The role of water dynamics in the glymphatic system through a holistic multi-scale mathematical model of the murine extracellular fluid systems

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Brain as a sponge

Brain water dynamics?
**Meningeal lymphatic vessels**

**Louveau et al. 2015, Nature**
Meningeal lymphatic system drain cerebrospinal fluid

MRI illustration of meningeal lymphatics in human. 3D-rendering of dural lymphatics (green) in a 47 year old woman from skull-stripped subtraction T1-black-blood images.

• Absinta, M. et al. Human and nonhuman primate meninges harbor lymphatic vessels that can be visualized noninvasively by MRI. eLife 2017
*Louveau, A. et al. Journal of Clinical Investigation 2017 “Understanding the functions and relationships of the glymphatic system and meningeal lymphatics”.*
Iliff, J. J. et al. Science Translational Medicine 2012 “A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β”.

Glymphatic system
Glymphatic system

Driving forces?

- Jessen, N. A. Neurochemical research 2015 “The glymphatic system: A beginner’s guide”.

• Para-Arterial Influx  • Convective Flux  • Para-Venous Efflux
Fluid systems

Holistic approach
Multi-scale mathematical model

**Zero-dimensional (0D)**

\[ V(t) \]

\[ d_t V = \sum_{in} q_i - \sum_{out} q_i \]

\[ p = p(V) + p_{ext} \]

**One-dimensional (1D)**

\[ A(x, t) \quad q(x, t) \]

\[ \begin{align*}
\partial_t A + \partial_x q &= 0, \\
\partial_t q + \partial_x \left( \alpha \frac{q^2}{A} \right) + \frac{A}{\rho} \partial_x p &= -\frac{f}{\rho}, \\
p &= p \left( \frac{A}{A_0} \right) + p_{ext}
\end{align*} \]
Mathematical model of the **murine** extracellular fluid system
• 253 Blood vessels (major arteries and veins)
• 112 Lumped parameter models
• 161 Connections between lumped parameter models

System of 779 equations

Hyperbolic Partial Differential Equations (PDEs)  \[ \partial_t Q_k + \partial_x F(Q_k) = S(Q_k), \]

Ordinary Differential Equations (ODEs)  \[ \frac{d}{dt} W = G(W, Q_1, \ldots, Q_n, t) \]
Mathematical model of the **murine** extracellular fluid system
Peripheral blood flow

Marjor veins: pressure and flow dynamics

R. subclavian vein III (131)

R. superior vena cava (84)

Azygos vein (129)

Inferior vena cava (85)

Inferior vena cava V (93)

R. external iliac vein (100)

L. subclavian artery II (17)

Ascending aorta (1)

Thoracic aorta I (12)

Abdominal aorta I (25)

L. external iliac artery (50)

Abdominal aorta V (33)

Marjor arteries: pressure and flow dynamics

Thoracic aorta I (12)

Abdominal aorta I (25)

L. external iliac artery (50)

Abdominal aorta V (33)
Modelled dynamics and mechanisms

- **Heart and pulmonary dynamics** (Sun et al. 1997, Liang et al. 2009)
- **Arterial and venous systems** (Müller and Toro 2014)
- **Brain and peripheral microcirculation** (Müller and Toro 2014)
- **Venous valves** (Mynard et al. 2012)
- **Intracranial Starling resistors** (Müller and Toro 2014)
- **Cerebrospinal fluid (CSF) dynamics** (Linninger et al. 2009, Linninger et al. 2017)
- **Modern concept of CSF/ISF dynamics** (Oreškovic et al. 2017, Linninger et al. 2017)
- **Brain lymphatic drainage**
- **Monroe-Kellie coupling**

Brain interactive fluid dynamics

CSF absorption by lymphatics and through arachnoid villi

Contarino, C. et al. IJNMB “A holistic multi-scale mathematical model of the murine extracellular fluid systems and study of the brain interactive dynamics”. In preparation
Validation of the mathematical model

- Validation with in-vivo intracranial pressure
- Validation with SPCP-MR flow measurements
- Validation with mouse model of Idiopathic Intracranial Hypertension
- Validation with existing literature values

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Validation with in-vivo intracranial pressure

Computational results vs In-vivo intracranial pressure

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Validation with SPCP-MR flow measurements

Ascending aorta (1)
- Mean reference MR flow measurements
- Mean ± 0.5 × SD MR flow measurements
- Mean ± SD MR flow measurements
- Computational result

L. common carotid artery (5)
- Mean reference MR flow measurements
- Mean ± 0.5 × SD MR flow measurements
- Mean ± SD MR flow measurements
- Computational result

Flow [mL/min]
Reference cardiac cycle [%]
Validation with SPCP-MR flow measurements

Flow [mL/min]

R. external jugular vein (155)

- Mean reference MR flow measurements
- Mean ± 0.5 × SD MR flow measurements
- Mean ± SD MR flow measurements
- Computational result

Reference cardiac cycle [%]
Interactive fluid systems

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Monroe-Kellie hypothesis: a mathematical model

The cranial compartment is incompressible and the volume inside the cranium is fixed.
Monroe-Kellie hypothesis: a mathematical model

- **Contarino, C. et al.** *IJNMB* “A holistic multi-scale mathematical model of the murine extracellular fluid systems and study of the brain interactive dynamics”. In preparation
Interactive fluid systems

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Idiopathic Intracranial Hypertension (IIH)

- Neurological disorder 2 per 100,000 people worldwide
- Abnormal increase of the intracranial pressure
- Causes Headache, tinnitus, papilledema
- 90% suffer from strictures in the transverse sinus (Farb et al. 2003)
Can an impairment of cerebral venous blood outflow affect waste product collection in the brain?
Validation with mouse model of Idiopathic Intracranial Hypertension

• Contarino, C. et al. Scientific Reports “Heart contraction, Starling forces and cerebrospinal fluid absorption drive the glymphatic system”. In preparation
Validation with mouse model of Idiopathic Intracranial Hypertension

Healthy

Bilateral ligation

- Contarino, C. et al. Scientific Reports “Heart contraction, Starling forces and cerebrospinal fluid absorption drive the glymphatic system”. In preparation
Validation with mouse model of Idiopathic Intracranial Hypertension

Computational results vs in-vivo intracranial pressure

- Contarino, C. et al. Scientific Reports “Heart contraction, Starling forces and cerebrospinal fluid absorption drive the glymphatic system”. In preparation
Effect of impairment of venous drainage on brain fluid dynamics

Contarino, C. et al. Scientific Reports “Heart contraction, Starling forces and cerebrospinal fluid absorption drive the glymphatic system”. In preparation
Impairment of cerebral venous blood outflow causes a local reduction of ISF efflux and CSF turnover, potentially leading to local accumulation of neurotoxins in the brain.

- Contarino, C. et al. Scientific Reports “Heart contraction, Starling forces and cerebrospinal fluid absorption drive the glymphatic system”. In preparation
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References

- **C. Contarino**, A. Louveau, S. Da Mesquita, D: Raper, I. Smirnov, N. Agarwal, V. Kurtcuoglu, J. Kipnis and E. F. Toro,
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