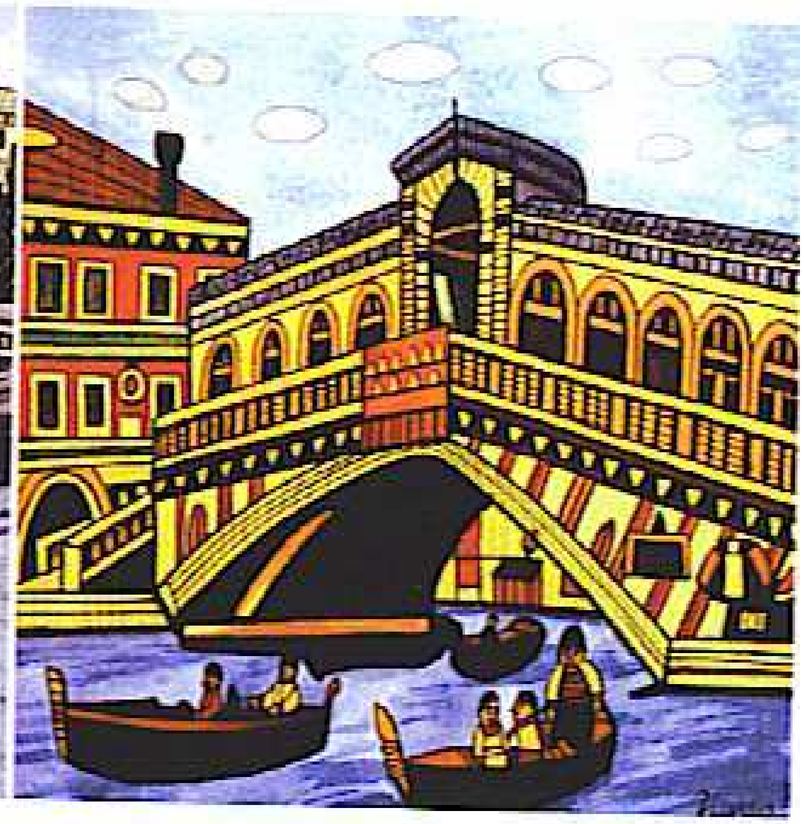
Paul-Elie Gernez aphasia 1940's

Before

After

Carolus Horn Alzheimer's 1960's

Before



After

Carolus Horn Alzheimer's 1960's


THANK YOU