Lagrangian Optimal Mass Transport with Applications to the Glymphatic System

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Abstract—In this work, a unified representation of all the time-varying dynamics is accomplished with a Lagrangian framework for analyzing regularized dynamical optimal mass transport (OMT) derived flows. Our Lagrangian framework is also applicable to the Fisher-Rao regularization because, as we show, it is equivalent to our regularized dynamical OMT formulation. The advantage of the Lagrangian framework is that the time-varying trajectories and particle attributes are displayed in a single visualization. This provides a natural capability to identify and distinguish flows under different conditions. Applying our Lagrangian analysis to the glymphatic system, we successfully distinguish between flow patterns under two different anesthetics. We should also note that the Fisher-Rao regularization makes direct contact with some of the very nice recent work on entropic regularization for the computation of optimal mass transport as well as the Schrödinger bridge theory. The latter provides a stochastic aspect to the approach described in the present work.

Index Terms—Lagrangian optimal mass transport, Glymphatic system.

I. INTRODUCTION

The problem of optimal mass transport (OMT) dates back to Monge in 1781, who posed the problem of finding the minimal transportation cost for moving a pile of soil from one location to another. OMT was given a modern and relaxed formulation in the work of Kantorovich, and so is now known as the Monge–Kantorovich problem. Applications include image processing and computer vision, econometrics, fluid flows, statistical physics, machine learning, expert systems, and meteorology; see [30], [31], [39] and the many references therein.

The dynamical version of OMT, put forth by Benamou and Brenier [1], opened up new possibilities for numerical solutions and extensions using tools from the field of fluid dynamics [5], [28]. Previously, Elkin et al. [10] considered a regularization of the Benamou-Brenier OMT formulation [1] by adding a diffusion term to the Euler equation in their framework (see our discussion below). The study of the resulting velocity field was carried out in an Eulerian framework, i.e., flow properties are considered at specific locations for each time point as compared to the Lagrangian framework, which tracks specific particles as they move over time; see Figure 1. Due to the unsteady nature of the flows, it will be advantageous to also consider taking a Lagrangian approach to this regularized flow. The trick to do this is based on the theory of Schrödinger bridges; see [7] and the references therein. In this work, we consider the glymphatic system from this point of view. It turns out that there are two equivalent ways to derive the Lagrangian coordinates of the optimal trajectories. The first is via a transformation of the advection-diffusion equation in the regularized problem, and the second by adding a Fisher-Rao information type term to the kinetic energy in [1]; see our discussion below. In either case, employing Lagrangian coordinates appears to give greatly improved visualizations of glymphatic system function and also reveals new disparate transport features in two different states of arousal that were previously difficult to discern. We should note that previously we considered an Eulerian approach without diffusion in Ratner et al. [32]. Because of the lack of diffusion in our model, we were essentially tracking noise in the later frames of our image sequences for the glymphatic system.

Waste products are removed from the brain through the glymphatic system (GS); a peri-vascular transit passage for cerebrospinal fluid (CSF) which facilitates mixing of CSF with interstitial fluid (ISF) via aquaporin 4 water channels positioned on glia cell’s end-feet [18]. Lack of sufficient waste clearance attributed to aberrant glymphatic function has been associated with the pathology of a rising number of neurological conditions including vascular dementia, Alzheimer’s Disease (AD) [29] and sleep deprivation [33]. Poor sleep architecture has been associated with greater accumulation of the metabolic waste product amyloid beta ($A_\beta$) in the human brain [35] and higher risk for AD and other dementias [2], [37].

The GS has been shown to accelerate waste clearance from the brain during slow wave sleep and anesthesia when compared to wakefulness [41]. It has been hypothesized therefore that the brain’s homeostatic need to clear metabolic waste serves as a biological driver for sleep. Preservation of GS function therefore has prodigious implications for maintaining general brain health across the age span. Interestingly, it was assumed that all drug-induced sleep states would increase GS function to the same extent when compared to wakefulness [41]. This concept, however, was challenged, as it was recently shown that unconsciousness induced with dexmedetomidine (DEXM) that mimics natural sleep enhances GS function to a greater extent when compared to deep anesthesia induced with isoflurane [3]. These results infer that hypnotic drugs that promote ‘natural’ sleep might be superior to deeper states of
The main contributions of this work are as follows:

1) We present a Lagrangian framework for analyzing flows derived from a regularized dynamical OMT problem.

2) For studying the lymphatic system, one must consider rather small diffusions. Employing the equivalence between the regularized dynamical OMT problem and the Fisher-Rao regularization, we can naturally handle this in our framework. This is in contrast to the Sinkhorn method for entropic regularization [9], which becomes unstable for small diffusive values. We should note that several authors have considered modifications of the Sinkhorn in order to get smaller values of the scaling parameter; see [34], [38] and the references therein. Nevertheless, because of the nature of the scaling, Sinkhorn type algorithms will fail to be stable for sufficiently small values of the diffusion parameter.

3) We successfully differentiate between lymphatic flows under two different anesthetics and provide additional flow attributes and insights that align with the biological understanding.

The Lagrangian methodology described in the present work is of course general and may be applied to any fluid problem for which the regularized OMT methodology is relevant; see Figure 2. In our case, our interest is primarily in the lymphatic system and other medical applications which include problems related to tumor vascularization, tractography, and autism [16]. This paper is organized as follows. In Section II, we provide a brief review of the OMT problem. We then present our Lagrangian framework for the regularized OMT problem in Section III, followed by a formal presentation of the fluid model with special considerations for medical images, and the GS in particular, in Section IV. Results with the numerical implementation of our Lagrangian framework are then shown in Section V before ending with a few comments about future directions in Section VI.

II. BACKGROUND

Optimal Mass Transport

As alluded to above, the problem of optimal mass transport (OMT) is concerned with moving mass from one site to another so that minimal ‘work’ is expended, and mass is preserved. The problem was originally put forth by Gaspard Monge [26], and much later relaxed by Leonid Kantorovich via the use of joint distributions [20]. In recognition of this, the modern formulation of the OMT problem is known as the Monge-Kantorovich problem (MKP). In the present work, we will use the terms OMT and MKP interchangeably. Recently, there have been a huge number of theoretical advancements together with applications to a wide array of disciplines [11], [30], [31], [39]. In particular, Brenier’s work using polar factorization to characterize optimal transport plans [4] led to an extension of the formalism to partial differential equations [6], [11]-[14]. This has proven to be a remarkable tool for the study and visualization of flows, creating renewed interest in the MKP (OMT). For an historical account of the transportation problem and its extensions, see [21] and references therein. For our purposes with respect to medical images, we recall the MKP for smooth densities defined on domains in Euclidean space.

Let $\mu_0$ and $\mu_1$ be non-negative density functions over a bounded, connected subspace $\mathcal{R}$ of $\mathbb{R}^d$ with the same total mass

$$\int_{\mathcal{R}} \mu_0(x) \, dx = \int_{\mathcal{R}} \mu_1(x) \, dx,$$

(2.1)

for $x \in \mathcal{R}$. We then consider mass preserving diffeomorphisms $\xi : \mathcal{R} \to \mathcal{R}$ describing how the mass distributed according to $\mu_0$ should be moved in order to match the distribution $\mu_1$, namely those satisfying the Jacobian equation

$$\mu_0 = \text{det}(D\xi) \mu_1 \circ \xi,$$

(2.2)

where $D\xi$ denotes the Jacobian of $\xi$.

In general, there may be many solutions to the Jacobian equation whose set of solutions we denote by $MP$. We seek to find an optimal one in some sense, which brings us to optimal mass transport. Namely, the $L^P$-MKP problem is given by finding

$$\inf_{\xi \in MP} \int_{\mathcal{R}} \mu_0(x) \|x - \xi(x)\|^p \, dx.$$

(2.3)

One may consider more general costs in the OMT formulation [31], [39], but here we take the cost (work) to be of the form $\|x - \xi(x)\|^p$. The most relevant cases are of course $p = 1, 2$. For fluid flow problems, and to guarantee uniqueness, we will only consider $p = 2$ in the present work. Indeed, Brenier [4] shows that the optimal map satisfying the MKP (2.2–2.3) is unique and has the form

$$\xi_{MK} = \nabla \eta_{MK},$$

(2.4)

where $\eta_{MK}$ is strictly convex (in other words, the optimal transport map is curl free); see [14], [40] for a proof. Substi-
tuting the transport map of the form (2.4) into the constraint (2.2) yields the following Monge-Ampere equation

\[ \det(H \eta) = \frac{\mu_0}{\mu_1 \circ \nabla \eta}, \]  

(2.5)

where \( H \eta \) denotes the Hessian of \( \eta \). As a result, numerical methods have been developed for solving the Monge-Ampere equation (2.5) for convex \( \eta : \mathcal{R} \to \mathcal{R} \), thereby obtaining the optimal transport map \( \xi_{MK} \) via the relationship (2.4); see [6], [11], [12] and the references therein.

For our purposes, perhaps the key approach to the quadratic MKP problem is due to Benamou and Brenier [1]. They propose an alternative numerical solution by introducing time and solving a partial differential equation constrained space-time minimization problem. This formulation has the geometric interpretation of finding geodesics [27] between the given densities \( \mu \) and \( \nu \), interpreted as the Hessian of \( H \eta \) where

\[ H \eta = \sum_{i=1}^{N} \left( \frac{\partial^2}{\partial x_i^2} \eta \right) \]  

Noticing that

\[ \int_{R^d} \mu \cdot \nabla \cdot (\mu) \, dx = \int_{R^d} \mu \cdot \nabla \cdot (\nu) \, dx \]  

we get the following conservation form of the constraint (2.13):

\[ \partial_t \mu + \nabla \cdot (\mu \nu) = \epsilon \Delta \mu, \]  

(3.20)

Analogous to (2.9), the Lagrangian coordinates of the flow \( X = X(t, x) \) corresponding to the minimizing velocity \( \nu_{min} \) is the solution of the differential equation

\[ X(0, x) = x, \quad \partial_t X = \nu_{min}(t, X(t, x)), \]  

(3.21)

where according to (3.16)

\[ \nu_{min} = \nu_{min} - \epsilon \nabla \log \mu_{min}. \]  

(3.22)

B. Regularized OMT

Explicit representation of the density’s evolution suggests exciting capabilities for improved image registration techniques to account for dynamical aspects of physiological processes with additional aptitude for analyzing interesting time-varying phenomena. This is particularly powerful for medical applications where a complete physical model is often impractical to implement. Following [10], we modify the original Benamou and Brenier OMT formulation by adding a diffusion term in the continuity equation to better model both advection and diffusion of the contrast agent. Further, the diffusion term regularizes the flow, and leads to smoother pathways when visualizing the lymphatic system.

Accordingly, we consider the following regularized OMT problem which will be used to motivate a Lagrangian framework for flow representation developed in the next section

\[ \inf_{\mu, \nu} \int_0^1 \int_{R^d} \mu(t, x) \|\nu(t, x)\|^2 \, dx \, dt \]  

(2.12)

subject to

\[ \partial_t \mu + \nabla \cdot (\mu \nu) = \epsilon \Delta \mu, \]  

(2.13)

\[ \mu(0, \cdot) = \mu_0(\cdot), \quad \mu(1, \cdot) = \mu_1(\cdot), \]  

(2.14)

\[ \epsilon > 0. \]  

(2.15)

It is interesting to note that this may also be regarded as a reformulation of the Schrödinger bridge problem [7] as we will indicate below.

III. LAGRANGIAN COORDINATES

We can define the optimal trajectory in Lagrangian coordinates for the regularized case as follows. Let \( \mu_{min} \) and \( \nu_{min} \) denote the minimum arguments of the action (2.12) subject to (2.13). Define the augmented velocity

\[ \nu(t, x) = \nu(t, x) - \epsilon \nabla \log \mu(t, x). \]  

(3.16)

Noticing that

\[ \nabla \cdot (\mu \nu) = \nabla \cdot [(\cdot) - \epsilon \nabla \log \mu(t, x)] \]  

(3.17)

\[ = \nabla \cdot (\mu \nu) - \epsilon \nabla \cdot (\mu \nu \log \mu(t, x)) \]  

(3.18)

\[ = \nabla \cdot (\mu \nu) - \epsilon \Delta \mu(t, x) \]  

(3.19)

we get the following constraint:

\[ \partial_t \mu + \nabla \cdot (\mu \nu) = 0. \]  

(3.20)

As referenced above, Benamou and Brenier give the following fluid dynamical version of the MKP over the normalized time interval \( t \in [0, 1] \) [1]:

\[ \inf_{\mu, \nu} \int_0^1 \int_{R^d} \mu(t, x) \|\nu(t, x)\|^2 \, dx \, dt \]  

(2.6)

subject to

\[ \partial_t \mu + \nabla \cdot (\mu \nu) = 0 \]  

(2.7)

\[ \mu(0, \cdot) = \mu_0(\cdot), \quad \mu(1, \cdot) = \mu_1(\cdot), \]  

(2.8)

where \( \mu = \mu(t, x) \in \mathcal{R} \) is the density interpolant between the given densities \( \mu_0 \) and \( \mu_1 \), assumed to have the same total mass (2.1), and \( \nu = \nu(t, x) \in \mathcal{R}^d \) is the velocity. Here we consider the kinetic energy (up to a factor of 1/2) associated with the transport (2.6) and require that the time-varying densities and velocities satisfy the continuity equation (2.7) with temporal endpoints matching the given densities (2.8) to enforce mass conservation.

The optimal \( \mu_{BB} \) and \( \nu_{BB} \) so that the infimum (2.6) is achieved do exist. In terms of Lagrangian coordinates, the trajectory \( X(t, x) \) of a particle with initial position \( x \in \mathcal{R} \) is given for time \( t \in [0, 1] \) by

\[ X(0, x) = x, \quad \partial_t X = \nu_{BB}(X(t, x), x). \]  

(2.9)

Moreover, the formulations given by (2.2–2.3) and (2.6–2.8) are equivalent [1], [39] in the sense that they both yield the same transport cost and for any \( x \in \mathcal{R} \) we have,

\[ X(1, x) = \xi_{MK}(x). \]  

(2.10)

Indeed, the geodesics described by (2.9) can be parameterized as follows,

\[ X(t, x) = x + t(\xi_{MK}(x) - x), \]  

(2.11)

where \( \xi_{MK} \) is the optimal transport map for the MKP.
A. Fisher-Rao regularization

It is very important to note that the regularized OMT problem is equivalent to a Fisher-Rao information theoretic regularization of OMT, which is very closely connected to the Sinkhorn approach [9], and is in fact a dynamic formulation of the Schrödinger bridge problem [7]. For small $\epsilon$ in the advection-diffusion equation above, Sinkhorn will become unstable, which is why one needs to employ a different approach in the medical imaging realm. We will therefore derive an equivalent Lagrangian formulation of regularized OMT via the Fisher-Rao regularized functional. We should note that there are a number of works demonstrating the equivalence of Fisher-Rao and OMT joint interpolation functional and regularized OMT including [7], [8], [24], [25]. We include some of the details of the computation since these are used in the numerical implementations given below, and the Lagrangian approach for studying the glymphatic system.

Following the notation of the previous section, we claim that the problem defined by (2.12-2.15) is equivalent to

$$\inf_{\mu, \nu} \int_0^1 \int_\mathcal{R} \mu(t,x)(||\dot{\nu}(t,x)||^2 + 2\epsilon^2 ||\nabla \log \mu(t,x)||^2) \, dx \, dt$$

(3.23)

subject to

$$\partial_t \mu + \nabla \cdot (\mu \dot{\nu}) = 0,$$

(3.24)

$$\mu(0, \cdot) = \mu_0(\cdot), \quad \mu(1, \cdot) = \mu_1(\cdot),$$

(3.25)

for time-varying densities $\mu = \mu(t,x) \in \mathbb{R}$ and velocities $\nu = \nu(t,x) \in \mathbb{R}^d$ where

$$H(\mu_1||\mu_0) := \int_\mathcal{R} \mu_1(x) \log \mu_1(x) - \mu_0(x) \log \mu_0(x) \, dx.$$  

(3.26)

Clearly, $H(\mu_1||\mu_0)$ is a constant.

Noting that

$$\dot{\nu}(t,x) + \epsilon \nabla \log \mu(t,x) = \nu(t,x),$$

(3.27)

and

$$\int_0^1 \int_\mathcal{R} \mu(t,x)||\dot{\nu}(t,x)||^2 \, dx \, dt$$

$$= \int_0^1 \int_\mathcal{R} \mu(t,x)||\dot{\nu}(t,x)||^2$$

$$+ 2\epsilon \mu(t,x)\dot{\nu}(t,x), \nabla \log \mu(t,x))$$

$$+ \epsilon^2 \mu(t,x)||\nabla \log \mu(t,x)||^2 \, dx \, dt,$$

we see that the claim will be verified once we show that

$$J := \int_0^1 \int_\mathcal{R} (\dot{\mu} \dot{\nu}, \nabla \log \mu) \, dx \, dt = H(\mu_1||\mu_0).$$

(3.29)

However, using integration by parts (i.b.p.) and equations (3.24-3.25) we see that

$$J = -\int_0^1 \int_\mathcal{R} \nabla \cdot (\mu \dot{\nu}) \log \mu \, dx \, dt$$

$$= \int_0^1 \int_\mathcal{R} \partial_t \mu \log \mu \, dx \, dt \quad \text{again using i.b.p.}$$

$$=-\int_0^1 \int_\mathcal{R} \mu \partial_t \log \mu \, dx \, dt + H(\mu_1||\mu_0).$$

(3.32)

Therefore, we will be done once we show that

$$\int_0^1 \int_\mathcal{R} \mu \partial_t \log \mu \, dx \, dt = 0.$$  

(3.33)

But

$$\int_0^1 \int_\mathcal{R} \mu \partial_t \log \mu \, dx \, dt = \int_0^1 \int_\mathcal{R} \mu \frac{\partial_t \mu}{\mu} \, dx \, dt$$

$$= \int_\mathcal{R} (\mu_1(x) - \mu_0(x)) \, dx$$

$$= 0.$$  

(3.36)

since the total masses of $\mu_1$ and $\mu_0$ are equal.

**Remarks:**

(i) Letting $\tilde{\nu}_{\min}$ denote the optimal vector field for (3.23-3.24), the Lagrangian coordinate solution is then exactly that given by (3.21) above.

(ii) As in the classical OMT setting, the optimization problem (3.23-3.24) admits an equivalent static formulation which amounts to minimizing a certain relative entropy functional. As noted above, there are very fast algorithms for solving such entropic regularized versions of OMT for sufficiently large $\epsilon$ [9]. Since, as we will see, we will need to consider small values $\epsilon$, we will need to apply an algorithm from [36] that we will detail below.

IV. Fluid model for glymphatic system

Suppose we are given dynamic contrast enhanced (DCE) images

$$\{\tilde{\mu}_{\min} : \mathcal{R} \to \mathbb{R}^+ \cup \{0\}\}_{m=0}^M,$$

(4.37)

($\{\tilde{\mu}_{\min}\}$ for short), over the compact subdomain $\mathcal{R} \subset \mathbb{R}^d$ (here, we consider $d = 3$) captured at times $t_0, t_1, \ldots, t_M$, normalized so that $t_0 = 0$ and $t_M = 1$. Image intensity is assumed proportional to contrast agent (tracer) density [22] and is therefore simply referred to as the density. Our goal is to model the glymphatic flow that occurs during the period of time between image acquisition, as captured by the apparent changes in the image intensity distributions. To this end,
Require: The respective initial and final observed tracer distributions $\mu_0$ and $\mu_1$, the diffusivity $\epsilon$
Ensure: Believed true interpolated tracer distributions $\mu(t_i)$ for $i = 1, ..., N$, the velocity field $\nu$ characterizing the tracer movement subject to the ADE (4.39)
Initialize cell-centered grid;
Initialize the velocity field with guess $\nu$;
for $i = 0$ to $N_{\text{iter}}$ do
Compute the interpolated tracer distributions $\mu(t_i)$ for $i = 1, ..., N$ according to the ADE (4.39);
Compute the gradient $g_F(\nu)$ of the objective function (4.40) with respect to the velocity $\nu$;
Compute the Hessian $H^F(\nu)$ of the objective function (4.40) with respect to the velocity $\nu$;
Solve the system $H^F(\nu)s = -g_F(\nu)$ for the Newton step $s$;
Perform line search: find $\alpha$ that minimizes $F(\nu + \alpha s)$; $\nu \leftarrow \nu + \alpha s$;
end for
return the velocity $\nu$

Algorithm 1 Generalized Regularized OMT

Require: The respective initial and final observed tracer distributions $\mu_0$ and $\mu_1$, the diffusivity $\epsilon$
Ensure: Believed true interpolated tracer distributions $\mu(t_i)$ for $i = 1, ..., N$, the velocity field $\nu$ characterizing the tracer movement subject to the ADE (4.39)
Initialize cell-centered grid;
Initialize the velocity field with guess $\nu$;
for $i = 0$ to $N_{\text{iter}}$ do
Compute the interpolated tracer distributions $\mu(t_i)$ for $i = 1, ..., N$ according to the ADE (4.39);
Compute the gradient $g_F(\nu)$ of the objective function (4.40) with respect to the velocity $\nu$;
Compute the Hessian $H^F(\nu)$ of the objective function (4.40) with respect to the velocity $\nu$;
Solve the system $H^F(\nu)s = -g_F(\nu)$ for the Newton step $s$;
Perform line search: find $\alpha$ that minimizes $F(\nu + \alpha s)$; $\nu \leftarrow \nu + \alpha s$;
end for
return the velocity $\nu$

Algorithm 2 Lagrangian Pathlines and Particle Attributes

Require: The optimal time-varying tracer density $\mu$ and velocity $\nu$, returned from the GR-OMT algorithm 1, the cell-centered grid spacing $\delta x$, time step $\delta t$ and diffusivity $\epsilon$
Ensure: Significant Lagrangian pathlines $X$, cluster reference for each pathline $C_l$, density pathlines $X_\mu$, speed pathlines $X_\nu$

Uniformly select $p$ pathline seeding points $x_l$ out of all voxels that satisfy the given criterion;
Initialize Lagrangian coordinates with particles’ starting positions: $X \leftarrow x_l$;
Initialize time: $t \leftarrow 0$;
for all $x_l$ do
for $i = 1 : N$ do
Update particle attributes:
$X_\mu \leftarrow \mu(t, X)$;
{ Interpolate density}
$\omega_\mu \leftarrow \nu(t, X)$;
{ Interpolate velocity}
$X_\nu \leftarrow ||\omega_\nu||$;
Compute augmented velocity (3.16):
$\tilde{\nu} \leftarrow \omega_\mu - \epsilon \nabla \log X_\mu$;
$X \leftarrow X + \delta t \tilde{\nu}$;
{ Update particle position}
t $\leftarrow t + \delta t$;
{ Update time}
end for
end for
Cluster pathlines by proximity with similar curvature and get the corresponding cluster index for each pathline $C_l$;
return Pathlines $X$, cluster indices $C_l$, density along pathlines $X_\mu$, speed along pathlines $X_\nu$
**Pathlines**

Elkin et al. [10] utilized an Eulerian framework to analyze the derived velocity field. This entailed computing streamlines, i.e., a family of curves that are everywhere parallel to the velocity vector at a fixed time. Streamlines provide informative descriptions of the tracer’s movement but require applying the procedure and individually viewing the trajectories for multiple time steps. In order to represent the characteristics of the flow over all time in one comprehensive figure, we propose using the Lagrangian framework to construct what are commonly known as *pathlines*. A pathline \( X(t, x) \) with initial position \( X(0, x) = x \) is given by (3.21) and traces the trajectory of an individual particle throughout the time interval. Specifically, additional information such as \( \% \)-signal from baseline is used to determine regions where flow is more likely to occur. Throughout this region of interest, \( p \) seeding points, denoted \( x_l \), are selected uniformly. Pathlines are then computed by integrating the augmented velocity (3.16) with initial positions \( x_l \). The speed \( |\nu(t, X(t, x_l))| \) of each particle is simultaneously computed along each pathline, referred to as the *speed pathline* and denoted \( X_\nu = X_\nu(t, x_l) \), by (tri)linearly interpolating the GR-OMT derived velocity field \( \nu \). We note that additional particle attributes such as density can be similarly obtained for further analysis of the flow dynamics. In order to extract pathlines that are representative of the flow behavior in specific anatomical regions, we subsequently cluster the pathlines by proximity and similar curvature using the QuickBundles algorithm [15]. Each pathline is returned with an associated cluster index \( C_l \) that can be used to group speed pathlines as well; see Algorithm 2. Algorithms 1 and 2 were implemented in MATLAB and run on a CPU cluster with 4592 nodes in total (128 gigabytes RAM per node). All 8 datasets (5 Dex, 3 Iso) of resolution \( 128 \times 128 \times 128 \) took approximately 10 hours to run.

**V. DISCUSSION**

While streamlines and pathlines are interchangeable for steady flows (i.e. time independent), the same cannot be said for unsteady flows (i.e. time dependent). A novel aspect of the Benamou-Brenier [1] dynamical OMT formulation is its explicit description of the density’s time-varying evolution, suggesting the need for Lagrangian analysis of this behavior. The Lagrangian approach provides an elegant framework to observe various attributes such as speed and density along the pathlines. Having a single representation for the history of a particle and its attributes across time lends itself to a natural means for differentiating between flows under different conditions. We show the capability of this framework as it pertains to the GS.

Glymphatic transport can be observed with dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) in combination with administration of paramagnetic contrast agents (e.g. DOTAREM) into the CSF [23]. However, supplementary analysis is required in order to extract and distinguish characteristics of the GS transport patterns and flow. Current techniques for quantifying GS transport include assessment of brain parenchymal solute uptake or clearance [18], kinetic analysis [23], and k-means cluster analysis [17], [19]. All of these analytical strategies are useful and have provided valuable information but are limited. Kinetic and cluster analysis strategies provide a static ‘snapshot’ of GS transport over 2-3 hours and dynamic information is lost. Solute uptake analysis only informs on GS ‘influx’ and visualization of the dynamic transport patterns in the brain are not derived [17], [25].

As briefly mentioned above, Elkin at al. [10] applied OMT analysis to study GS transport in the rat brain based on DCE-MRIs and were able to discern two new GS transport features not previously captured: Dynamic CSF streamlines penetrating into the brain parenchyma as well as new solute exit (drainage) pathways. Here, we present an improved Lagrangian framework for analyzing GS transport flows derived from a regularized dynamical OMT problem. We apply this new analytical pipeline to measure GS function based on DCE-MRIs acquired in rats while under two different states of unconsciousness - ‘light’ sleep/hypnosis with DEXM versus deep sleep/anesthesia with isoflurane based on data from [3]. Specifically, we tested the new Lagrangian OMT framework’s ability to differentiate GS function between these two different states of arousal.

Cluster pathlines derived from our Lagrangian framework are shown in Figure 3. It is evident, based on the cluster pathlines patterns observed in the rats anesthetized with the two anesthetics, that glymphatic transport function is very different. With DEXM anesthesia, glymphatic transport in the brain is highly efficient as noted by the density of cluster pathlines reaching into the hippocampus, hypothalamus and the brain stem. In contrast, in the rat anesthetized with isoflurane, glymphatic transport is inhibited and CSF (and cluster pathlines) is not penetrating as much into brain parenchyma. This is most clearly visualized by the vigorous and premature ‘exit’ of CSF along the olfactory nerves (cobalt blue clusters), which over 30 minutes is very prominent in the ISOFLURANE but not in the DEXM anesthetized rat.

Figure 4 captures pathline speed (integrated over 30 minutes) through the GS in rats anesthetized with either DEXM or isoflurane. The speed pathlines associated with the whole brain are shown as a 3D volume rendered color-coded map overlaid on the corresponding 3D volume rendered anatomical rat brain. Higher and lower magnitudes of speed in a given pathline are represented by red and blue colors, respectively. Note that with both anesthetics, pathline speed is lower in areas associated with the basal cisterns and higher towards the olfactory bulb and frontal cortex. In the isoflurane anesthetized state, pathline speed is high along the olfactory nerves. In the DEXM anesthetized rats, only a few speed lines reach out into the nasal cavity, however, their speed appears to be identical to those of the isoflurane anesthesia. In Figure 5, we have listed the average speed in each of the clusters defined in Figure 4. As can be observed, the average speed in clusters within the key anatomical areas appears to be within the same range for the two anesthetics. It is interesting to note that the speed of pathlines within the olfactory bulb versus along the olfactory nerves is similar. This new analytical modality provides a way to capture GS features which have not previously been revealed.
Fig. 3. Glymphatic transport is visualized using cluster pathlines derived from the Lagrangian framework analysis. This approach now allows us to view the glymphatic transport over 30 minutes in one figure. Specifically, the figure shows glymphatic transport of DOTA (Gd-Dota) in the brains of rats during anesthesia with DEXM (Figures 3B-D) and Isoflurane (Figures 3E-H). 3A, B, E, F: 3D volume rendered rat brains with color coded cluster pathlines overlaid. In 3A and 3E, the 3D brain is solid-appearing, so that only cluster pathlines on the surface entering or exiting the brain can be highlighted. In 3B and 3F, the brain parenchyma has been rendered transparent so that cluster pathlines penetrating into the tissue can be appreciated. Each cluster is color coded to highlight anatomical areas of interest: Turquoise: cluster pathlines associated with the cisterna magna (CM) and spinal cord. Blue: cluster pathlines associated with the basal cisterns; Magenta: cluster pathlines associated with CSF penetrating into the ventral hippocampus; Red: cluster pathlines associated with CSF surrounding the pineal recess; Purple: cluster pathlines associated with the hypothalamus and ventral surfaces; Cobalt blue: cluster pathlines associated with the olfactory bulb; Green: Cluster pathlines associated with the rhinal fissure (RF). 3C-D, 3G-H are 2D T1-weighted MRIs of each rat presented in the sagittal plane showing anatomical landmarks of interest. Pi=pineal gland; Cb=cerebellum; Spi=spinal cord; Hyp=hypothalamus; Pit=pituitary; Olf=olfactory.

Table I provides an estimate of average speed in rats anesthetized with isoflurane (N=3) and DEXM (N=5) and confirms that the speed range across groups are identical. Data are mean ± SD.

VI. CONCLUSION AND FUTURE WORK

We have introduced a Lagrangian OMT framework to represent time-varying dynamics and various attributes in a single visualization. A theoretical proof for the connection between the regularized OMT problem and the Fisher-Rao regularization was also provided which allows efficient computation using small diffusive values $\epsilon$. The resultant framework was then used to capture known GS transport flow patterns and provide additional insights in distinguishing GS function under different anesthetic conditions.

In the future, we will extend the proposed framework to differentiate between healthy and pathological (e.g. Alzheimer’s disease, vascular diseases, autism) cases. Specifically, given enough datasets, the computed particle attributes can be used as features in machine learning algorithms to differentiate and
classify various transport related flow patterns for diagnostic purposes. Moreover, we will also add a source term into the GR-OMT formulation to account for dynamics during tracer infusion; this will allow us to identify tracer particles by their initial position and the first time they appear. This can then help focus specifically on tracking these particles over time which naturally suggests using a Lagrangian representation of their trajectories. With this motivation, we will formulate a Lagrangian method for solving this regularized (source-term added) OMT in the future.

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