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A mathematical model for neuronal fibers

Antonio Marigonda, Giandomenico Orlandi

Dipartimento di Informatica, Facoltà di Scienze MM.FF.NN.
Università degli Studi di Verona, Strada Le Grazie 15, 37134 Verona, Italy
antonio.marigonda@univr.it
giandomenico.orlandi@univr.it

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Abstract

Diffusion Magnetic Resonance Imaging (MRI) is a powerful non-invasively method producing images of biological tissues exploiting the water molecules diffusion into the living tissues under a magnetic field. This technique enhances the highly non–homogenous character of the diffusion medium, revealing underlying microstructure. Recently, this method has been widely applied to the study of the neuronal fibers in the brain white matter, and several methods have been proposed to reconstruct the fiber paths from such data (tractography). Results rely on the model chosen to represent water molecules diffusion into an MRI voxel: among all the proposed model, we recall the Diffusion Spectrum Imaging (DSI) model, which describes the diffusion inside each voxel as a probability density function defined on a set of predefined directions inside the voxel. DSI is able to successfully describe more complex tissue configurations than other models as, for example, Diffusion Tensor Imaging (DTI), but lacks to consider the density of fibers going to make up a bundle trajectory among adjacent voxels, preventing any evaluation of the real physical dimension of neuronal fiber bundles.

We describe here a new approach, based on ideas from mass transportation theory, that takes into account the whole information given by DSI in order to reconstruct the underlying water diffusion process, and recover the actual distribution of neuronal fibers. In this paper we review and summarize results in [1], to which we defer the reader for complete arguments, further details, and full proofs.

Keywords: `DSI images, tractography, optimal mass transportation.`

AMS Subject Classification: `49L25, 65K10`

1. Introduction.

1.1. *General introduction.*

Diffusion magnetic resonance imaging (MRI) is a powerful imaging modality for non-invasive and in vivo study of the anatomy of the brain white matter. Starting from the observation that water molecules diffusion in living tissues is highly affected by the cellular organization of the observed tissue, MRI exploits this dependency to probe tissue structure architecture

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at a microscopic scale far beyond the usual imaging resolution. Moreover, since it is well known that in the brain there is a strong relationship between water diffusion and axonal orientations [2–4], in the last decade diffusion MRI has been widely applied to the study of fiber bundle trajectories into the brain white matter yielding a high number of "tractography" or "fiber-tracking" methods. In general terms, a fiber-tracking algorithm exploits water diffusion data of each 3D resolution element (voxel) in order to reconstruct the fiber bundle trajectories present into the brain white matter. Various models are used to describe the water molecules diffusion at the scale of an MRI voxel.

In the simplest case of Diffusion Tensor Imaging (DTI), displacements of water molecules subject to magnetic field are assumed to follow a Gaussian distribution and therefore in each voxel there will be only one direction of maximum diffusion. On the contrary, in the state-of-the-art technique Diffusion Spectrum Imaging (DSI), the diffusion at each voxel is described by a displacement distribution or equivalently by a probability density function (DDF) defined for a set of predefined directions inside the voxel. The probability density function DDF is reduced to an orientation distribution function (ODF) by summing the probabilities of diffusion in each direction. As opposed to DTI, hence, DSI is able to successfully characterize more complex axonal configurations, such as fiber crossing, fanning and bending.

Despite some important progresses made by recent studies focused on assessing the ability of diffusion tractography to estimates anatomically correct fiber bundles, the *validation* of reconstructed fiber trajectories and their *interpretation* remain the two major shortcomings. As regards the interpretation of tractography results, present fiber-tracking methods, DSI-based included, build fiber trajectories disregarding the "quantity" of fibers going to make up a bundle trajectory among adjacent voxels, thus preventing any evaluation, for example, of the real physical dimension of a fiber bundle or the global quantity of fibers crossing a brain region.

1.2. *Related work.*

In the literature, diffusion fiber-tracking algorithms are generally divided into two major classes: deterministic and probabilistic ones.
Deterministic tractography algorithms [5–7] incrementally reconstruct fiber trajectories starting from a seed point and following the maximum local diffusion information (i.e., a streamline process). Such algorithms are relative fast and easy to compute, but lack of robustness and errors are propagated exponentially.

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To overcome the shortcomings of deterministic tractography in dealing with the uncertainty in fiber orientations, *probabilistic* algorithms have been introduced [8–10]. They generate multiple trajectories from a given seed point (up to thousands) by independently repeating a streamline tracking process and randomly choosing the next direction to follow at each step. Some of the reconstructed paths will correspond to anatomically meaningful fiber bundles, others will not. The output of such algorithms is not a trajectory, but a map of "probability" for a given point to be traversed by an anatomically genuine fiber bundle. The computation of these maps is burdensome, and their interpretation is still controversial.

More recently, a new approach called *global tractography* has been proposed by means of some fiber-tracking algorithms [11–15]. These algorithms share the idea of searching a fiber path as a global parameter optimization process in order to improve robustness to the noise or to local errors of diffusion directions. In [11], the authors model fiber trajectories as spline curves having control points randomly drawn as a Bayesian based distribution. The obtained results are interesting, but the method is computational expensive because the initialization of the control points and the sampling process are two very time-consuming processes. Another recent promising approach has been introduced by [14] and [15], in which each fiber bundle trajectory is obtained by minimizing Ising spin glass-type model. In general, such approach requires a very high computational time.

1.3. *The optimal mass transport approach.*

In this paper we describe a model introduced in [1] that takes the microstructural information into account during the fiber trajectories building process in the case of DSI tractography. Exploiting microstructural information, this model can be used to investigate some ambiguities that often occur in white matter and are difficult to deal with, e.g. distinguish between fiber crossing and kissing, improving the specificity and accuracy of tractography results.

The considered model aims to take into account the whole information given by the MRI data in order to reconstruct the actual underlying water diffusion process, which as observed above is highly anisotropic and takes place essentially along the fiber paths. This anisotropy is encoded in the highly non-spherical symmetry of the DDF. Another aspect of this process, enhanced by physical evidence, is total water mass conservation during diffusion.

The knowledge of the underlying water diffusion process allows in principle to reconstruct the whole fiber net by considering the streamlines corresponding to the regions where the density of diffused water is higher. These should correspond to the actual fibers. Moreover, the ratio between the actual number of fibers crossing in a point associated to different directions will be equal to the ratio between the water density in the corresponding streamlines. Another constraint to take into account is that each fiber has no endpoints in the interior of the brain white matter: in other words, the distribution of the unit tangents to each fiber is divergence free.

Having in mind the previous considerations, we will focus on the problem of finding the bundle of fibers connecting two given cerebral regions, by considering it as the superposition of paths that fulfill the following requirements: they lie in the higher water density regions, and the distribution of their tangents fits as much as possible with the velocity distribution given by the DDF.

We hence consider two given regions, assign to each one (water) mass distributions having the same total mass, and consider the problem of steering the first mass distribution to the second one by respecting as much as possible the probability distribution on the velocities given by DDF, thus simulating the actual water diffusion process between the two regions as measured by the MRI.

The masses assigned to initial and final regions must be equal because conservation of total mass has to hold at each time of the process, since neither sources nor sinks are present along the fibers.

This constraint provides a link between the density of the water molecules and their velocities, quantitatively expressed by the continuity equation.

We may thus assign a cost to each diffusive process satisfying the continuity equation and steering the initial mass configuration to the final one along a family of paths. This cost will be higher for velocities that are far from the set of averaged observed velocities given by the DDF.

The processes which minimize this cost give as a byproduct a reasonable picture of the neuronal fiber bundle connecting the two regions.

This kind of problem is known as an optimal mass transportation problem, and in general it admits a solution under mild hypothesis. However, without some regularity assumption, solutions turn out to be difficult to interpret.

In the regular cases, the optimal transport solutions can be viewed as a superposition of noncrossing trajectories (transport paths) starting from the initial to the final configuration (in our situation, they are the trajectories followed by each water molecule), and the cost function can be expressed as an integral of cost functions assigned to every single trajectory.

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The optimization procedure then reduces to minimize the cost of every trajectory. This can be done with standard techniques in the framework of optimal control theory. The superposition of optimal trajectories will give us the picture of the bundle of fibers connecting the two considered regions.

In [1], are proposed two different cost functions, which are described in Section 2.3 and 2.4, and which provide optimal transport paths solutions between the two region thanks to Theorem 2.2 below (in its strongest version).

Along the same lines we are able to provide also a *quantitative* criterion that measures the connectivity between two localized cerebral regions (see formula (6)), extending similar criteria in [14,16]. Roughly speaking, we compare the Euclidean distance of points belonging to the distinct regions with the geodesic distance measured along the corresponding optimal transport paths, which in turn corresponds to the length of the fibers connecting the two regions.

In [16], the authors face the same problem as a *front propagating problem*, and perform accordingly an analysis of an underlying control problem. However, their approach does not take in account at all the physical relevant information about the density of fibers, and cannot be used for a non-pointwise connectivity criterion (i.e. to study the connectivity between *regions* and not only between a point and a fixed region). For a detailed and more technical discussion about this point, we refer to [1].

In the next section we first consider and analyze those quantities related to the MRI data that will enter in the proposed modelization, then we recall basic theoretical background on mass transportation theory and its relation with optimal control and Hamilton-Jacobi PDE's, and finally we discuss two kind of cost functions for our problem and analyze their regularity properties to ensure existence of optimal transport paths solutions according to Theorem 2.2.

The final section is devoted to the discussion on advantages and shortcomings of the considered model, together with further remarks and open problems.

2. Optimal transportation–based models.

2.1. *Discussion of the DSI data.*

The DDF function assigns to each voxel a probability distribution on the space of velocities. A voxel is represented by the set $Q(\alpha)$, defined as the unitary cube centered at $\alpha \in \mathbb{Z}^3$. For each $(\alpha, v) \in \mathbb{Z}^3 \times \mathbb{R}^3$, let $N(\alpha)$

be the total number of molecules contained in $Q(\alpha)$, and $N(\alpha, v)$ be the number of molecules in $Q(\alpha)$ displaced of $v\delta t$ in the time δt. Define the *(averaged) displacement density function* $f_D : \mathbb{Z}^3 \to [0, +\infty[$ by setting:

$$f_D(\alpha, v) := \frac{N(\alpha, v)}{N(\alpha)}.$$

Due to highly anisotropic character of the medium where diffusion occurs, the fraction of molecules displacing in the direction of a fiber will be significatively different from the fraction of molecules displacing in the orthogonal directions. Moreover, multiple fiber aligned in the same direction will produce an higher value of the DDF rather than a single fiber.

By construction, we have trivially

$$\int_{\mathbb{R}^3} f_D(\alpha, v)\, dv = 1,$$

hence $f_D(\alpha, \cdot) \in L^1(\mathbb{R}^3)$ is a probability density on $\mathbb{R}^3$. This means that if we consider all possible displacements $v \in \mathbb{R}^3$ and sum all the fractions of molecules which moved in that directions, we recover the whole of the initial number of molecules in $Q(\alpha)$. The main properties of f_D are the following:

1. if we fix α and a direction $w \in \mathbb{S}^2 := \{p \in \mathbb{R}^3 : |p| = 1\}$ (i.e. the unit sphere of $\mathbb{R}^3$), we have that the probability of a displacement in direction w follows a normal distribution according to its magnitude;
2. for α fixed, we have that if two directions are sufficiently near each others, the respective distribution are close, i.e. $w \mapsto f_D(\alpha, w)$ is continuous;

Of particular significance for the construction of this model is the set $M(\alpha)$ of displacement with cumulative probability less or equal $1/2$. Remark that this set may be different from the graph of the ODF usually considered in current models.

The set $M(\alpha)$ contains the origin and its boundary is constituted by vectors v whose modulus is the median of the magnitudes of observed displacements in the direction $v/|v|$. This set in general is nonconvex, however it is symmetric with respect to the origin. We can think to the boundary of the set as a collection of averaged observed velocities.

We associate this set to the center of the voxel. Assuming that the distribution assigned to each voxel is the average on the voxel of an analogous distribution defined at each point of the voxel, we may define accordingly at each point of the voxel the set of averaged observed velocities. In other words, we set

$$f_D(\alpha, v) = \int_{Q(\alpha)} f(x, v)\, dx$$

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where $f:\mathbb{R}^3\times\mathbb{R}^3\to\mathbb{R}$ has a behavior similar to $f_D(\alpha,v)$ for $x\in Q(\alpha)$. Since f is the result of an averaging procedure, we can assume that if two points are sufficiently close, the probability distribution is almost the same, i.e. we take f continuous. We set for every $\lambda\in\mathbb{R}$, $w\in\mathbb{S}^2$

$$f\left(x,\lambda w\right)=a(x,w)e^{-\frac{\lambda^2}{2r(x,w)}},$$

where $a,r:\mathbb{R}^3\times\mathbb{S}^2\to]0,+\infty[$ are continuous strictly positive functions bounded away from 0 such that

$$\int_{w\in\mathbb{S}^2}\int_0^{+\infty}f(x,\lambda w)\lambda^2\,d\lambda\,d\Sigma(w)=1,$$

with $d\Sigma$ the area element of $\mathbb{S}^2$. We assume that, for fixed x, $w\mapsto r(x,w)$ and $w\mapsto a(x,w)$ are Lipschitz continuous functions.

We may hence define the following set of displacements for any $x\in\mathbb{R}^3$:

$$\begin{aligned}M(x)&:=\left\{v\in\mathbb{R}^3\setminus\{0\}:\ \int_0^{|v|}f\left(x,s\frac{v}{|v|}\right)\,ds\le\int_{|v|}^{+\infty}f\left(x,s\frac{v}{|v|}\right)\,ds\right\}\cup\{0\}\\&=\left\{v\in\mathbb{R}^3\setminus\{0\}:\ |v|\le\sqrt{2r\left(x,\frac{v}{|v|}\right)\mathrm{Erf}^{-1}(1/2)}\right\}\cup\{0\},\end{aligned}$$

where Erf^{-1} is the inverse function of

$$\mathrm{Erf}(s):=\frac{2}{\sqrt{\pi}}\int_0^s e^{-x^2}\,dx.$$

Boundary points of this set are precisely those displacement with cumulative probability function $1/2$. The sets $M(x)$ inherit from f some regularity properties: $x\mapsto M(x)$ is a continuous mapping from $\mathbb{R}^3$ with the Euclidean norm to $2^{\mathbb{R}^3}$ endowed with Hausdorff distance, moreover for every $x\in\mathbb{R}^3$ we have that the compact set $M(x)$ is a neighborhood of the origin and is strictly star–shaped and symmetric with respect to $0\in\mathrm{int}\big(M(x)\big)$. These properties of $M(x)$ will be crucial in the regularity issues for the optimal mass transportation model, defined in term of the sets $M(x)$, that we discuss in the next sections. In [1] some further properties of sets $M(x)$ are discussed.

2.2. *Optimal transportation background.*

For an extensive introduction to the *dynamical reformulation* of the Monge-Kantorovich optimal transportation problem due to Benamou and Brenier, we refer to [17], [18], and Chapter 8 in [19].

Assume to have a fluid made by particles and denote by ρ_0 and ρ_1 the initial and final density of the particles. The problem is to transport the mass from the initial to the final configuration minimizing a suitable cost, which depends on the path followed by particles, under some constraints. We adopt an Eulerian point of view, denoting by $v_t(x)$ the vector field of the velocities of the particle which at time t is at position x.

The first physical requirements is that during the transportation process, the total mass at every time must remain unchanged. This implies that the density of particles ρ_t at time t and vector field velocity are related by the *continuity equation*:

$$\partial_t \rho_t + \mathrm{div}(v_t \rho_t) = 0. \tag{1}$$

We consider then the following minimization problem:

$$\text{minimize} \int_0^T \int_{\mathbb{R}^3} L(x, v_t(x)) \rho_t \, dx \, dt, \tag{2}$$

among all the solutions $t \mapsto \rho_t$ of the continuity equation (1) (which must be understood in the weak sense) such that $t \mapsto \mu_t := \rho_t \, dx$ is an absolutely continuous curve in the space of measures, converging in the sense of measure to the initial datum $\mu_0 := \rho_0 \, dx$ for $t \to 0^+$, and to the final datum $\mu_1 := \rho_1, \, dx$ for $t \to T^-$. We will take ρ_0 and ρ_1 to be compactly supported. Function $L : \mathbb{R}^3 \times \mathbb{R}^3 \to [0, +\infty[$ will be a suitable *current cost* related to our problem. It will penalize the velocities with lower probability according to DSI data. If vector field v_t is sufficiently smooth, it is possible to consider the *characteristic system*

$$\begin{cases} \dfrac{d}{dt} T_t = v_t \circ T_t \\ \\ T_{t=0} = \mathrm{id}_{\mathbb{R}^3}, \end{cases}$$

and for each initial datum μ_0 we have that the solution μ_t is given by $\mu_t = T_t \sharp \mu_0$, where $T_t \sharp \mu_0$ denotes the push forward of the measure μ_0 by the vector field T_t, namely

$$\int_{\mathbb{R}^3} \varphi(x) \, d\mu_t(x) = \int_{\mathbb{R}^3} \varphi(T_t(x)) \, d\mu_0(x).$$

In this case (2) reduces to

$$\inf \left\{ \int_0^T \int_{\mathbb{R}^3} L(T_t(x), \dot{T}_t(x)) \, d\mu_0 \, dt : T_0(x) = x, \, T_1 \sharp \mu_0 = \mu_1 \right\},$$

which can be rewritten as:

$$\inf\left\{\int_{\mathbb{R}^3}\int_0^T L(\gamma_x(t),\dot\gamma_x(t))\,dt\,d\mu_0 : \gamma_x(0)=x,\ \gamma_x(T)\sharp\mu_0=\mu_1\right\}.$$

If we introduce the cost:

$$c(x,y):=\inf\left\{\int_0^T L(\gamma_x(t),\dot\gamma_x(t))\,dt, \gamma_x(0)=x,\ \gamma_x(T)=y\right\},$$

the problem can be recasted in the Monge's form:

$$\inf\left\{\int_{\mathbb{R}^3} c(x,\gamma_x(T))\,d\mu_0 : \gamma_x(0)=x,\ \gamma_x(T)\sharp\mu_0=\mu_1\right\}.$$

It is well known that in general Monge's problem has no solution, needing some smoothness to be solved, moreover due to lack of compactness we cannot in general restrict ourselves to the class of absolutely continuous measures. The relaxation of the problem, introduced by Kantorovich in 1942, involves the framework of probability measures and the notion of *transporting plans* rather than optimal transport vector fields, leading to generalized solutions of the problem. In what follows, we will denote by $\mathcal{P}(X)$ the space of probability measures on an Euclidean space X. Consider the set of *transport plans* from μ_0 to μ_1 defined by

$$\Pi(\mu_0,\mu_1)=\left\{\pi\in\mathcal{P}(\mathbb{R}^3\times\mathbb{R}^3) : \begin{array}{l}\pi(A\times\mathbb{R}^3)=\mu_0(A),\ \text{for all } \mu_0\text{-measurable } A\\ \pi(\mathbb{R}^3\times B)=\mu_1(B),\ \text{for all } \mu_1\text{-measurable } B\end{array}\right\},$$

and the following class of functions:

$$\begin{aligned}\mathcal{F}(\mu_0,\mu_1,c):=\{(f,g)\in & L^1(\mathbb{R}^3,\mu_0)\times L^1(\mathbb{R}^3,\mu_1)\\ & : f(x)+g(y)\le c(x,y) \text{ for } \mu_0\text{-a.e. } x,\ \mu_1\text{-a.e. } y\}.\end{aligned}$$

The Kantorovich's problem is to find

$$\inf_{\pi\in\Pi(\mu_0,\mu_1)}\int_{\mathbb{R}^3\times\mathbb{R}^3} c(x,y)\,d\pi(x,y).$$

This is of course a relaxation of the Monge's problem: indeed if $\gamma_x(T)$ is optimal in the Monge's problem, then $(\mathrm{id}\times\gamma_x(T))\sharp\mu_0$ is optimal in the Kantorovich's problem. We recall the following result (see Theorem 1.3 in Ref. [19]) ensuring existence of a solution for Kantorovich's problem:

Theorem 2.1. *Let μ_0, μ_1 be probability measures on $\mathbb{R}^3$, and let $c:\mathbb{R}^3\times\mathbb{R}^3\to[0,+\infty]$ be a lower semicontinuous cost function. Then*

$$\inf_{\pi\in\Pi(\mu_0,\mu_1)}\int_{\mathbb{R}^3\times\mathbb{R}^3} c(x,y)\,d\pi(x,y)=\sup_{(f,g)\in\mathcal{F}(\mu_0,\mu_1,c)}\int_{\mathbb{R}^3} f\,d\mu_0+\int_{\mathbb{R}^3} g\,d\mu_1. \tag{3}$$

Moreover the infimum in the left hand side is attained, and to compute the supremum in the right hand side we can restrict to bounded and continuous functions in $\mathcal{F}(\mu_0, \mu_1, c)$.

In order to recover a solution of our original problem, we must:

a. characterize the optimal transportation plan given by existence theorem;
b. prove some regularity properties in order to solve the problem in the Monge formulation;
c. ensure that v_t is a sufficiently smooth vector field to have existence and uniqueness of the solutions for the characteristic system.

Some remarks and alternative strategies are discussed in the last section.

The characterization of optimal transport plans needs the notions of c-transform and c-concave function: according to Definition 2.33 in [19], we introduce the c-transform of a function ψ by setting

$$\psi^c(y) := \inf_{x\in\mathbb{R}^3}\{c(x,y) - \psi(x)\},$$

and we say that f is c-concave if there exists a function ψ such that $f(y) = \psi^c(y)$.

These functions possesses a PDE characterization that turns out to be extremely useful in our setting. We denote by $AC(\mathbb{R}^+;\mathbb{R}^3)$ the set of absolutely continuous curves from $\mathbb{R}^+$ to $\mathbb{R}^3$. Taken a Lipschitz continuous function ζ and considered the function

(4)
$$\varphi(t,x) = \inf\left\{\zeta(\xi(0)) + \int_0^t L(\xi(s),\dot{\xi}(s))\,ds : \xi \in AC(\mathbb{R}^+;\mathbb{R}^3), \xi(t) = x\right\},$$

we have that $\varphi(t,x)$ is the viscosity solution of the following Hamilton-Jacobi equation:

$$\begin{cases}\partial_t\varphi(t,x) + H(x, D_x\varphi(t,x)) = 0,\\ \varphi(0,x) = \zeta(x),\end{cases} \tag{5}$$

where H is the Legendre-Fenchel transform of L, we have that $\varphi(T,x)$ is c-concave (we refer to [20] for a comprehensive introduction to the theory of viscosity solutions of Hamilton-Jacobi equations) foe every fixed T.

We recall the following theorem, referring to Section 2.4 in Ref. [19] and [21] for proof and further references:

Theorem 2.2. *Let c as in the statement of Theorem 2.1. Assume that there exists a μ_0-measurable function $c_1 : \mathbb{R}^3 \to \mathbb{R}$ and a μ_1-measurable function*

$c_2 : \mathbb{R}^3 \to \mathbb{R}$ *such that* $c(x, y) \leq c_1(x) + c_2(y)$ *for all* $(x, y) \in \mathbb{R}^3 \times \mathbb{R}^3$ *and that*

$$\inf_{\pi \in \Pi(\mu_0, \mu_1)} \int_{\mathbb{R}^3 \times \mathbb{R}^3} c(x, y)\, d\pi(x, y) < +\infty.$$

Then:

1. *there exists a c-concave function* $f \in L^1(\mathbb{R}^3, \mu_0)$ *such that its c-trasform* $f^c \in L^1(\mathbb{R}^3, \mu_1)$*, and* (f, f^c) *achieves the supremum in* (3)*.*
2. *Kantorovich's problem has a solution, and a plan* $\pi \in \Pi(\mu_0, \mu_1)$ *is optimal iff* π *is concentrated on the set*

$$\{(x, y) \in \mathbb{R}^3 \times \mathbb{R}^3 :\ f(x) + f^c(y) = c(x, y)\}.$$

3. *If* $c(x, y)$ *is continuous, bounded below, and* μ_0*,* μ_1 *are compactly supported, then* f, f^c *are upper semicontinuous. If* $x \mapsto c(x, y)$ *is locally Lipschitz on a set* U *and the Lipschitz constant is locally independent of* y*, then* f *can be chosen to be locally Lipschitz on* U*.*

In our case, the initial datum ζ of the PDE characterization of c-concavity, will be the function f given by Theorem 2.2. For further details on this, we recall Subsection 2.5.2, Subsection 5.4.6 in Ref. [19]. If φ is sufficiently smooth, from classical mechanics it is known that derivatives of φ w.r.t. the state variables x_i give the momenta p_i, and if the relation $\nabla_v L(\gamma(t), \dot{\gamma}(t)) = p(t)$ is invertible, we can recover the optimal velocities. In the same way, according to Chapter 13, Equation 13.5 in Ref. [22], the optimal interpolation velocity vector field v_t is implicitly given by $\nabla_v L(x, v_t(x)) = D_x\varphi(t, x)$ or $v_t(x) = \nabla_p H(x, D_x\varphi(t, x))$. In order to have the regularity needed to perform these computations we need to choose L (and hence H, c) such that:

1. the PDE characterization of c-concave functions holds (hence f in Theorem 2.2 may be chosen Lipschitz);
2. function $p \mapsto H(x, p)$ is C^1;
3. the gradient $D_x\varphi(t, x)$ of solution φ of Equation (5) is Lipschitz continuous.

In order to have $C^{1,1}$ solutions φ it turns out the notion of *semiconcave functions*: a function $h(x)$ is semiconcave if there exist $C > 0$ such that the function $x \mapsto h(x) - C|x|^2$ is concave. Let Ω be an open subset of $\mathbb{R}^d$ and $T > 0$. Under mild hypothesis on H (we require $H \in \mathrm{Lip}_{\mathrm{loc}}(]0, T[\times \Omega \times \mathbb{R} \times \mathbb{R}^n)$, see Theorem 5.3.8 in Ref. [23]), we have that viscosity solutions of Equation (5) are locally semiconcave in $]0, T[\times\Omega$. If also $-\varphi$ solves Equation (5), we have that $\pm\varphi$ are semiconcave, hence $\varphi \in C^{1,1}$ (see [23] for details on properties of semiconcave functions). This can be ensured by requiring some symmetry in L, i.e. $L(x,q) = L(x,-q)$. In the proposed model, we will penalize the deviations of velocities from being on the boundary of $M(x)$. Partially following ideas from [24] and [21], our aim is to embed the transport problem (2) into an optimal control problem, where solution φ of Equation (5) will play the role of *value function*. We refer to [1] for further details about the regularity issues of H and φ.

2.3. *Averaged speed model.*

We start discussing the first model of [1] where the transport cost is given by:

$$\begin{aligned} c_1(x,y) := \inf\{T>0:\ &\text{there exists } \gamma:[0,T]\to\mathbb{R}^3 \text{ such that} \\ &\gamma(0)=x,\ \gamma(T)=y, \dot\gamma(t)\in M(\gamma(t)) \text{ for a.e. } t\in[0,T]\}, \end{aligned}$$

i.e. c_1 is the minimum time needed to steer x to y with absolutely continuous curves $\xi(\cdot)$ satisfying $\dot\xi(t) \in M(\xi(t))$ for a.e. t. According to Aumann's Theorem (see e.g. Theorem 5.15 in Ref. [25]), we can replace $M(x)$ with its convex hull. If we set $H_1(x,p) = \delta_{M(x)}(-p) - 1$, where $\delta_C(p) := \sup_{q\in C} q\cdot p$ is the support function, it is known (see Proposition IV.2.3 and Theorem IV.2.6 in [20] for the proof) that for fixed x, the function $y \mapsto c_1(x,y)$ is the unique continuous and bounded below viscosity solution of $H_1(y, Du(y)) = 0$ for $y \in \mathbb{R}^3 \setminus \{x\}$ coupled with $u(x) = 0$. Moreover c_1 is a metric on $\mathbb{R}^3$ and there are constants $k_1, k_2 > 0$ such that $k_1|x-y| \le c_1(x,y) \le k_2|x-y|$. Unfortunately H does not enjoy strict convexity property, whence the solution of (5) may not enjoy the regularity needed to perform the computation discussed in the previous section. To tackle this difficulty, we add a quadratic perturbation depending on a smooth parameter $\varepsilon > 0$ in order to obtain approximate smooth solutions:

$$\begin{aligned} c_1^\varepsilon(x,y) := \inf\Bigg\{\int_0^T \left(1+\varepsilon\frac{|\dot z(t)|^2}{2}\right)dt:\ & z:[0,T]\to\mathbb{R}^3, \\ & z(0)=x,\ z(T)=y, \dot z(t)\in M(z(t)) \text{ for a.e. } t\in[0,T]\}. \end{aligned}$$

Notice that for $\varepsilon \to 0^+$ we have $c_1^\varepsilon(x,y) \to c_1(x,y)$. For every fixed x, the function $v \mapsto L_1^\varepsilon(x,v) := 1 + \varepsilon|v|^2/2$ is strictly convex, and denote by $p \mapsto H_1^\varepsilon(x,p)$ its Legendre transform. We set for given probability measures μ_0, μ_1:

$$W_2^{c_1^\varepsilon}(\mu_0,\mu_1) = \inf_{\pi\in\Pi(\mu_0,\mu_1)} \left\{\int_{\mathbb{R}^3\times\mathbb{R}^3} c_1^\varepsilon(x,y)\,d\pi\right\}^{1/2}.$$

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We notice that Theorem 2.2 applies in its stronger form, hence we can use also the PDE characterization of c_1^ε-concavity, moreover with this choice of the functional, it provides a semiconcave solution φ_ε. By the symmetry of the Lagrangian, we have that indeed φ_ε is $C^{1,1}$ so the intermediate vector field is given by $v_t^\varepsilon(x) = \nabla_p H_1^\varepsilon(x, D_x\varphi(t,x))$ for a.e. x.

2.4. *Intrinsic metric model.*

In the second model of [1], the infinitesimal metric on $\mathbb{R}^3$ is modified in order to take into account the nonisotropic character of the diffusion by penalizing the choice of $v_t(x)$ if far from $M(x)$. Due to technical reasons, we relax the problem replacing the set $M(x)$ with its convex hull. We introduce the *gauge (Minkowski) function* : for a generic set K with $0 \in \mathrm{int}(K)$, we set $\gamma_K(q) = \inf\{\lambda > 0 : q/\lambda \in K\}$.

We define the following cost function for $x, y \in \mathbb{R}^3$:

$$c_2(x,y) := \inf\left\{\int_0^T \gamma^2_{\overline{\mathrm{co}}M(z(t))}(\dot z(t))\,dt : z(0) = x, z(T) = y\right\},$$

and accordingly we set

$$W_2^{c_2}(\mu_0,\mu_1) = \inf_{\pi\in\Pi(\mu_0,\mu_1)}\left\{\int_{\mathbb{R}^3\times\mathbb{R}^3} c_2(x,y)\,d\pi\right\}^{1/2}.$$

In this case we have no constraints on velocities, hence the Hamiltonian H_2 associated to the Lagrangian $L_2(x,v) := \gamma^2_{\overline{\mathrm{co}}M(x)}(v)$ is simply given by

$$H_2(x,p) := \sup\{\langle p, v\rangle - \delta^2_{Z(x)}(v) : v \in \mathbb{R}^3\},$$

where $Z(x) := \{p \in \mathbb{R}^3 : \langle q, p\rangle \le 1 \text{ for all } q \in M(x)\}$ is the dual set of $M(x)$.

For fixed x, $v \mapsto L(x,v)$ is strictly convex, hence $p \mapsto H_2(x,p)$ is strictly convex and everywhere differentiable. We can apply also in this case Theorem 2.2 in its stronger version, obtaining a solution of the Monge-Kantorovich problem. As above, we can use also the PDE characterization of c_2-concavity, which yields a semiconcave solution φ. By the symmetry of the Lagrangian, actually φ turns out to be $C^{1,1}$, whence the intermediate vector field is given by $v_t(x) = \nabla_p H_2(x, D_x\varphi(t,x))$ for a.e. x.

3. Final remarks and open problems.

In this section we discuss some issues related to the considered, and present some directions that need further investigation.

3.1. *Advantages of the proposed model.*

It is an experimental fact that the measurements in each voxel enjoy very poor robustness properties, and sometimes we can have a voxel where no information is available, surrounded by regular voxels. This *missing cell problem* is not adequately faced by classical models, since they assume that no fibers can cross such voxels. In order to avoid this situation, we propose to assign to each empty voxel Q_α a constant profile $M(\alpha)$ given by a ball, whose radius should be determined by experimental data. In this way, the missing information in the voxel will be in some sense *reconstructed* by the information contained in the neighboring ones. Indeed, in our construction, if the infinitesimal metric is given by (the dual of) a ball, it will not change the direction of integral lines hence will not affect the data coming from the neighborhood. So fibers will be propagated in the missing voxel according to the behavior in the nearby ones. The smaller the radius of the assigned ball, the stronger must be the surrounding information to have a fiber passing through the missing cell. The lowest possible radius is given by the sensitivity of instruments.

From a medical point of view, it turns out to be important to know not only whether or not two regions are connected by a fiber bundle, but also the quantity of fibers forming that connecting bundle. This *connecting regions problem* is relevant in particular to describe situations where, due to medical pathologies, we have two cerebral areas connected by fibers that pass through a damaged region where the connection is interrupted or strongly hampered: if the connection was ensured by several fibers, the damaged area will not jeopardize the connection between the two given areas as much as in the case of a scarce number of connecting fibers.
We suggest the following criterion in order to quantitatively estimate the robustness of the connection between two regions D_0 and D_1, involving the transport distance $W_2^{c_i}$: let μ_0 and μ_1 be two measures having same mass and be absolutely continuous w.r.t. the Lebesgue measure. Assume their density is constant and their support coincides respectively with D_0 and D_1. Define the ratio

$$Q(D_0, D_1) = \frac{W_2^{c_i}(\mu_0, \mu_1)}{d_H(D_0, D_1)} \tag{6}$$

$(i = 1, 2)$, of the transport distance $W_2^{c_i}$ (related to the transport cost c_i defined in section 2.3 and 2.4) between μ_0 and μ_1 and the Hausdorff distance d_H (related to the Euclidean metric) between D_0 and D_1. A small quotient in (6) implies a high fiber density connection between D_0 and D_1.

This kind of information is apparently not provided by other tractography models that ignore information on fiber density.

3.2. *Mathematical issues and drawbacks.*

From a mathematical point of view, the main delicate issue here is to provide from an optimal transfer plan, solution of the Monge-Kantorovich problem, a (possibly) unique displacement interpolation describing the evolutive process. The obstruction is given by the *lack of smoothness* of the velocity vector field v_t (due to the presence in a voxel of multiple fibers crossing along different directions). The strategy that can be used to overcome these difficulties are based on explicit representation formulas for the solutions, regularization procedures and, in the case of nonuniqueness, also on selection principles (e.g. selecting the smoothest among all the solutions). We refer to [26] and [27] for a complete analysis of these topics, just recalling that the use of selection principles with respect to certain criteria (e.g. curvature of fibers) is extensively used also in other tractography models (e.g. [12]).

In the second model described in section 2.4, the problem was relaxed by making a *convexification* of the sets $M(x)$ in order to obtain a description of intermediate–time optimal displacements by mean of characteristic curves. This relaxation has no physical meaning, since the sets $M(x)$, giving the average displacement probabilities, are characterized by strong anisotropy. Moreover, in certain cases it is not even required to have a suitable notion of solution of Hamilton-Jacobi equation. However, in the nonconvex case, since Lax-Hopf's formula no longer holds, it is not possible in general to define a intermediate–time optimal velocity vector field based on characteristic curves. For details and counterexamples on this delicate point, we refer to [28].

3.3. *Work in progress.*

Reconstructing a reliable picture of the whole fiber net using the quantitative connectivity criterion will actually require a large number of implementations of the considered model, starting from different brain areas to be carefully chosen according to experimental data. However, the algorithmic implementation and the numerical validation of it are currently still under investigation. Our aim is to provide also an equivalent description of this model in the framework of *mean field games*, and take advantage of the associated numerical methods (see e.g. [29]).

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