Assessing glymphatic transport velocities by adjoint methods

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Abstract

1 Introduction

The discovery of the paravascular pathway in 2011 [**?**] propose a novel component crucial to the metabolism of the brain which may potientially provide an explanation for the accumulation of waste such as amyloid beta in elderly, ultimately leading to diseases such as Alzheimer and Parkinson. In the rest of our body, the lymphatic system plays an important role in the clearance of metabolic waste, but there are no lymphs within the brain. This fact is puzzling in particular because the brain requires around 10 times more energy per volume than the result of the body. The paravascular pathway is proposed important to waste clearance and has therefore been named the *glymphatic system*.

The pioneering works of Syková and Nicholson [**?**] demonstrated that diffusion was a governing transport mechanism in the brain. However, the clearance of CSF-tracers during sleep [**?**] in mice demonstrated transportation much faster what could be explained by diffusion and it was proposed that arterial pulsation powered accelrated perivascular flow combined convective interstitial flow. Several modelling attempts have put the theory to the test [**?**, **?**, **?**], but so far computational modeling have failed to adequately described the mechanism.

Transportation by diffusion is in the order of XXXLars: hente fra R. Thorne / Nicholson. However, in [**?**] a 6020 minutes. As such, the transportation is XXX faster than what diffusion would provide. Furthermore, in [**?**] it was demonstrated that X Da Gadovist was brainwide in 8 hours after injection in the lumbar region.

Paragraph about timescales etc.

The purpose of this paper is to attempt to assess transportation speed in terms of an apparent diffusion coefficient by using adjoint methods provided

by [] for optimizing the coefficient with respect to data. As such a coefficient larger than commonly reported values of diffusion would suggest that at the timescale of minutes to hours there is indeed a glymphatic transportation which may potentially be responsible for metabolic waste.

An outline of the paper is as follows. In Section 2 we descibe the medical images and their modality, and the mathematical methodology used for determining the apparent diffusion coefficients.

2 Methods

Data

Mathematical Model

The objective function was defined as

$$\min_{u,g} F = \sum_{i}^{n} \int_{\Omega} |u(t_i) - u_{obs}(t_i)| \mathrm{d}\Omega + \frac{\alpha}{2} \int_{0}^{T} ||g||_{L^2(\partial\Omega)} \mathrm{d}t + \frac{\beta}{2} \int_{0}^{T} ||\dot{g}||_{L^2(\partial\Omega)} \mathrm{d}t \tag{1}$$

subjugated by

$$\begin{aligned} \frac{\partial u}{\partial t} &= \nabla \cdot D_i \nabla u \qquad \text{in} \qquad \Omega \times \{0, T) \\ u &= g(t) \qquad \text{on} \qquad \partial\Omega \times \{0, T) \end{aligned} \tag{2}$$

with the domain Ω contains three sub domains, each with a different diffusion coefficient. We denote the Cerebral Spinal fluid (CSF) domain as Ω_1, the grey matter as Ω_2 and the white matter as Ω_3.

The manufactured observations was obtained by forward computation of Eq.2 with the Dirichlet boundary condition defined as

$$g(t)_{\partial\Omega_1} = 0.3 + 0.167t - 0.007t^2 \qquad 0 \leq t \leq 24. \tag{3}$$

The timestep was $dt = 0.02$, and the diffusion coefficients were selected to be

$$D_{\Omega_1} = 1000 \quad , \quad D_{\Omega_2} = 4.0 \quad , \quad D_{\Omega_3} = 8.0 \tag{4}$$

The magnitude order of the diffusion coefficient are chosen so that they resemble diffusion coefficient in csf, grey and white matter. The forward simulation gave a total of 120 possible observation time points. These points will be denoted as τ.

The mesh was constructed by using the MRI of a patient diagnosed with iNPH. The software Freesurfer was used in segmentation and creating the polyhedral surfaces of the white and grey matter. Then the use of T2 weighted MRI was used to segment the csf compartment surrounding the cerebral. The polyhedral surfaces was use of CGAL [?], was used to

construed the the mesh. The computational requirement for the resulting mesh was significant, therefore a submesh was also constructed, see Fig. ?? .

P1 finite elements were used, and the dolfin adjoint [?] was used to construct a reduced function. Furthermore, the scipy optimize library was used to minimize the functional using L-BFGS-B algorithm.

Non-linear relation

The MR images that are provided by Oslo University Hospital Rikshospitalet and can be seen in Fig.?? .

The software Freesurfer was used to segment and align each of the observations, which made it possible to estimate voxelwise intensity increase due to tracer concentrations.

The relation between intensity and concentration is non-linear, and best be de

- describe the imaging, shortly with ref to JCI
- describe the abstract mathematical problem to be solved, ie. PDE constrained opt problem where we address coefficients and bc
- the details: finite element, reduced problem, BFGS,

Lars: bilde av konkret mesh

3 Results

- 2D experiments as have already been done (with and without noise/ with and without observations everywhere in time)
- 2D experiments should highlight the impact of the regularization parameter wrt number of iterations and diffusion coeff
- 3D experiments based on data generated
- 3D experiments based on real data (lars: we need to try testing this)

The results.

The optimal relaxation parameters was investigated by using 10 evenly spaced time points as observations. Then estimate the corresponding controls, while varying the relaxation parameters.

The dependency on the spacing and distribution of tau was done by using the optimal relaxation parameters and consider number of time points equal to the number of observations.

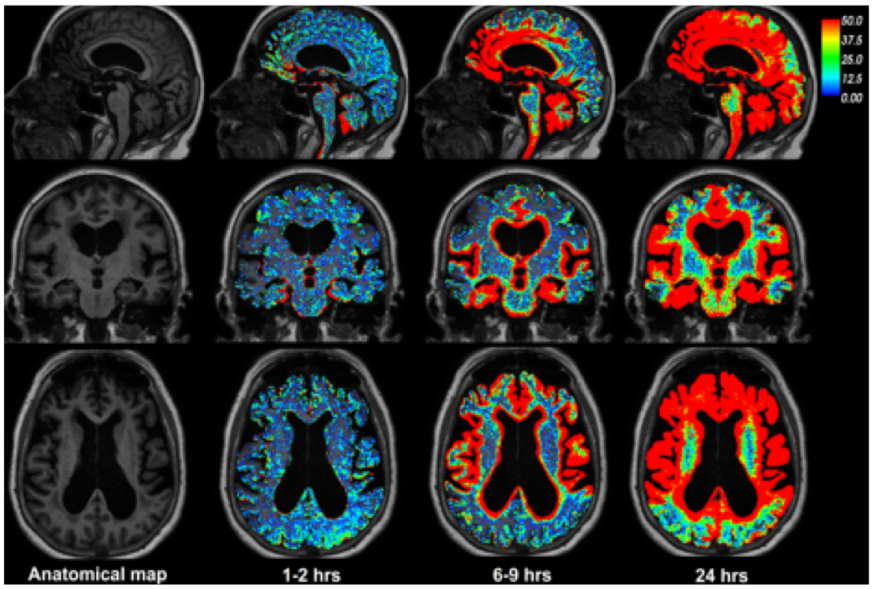

Figure 1: lars, we will need some new images since I believe this is stolen from JCI

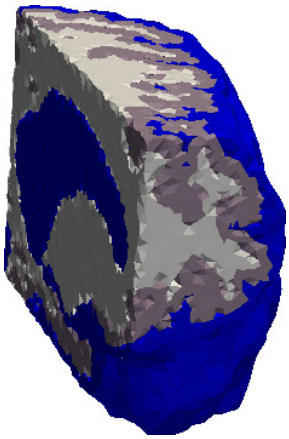

Figure 2: lars, we will need some new images since I believe this is stolen from JCI

The dependency of time steps were computed by increasing the times

The dependency on noise was done by adding randomly distributed noise to the observations.

There are some extreme cases that require some considerations, namely :

no observations around 12, i.e. can the parameters be estimated if there exists a hole in the observations.

Is estimating parameters between 2

4 Discussion

The L-BFGS-B algorithm does not scale the control parameters, thus the step size . This poses a problem with a large difference in the control parameters,

There is a need for observable change in order to estimate the parameters. But considering the magnitude difference between diffusion coefficients. It is clear that the observable change is in different timescales. This prompted that in using actual data, we will only consider a mesh with 2 subdomains that have diffusion coefficient of similar magnitude.

Table 1:

α	β	k	τ	iter	$D_{\Omega_1} = 1000$	$D_{\Omega_2} = 4.0$	$D_{\Omega_3} = 8.0$
1.0	1.0	10	10	801	3152.55150305	5.66843317507	9.10176601537
1.0	0.1	10	10	846	2890.10652122	5.8333990243	9.14516904881
1.0	0.01	10	10	1001	2374.75510786	5.90748588887	9.1624514977
1.0	0.001	10	10	987	3012.94145621	5.84828588848	9.14780994071
1.0	0.0001	10	10	1001	2846.67368004	5.86716070687	9.1516059019
1.0	1e-05	10	10	1001	2488.99687704	5.89553108585	9.16094907807
1.0	1e-06	10	10	1001	2572.74685463	5.88550285289	9.15701445733
0.1	1.0	10	10	525	1165.00025805	4.55541673123	8.51469574502
0.1	0.1	10	10	899	1098.5603179	4.5965351918	8.60353462124
0.1	0.01	10	10	792	1148.68286947	4.58961131725	8.60923608344
0.1	0.001	10	10	768	1133.11485657	4.59512891707	8.61427396989
0.1	0.0001	10	10	840	1152.61459776	4.5895138786	8.61107565287
0.1	1e-05	10	10	739	1145.12699776	4.59168203791	8.61245925367
0.1	1e-06	10	10	697	1127.51137739	4.59724924241	8.6163255093
0.01	1.0	10	10	130	1000.69417631	4.45194182806	8.48016213899
0.01	0.1	10	10	204	1001.45906364	4.44288397852	8.55964437402
0.01	0.01	10	10	384	1004.91771072	4.44039285507	8.57773362809
0.01	0.001	10	10	455	1006.92821746	4.4401364227	8.57964644068
0.01	0.0001	10	10	382	1005.46132856	4.44059403278	8.58161935877
0.01	1e-05	10	10	389	1005.48872458	4.44091328174	8.58070451064
0.01	1e-06	10	10	320	1003.88180045	4.44140148563	8.57914151398
0.001	1.0	10	10	144	1000.72690068	4.43617090765	8.47356658247
0.001	0.1	10	10	188	1001.11632883	4.42560354452	8.55339645884
0.001	0.01	10	10	242	1002.06937059	4.42388003439	8.57511846108
0.001	0.001	10	10	332	1005.24945351	4.42278572482	8.58013052115
0.001	0.0001	10	10	432	1008.05660576	4.42186842634	8.58305135552
0.001	1e-05	10	10	360	1006.05061062	4.42295196846	8.57964172911
0.001	1e-06	10	10	363	1006.70468432	4.42251369108	8.58151348789
0.0001	1.0	10	10	157	1000.83218743	4.43452507573	8.47318916943
0.0001	0.1	10	10	131	1000.56624899	4.42351929725	8.55256760219
0.0001	0.01	10	10	174	1001.0091989	4.42260942583	8.57478259945
0.0001	0.001	10	10	136	1000.57577092	4.4239534819	8.57151355191
0.0001	0.0001	10	10	283	1003.03255695	4.42248562737	8.5786695754
0.0001	1e-05	10	10	284	1003.54402535	4.42227734882	8.58311915306
0.0001	1e-06	10	10	289	1003.03642353	4.42224580212	8.58006825258
1e-05	1.0	10	10	151	1000.79310038	4.43448500449	8.47338153139
1e-05	0.1	10	10	140	1000.70858373	4.42340629909	8.55312689863
1e-05	0.01	10	10	203	1001.34714912	4.42253540005	8.57470943099
1e-05	0.001	10	10	215	1001.75591211	4.42292580709	8.58079455564
1e-05	0.0001	10	10	208	1001.41103854	4.42264942624	8.58064686718
1e-05	1e-05	10	10	218	1001.73103534	4.42318548221	8.57843152546
1e-05	1e-06	10	10	191	1001.33680306	4.42244263068	8.58128891831
1e-06	1.0	10	10	115	1000.47868283	4.43456295486	8.47226911091
1e-06	0.1	10	10	158	1000.8203239	4.42368702618	8.55236552474
1e-06	0.01	10	10	142	1000.64224198	4.42327990324	8.57047799569
1e-06	0.001	10	10	149	1000.64956243	4.42317461499	8.57554522252
1e-06	0.0001	10	10	179	1001.07075407	4.42262619987	8.57788936678
1e-06	1e-05	10	10	254	1002.49656481	4.42254606227	8.58162265954
1e-06	1e-06	10	10	228	1001.78781526	4.42297193581	8.57946804203