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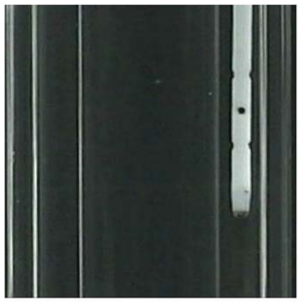

Fluid Dynamics of Drug Spread in the Intrathecal Space

Navid Borhani

Radboud M. Nelissen
Eric Buchser & team at Morges Hospital
Peter A. Monkewitz
Medtronic Europe Sarl
CTI Medtech

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Outline of talk

- Clinical observations of bolus effects
- CSF flow parameters
- Experimental laboratory model
- Drug spread mechanisms
    - Molecular diffusion
    - Enhanced diffusion
    - Steady streaming - Subarachnoid space
    - Steady streaming - Catheter
    - Buoyancy effects
- Summary
- Conclusions

Clinical Background

1. A high dose of local anaesthetic continuously administered intrathecally does not:
   - Improve pain relief
   - Produce neurological changes

2. A low, clinically insignificant, dose of local anaesthetic administered intrathecally as a *fast* bolus:
   - Improves pain relief
   - Produces neurological changes

These observations:

- Cannot be explained by current pharmacokinetics
- May be due to fluid dynamics occurring within the CSF

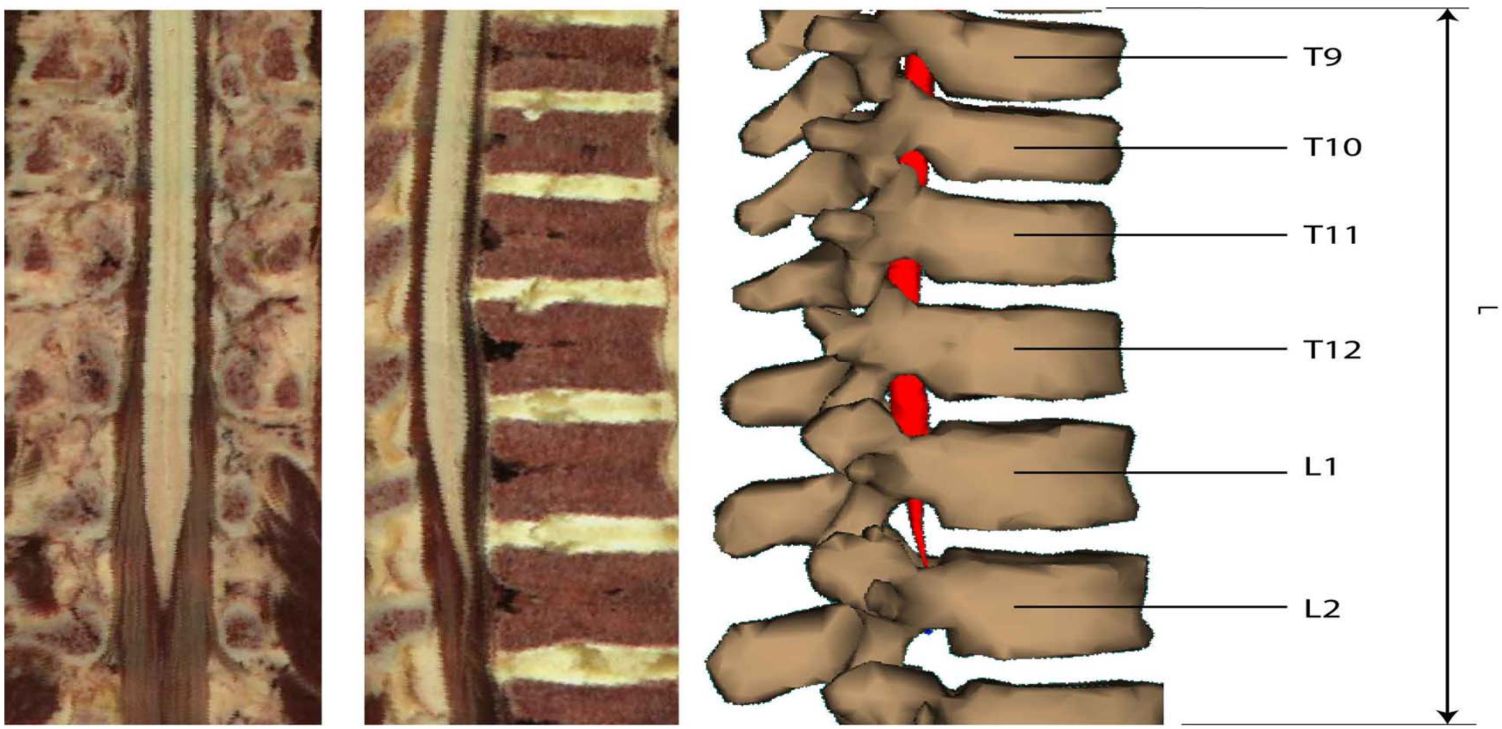
Fluid Dynamic Mechanisms of Intrathecal Drug Delivery

The history of a drug from the time it leaves the pump until it reaches the surface of the spinal cord is governed entirely by fluid mechanics.

The fluid mechanics of drug spread in an oscillating flow field, as found in the intrathecal space, depends on a number of competing factors of different strength. These include:

- Molecular diffusion due to Brownian motion
- Enhanced diffusion due to the oscillating shear flow
- Steady streaming secondary flows induced by nonlinear effects
- Buoyancy effects due to density mismatch
- Injection parameters such as direction, flow rate and concentration

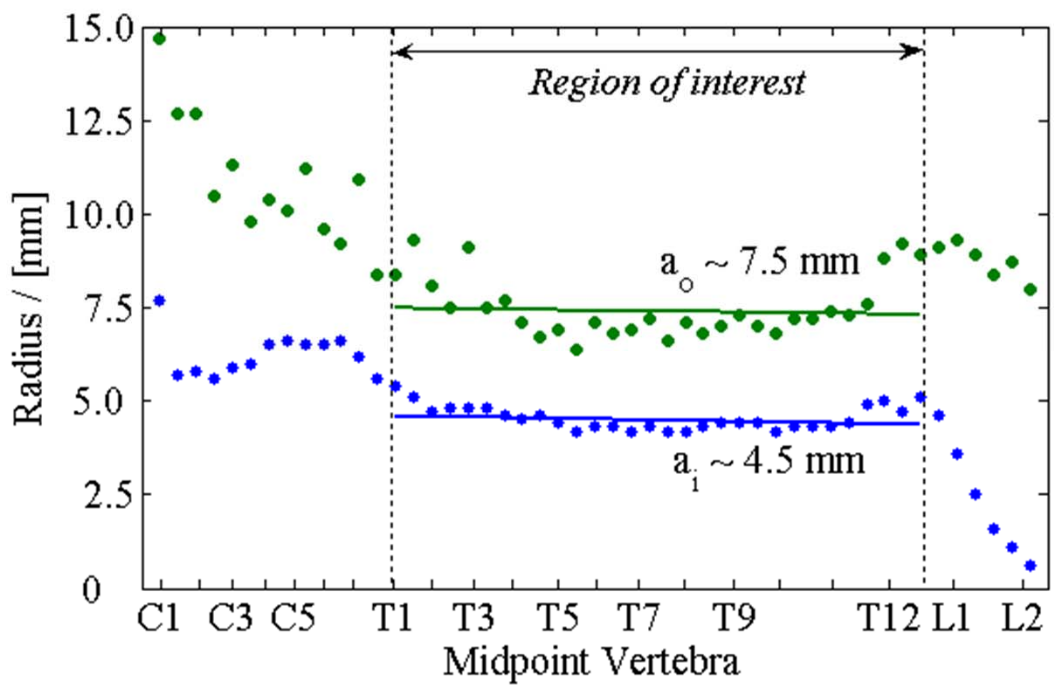
CSF flow parameters - Geometry of the subarachnoid Space

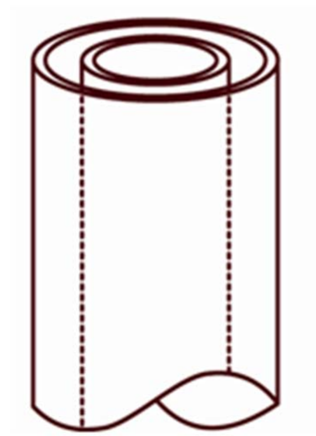


(1) Data extracted from Visible human database

CSF flow parameters - Modelling of the human spinal canal

As a first approximation the thoracic part of the subarachnoid space can be modeled by the annular gap between two concentric cylinders[1].

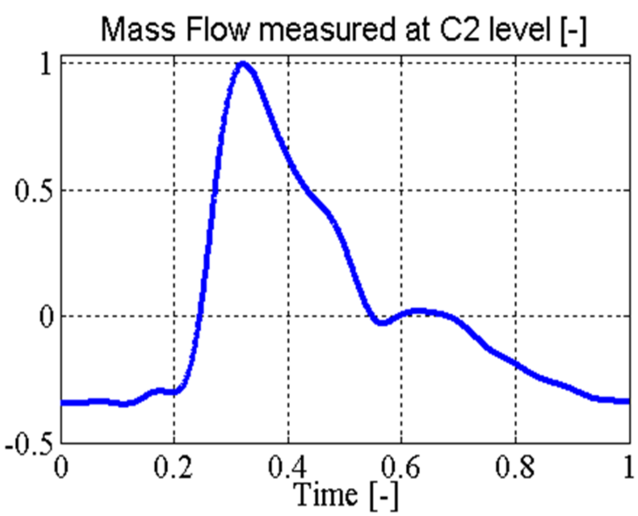




(1) Data extracted from Visible human database

CSF flow parameters - Oscillating velocity profile

The CSF mass flow has been measured in healthy subjects[1]



	Symbol	Model
Displacement amplitude (pp)	d_{osc}	< 13 mm
Displacement amplitude	$A_{osc} = \frac{d_{osc}}{r_H}$	< 4.3
Peak velocity	U_{osc}	80 mm/s
Angular frequency	$\omega = 2\pi f_{osc}$	4.5 – 12 rad/s
Relative viscosity	$\frac{\upsilon_{CSF}}{\upsilon_{H_2O}}$	0.7 – 1

Oscillation is primarily driven by heart beat, respiration and movement

(1) Loth *et al*. 2001, J. of Biomech. Eng.

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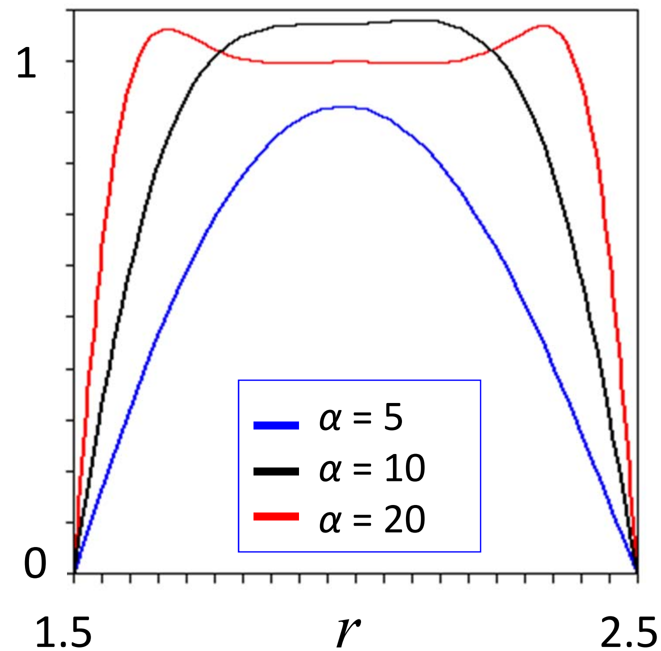
CSF flow parameters - Oscillating flow in an annular gap

	Definition	Model
Stokes' layer thickness	$\propto \sqrt{\frac{\upsilon}{\omega}}$	0.32 mm
Womersley #	$\alpha = r_H \sqrt{\frac{\omega}{\upsilon}}$	< 10
Reynolds #	$Re = \alpha^2 A_{osc}$	< 430
Stability Parameter	$\beta = \alpha\, A_{osc}$	< 43

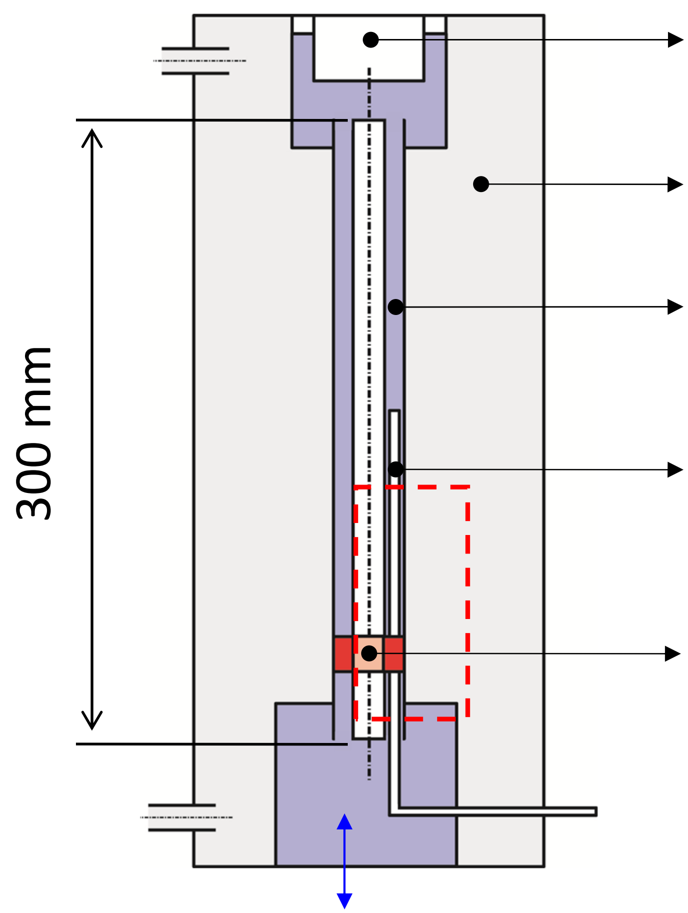
RMS velocity profile



- For relevant α, viscous effects dominate
- Based on the instantaneous Re and β, the flow is laminar and stable (1)

(1) Kurzweg U.H *et al*. 1989 Phys. Fluids 1(12), p. 1972.

Experimental laboratory model



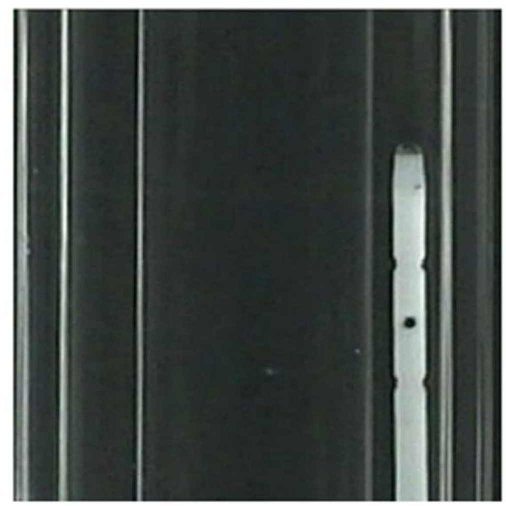
Optical access

Re-circulating temperature bath (37°C)

Annular gap formed by concentric glass tubes

Injection catheter

Annular piston



Molecular Diffusion - D_{mol}

- Molecular diffusion is driven by random Brownian motion
- Molecules move from areas of high concentration to lower concentration
- Influence in a flow is determined by Schmidt number: $Sc = \frac{\upsilon}{D_{\text{mol}}}$ (ratio between viscous to molecular diffusion)
- The molecular diffusion coefficient D_{mol} is extremely low for liquid-liquid diffusion, thus very high Schmidt number: Particle behaviour

$$D_{mol\ \text{bupi-CSF}} = 0.67 \cdot 10^{-9}\ \text{m}^2/\text{s}$$

- Theoretical spread due to molecular diffusion:

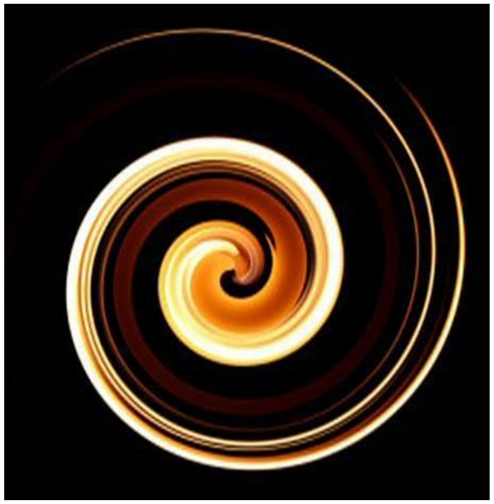
distance of *O*(cm) takes *O*(days)

- Molecular diffusion can be enhanced by increasing the temperature

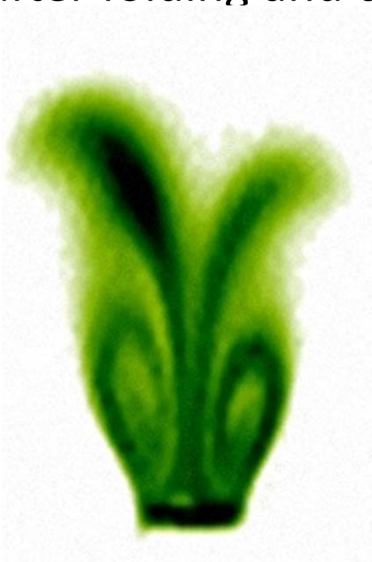
Molecular Diffusion - D_{mol}

- Vortical structures in the CSF stretch and fold the drug mass, increase its surface area to volume ratio, and distribute it through out the bulk liquid by convection

- Full homogenous mixing and interaction with surfaces is eventually achieved only through molecular diffusion after folding and convection



Coffee and cream



Injected drug bolus

Enhanced Mixing due to oscillating shear flow - D_{enh}

- First described by G.I. Taylor in 1953, to account for enhanced mixing in oscillatory shear flows. Elad *et al*. defined the ratio of enhanced diffusion D_{enh} to molecular diffusion D_{mol} as:

$$\frac{D_{enh}}{D_{mol}} \propto \sqrt{f_{osc}} \cdot A_{osc}^{2}$$

where f_{osc} : oscillation frequency = BPM / 60

A_{osc} : oscillation amplitude

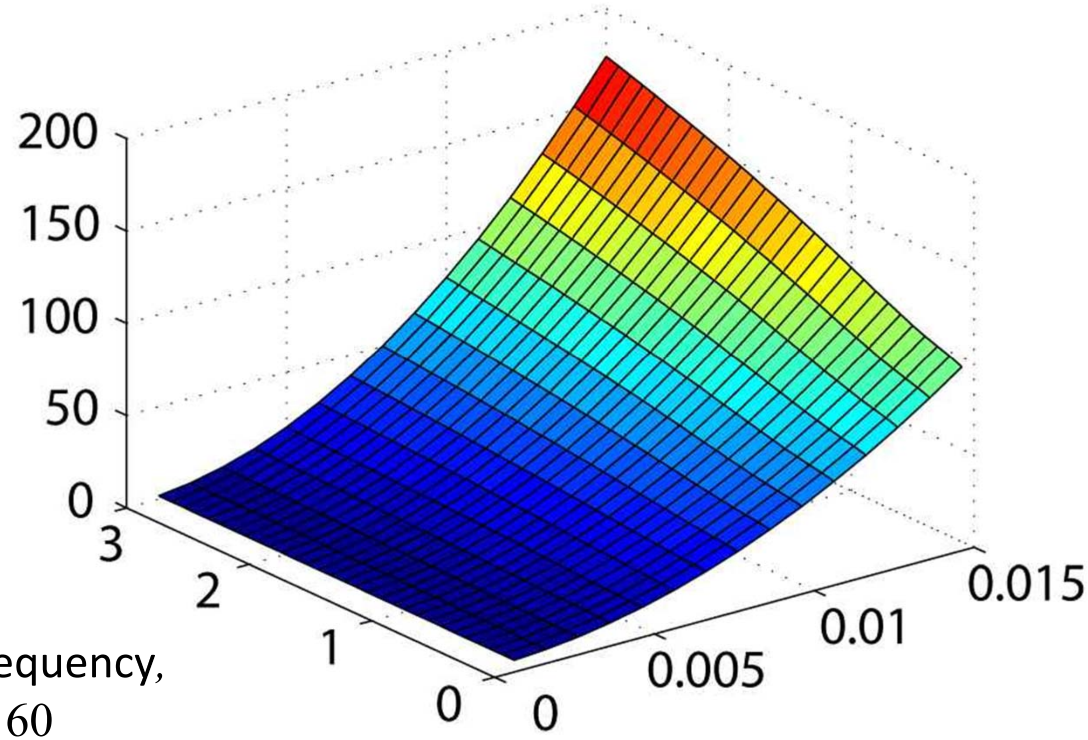
- Theoretical spread due to enhanced diffusion:

distance of *O*(cm) takes *O*(hours)

- Magnitude of enhanced diffusion can be increased by increasing heart rate and/or increasing blood pressure

Enhanced Mixing due to oscillating shear flow - D_{enh}

Ratio between axial and radial diffusion, $D_{\text{enh}} / D_{\text{mol}}$



CSF Oscillation frequency, f_{osc} [Hz] = BPM / 60

CSF Oscillation amplitude, A_{osc} [m]

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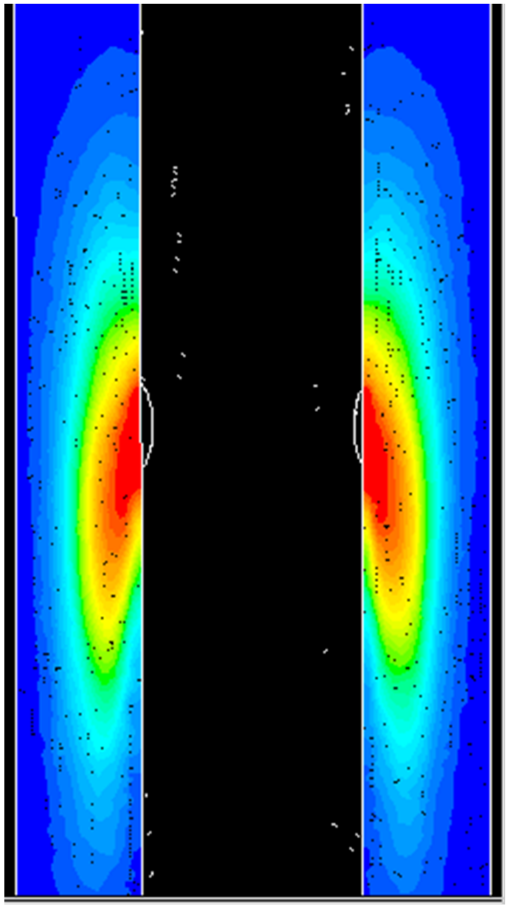
Enhanced Mixing due to oscillating shear flow - D_{enh}



Frequency: f_{osc} = 1 Hz = 60 BPM

Amplitude: A_{osc} = 4 mm

↓

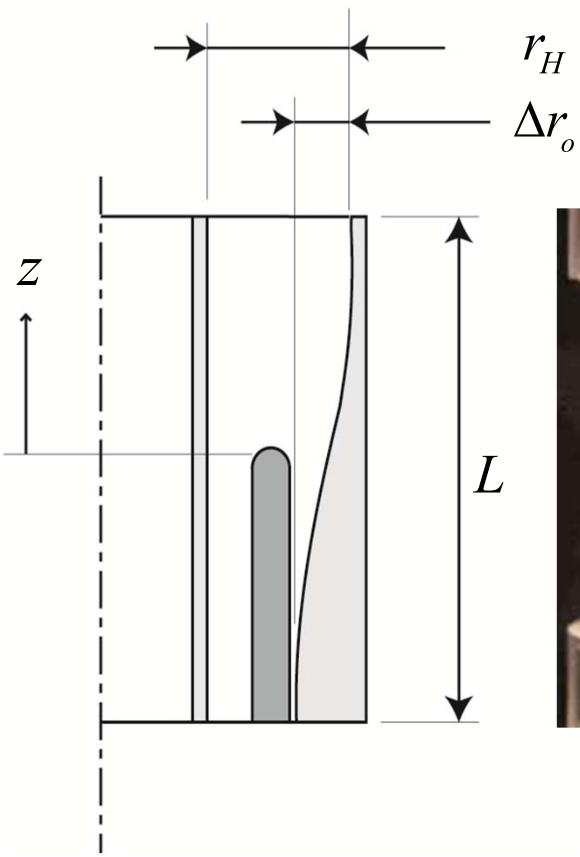
Results in an enhanced axial diffusion of the drug: D_{enh} / D_{mol} = **8**

Steady Streaming

- Steady streaming is the non-zero mean velocity induced by oscillatory flow when flowing over a curved surface, such as:
    - Changes in spinal canal cross-section
    - The presence of the catheter
    - Nerve branches, etc…
- Implies fluid elements do not return to their original positions after an oscillation period, thus forming vortices
- Each structural element creates its own vortex structure of different strengths, these then combine to form a complex vortex array
- Steady streaming velocity can be increased by increasing heart rate and/or increasing blood pressure
- The theoretical spread due to streaming depends entirely on the ‘shape’ of the perturbation

distance of O(cm) takes O(minutes)

Steady streaming – Subarachnoid space - Model



- Radius of a slowly varying outer wall representative of the vertebral structure modelled as

$$r = r_o \pm \frac{\Delta r_o}{2}\left(1 - \cos\left(\pi\, z / L\right)\right)$$

- Characteristic slope:

$$\delta = \frac{\Delta r_o}{L}$$

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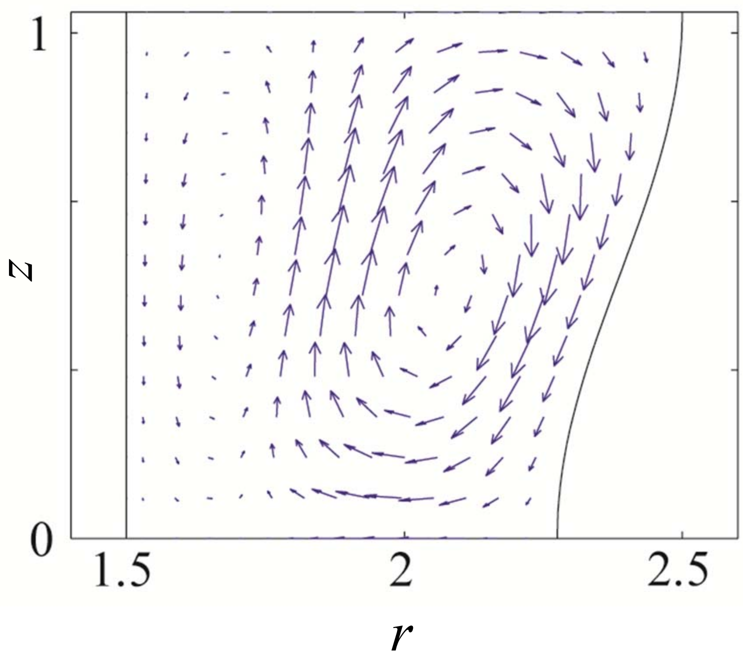
Steady streaming – Subarachnoid space - Theoretical

Axi-symmetric analytic model



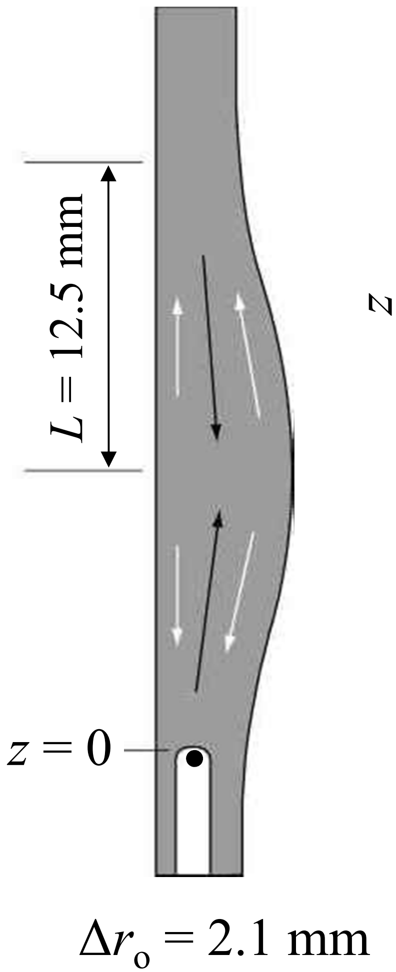
- For $\delta < 1$, $\delta.Re < 1$ and moderate α, the steady streaming velocity on the midline of the geometry is in the direction of the wider section, and in the opposite direction near the walls

- This was theoretically shown using a standard perturbation analysis for annular and planar gaps [1,2]

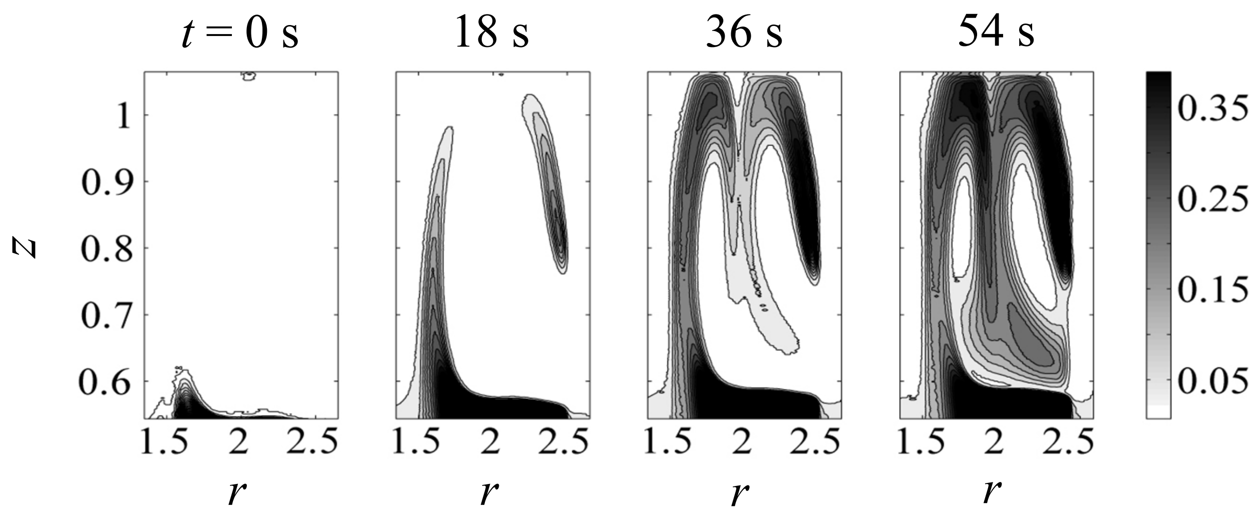
(1) Sarkar, A. and Jayaraman,G. J. of Biomechanics, 31(9):781-791, 1998

(2) Grotberg, J.B. JFM, 141(APR):249-264, 1998.

Steady streaming – Subarachnoid space - Experimental



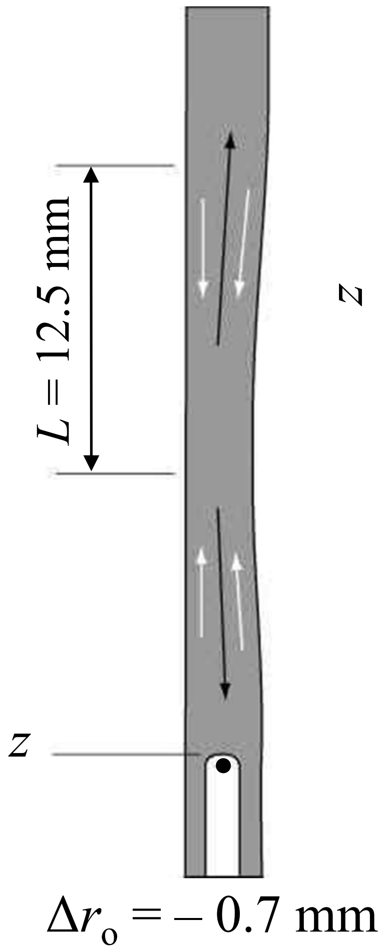
Effect of catheter location



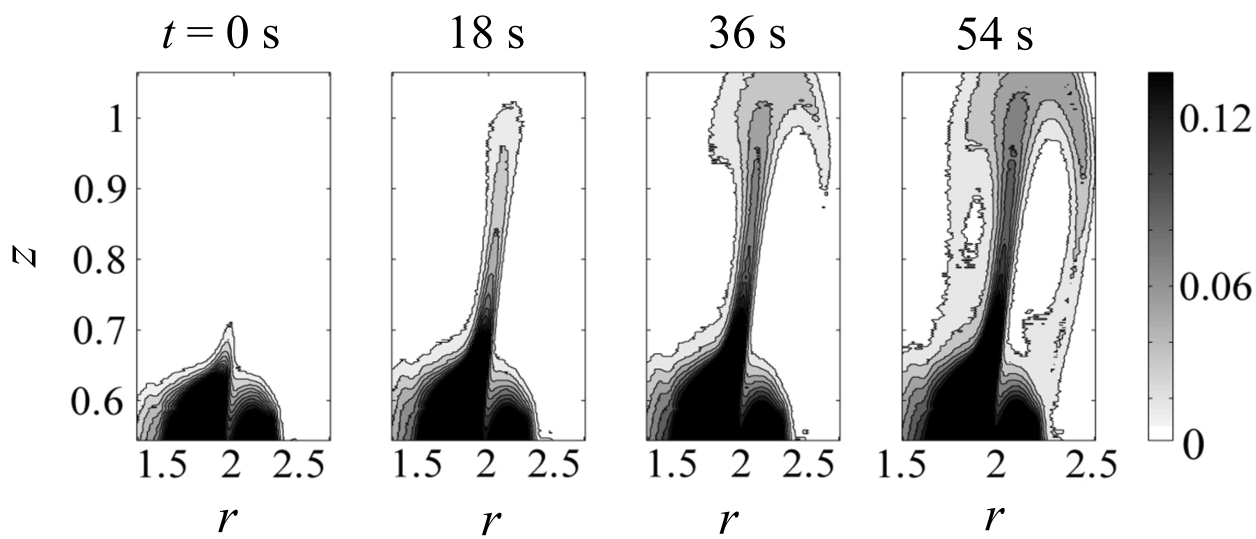
f_{osc}= 1 Hz = 60 BPM, A_{osc}= 5.1 mm

- The dye follows the theoretical streamlines of the steady streaming
- Although steady streaming velocities are small, they extend over the entire varying cross section

Steady streaming – Subarachnoid space - Experimental



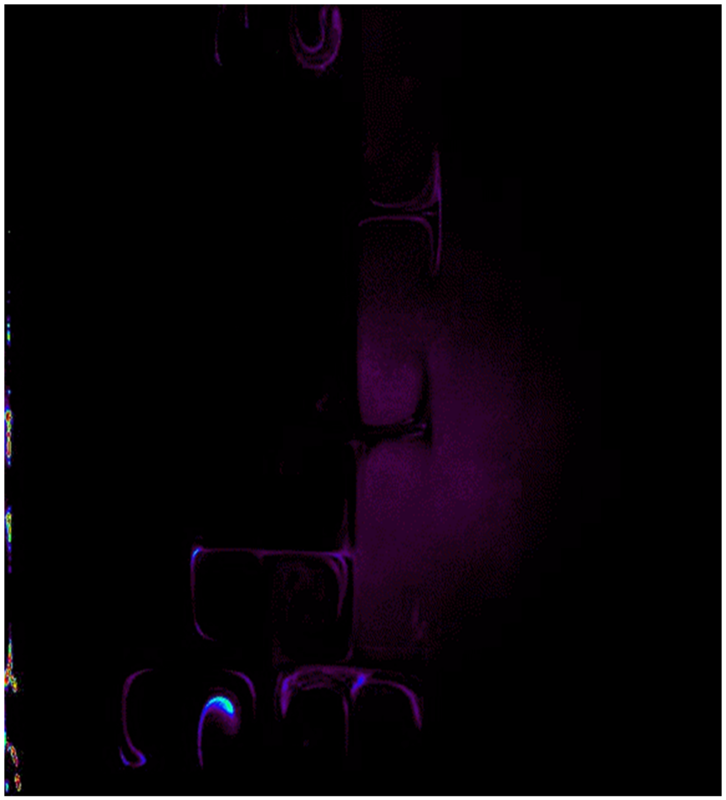
Effect of catheter location



f_{osc}= 1 Hz = 60 BPM, A_{osc}= 5.1 mm

- Even for smaller variations of cross section, the influence of steady streaming on dispersion is an order magnitude larger than the influence of enhanced diffusion

Steady streaming – Subarachnoid space – Vortex array mixing

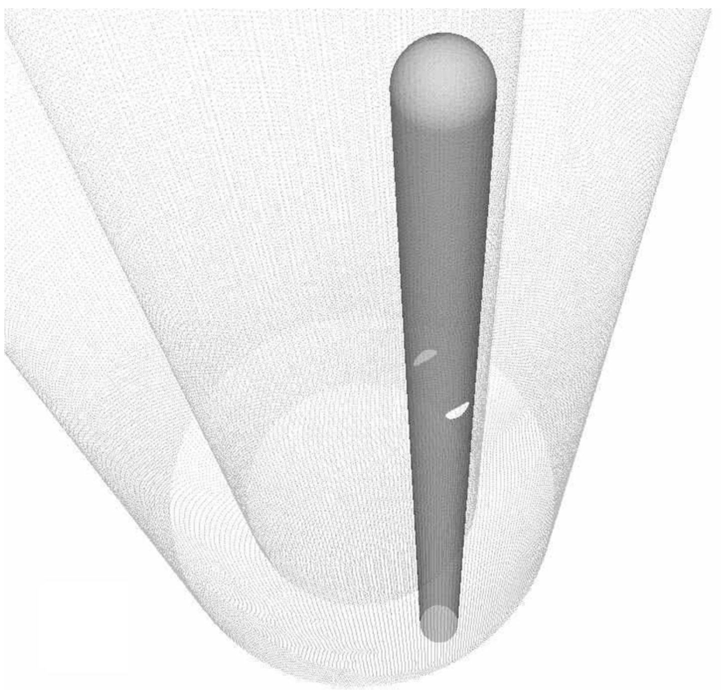


Injection location

- There is no requirement for a net axial flow of CSF, or even its creation and absorption
- Each anatomical feature generates its own vortex structure due to steady streaming
- These structures then combine to form complex vortex arrays, thus creating *'fluid paths'* within the enclosed intrathecal space
- These can rapidly transport the injected drug through the intrathecal space

Steady streaming – Catheter - Numerical

Geometry and computation mesh

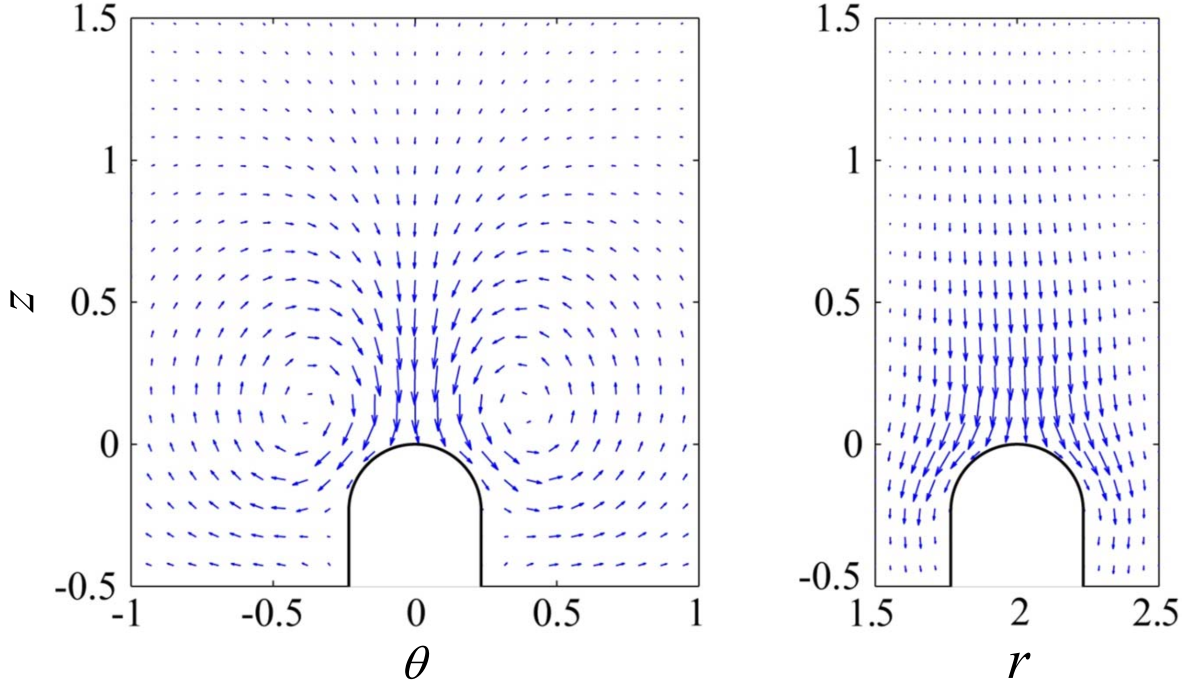


Numerical computations

- 3D model of experiment
- Perfectly straight catheter
- Singly harmonic oscillation waveform
- Straight walls

Steady streaming – Catheter - Numerical

- The mean velocity around the catheter tip is 3 dimensional
- A 'mushroom shaped' vortex is formed at the catheter tip
- The mean velocity directly above the catheter is downwards



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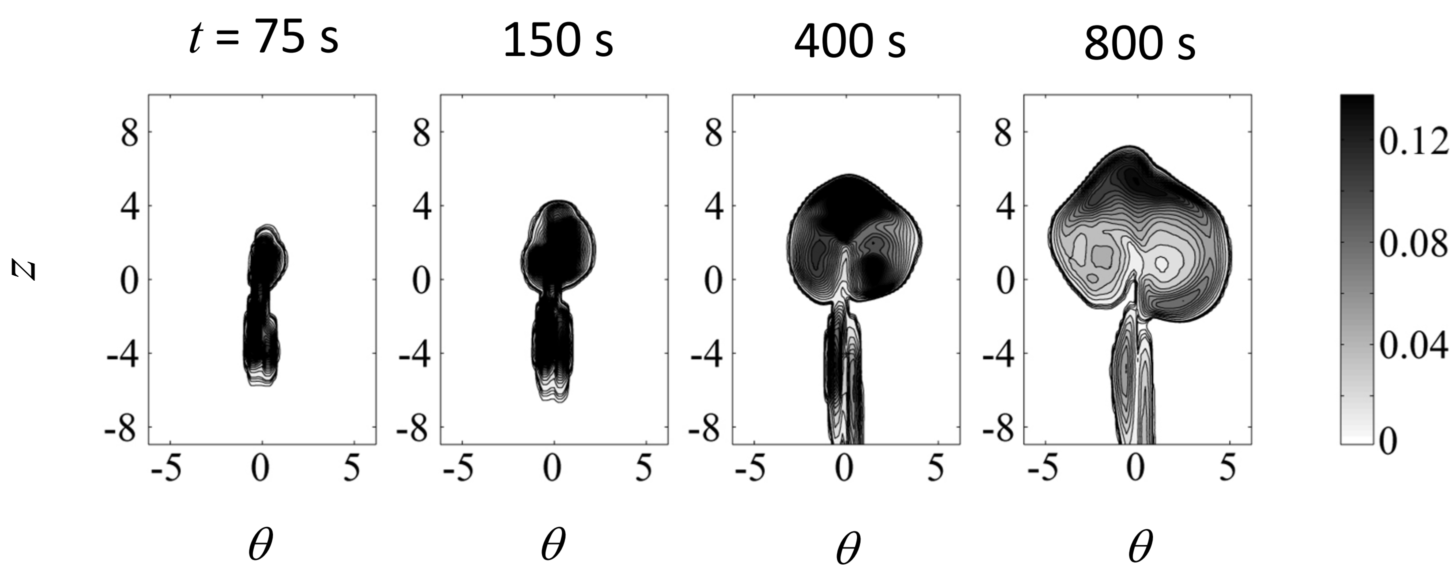
Steady streaming – Catheter – Experimental injection profile

Bolus injection rate of 50 microlitres in 143 seconds, oscillation 1 Hz = 60 BPM

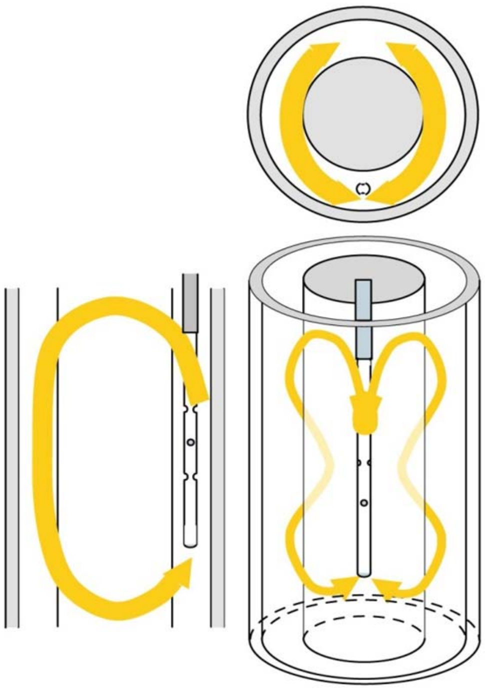
Note at these realistic drug flow rates there is no jet!

Steady streaming – Catheter - Experimental

- As numerically predicted, the dye has a tendency to form a mushroom shaped cloud around the catheter tip, and to become pulled down the length of the catheter
- Example: Bolus 60 µl @ 24 µl/min, f_{osc}= 1 Hz = 60 BPM, A_{osc}= 5.1 mm
- Uniform annular gap



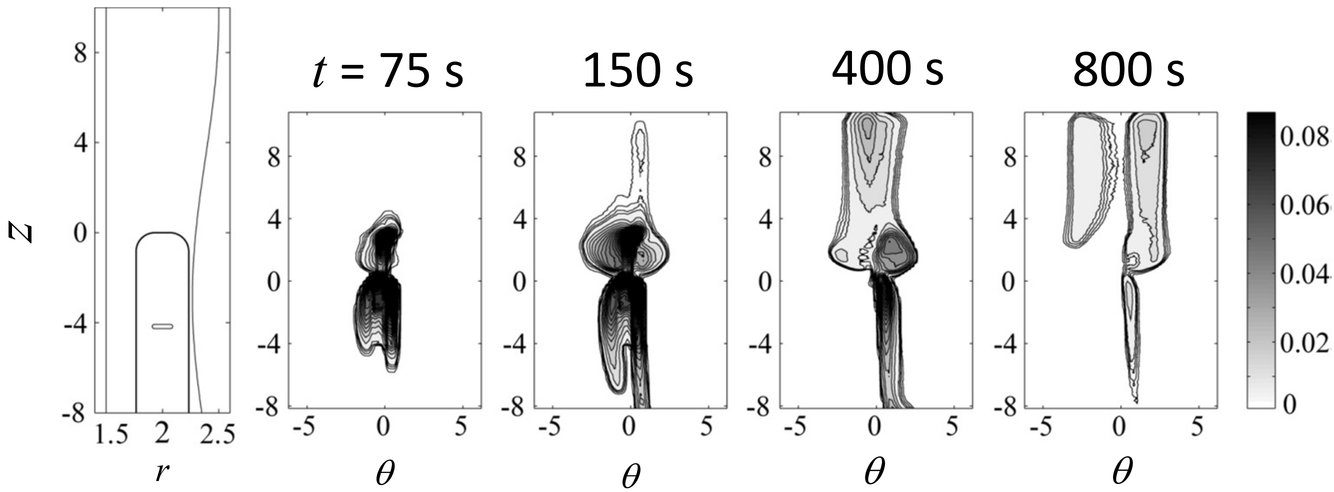
Steady streaming – Catheter – Experimental 3D



Due to steady streaming, the drug is convected around the spinal cord axis

Steady streaming – Catheter & subarachnoid space - Experimental

- Steady streaming velocities induced by subarachnoid geometry are small. However, the mushroom cloud of drug at the catheter tip becomes drawn up into the wider cavity, thus increasing the axial dispersion of the drug relative to a uniform annular geometry
- Once again, a large volume of the injected drug is drawn down the length of the catheter soon after injection
- Example: 60 µl @ 24 µl/min, f_{osc}= 1.5 Hz = 90 BPM, A_{osc} = 4.49 mm



Buoyancy effects

- Effect of buoyancy related to difference in density $\Delta\rho$:

$$\propto \left(\frac{\Delta\rho}{\rho}\right)^2$$

- Buoyancy is notoriously difficult to quantify:
  - Drug 'cloud' deforms when traveling
  - Drug diffusion reduces local baricity

- Buoyancy can radically increase initial drug spread along the spinal canal depending on the position of the patient. However, it is hard to control.

O(cm) is O(minutes)

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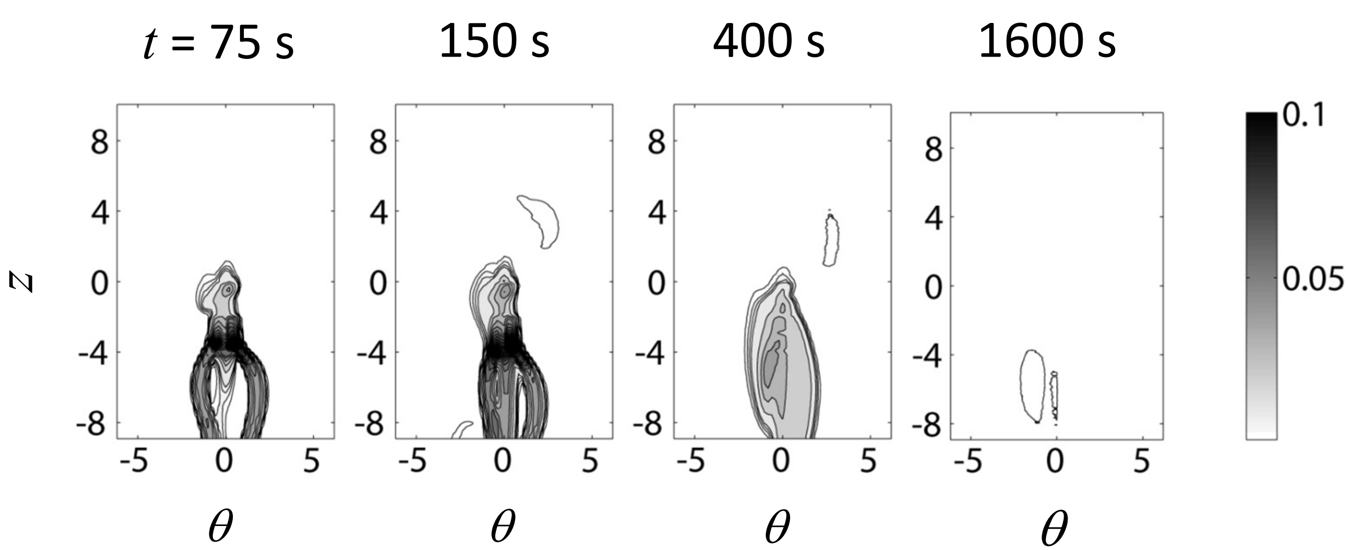
Buoyancy effects

- High injection rate, high A_{osc} , 0.3% glucose
- Dye travels downwards due to its buoyancy



Summary of drug spread mechanisms

Mechanism	***Typical time scale to spread 1cm***
Molecular diffusion	**Day**
Enhanced diffusion	**Hour**
Steady Streaming	**Minutes**
Buoyancy effects	**Minutes**

Conclusions

- Geometry induced steady streaming is the primary driver of drug spread
- Fluid dynamic 'vortical structures' are ultimately responsible for drug spread in the subarachnoid space, they provide the roads
- These structures are imposed purely by the geometry of the subarachnoid space, the catheter, and factors affecting the characteristics of the CSF oscillation
- The actual long-term spread of the drug for a given case depends sensitively on the flow rate, location, and direction of the injected drug into these vortical structures. Drug is the car guided by the roads
- Drug spread is a non-linear phenomena and therefore very sensitive to conditions
- Patient tuned therapy requires: accurate patient anatomical data, and knowledge of the exact catheter and injection port locations

Thank You

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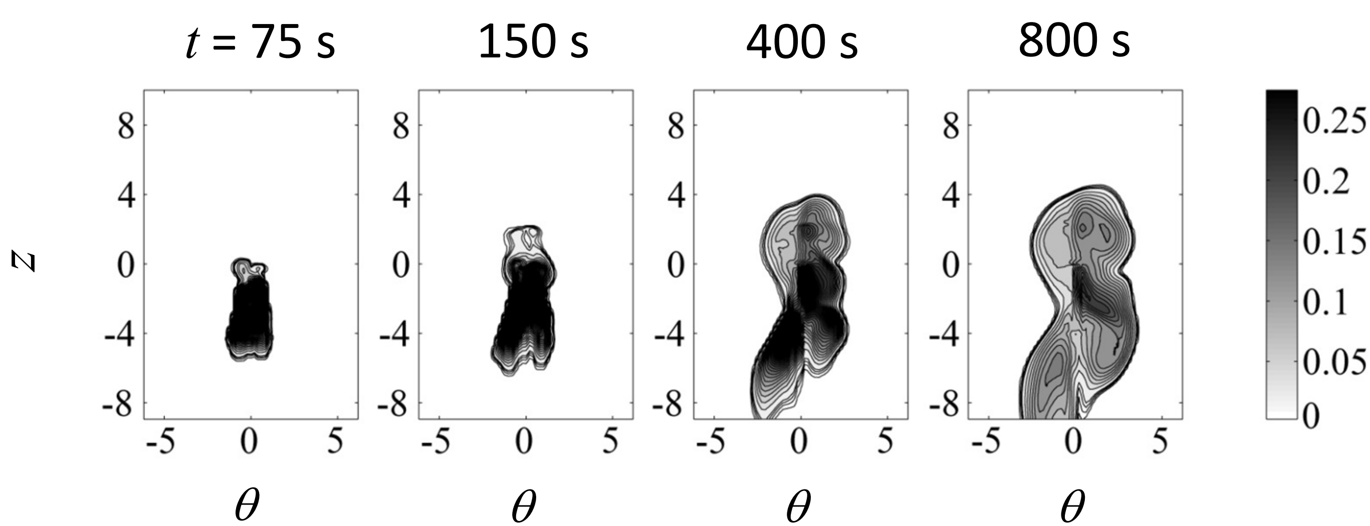
Steady streaming – Catheter - Experimental

Effects of ‘perturbations’ on drug spread

- Same injection/oscillation characteristics as before, but different catheter, orientation and position
- Uncontrollable parameters have a great influence on drug spread
- Parameters include: Catheter inclination, injection direction and location, injection rate…



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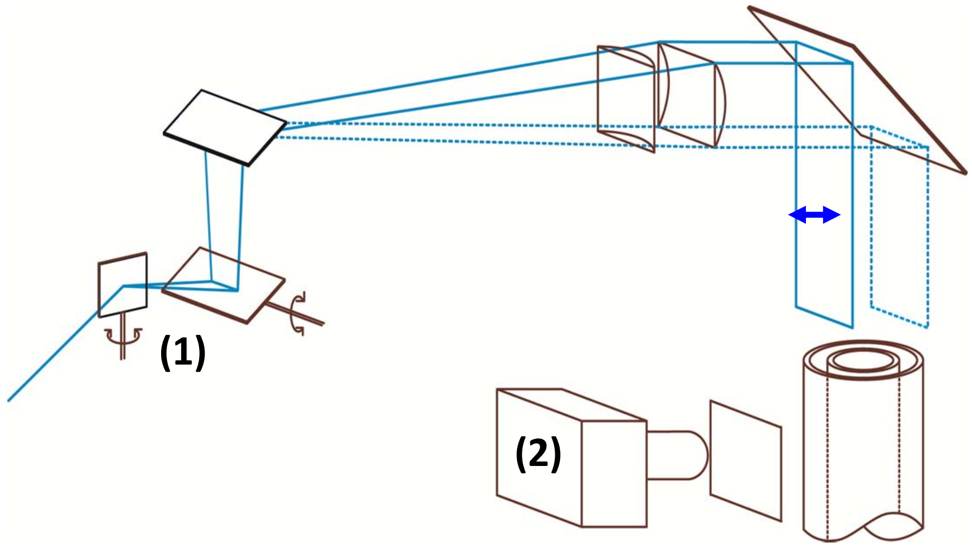
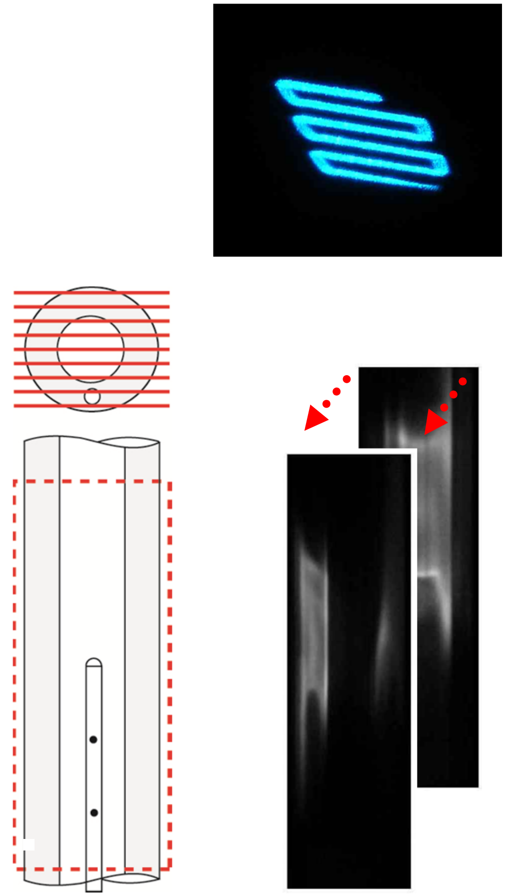
Experimental laboratory model





- A fluorescent dye used to model the drug
- 3 dimensional volumetric spread of injected drug was recorded with time, using a (1) Galvanometric rotating mirrors at 800 Hz and (2) high speed camera at 400 Hz