Department of Engineering Science
Institute of Biomedical Engineering
Fluidics and Biocomplexity Group
St. Cross College

Water Transport in Brain:

Cerebrospinal Fluid, Capillaries and Glial Cells

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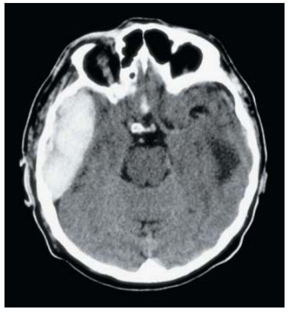
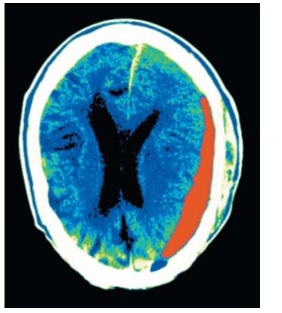
(M. McKinley, V. D. O'Loughlin, Human Anatomy 7th)

Cerebrospinal Fluid (CSF)



Epidural

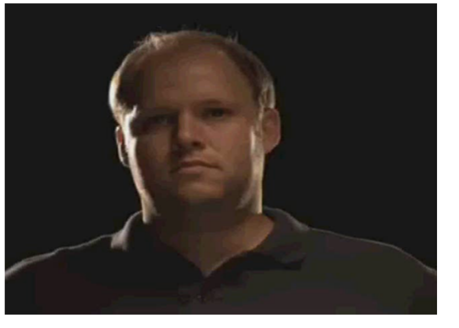


Subdural haemorrhage

- Buoyancy
  - Reduce the net weight from 1400 g to 25 g
- Protection
  - Prevent contact between delicate neural structures and the surrounding bones
  - Protect from injuries, EX: Jolt, hit
- Transport
  - Nutrients, Chemical messengers, and Metabolic waste products

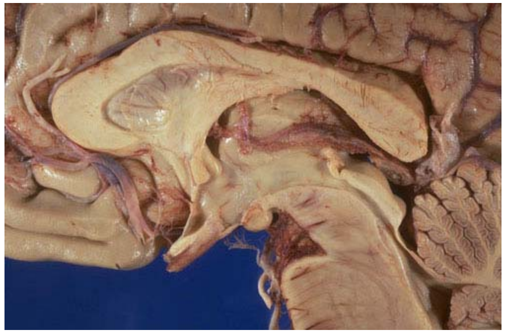
http://blog.iilm.edu/2012/11/the-rest-is-history/footer_newton/

http://egoscueportland.wordpress.com/2010/12/26/the-cause-and-effect-of-football-tackling/

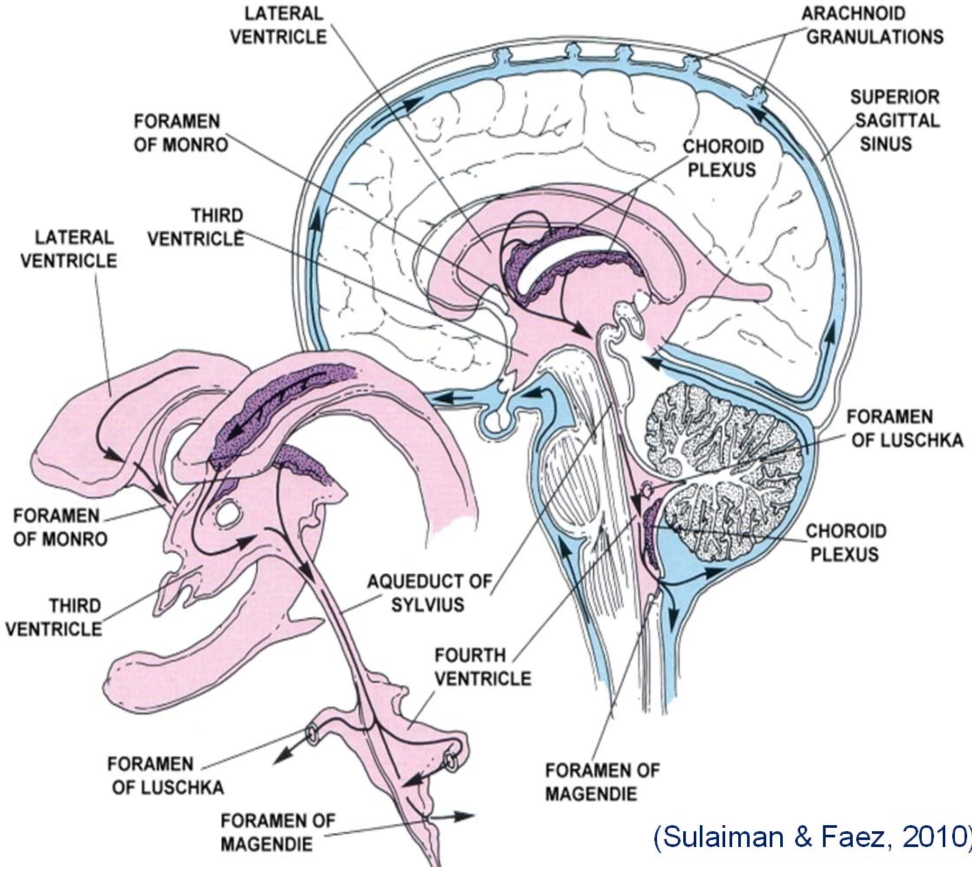


http://www.expertboxing.com/boxing-strategy/counter-punching/7-easy-boxing-counters-punches

Cerebrospinal Fluid (CSF)

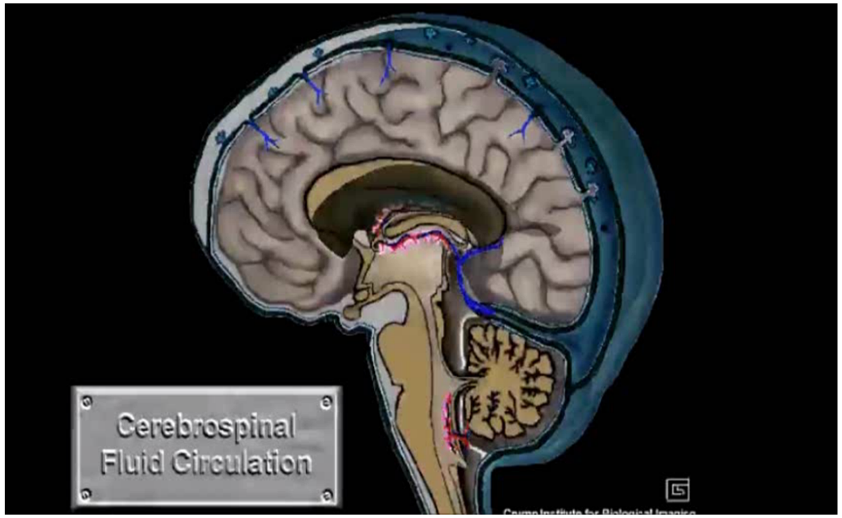


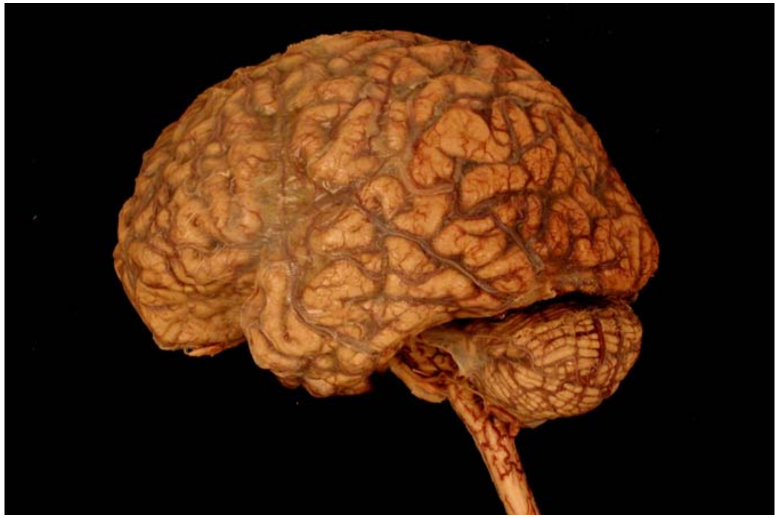
- The choroid plexus produces CSF at a rate of around 500 ml/day
- The total volume of CSF at any given moment is around 150 ml
- Entire volume of CSF is replaced approximately every 8 hours
- CSF circulation path

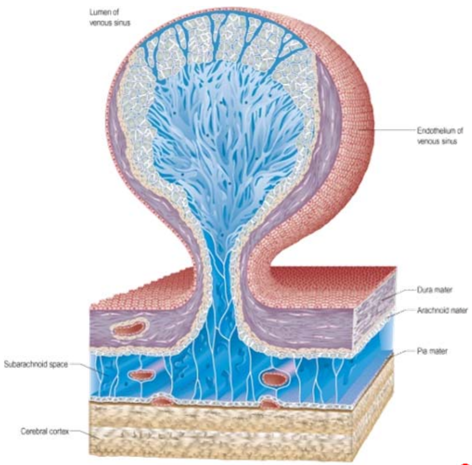


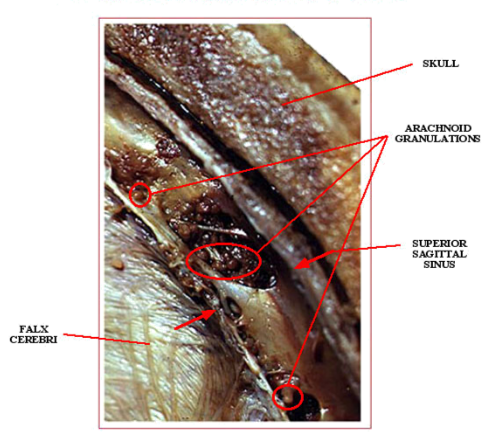
(Sulaiman & Faez, 2010)

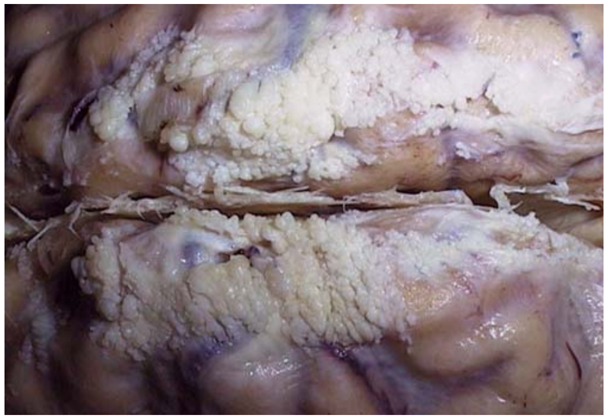
Cerebrospinal Fluid (CSF) - Circulation



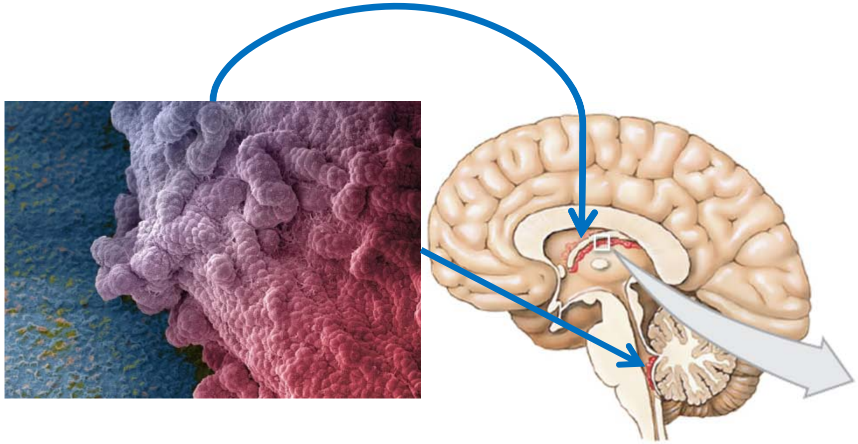


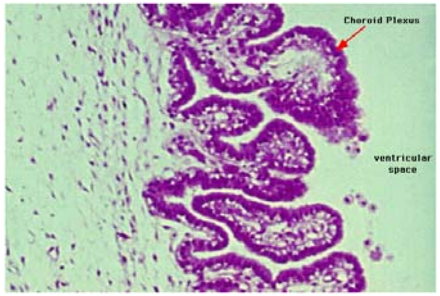


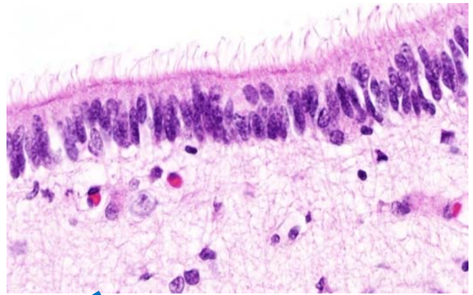


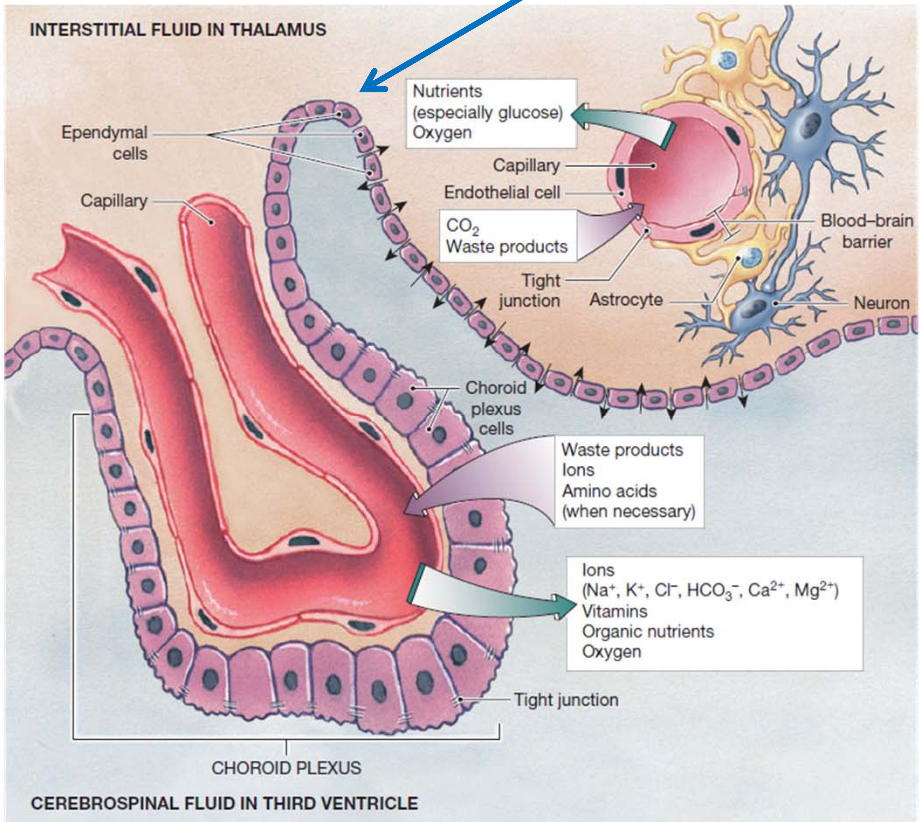


Choroid Plexus (CP)







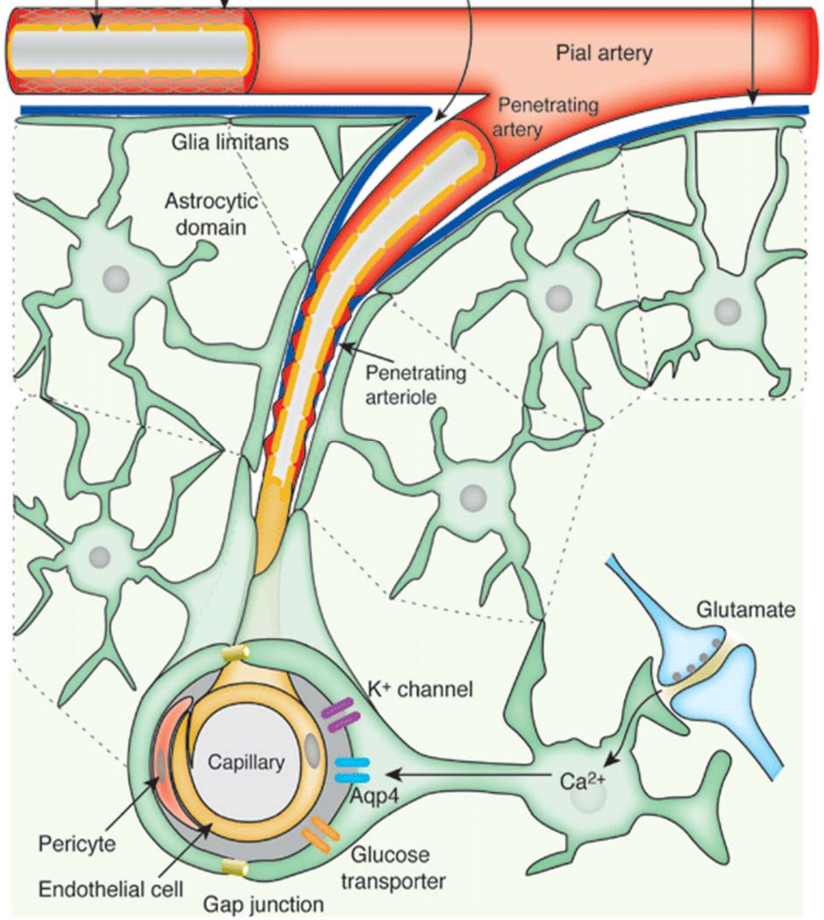


(M. McKinley and V. D. O'Loughlin, Human Anatomy 3rd)

- There are four choroid plexi in each ventricles.
- The CP acts as a blood-CSF barrier (filtration system).
- The CP plays an important role to maintain the delicate extracellular environment

Capillaries

- Around 5-10 µm in diameter
- Smallest blood vessels in brain
- Connect arterioles and venulae
- Site of mass transfer between blood and surrounding tissue, such as oxygen, carbon dioxide, water, ions and so on
- The regulation of behaviour via water channel, AQP4, is one of important issues that we are considering in this research



Costantino Iadecola & Maiken Nedergaard
Nature Neuroscience **10**, 1369 - 1376 (2007)

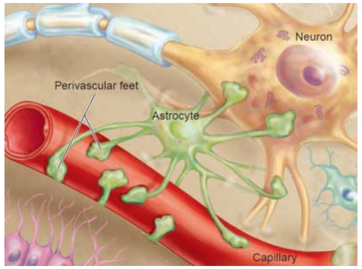
Glial Cells (Neuroglia)

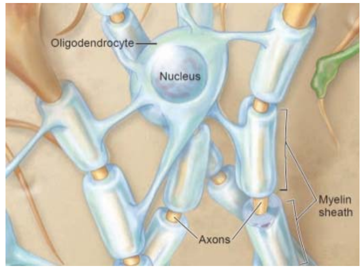
Central Nervous System (CNS)

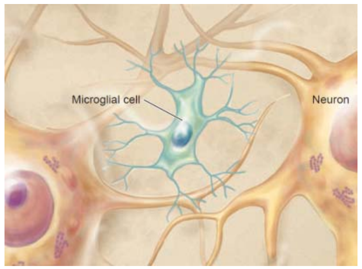
- Astrocytes
  - Maintain Blood-Brain Barrier
  - Provide structural framework
  - Regulate ions and nutrients
  - Absorb and recycle neurotransmitters
- Oligodendrocytes
  - Mylinate CNS axons
  - Provide structural framework
- Microglia Cells
  - Remove cell debris, waste products, pathogens by phagocytosis
- Ependymal Cells
  - Assist for producing and circulating CSF

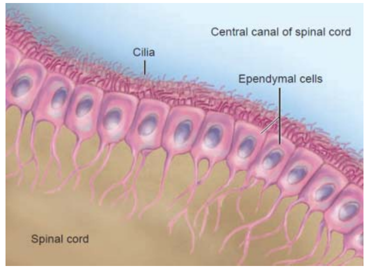
Peripheral Nervous System (PNS)

- Satellite Cells
- Schwann Cells





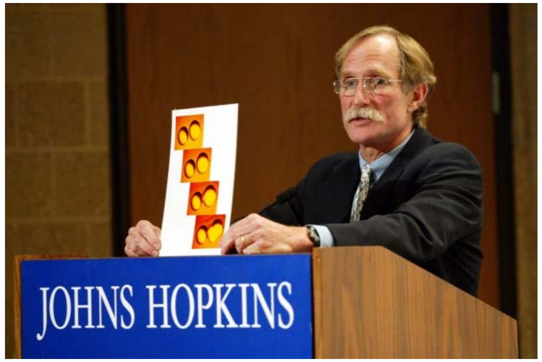




(M. McKinley and V. D. O'Loughlin, Human Anatomy 3rd)

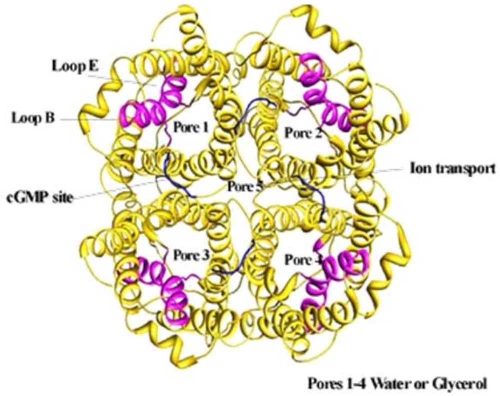
Aquaporins (AQPs)

- Discovery aquaporin – Peter Agre
  - the biochemical properties of the Rh proteins from the erythrocyte membrane
  - Reveal the homology with MIP by cloning the full-length cDNA sequence

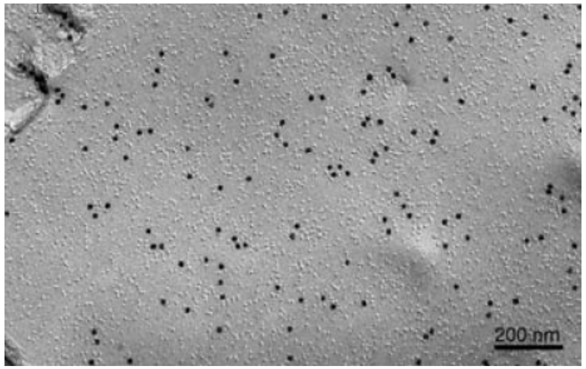


(http://www.hopkinsmedicine.org/press/2003/october/031008a.htm)

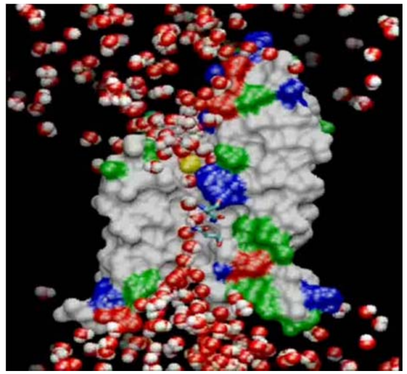
- The structure of aquaporin



(PubMed:18678926, 2008)

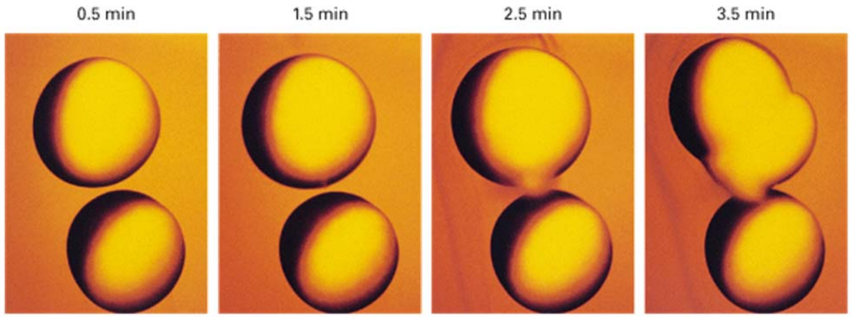


(Suzuki H, Nishikawa K, Hiroaki Y, Fujiyoshi Y., 2008)



(TCB Group, UIUC)

Aquaporins (AQPs)



(H. Lodish, Molecualr Cell Biology 7th, 2012)

- Effects of AQPs
  - Expression of water permeability of AQP 1 in *Xenopus laevis* oocytes
  - The upper oocytes were injected with mRNA encoding AQP in each photo transfer from an isotonic salt solution to a hypotonic salt solution
  - The lower oocytes in each photo are normally not permeable to water (without AQP 1 expression)
  - From 2.5 min to 3.5 min, the lower oocytes continue to keep their original shape because of impermeability. However, the upper oocytes continue to swell due to osmotic water flux-in. This phenomenon implies that AQP is a water channel protein (WCP)

Aquaporins (AQPs)

- Phylogenetic tree of Aquaporins

Mammalian Aquaporins	Mammalian Aquaglyceroporins	Mammalian Superaquaporins	Other Aquaporins
AQP0	AQP3	AQP11	SoPIP2;1 Plant aquaporin
AQP1	AQP7	AQP12	GlpF Bacterial Aquaglyceroporin
AQP2	AQP8		AQPZ Bacterial Aquaporin
AQP4	AQP9		AQPM Archaebacterial aquaporin
AQP5	AQP10		
AQP6			

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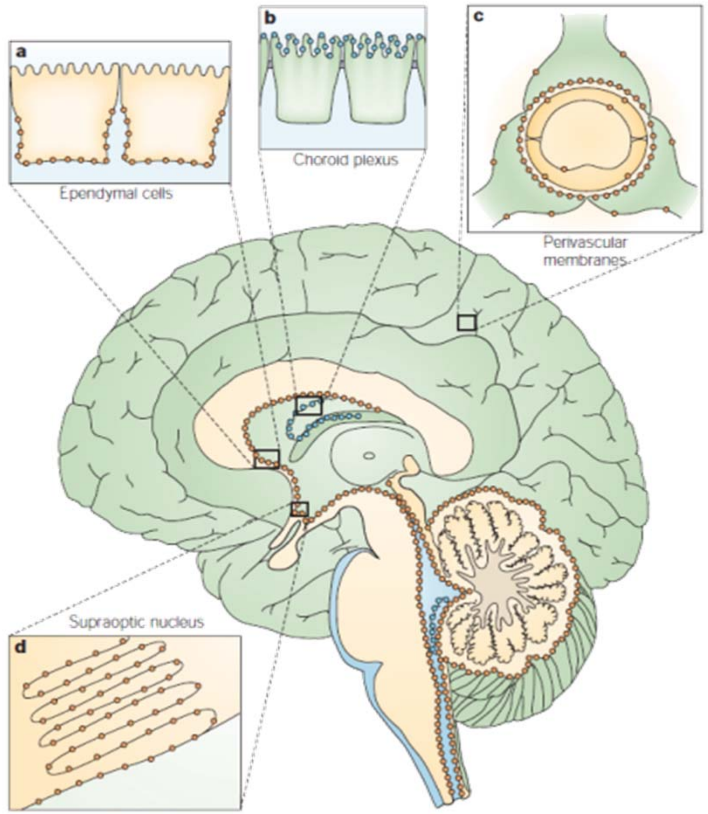
Aquaporins (AQPs)

AQPs in CNS	Astrocytes	AQP1, AQP3, AQP4, AQP5, AQP9
	Oligodendrocytes	AQP8
	Microglia cells	AQP9
	Ependymal cells	AQP1, AQP4, AQP9
	Neurons	AQP1, AQP5, AQP8

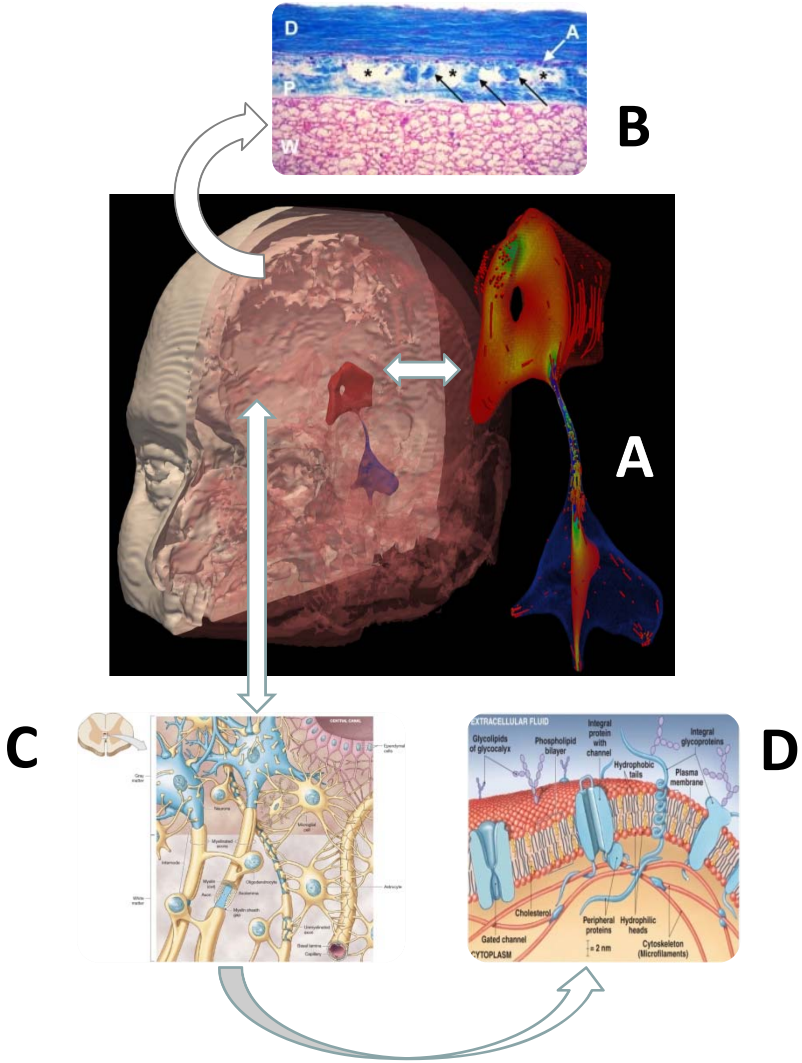


Owler, B, Pitham, T, Dongwei, W. (2010). Aquaporins: relevance to cerebrospinal fluid physiology and therapeutic potential in hydrocephalus. *Cerebrospinal Fluid Research* . 7 (15), 1-12

Multiscale Platform

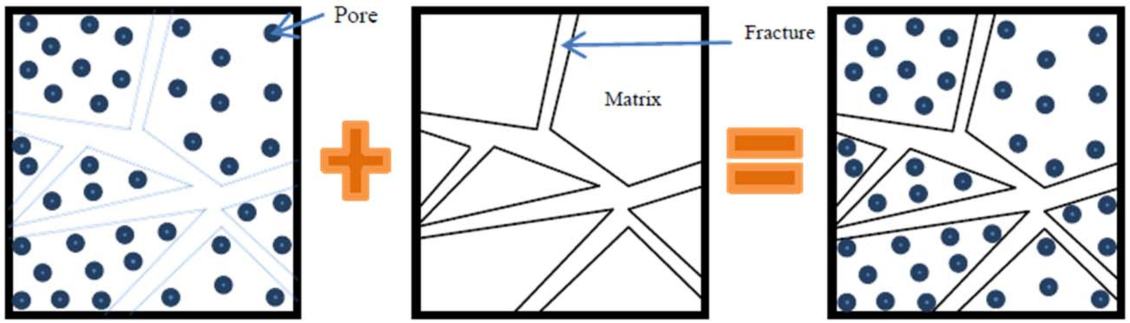
The inherent multiscalarity of the cerebral water flow environment

ventricles and aqueducts	the subarachnoid space	Glial cells and capillaries	Channels and tight junctions
A:cm-mm	B:mm-µm	C:µm-nm	D:nm-below



Multiple-Network Poroelastic Theory (MPET) Model

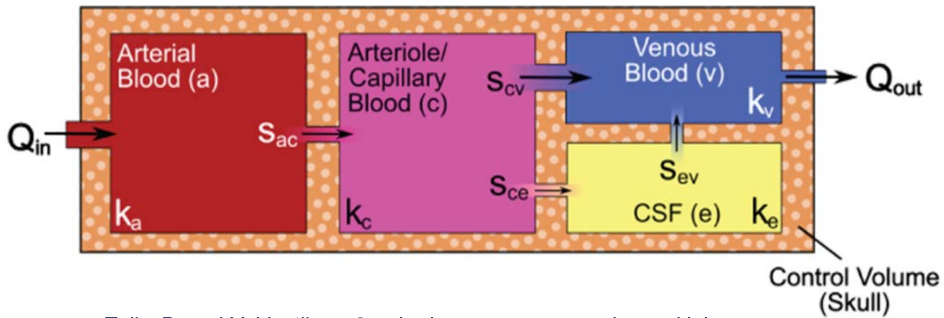
- The concept of MPET comes from geotechnical engineering in order to describe fluid transport phenomena in soil and rock
- It is assembled by deformable elastic matrix and multiple fluid networks of pores and fissures
- This porous media model vary with porosity and permeability
- Equations are built by treating the different fluid networks as separate compartments which are in communication each other



Biological MPET Model

- The concept of MPET model can capture the dynamics of all fluids transfer in the brain
- Extend to include independent networks for cerebral blood and CSF
- Distinguish four network compartments

1. Arterial blood
2. Arteriole/Capillary blood
3. Cerebrospinal fluid
4. Venous blood



Tully, B. and Y. Ventikos, *Cerebral water transport using multiple-network poroelastic theory: application to normal pressure hydrocephalus.* Journal of Fluid Mechanics, 2011

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Biological MPET Model

- Two governing equations of motion for a unit volume

a. Solid-fluid equation of motion

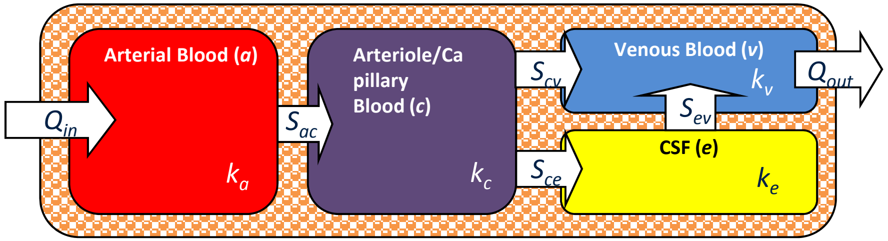
$$\nabla \bullet \sigma^{M} + \rho_{f}\left(f^{b} - \frac{\partial^{2} x}{\partial t^{2}} \right) - \sum_{a=1}^{A} \alpha^{a} \nabla p^{a} = 0$$

b. Fluid equilibrium and conservation (each network *A= 1,…,a*)

$$\frac{1}{Q^{a}} \frac{\partial p}{\partial t} + \alpha^{a} \frac{\partial (\nabla \bullet x)}{\partial t} - \sum_{b=1, b\neq a}^{A} \dot{S}_{b\to a} + \nabla \bullet \left[\kappa^{a} \bullet \rho_{f}^{a} \left(f^{b} - \frac{\partial^{2} x}{\partial t^{2}} \right) - \kappa^{a} \bullet \nabla p^{a} \right] = 0$$

Setting *A=4* from previous slide and assuming a linear stress-strain relationship, we have following *u-p* formulations

Biological MPET Model



- Linear stress strain equation (Hooke's law) inverted for stress and then stress is represented as a function of displacement and where the permeability is isotropic

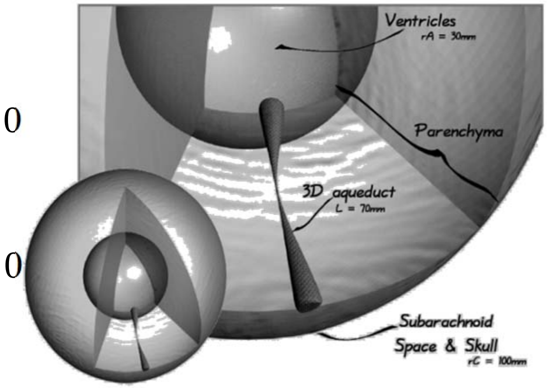
$$\nabla \bullet \boldsymbol{\sigma}^M = G\nabla^2 \boldsymbol{x} + \frac{G}{1-2\nu}\nabla(\nabla \bullet \boldsymbol{x}) \quad \nabla \bullet \boldsymbol{\sigma}^M + \rho_f\left(\boldsymbol{f}^b - \ddot{\boldsymbol{x}}\right) - \alpha^a \nabla p^a - \alpha^e \nabla p^e - \alpha^c \nabla p^c - \alpha^v \nabla p^v = 0$$

$$\frac{1}{Q^a}\frac{\partial p^a}{\partial t} + \alpha^a \frac{\partial(\nabla \bullet \boldsymbol{x})}{\partial t} - \dot{S}_{c\to a} - \dot{S}_{e\to a} - \dot{S}_{v\to a} + \nabla \bullet \left[\kappa^a \bullet \rho_f^a\left(\boldsymbol{f}^b - \ddot{\boldsymbol{x}}\right) - \kappa^a \bullet \nabla p^a\right] = 0$$

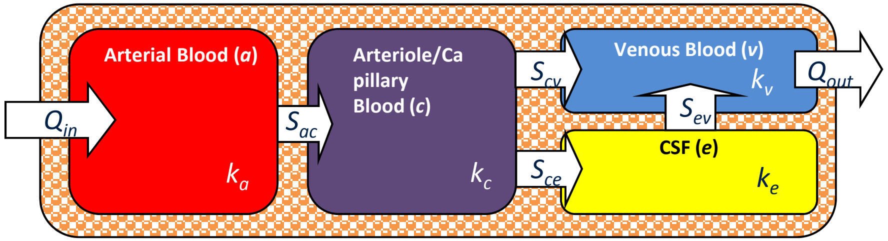
$$\frac{1}{Q^e}\frac{\partial p^e}{\partial t} + \alpha^e \frac{\partial(\nabla \bullet \boldsymbol{x})}{\partial t} - \dot{S}_{a\to e} - \dot{S}_{c\to e} - \dot{S}_{v\to e} + \nabla \bullet \left[\kappa^e \bullet \rho_f^e\left(\boldsymbol{f}^b - \ddot{\boldsymbol{x}}\right) - \kappa^e \bullet \nabla p^e\right] = 0$$

$$\frac{1}{Q^c}\frac{\partial p^c}{\partial t} + \alpha^c \frac{\partial(\nabla \bullet \boldsymbol{x})}{\partial t} - \dot{S}_{a\to c} - \dot{S}_{e\to c} - \dot{S}_{v\to c} + \nabla \bullet \left[\kappa^c \bullet \rho_f^c\left(\boldsymbol{f}^b - \ddot{\boldsymbol{x}}\right) - \kappa^c \bullet \nabla p^c\right] = 0$$

$$\frac{1}{Q^v}\frac{\partial p^v}{\partial t} + \alpha^v \frac{\partial(\nabla \bullet \boldsymbol{x})}{\partial t} - \dot{S}_{a\to v} - \dot{S}_{e\to v} - \dot{S}_{c\to v} + \nabla \bullet \left[\kappa^v \bullet \rho_f^v\left(\boldsymbol{f}^b - \ddot{\boldsymbol{x}}\right) - \kappa^v \bullet \nabla p^v\right] = 0$$



Biological MPET Model



- The one-dimensional spherically symmetric system equations:

$$\frac{\partial^2 x}{\partial r^2}+\frac{2}{r}\frac{\partial x}{\partial r}-\frac{2}{r^2}x=\frac{1-2\nu}{2G(1-\nu)}\left[\alpha^a\frac{\partial p^a}{\partial r}+\alpha^e\frac{\partial p^e}{\partial r}+\alpha^c\frac{\partial p^c}{\partial r}+\alpha^v\frac{\partial p^v}{\partial r}-\rho_f\left(f_r^b-\ddot{x}\right)\right]$$

$$\frac{1}{Q^a}\frac{\partial p^a}{\partial t}+\alpha^a\frac{\partial}{\partial t}\left(\frac{\partial x}{\partial r}+\frac{2}{r}x\right)-\dot{S}_{c\to a}-\dot{S}_{e\to a}-\dot{S}_{v\to a}+\frac{2}{r}\rho_f^a\left(f_r^b-\ddot{x}\right)-\kappa^a\left(\frac{\partial^2 p^2}{\partial r^2}+\frac{2}{r}\frac{\partial p^a}{\partial r}\right)+\kappa^a\left(\frac{\partial\rho_f^a\left(f_r^b-\ddot{x}\right)}{\partial r}\right)=0$$

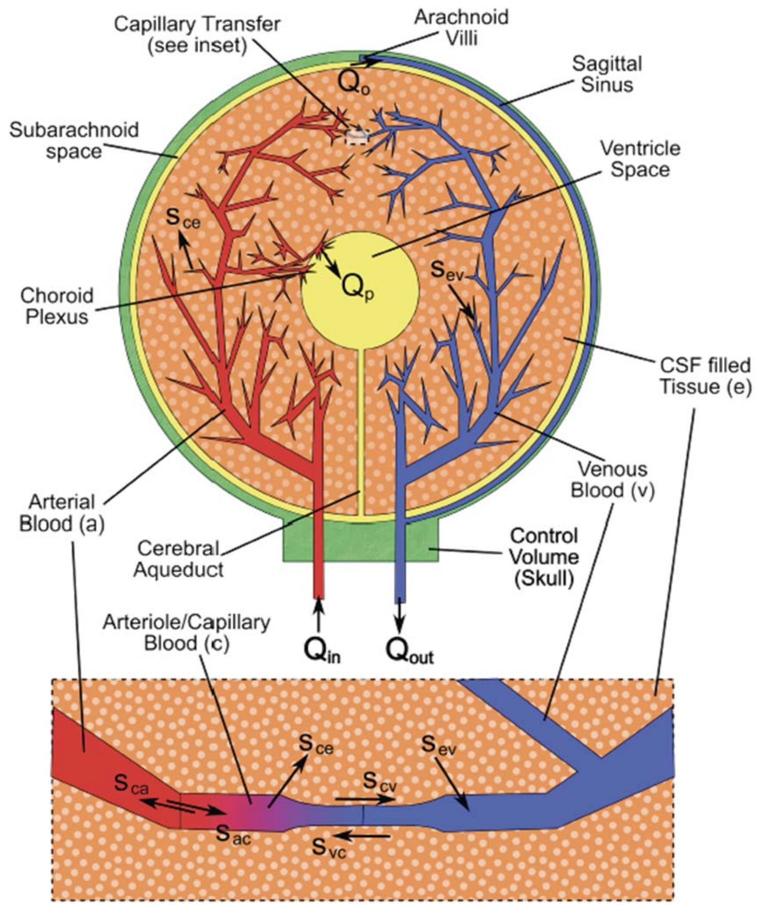
$$\frac{1}{Q^e}\frac{\partial p^e}{\partial t}+\alpha^e\frac{\partial}{\partial t}\left(\frac{\partial x}{\partial r}+\frac{2}{r}x\right)-\dot{S}_{a\to e}-\dot{S}_{c\to e}-\dot{S}_{v\to e}+\frac{2}{r}\rho_f^e\left(f_r^b-\ddot{x}\right)-\kappa^e\left(\frac{\partial^2 p^2}{\partial r^2}+\frac{2}{r}\frac{\partial p^e}{\partial r}\right)+\kappa^e\left(\frac{\partial\rho_f^e\left(f_r^b-\ddot{x}\right)}{\partial r}\right)=0$$

$$\frac{1}{Q^c}\frac{\partial p^c}{\partial t}+\alpha^c\frac{\partial}{\partial t}\left(\frac{\partial x}{\partial r}+\frac{2}{r}x\right)-\dot{S}_{a\to a}-\dot{S}_{e\to c}-\dot{S}_{v\to c}+\frac{2}{r}\rho_f^c\left(f_r^b-\ddot{x}\right)-\kappa^c\left(\frac{\partial^2 p^2}{\partial r^2}+\frac{2}{r}\frac{\partial p^c}{\partial r}\right)+\kappa^c\left(\frac{\partial\rho_f^c\left(f_r^b-\ddot{x}\right)}{\partial r}\right)=0$$

$$\frac{1}{Q^v}\frac{\partial p^v}{\partial t}+\alpha^v\frac{\partial}{\partial t}\left(\frac{\partial x}{\partial r}+\frac{2}{r}x\right)-\dot{S}_{a\to v}-\dot{S}_{e\to v}-\dot{S}_{c\to v}+\frac{2}{r}\rho_f^v\left(f_r^b-\ddot{x}\right)-\kappa^v\left(\frac{\partial^2 p^2}{\partial r^2}+\frac{2}{r}\frac{\partial p^v}{\partial r}\right)+\kappa^v\left(\frac{\partial\rho_f^v\left(f_r^b-\ddot{x}\right)}{\partial r}\right)=0$$

Biological MPET Model Assumptions

- Spherically symmetric geometry
- No external forces on the system
- Gravity is neglected
- Use a stationary reference frame
- Long time scale for development of hydrocephalus so the system is assumed as quasi-steady
- Transfer of fluid between networks does not break laws of continuity for the system, hence directional transport is important ($|\dot{S}|$>0 is a loss from the system)



Tully, B. and Y. Ventikos, *Cerebral water transport using multiple-network poroelastic theory: application to normal pressure hydrocephalus.* Journal of Fluid Mechanics, 2011

Aquaporins Effect

- Darcy Flow

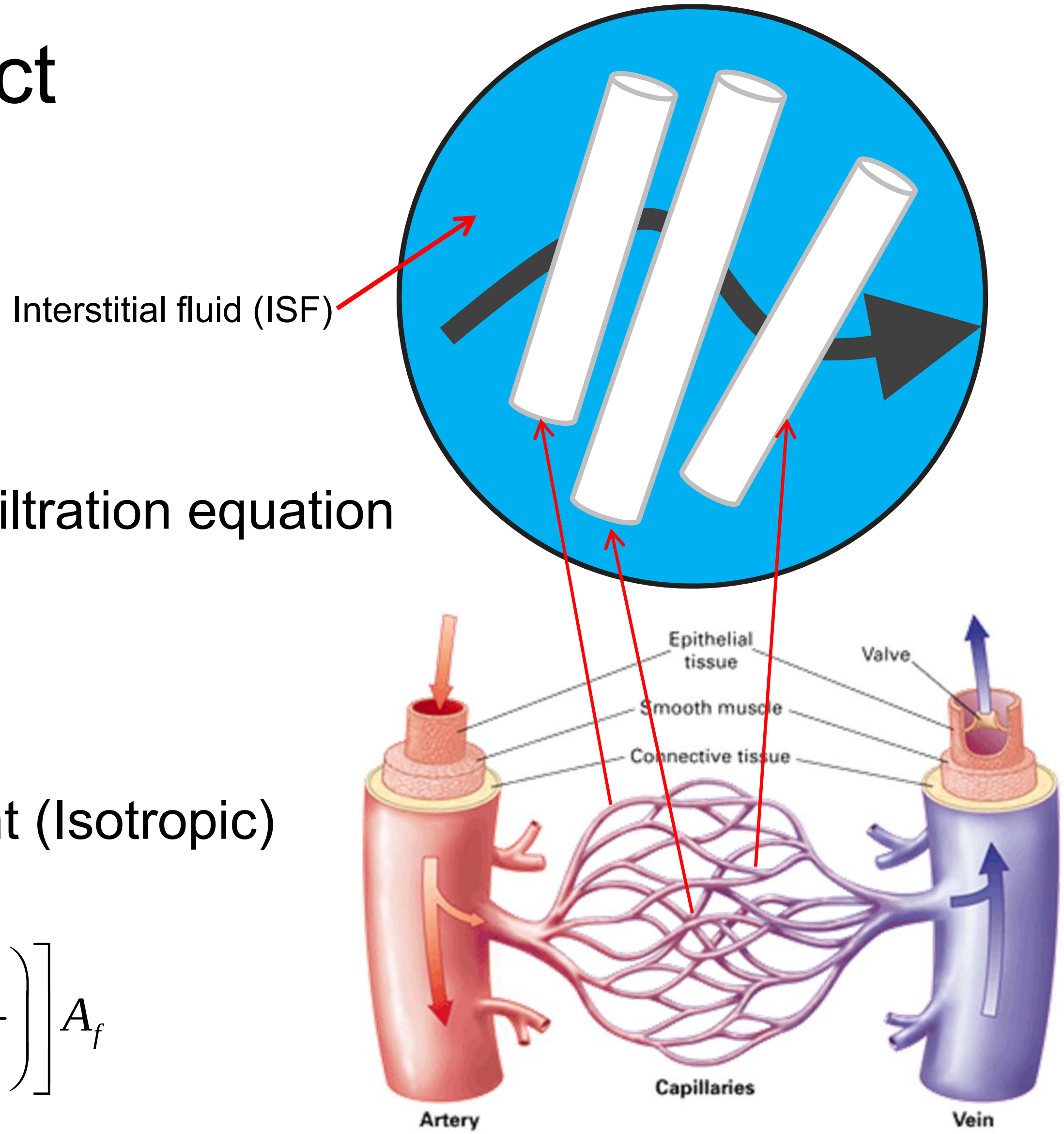
$$Q = -\frac{\kappa}{\mu} \cdot A \cdot \Delta p$$

- The Starling's Law of filtration equation

$$J_v = L_p \tilde{S} \left(\Delta p - \Delta \Pi \right)$$

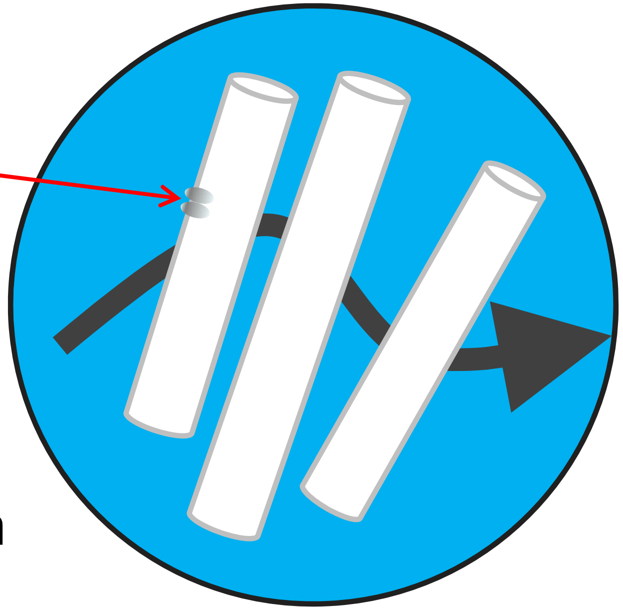
- Permeability coefficient (Isotropic)

$$\kappa_{AQP} = \left(\frac{\kappa_e}{\mu_e} \right) \left[1 - \left(\frac{p_e - p_{ref}}{p_{ref}} \right) \right] A_f$$



www.pycnogenall.com/?p=178

Aquaporins Effect



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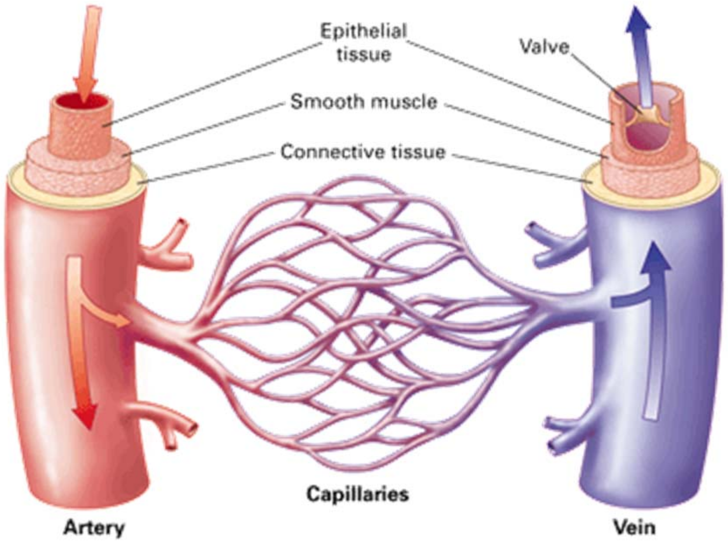

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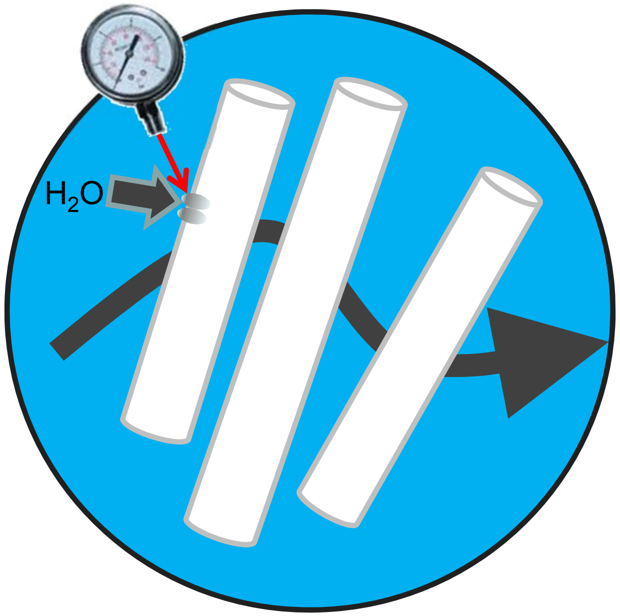
Aquaporins Effect



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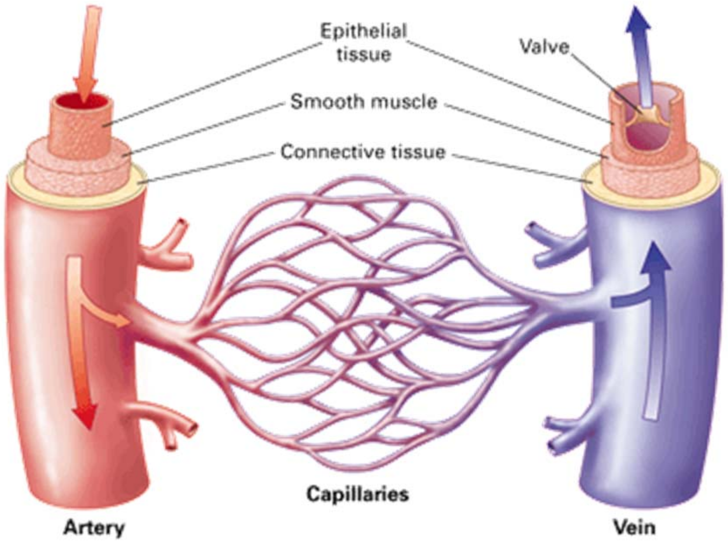

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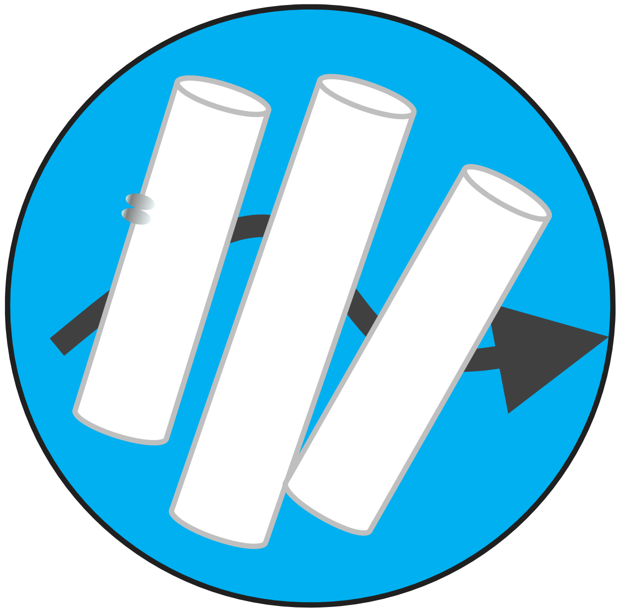
Aquaporins Effect



- Darcy Flow

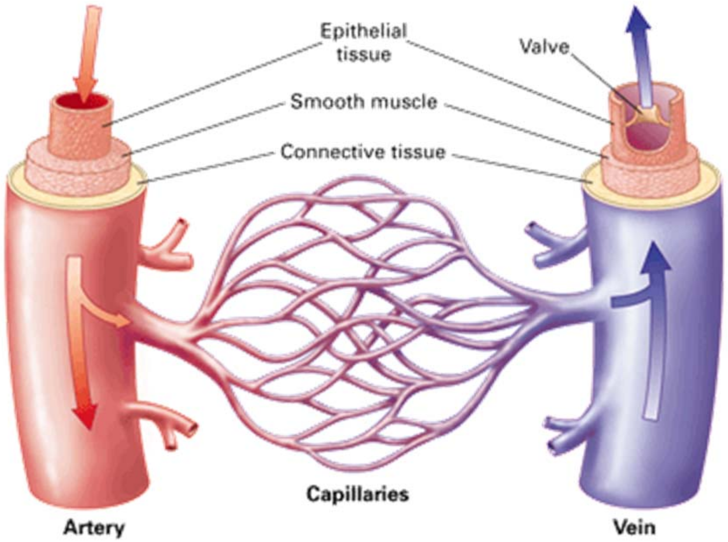
$$Q = -\frac{\kappa}{\mu} \cdot A \cdot \Delta p$$

- The Starling's Law of filtration equation

$$J_v = L_p \tilde{S} \left(\Delta p - \Delta \Pi \right)$$

- Permeability coefficient (Isotropic)

$$\kappa_{AQP} = \left(\frac{\kappa_e}{\mu_e} \right) \left[1 - \left(\frac{p_e - p_{ref}}{p_{ref}} \right) \right] A_f$$



www.pycnogenall.com/?p=178

MPET Model – Currently Progress

- After the assumptions discussed, the MPET governing equations can be cast as following:

$$\frac{\partial^2 x}{\partial r^2}+\frac{2}{r}\frac{\partial x}{\partial r}-\frac{2}{r^2}x=\frac{1-2\nu}{2G(1-\nu)}\left[\alpha^a\frac{\partial p^a}{\partial r}+\alpha^e\frac{\partial p^e}{\partial r}+\alpha^c\frac{\partial p^c}{\partial r}+\alpha^v\frac{\partial p^v}{\partial r}-\rho_f\left(f_r^b-\ddot{x}\right)\right]$$

$$-\kappa^a\left(\frac{\partial^2 p^a}{\partial r^2}+\frac{2}{r}\frac{\partial p^a}{\partial r}\right)+\left|\dot{S}_{a\to c}\right|=0$$

$$J_v=L_p\tilde{S}\left(\Delta p-\Delta\Pi\right)$$

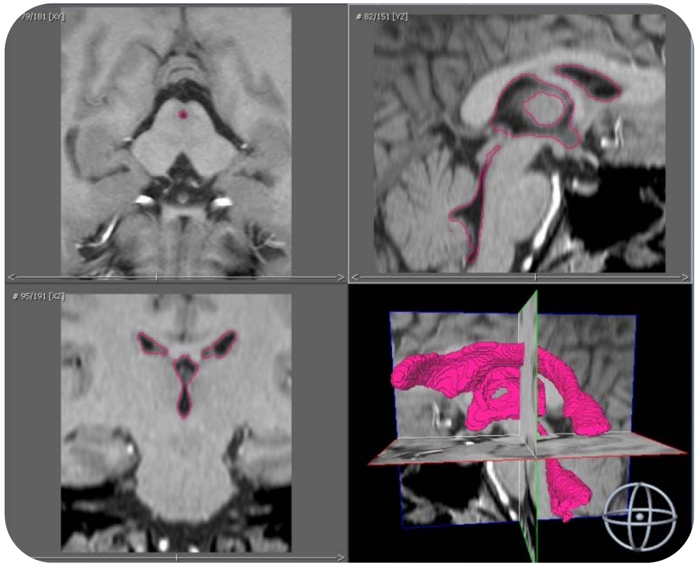
$$\kappa_{AQP}=\left(\frac{\kappa_e}{\mu_e}\right)\left[1-\left(\frac{p_e-p_{ref}}{p_{ref}}\right)\right]A_f$$

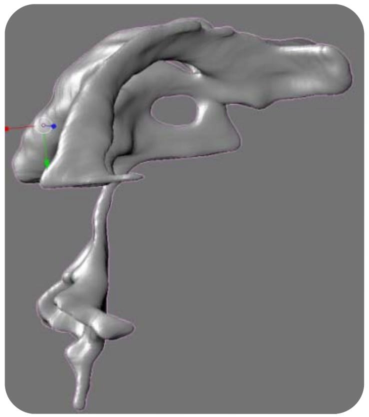
$$-\kappa^e\left(\frac{\partial^2 p^e}{\partial r^2}+\frac{2}{r}\frac{\partial p^e}{\partial r}\right)-\left|\dot{S}_{c\to e}\right|+\left|\dot{S}_{e\to v}\right|=0$$

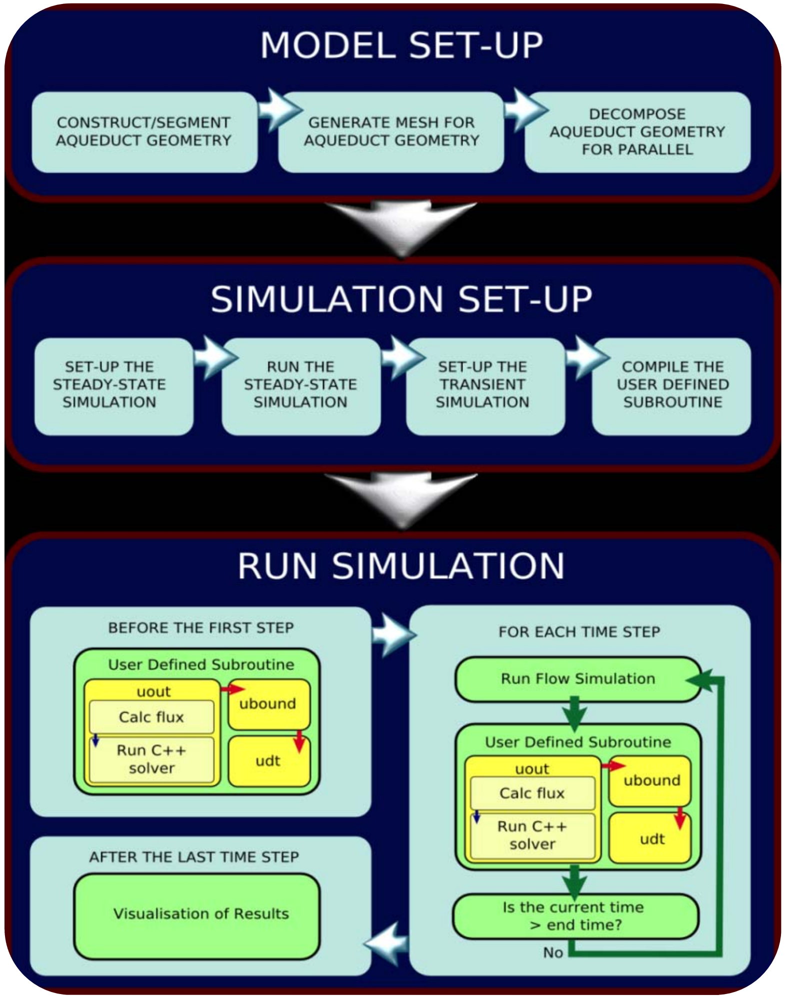
$$-\kappa^c\left(\frac{\partial^2 p^c}{\partial r^2}+\frac{2}{r}\frac{\partial p^c}{\partial r}\right)-\left|\dot{S}_{a\to c}\right|+\left|\dot{S}_{c\to e}\right|-\left|\dot{S}_{c\to v}\right|=0$$

$$-\kappa^v\left(\frac{\partial^2 p^v}{\partial r^2}+\frac{2}{r}\frac{\partial p^v}{\partial r}\right)-\left|\dot{S}_{e\to v}\right|-\left|\dot{S}_{c\to v}\right|=0$$

MPET Model Processes





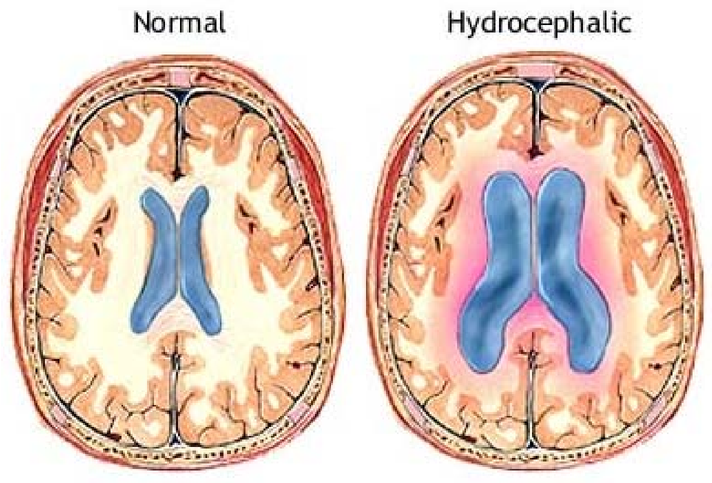


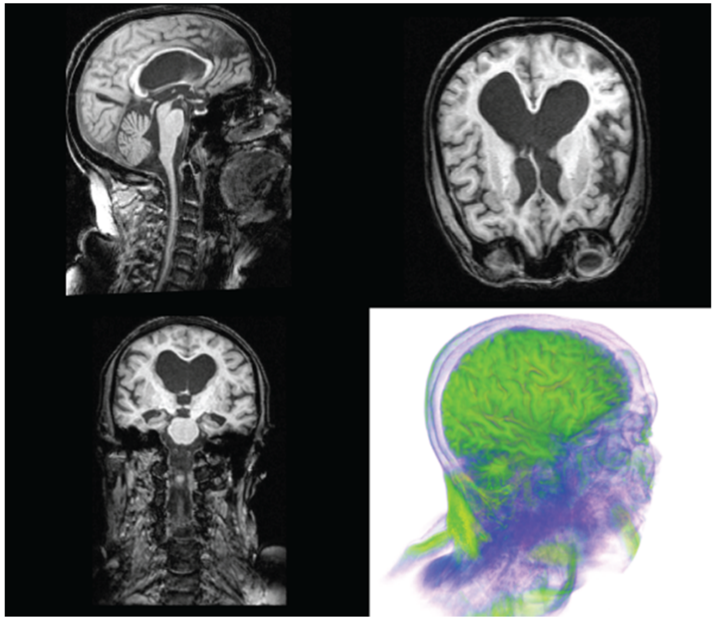
Biological MPET Model – What we would like to do?

- Assist to explore numerous cerebral pathologies
  - brain oedema
  - brain trauma
  - brain tumors
  - stroke,
  - Hydrocephalus
  - Migraines
  - other neurological pathologies, such as multiple sclerosis (MS) and neuromyelitis optica (NMO)
- Aims to make a tangible contribution to the understanding of cerebral or neurological pathologies, but also to pharmaceuticals development.

Hydrocephalus (HCP)

- HCP can be described as the abnormal accumulation of CSF with in the brain.
- Types of HCP:
  a. Obstructive HCP
  b. Communicating HCP
  c. Normal Pressure Hydrocephalus (NPH)
- Symptoms in adults:
  a. Headache
  b. Vomiting
  c. Altered level of consciousness
  d. Visual obscurations
  e. Cognitive impairment, poor concentration, gait disturbance





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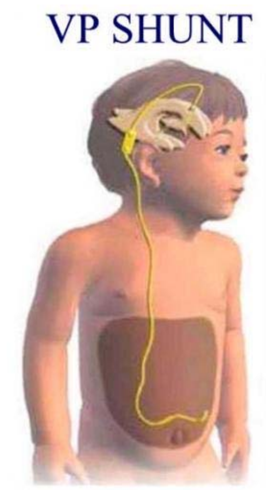
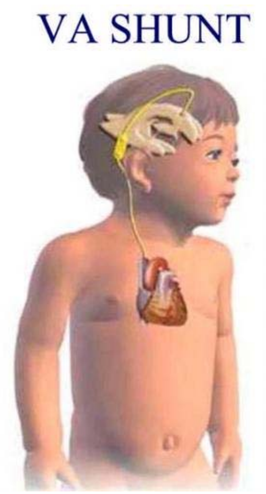
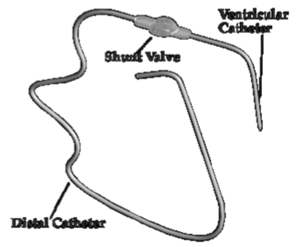
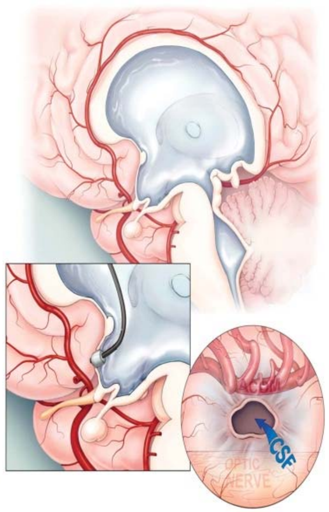
Hydrocephalus (HCP)

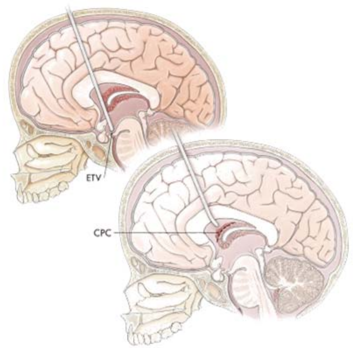
Treatment	Location of Fluid Drain
Ventriculo-peritoneal shunt (VP shunt)	Peritoneal cavity
Ventriculo-atrial shunt (VA shunt)	Right atrium of the heart
Ventriculo-pleural shunt (VPL shunt)	Pleural cavity
Endoscopic third ventriculostomy (ETV) Choroid plexus cauterization (CPC)	The floor of the 3rd ventricle Choroid plexus cauterization











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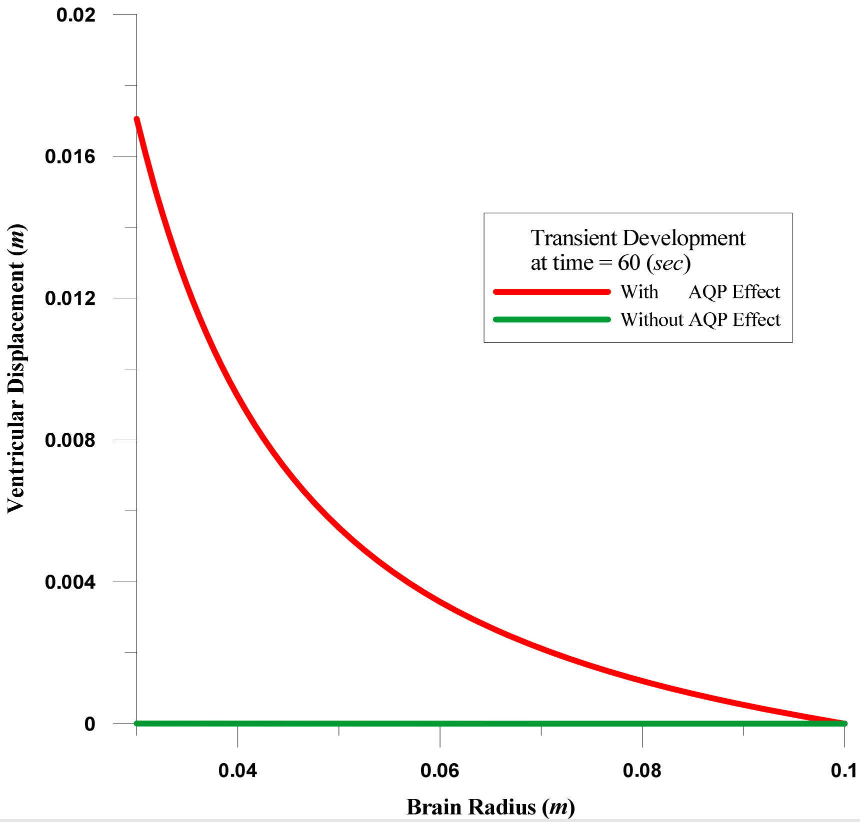
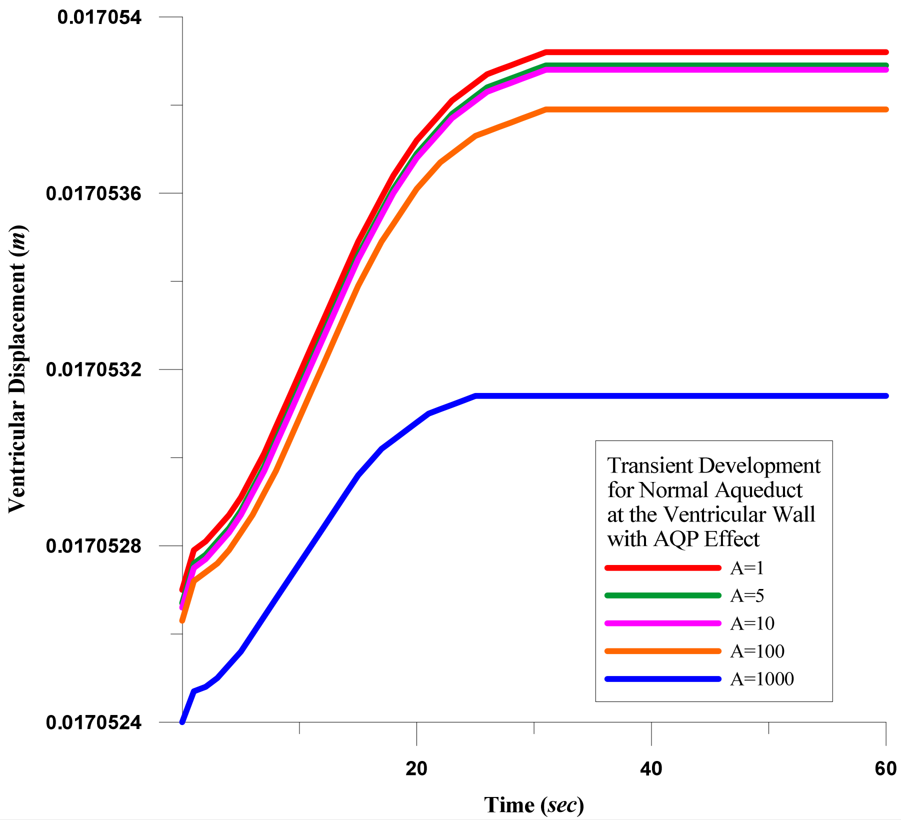
Current Results

Comparing the effect of AQP presence on the ventricular displacement in a case involving an open cerebral aqueduct

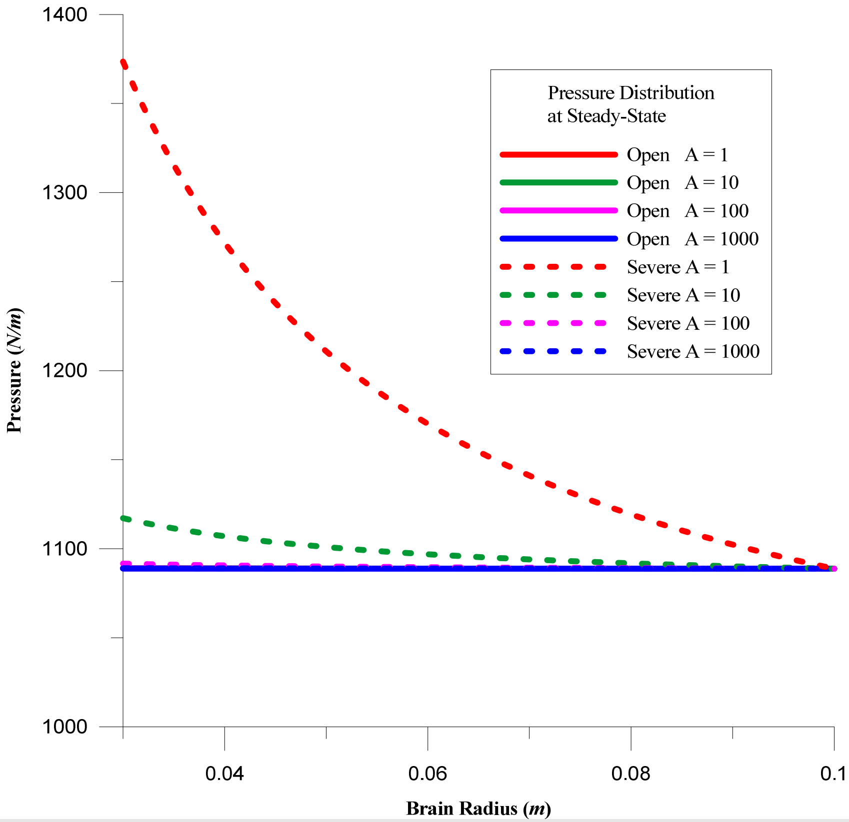


Comparing different amplification factors for the ventricular displacement in transient development

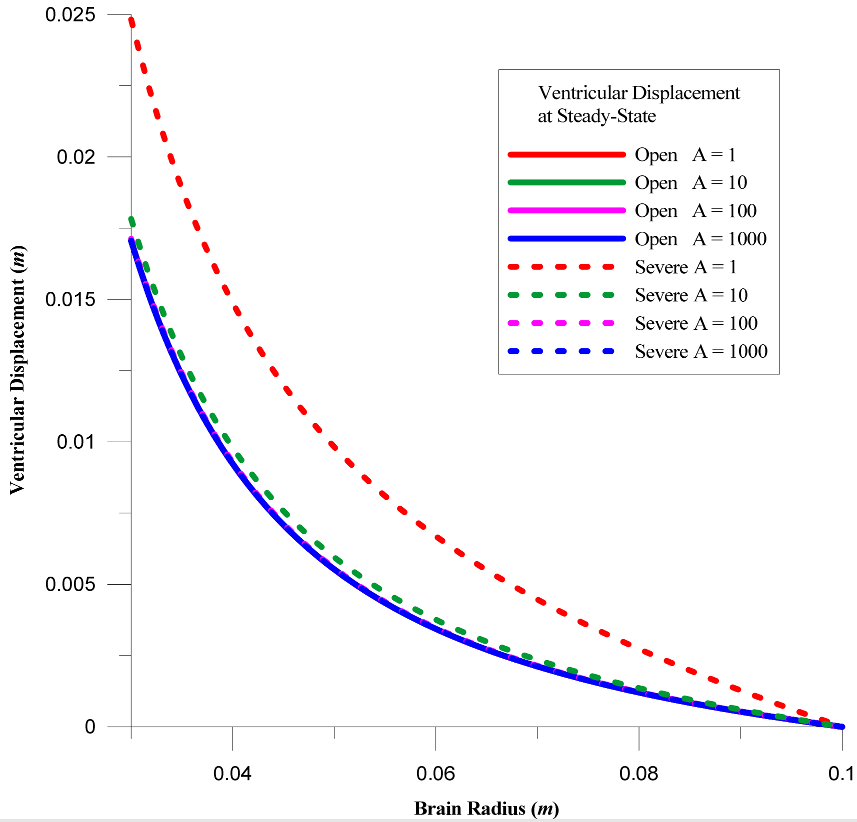


Current Results

Comparing the effect of AQP presence on the ventricular pressure in a case involving an open/severe cerebral aqueduct

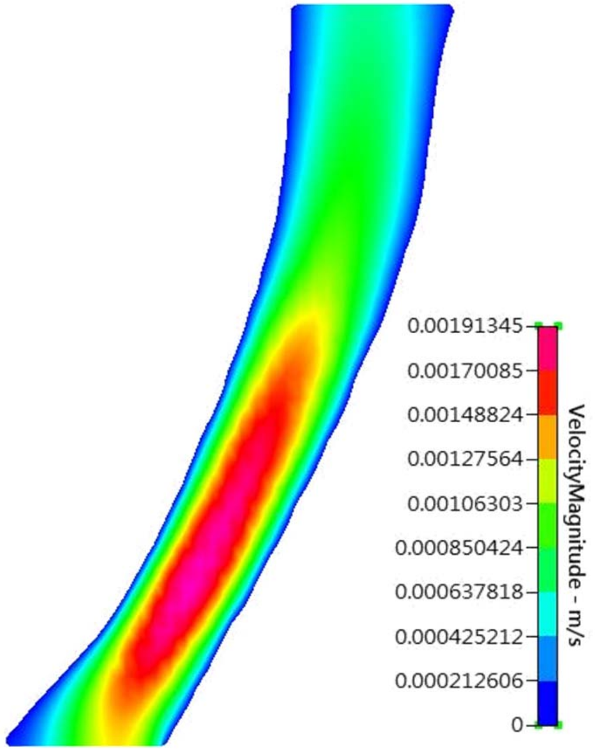


Comparing the effect of AQP presence on the ventricular displacement in a case involving an open/severe cerebral aqueduct

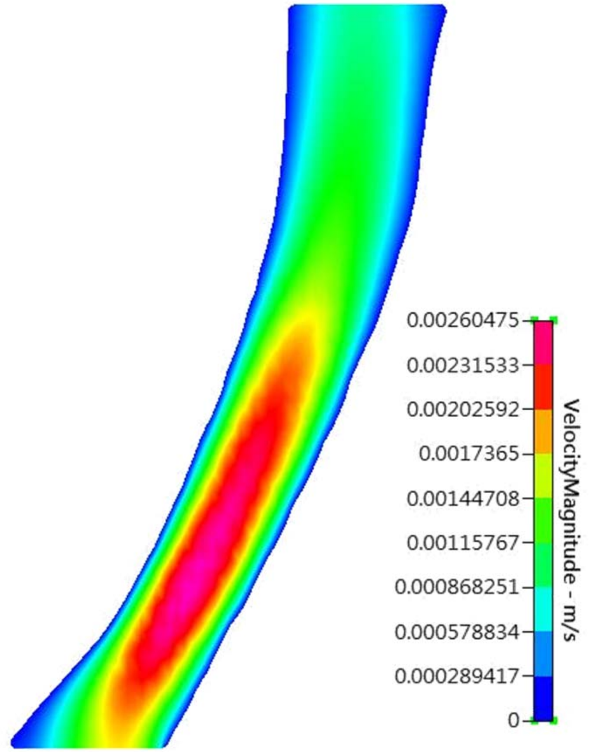


Current Results

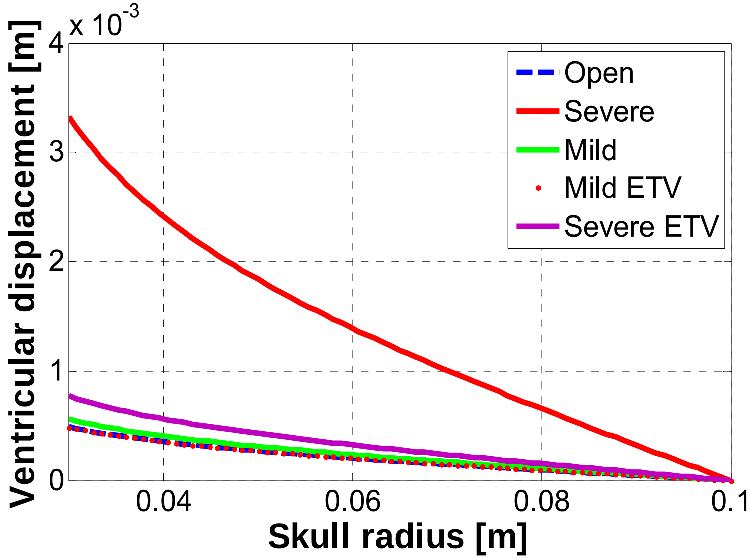
Velocity distribution in open cerebral aqueduct with AQP effect

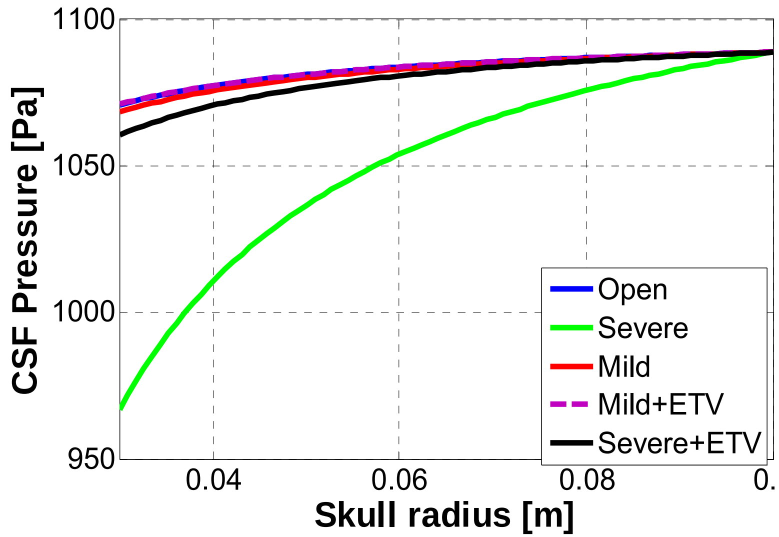


Velocity distribution in open cerebral aqueduct without AQP effect



Current Results : Choroid Plexus + ETV

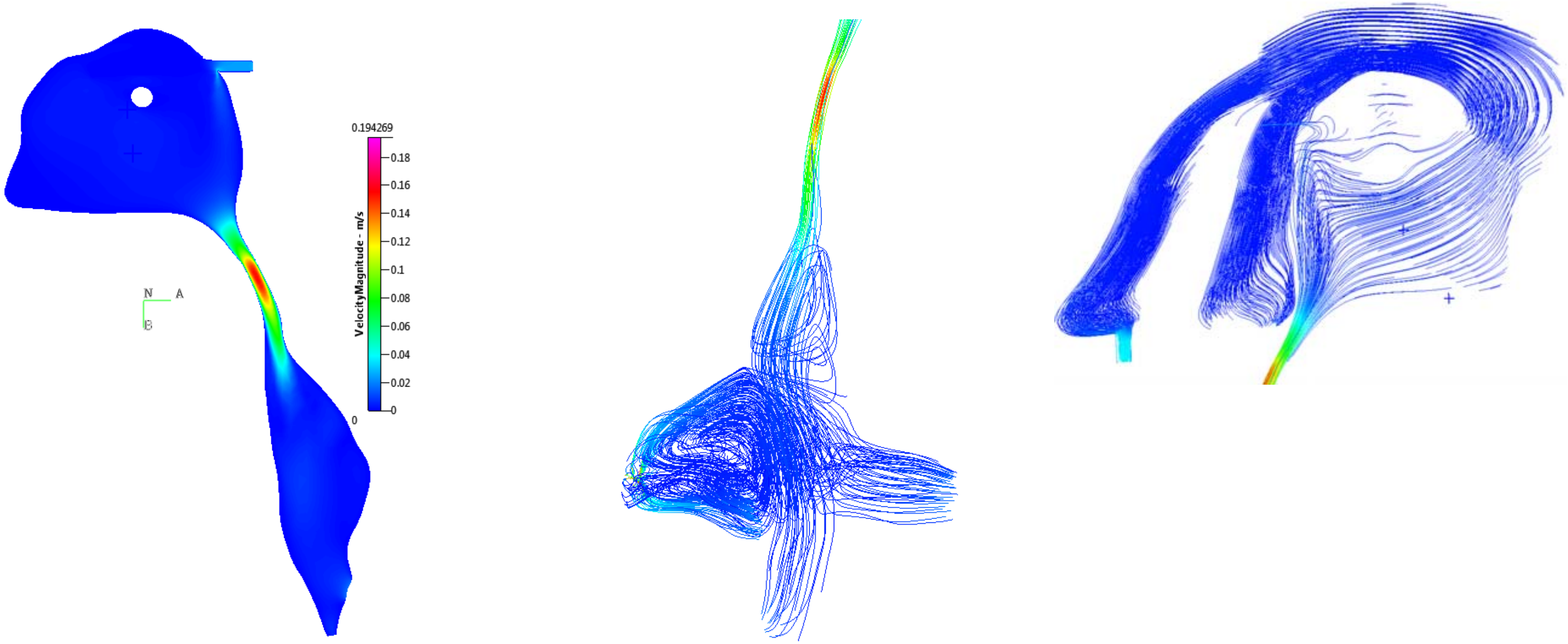




- The severe case causes a ventricular displacement of just over 3.3 mm, mild (0.55mm), open case (0.5 mm)
- ETV significantly reduces displacement of mild stenosis to the open level

- CSF pressure is lowest in severely stenosed case (966 Pa)
- Open and mild cases exhibit similar pressure distributions (1070-1072 Pa). All converge to 1089 Pa at skull
- ETV reduces the pressure in both mild and severe cases

Current Results



- (Left) Sagittal view of a z-slic of the unobstructed ventricular system
- (Centre) Rotated view of lines tangent to the instantaneous velocity vector in the AS and 4th ventricle (open case)
- (Right) Sagittal view of lines tangent to the instantaneous velocity vector in the 3rd ventricle and both LV's

Impact & Applications

- Scientific impact
    a. To develop a completely new understanding of brain water balance
    b. Virtual Physiological Brain (VP-Brain) is its target of the development of virtual optical instrumentation
- Clinical impact
    a. To improve diagnosis, intervention planning and therapy design
    b. To facilitate targeted clinical interventions, which reduces the risk of ineffective, or harmful, treatment, and improves patient safety and clinical outcomes
- Industrial impact
    a. Three targeted industrial applications
        1. Accurate characterisation of brain injury by modelling head impact
        2. Development and deployment of a novel combined ICP-NIRS probe
        3. Design of novel shunting devices
    b. The pharmaceutical industry can realise new product development

Thanks !!

Questions, please!!

Acknowledgement

- FBG in Oxford
- ESI-Group

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