Towards continuous monitoring of the glymphatic system of the human brain

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Towards continuous monitoring of the glymphatic system of the human brain

Outline

- Glymphatic system
  - Blood brain barrier (BBB) and brain clearance

- Multimodal human brain monitoring in Oulu
  - BBB disruption monitoring
  - Multimodal human imaging in Magnetic Resonance Imaging (MRI)

- Towards wearable monitoring
  - A combined opto-capacitive-microwave imaging device
  - Sensing method
  - Validation experiments
(G)lymphatic system

- Lymphatic vessels are present throughout the body
- Density of lymph vessels correlates with the rate of tissue metabolism
- Lymphatic flow is responsible for flushing out harmful fluids from the body system, such as
  - toxins
  - metabolic waste products
  - soluble proteins

Source: https://www.extremetech.com/
The Glymphatic system is the counterpart of the lymphatic system elsewhere in the body.

As a whole, it is responsible for flushing out toxins, metabolic waste products, soluble proteins and other harmful fluids from the body system into the CSF drainage.

Glymphatic system

- CSF flows from perivascular space via astroglial cell aquaporin channels (AQP4), through brain tissue.

Source: http://biofoundations.org/
BBB and Brain clearance

Focused ultra sound (FUS) Alzheimer disease therapy, 2014

Figure 1

![MRI images comparing non-Tg and TgCRND8 groups before and after FUS therapy.](image)

Bar charts showing time in novel arm and maximum alternation index for non-Tg and TgCRND8 groups before and after FUS therapy. Asterisks indicate statistically significant differences.
Scanning ultrasound removes amyloid-β and restores memory in an Alzheimer's disease mouse model

Gerhard Leinenga and Jürgen Götz*

**ALZHEIMER'S DISEASE**

**BBB and Brain clearance**

**RESEARCH ARTICLE**

**Fig. 1**

A. Striatal section

B. Hippocampal section

C. Bright-field and LI-COR

D. Histology/Western blot/ELISA

E. No of plaques/section

F. Spontaneous alternation [%]

G. Plaque burden (% surface area)

H. No of arm entries

I. Analysis

J. Sacrifice after 3 days

K. Time (weeks)

L. 10/10 APP23

M. Sham SUS

N. No. of plaques/section

O. Plaque burden

P. (% surface area)

Q. Non-Tg

R. APP23

S. APP23 SUS

T. Sham

U. SUS

V. Analysis

W. Histology/Western blot/ELISA

X. Bright-field and LI-COR

Y. Sacrifice after 3 days

Z. Time (weeks)

AA. 10/10 APP23

BB. Sham SUS

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GG. APP23

HH. APP23 SUS

III. Sham

JJ. SUS

KK. Analysis

LL. Histology/Western blot/ELISA

MM. Bright-field and LI-COR

NN. Sacrifice after 3 days

OO. Time (weeks)

PP. 10/10 APP23

QQ. Sham SUS

RR. No. of plaques/section

SS. Plaque burden

TT. (% surface area)

UU. Non-Tg

VV. APP23

WW. APP23 SUS

XX. Sham

YY. SUS

ZZ. Analysis

AABB. Histology/Western blot/ELISA

CCDD. Bright-field and LI-COR

EFFF. Sacrifice after 3 days

GGGG. Time (weeks)

HHHH. 10/10 APP23

IIII. Sham SUS

JJJJ. No. of plaques/section

KKKK. Plaque burden

LLLL. (% surface area)

MMMM. Non-Tg

NNNN. APP23

OOOO. APP23 SUS

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TTTT. Bright-field and LI-COR

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WWWW. 10/10 APP23

XXXX. Sham SUS

YYYY. No. of plaques/section

ZZZZ. Plaque burden

AABBCC. (% surface area)

D. Sham

EE. SUS

F. Plaque burden

GG. (% surface area)

HH. Sham

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The BBB forms a major obstacle for brain drug delivery, especially in the treatment of brain tumours. A method involving BBB disruption (BBBD) induced with intra-arterial mannitol infusion, developed at the University of Portland, is exploited at the Oulu University Hospital to treat CNS lymphoma.

Grand average DC-EEG and average NIRS traces illustrating characteristic responses evoked by intra-arterial mannitol infusion

Multimodal imaging in MRI
- Towards continuous monitoring of the glymphatic system

- **Drivers of lymphatic and CSF flow**
  - Body movements, muscle contractions
  - Cardiovascular system, arterial and cardiac pulsations
  - Blood pressure, which indirectly maintains force of pressure in the lymphatic channels
  - Respiratory pulsations induce counter pulsations probably cleaning the perivenulous accumulations
  - Very low frequency (VLF) waves modulate CSF convection

=> simultaneous measurement of brain and physiological signals are of interest
Multimodal imaging in MRI  
-Towards continuous monitoring of the glymphatic system

Functional ultrafast MRI, **NIRS**, **blood pressure**, EEG, ECG, CO2 expiration and oxygen saturation (SpO2) recordings simultaneously.

A collaboration project in Oulu
- Oulu University Hospital
- Medical Research Center (Oulu Neuroimaging group, OFNI)
- Oulu Biocenter
- University of Oulu (Optoelectronics and Measurement Techniques Unit)


Continuous monitoring of the glymphatic system

The glymphatic system is more active during sleep

=> For sleep studies, a wearable, over-night monitoring method needed

Requirements:

- easy to use (small)
- suitable for long-term measurements
- doesn’t affect sleep quality
- completely safe method
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Continuous monitoring of the glymphatic dynamics
- By measuring of CSF in the subarachnoid space

Dynamics of CSF volume and flow in subarachnoid space reflect dynamics of the glymphatic system?

- CSF acts as a cushion behind the skull, providing basic mechanical as well as immunological protection to the brain.
- Cerebrospinal fluid (CSF) is a clear, colourless liquid including water (H2O) approximately with a concentration of 99%.

Monte Carlo simulation of a multilayered brain. Photon trajectory maps for 830 nm for source-detector separations of 30 mm (left) and 40 mm (right).

NIRS sensing

Isosbestic point for oxy- and deoxy Hb

Isosbestic point for oxy Hb and water

The Beer-Lambert law
Capacitive sensing

- Dielectric properties of tissue are well studied, however, utilization of a capacitive sensor for non-invasive CSF sensing are not reported

  • Capacitors are sensitive to change in volume of fluid, and even flow
  • Can measure total water volume (in blood and CSF)
  • Low manufacturing costs
  • Skin (electrical) conductance not needed
Capacitive sensor

The basic construction of the capacitance measuring device.

- Basic operation principle: creating step excitations to the unknown capacitance CX by using a fixed resistor RC with known voltage values and measuring the time interval of each charge time constant which is dependent on CX.
- The exact value of the unknown CX, which is the capacitive field over the sensor plates, can be determined with the obtained results.
Capacitive sensor

\[
C_x = \frac{T}{\ln \left( \frac{V_{tresh}}{V_{trig}} \right) + \ln \left( \frac{V_{tresh}}{V_{outk}} \right)} \times R_C - C_{ref}
\]

\(T = \) time periods of the square wave. \(T\) is 0.34 ms when \(C_x\) is not connected which corresponds frequency of 2.9 kHz.

- The time of high and low periods of the square wave (charging and discharging sequences), shown in Fig below, is read by a counter using 80 MHz clock frequency.
- The value of \(C_x\) can be determined using the equation on left if a reference capacitor is in parallel with \(C_x\).

Vouth: 3.1 V

Voutl: 0.2 V

Vtrig: 1.14 V

Vthresh: 2.27 V

Vcap: voltage over the unknown capacitance.

Vout: timers output (charging) voltage.

Fig. Signals and voltages of the capacitance measuring device.
Capacitive sensor

Capacitance measurement device connected to a multiplexer. Cx can be selected from eight different sources (channels 0 i/o - 7 i/o).

In addition, the device uses a multiplexer (Texas Instruments CD4051) which enables selecting Cx from eight different sources.
Microwave imaging technique

- One recent example is wideband microwave head imaging system for on-the-spot detection of intracranial hemorrhage. The dielectric contrast between healthy brain tissues and a hemorrhage that causes a strong microwave scattering.*
- The system uses a compact sensing antenna with directional radiation, and a portable, compact microwave transceiver for signal transmission and data acquisition.
- System operates from 0.75–2.55 GHz.
- The collected data is processed to create a clear image of the brain using an improved back projection algorithm.

Validation of sensitivity

- 3D simulations using
  - COMSOL Multiphysics for capacitive technique
  - Cone-Shaped Distribution (CSD) for microwave technique
  - Monte Carlo for optical technique

- Multilayered phantom measurements
  - Mimicking both optical and dielectric properties of brain tissues

- In vivo measurements in MRI
Simulations

- Geometric setup: a capacitor is placed on top of a human head with layers of skin, skull and cerebrospinal fluid

Geometric setup (*left*). The change in volume of the CSF is plotted against the change in capacitance for different configurations of the capacitor (*right*).
Phantom experiments

- Capacitive sensor test and simulation was done using the same geometric setup and method.
- Both simulation and real measurement show that small changes in water volume can be detected.

![Graph showing the average response of the capacitive sensor compared to simulation result.](image)

Average response of the capacitive sensor (right) and the simulation result (left). The thickness of the layer of water was varied from 1 mm to 10 mm.

## Phantom experiments

### Human Skull Electrical and Mechanical Parameters

<table>
<thead>
<tr>
<th>Layer</th>
<th>Thickness [mm]</th>
<th>$\mu_a$ [mm$^{-1}$]</th>
<th>$\mu's$ [mm$^{-1}$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>skin (dermis)</td>
<td>1 – 3</td>
<td>0.036</td>
<td>1.2</td>
</tr>
<tr>
<td>skull</td>
<td>5 – 7</td>
<td>0.05</td>
<td>1.4</td>
</tr>
<tr>
<td>CSF</td>
<td>1 – 2</td>
<td>0.005</td>
<td>0.25</td>
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<tr>
<td>grey matter</td>
<td>4 – 6</td>
<td>0.06</td>
<td>0.63</td>
</tr>
<tr>
<td>white matter</td>
<td>10 – 15</td>
<td>0.2</td>
<td>3.16</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Source</th>
<th>@1900 MHz</th>
<th>Elec. Cond. (S/m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Skin (Dry)</td>
<td>38.71429860635464</td>
<td>1.224532125743767</td>
</tr>
<tr>
<td>Skull Cancellous</td>
<td>Bone Cancellous</td>
<td>19.213035781740164</td>
<td>0.6199036157247495</td>
</tr>
<tr>
<td>Skull Cortical</td>
<td>Bone (Cortical)</td>
<td>11.716472852861365</td>
<td>0.292341961945009</td>
</tr>
<tr>
<td>Cerebrospinal Fluid</td>
<td>Cerebrospinal Fluid</td>
<td>67.05564806810452</td>
<td>2.9972739179098724</td>
</tr>
<tr>
<td>Brain</td>
<td>Cerebellum</td>
<td>45.884888803827074</td>
<td>1.7652286689074284</td>
</tr>
<tr>
<td>Brain (Grey Matter)</td>
<td>Brain (Grey Matter)</td>
<td>49.88199397536683</td>
<td>1.4502995498876796</td>
</tr>
<tr>
<td>Brain (White Matter)</td>
<td>Brain (White Matter)</td>
<td>36.8683967651613</td>
<td>0.9575054584828246</td>
</tr>
</tbody>
</table>

Source
https://www.itis.ethz.ch/virtual-population/tissue-properties/database/dielectric-properties/
Acknowledgement

- Oulu Functional Neuro-Imaging group (OFNI)
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