Open challenges in tractography: addressing tractography biases and tackling the false-positive problem

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Sherbrooke Connectivity Imaging Lab (SCIL)







2 branches in diffusion MRI



2 branches in diffusion MRI

Tract-based Tractography Tractometry Connectomics





Probabilistic V1-A1

2 branches in diffusion MRI

Tract-based Tractography Tractometry Connectomics







Tissue properties local modelling microstructure (axon diameter, intra/extra axonal VF, g-ratio)



Towards quantitative connectomics

Tract-based Tractography Tractometry Connectomics



Tissue properties local modelling microstructure (axon diameter, intra/extra axonal VF, g-ratio)



[Daducci, Descoteaux et al. Frontiers 2016]

Different family of algorithms

- Streamline deterministic
- Streamline probabilistic
- Probabilistic
- Global techniques



[e.g. Aganj et al., MIA, 2010; Behrens et al., Nimg, 2007; Cambell et al., Nimg, 2005; Collins et al., ACCV, 2010; Descoteaux et al., TMI, 2009; Fillard et al., MICCAI, 2009; Fillard et al., NImg, 2011; Iturria-Medina et al., Nimg, 2008; Jbabdi et al., NImg, 2007; Jbabdi et al., J. Bio. Img., 2008; Jeurissen et al., Hum. Brain Mapp., 2011; Jones, TMI, 2008; Merlet et al., MICCAI, 2012; Oguz et al., MICCAI, 2012; Pontabry and Rousseau, MICCAI, 2011; Reisert et al., NImg, 2010; Sherboody et al., MICCAI, 2010; Satiropoulos et al., Nimg, 2010; Smith et al., Nimg, 2013; Tournier et al., Nimg, 2007; Tournier et al., J. Img. Sys. 2012; Takemura et al., Plos Comp. Bio., 2016; Zalesky et al., TMI, 2008]



Tractography challenges & open questions

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Tractography challenges

- No connections
- Tractography biases
 - Length bias
 - Size bias
 - Shape bias
 - Position bias (gyral bias, partial volume areas)
- Invalid connections

[Jbabdi Brain Connectivity 2011 Jones et al 2013 Chamberland Frontiers 2014]

Shape/length/size bias

[Jbabdi Brain Connectivity 2011 Jones et al 2013 Chamberland Frontiers 2014]

Shape/length/size bias

Some bundles are easier/harder to track

Optimal tracking parameters vary across the brain



[Jbabdi Brain Connectivity 2011 Jones et al 2013 Chamberland Frontiers 2014]

Shape/length/size bias

Some bundles are easier/harder to track

- Optimal tracking parameters vary across the brain
- Bigger, longer, straighter bundles
 - have more seeds in them





"seeding the whole white matter"



"seeding the whole white matter"



"seeding the whole white matter"



"seeding the whole white matter"



"seeding the whole white matter"



"seeding the whole white matter"

Solution: gm/wm interface seeding



Seeding from the wm/gm interface

reduces the shape, size & length biases

[Smith et al. NeuroImage 2012-2014] [Girard et al. NeuroImage 2014]

- Streamlines
 - near the cortex
 - in deep structures (nucleii, brainstem)
 - in & out of the cerebellum

are an **open challenge**:

- harder to track
- under-represented in the tractogram





Particle filtering tractography (PFT)

Reducing shape bias

Better management of boundaries, curving & stopping criteria



Particle filtering tractography (PFT)

Reducing shape bias

Better management of boundaries, curving & stopping criteria



Particle filtering tractography (PFT) with anatomical priors with interface seeding with PVE maps for stopping



[Gabriel Girard]

helps to reduce the positional bias [Girard et al Neurolmage 2014]



NeuroImage Volume 98, September 2014, Pages 266–278



Towards quantitative connectivity analysis: reducing tractography biases

Gabriel Girard^{e, a.}

Connectomics -Structural connectivity



tractogram





DWI

tractogram



DWI

+ T1



Cortical parcellation

tractogram



Cortical parcellation

Structural connectivity reproducibility through multiple acquisitions

Authors: Girard, G., Whittingstall, K., Deriche, R., Descoteaux, M.

- 11 subjects 3 times points
- Tractography (det/prob, wm/int)
- 150 cortical regions dilated by 2mm of the Destrieux atlas (Freesurfer) without subcortical areas
- Count tracts between ROIs to produce 150x150 connectivity matrix



Normalized tract count sum(C_{ij}) = 1



Cii



Cij

[Girard, Descoteaux et al., HBM 2015]

Normalized tract count sum(C_{ij}) = 1







[Girard, Descoteaux et al., HBM 2015]

One of the 11 subjects scanned 1 year later -Can you find him?


One of the 11 subjects scanned 1 year later -Can you find him?





0

One of the 11 subjects scanned 1 year later -Can you find him?



23.2%

1.39

29.4%

1.36

Intra-subject distance

Dunn index

)6

16.8%

1.63

19.9%

1.64

)0

3 subjects4 time points

3 subjects4 time points

At best, 15% from myself

30% from neighbor

Open challenge! Reducing variability

3 subjects4 time points

At best, 15% from myself

30% from neighbor

Tractography challenges

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- Invalid connections

Position bias : the gyral bias

Parasagittal MRI slice

What may exist (simplified)

Diffusion imaging orientations

Tractography streamlines

Surface-Enhanced Tractography

Etienne St-Onge^a, Alessandro Daducci^b, Gabriel Girard^a, Maxime Descoteaux^a

Reducing gyrial bias

- More uniform cortical coverage by streamlines
- Improves test-retest of connectome (better reproducibility) increases the inter/intra ratio from 1.6 to 2.0
- Reduces number of small 'broken' streamlines, better reconstruction of longe-range connections

[St-Onge et al ISMRM NeuroImage (under minor review)]

Open challenge (40% of empty cortex)

Tractography challenges

- No connections
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 - Length bias
 - Size bias
 - Shape bias
 - Position bias (gyral bias, partial volume areas)
- Invalid connections

invalid connections (false positives)

Dense Invalid Connections

- Connecting invalid cortical or subcortical regions
- Connecting valid regions but through a wrong path

[Cote, Girard et al., MIA, 2013]

Dense Invalid Connections

• ?%

- Connecting invalid cortical or subcortical regions
- Connecting valid regions but through a wrong path

The false positive problem

 Recent studies have shown that false positives are a major problem for tractography and connectomics

Anatomical accuracy of brain connections derived from diffusion MRI tractography is inherently limited

Cibu Thomas^{a,h,1}, Frank Q. Ye^{c,d}, M. Okan Irfanoglu^{a,b}, Pooja Modi^a, Kadharbatcha S. Saleem^a, David A. Leopold^{C,d}, and Carlo Pierpaoli^{a,b}

*Program on Pediatric Imaging and Tissue Sciences, Eurice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD, 20892; *Center for Neuroscience and Regenerative Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD 20814; *Neurophysiology Imaging Facility, National Institute of Mental Health, National Institute of Neurological Disorders and Stroke, and National Eye Institute, Bethesda, MD 20892; *Section on Cognitive Neuroscience, Laboratory of Neuropsychology, National Institute of Mental Health, Bethesda, MD, 20892; *Section on Cognitive Neuroscience, Laboratory of Neuropsychology, National Institute of Mental Health, Bethesda, MD, 20892; *Section on Cognitive Neuroscience, Laboratory of Neuropsychology, National Institute of Mental Health, Bethesda, MD, 20892; *Section on Cognitive Neuroscience, Laboratory of Neuropsychology, National Institute of Mental Health, Bethesda, MD, 20892; *Section on Cognitive Neuroscience, Laboratory of Neuropsychology, National Institute of Mental Health, Bethesda, MD, 20892; *Section on Cognitive Neuroscience, Laboratory of Neuropsychology, National Institute of Mental Health, Bethesda, MD, 20892; *Section on Cognitive Neuroscience, Laboratory of Neuropsychology, National Institute of Mental Health, Bethesda, MD, 20892; *Section on Cognitive Neuroscience, Laboratory of Neuropsychology, National Institute of Mental Health, Bethesda, MD, 20892; *Section on Cognitive Neuroscience, Laboratory of Neuropsychology, National Institute of Mental Health, Bethesda, MD, 20892; *Section on Cognitive Neuroscience, Laboratory of Neuropsychology, National Institute of Mental Health, Bethesda, MD, 20892; *Section On Cognitive Neuroscience, Laboratory of Neuropsychology, National Institute of Mental Health, Bethesda, MD, 20892; *Section On Cognitive Neuroscience, Laboratory of Neuropsychology, National Institute of Mental Health, Bethesda, MD, 20892; *Section On Cognitive Neuroscience, Laboratory of Neuropsychology, National Health, Bea

Connectome sensitivity or specificity: which is more important?

Andrew Zalesky ^{A,*}, Alex Fornito^b, Luca Cocchi^c, Leonardo L. Gollo^c, Martijn P. van den Heuvel^d, Michael Breakspear^{c,e}

How often do invalid bundles/connections occur?

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Tractography-based connectomes are dominated by false-positive connections

Klaus H. Maier-Hein, Peter Neher, Jean-Christophe Houde, Marc-Alexandre Côté, Eleftherios Garyfallidis, Jidan Zhong, Maxime Chamberland, Fang-Cheng Yeh, Ying-Chia Lin, Qing Ji, Wilburn E. Reddick, John O. Glass, David Qixiang Chen, Yuanjing Feng, Chengfeng Gao, Ye Wu, Jieyan Ma, H Renjie, Qiang Li, Carl-Fredrik Westin, Samuel Deslauriers-Gauthier, J. Omar Ocegueda González, Michael Paquette, Samuel St-Jean, Gabriel Girard, François Rheault, Jasmeen Sidhu, Chantal M.W. Tax, Fenghua Guo, Hamed Y. Mesri, Szabolcs Dávid, Martijn Froeling, Anneriet M. Heemskerk, Alexander Leemans, Arnaud Boré, Basile Pinsard, Christophe Bedetti, Matthieu Desrosiers, Simona Brambati, Julien Doyon, Alessia Sarica, Roberta Vasta, Antonio Cerasa, Aido Quattrone, Jason Yeatman, Ali R. Khan, Wes Hodges, Simon Alexander, David Romascano, Muhamed Barakovic, Anna Auría, Oscar Esteban, Alia Lemkaddem, Jean-Philippe Thiran, H. Ertan Cetingul, Benjamin L. Odry, Boris Mailhe, Mariappan S. Nadar, Fabrizio Pizzagalli, Gautam Prasad, Julio E. Villalon-Reina, Justin Galvis, Paul M. Thompson, Francisco De Santiago Requejo, Pedro Luque Laguna, Luis Miguel Lacerda, Rachel Barrett, Flavio Dell'Acqua, Laurent Petit, Emmanuel Caruyer, Alessandro Daducci, Tim B. Dyrby Tim Holland-Letz, Bram Stieltjes, **Maxime Descoteaux**

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The challenge of mapping the human connectome based on diffusion tractography

Klaus H. Maier-Hein, Peter Neher, Jean-Christophe Houde, Marc-Alexandre Côté, Eleftherios Garyfallidis, Jidan Zhong, Maxime Chamberland, Fang-Cheng Yeh, Ying-Chia Lin, Qing Ji, Wilburn E. Reddick, John O. Glass, David Qixiang Chen, Yuanjing Feng, Chengfeng Gao, Ye Wu, Jieyan Ma, H Renjie, Qiang Li, Carl-Fredrik Westin, Samuel Deslauriers-Gauthier, J. Omar Ocegueda González, Michael Paquette, Samuel St-Jean, Gabriel Girard, François Rheault, Jasmeen Sidhu, Chantal M.W. Tax, Fenghua Guo, Hamed Y. Mesri, Szabolcs Dávid, Martijn Froeling, Anneriet M. Heemskerk, Alexander Leemans, Arnaud Boré, Basile Pinsard, Christophe Bedetti, Matthieu Desrosiers, Simona Brambati, Julien Doyon, Alessia Sarica, Roberta Vasta, Antonio Cerasa, Aido Quattrone, Jason Yeatman, Ali R. Khan, Wes Hodges, Simon Alexander, David Romascano, Muhamed Barakovic, Anna Auría, Oscar Esteban, Alia Lemkaddem, Jean-Philippe Thiran, H. Ertan Cetingul, Benjamin L. Odry, Boris Mailhe, Mariappan S. Nadar, Fabrizio Pizzagalli, Gautam Prasad, Julio E. Villalon-Reina, Justin Galvis, Paul M. Thompson, Francisco De Santiago Requejo, Pedro Luque Laguna, Luis Miguel Lacerda, Rachel Barrett, Flavio Dell'Acqua, Laurent Petit, Emmanuel Caruyer, Alessandro Daducci, Tim B. Dyrby Im Holland-Letz, Bram Stieltjes, **Maxime Descoteaux**

- Includes 25 well-known ground truth bundles
- Exact ground truth connectivity (terminations)
- Covers ~70% of the white matter

Diffusion

Tensor Imaging

ISMRM 2015 Tractography challenge data

FiberFox: Neher, Laun, Stieltjes, Maier-Hein. MRM (2014)

- Includes 25 well-known ground truth bundles
- Exact ground truth connectivity (terminations)
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Diffusion

Tensor Imaging

ISMRM 2015 Tractography challenge data

FiberFox: Neher, Laun, Stieltjes, Maier-Hein. MRM (2014)

Evaluation with the Tractometer (comparison with ground truth)

[Tractometer: Côté et al Descoteaux. Medical Image Analysis (2013)]

http://www.tractometer.org/ismrm_2015_challenge/

Overview of frequently occurring valid (red) & invalid (blue) bundles.

 Invalid bundles detected by more than half of the submissions

The tractography algorithms found most existing valid bundles, but ...

http://www.tractometer.org/ismrm_2015_challenge/

The tractography algorithms found most existing valid bundles, but ...

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Tracking on ground truth directions helps on some measures but not for false positives

http://www.tractometer.org/ismrm_2015_challenge/

Tracking on ground truth directions helps on some measures but not for false positives

http://www.tractometer.org/ismrm_2015_challenge/

What do false positives look like?

Examples of invalid bundles from HARDI probabilistic

Examples of invalid bundles from HARDI probabilistic

benee & thick in locations not in the data

What's happening?







[Maier-Hein et al, NatureComm 2017]



SLF, CST, Cg, CC





Easy to track un-existent bundles!

[Maier-Hein et al, NatureComm 2017]





Local orientations are not enough!



Local orientations are not enough!



Local orientations are not enough!



Advanced streamline-weighting/filtering to reduce invalid connections

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Advanced streamline filtering techniques

- SIFT1, SIFT2, LIFE, COMMIT
 [Smith et al 2014-2015, Pestilli et al 2014, Daducci et al 2014]
- Remove streamlines that do not explain the diffusion MRI data (or assign a low weight to streamlines not explaining data)

Advanced streamline filtering techniques

- SIFT1, SIFT2, LIFE, COMMIT
 [Smith et al 2014-2015, Pestilli et al 2014, Daducci et al 2014]
- Remove streamlines that do not explain the diffusion MRI data (or assign a low weight to streamlines not explaining data)
- Tractometer reveals that they reduce invalid connections but at the price of removing some valid connections

Advanced streamline filtering techniques

- SIFT1, SIFT2, LIFE, COMMIT
 [Smith et al 2014-2015, Pestilli et al 2014, Daducci et al 2014]
- Remove streamlines that do not explain the diffusion MRI data (or assign a low weight to streamlines not explaining data)
- Tractometer reveals that they reduce invalid connections but at the price of removing some valid connections
- Global tractography shows similar trends

Prior1: Streamlines are not just lines!



- They have a volume
- There must be a conservation of density in space





"Density" map Gives the total intra-axonal volume fraction in each voxel (NODDI)

Streamlines have "volume" Every fiber contributes by its length

Prior1: Streamlines are not just lines!



- They have a volume
- There must be a conservation of density in space



Streamlines have "volume" Every fiber contributes by its length



"Density" map Gives the total intra-axonal volume fraction in each voxel (NODDI)

NOTE

This map might come <u>from any modality</u>, *e.g. myelin, T1, qMRI*

- Prior 2: Fibers are organized in bundles
 - Streamlines are not independent





[Curtesy of A Daducci & Mateo Frigo MSc]

- Prior 2: Fibers are organized in bundles
 - Streamlines are not independent

 COMMIT implementation with priors1 (conversation of density in space) priors2 (group sparsity)



[Curtesy of A Daducci & Mateo Frigo MSc]



False positives identification with COMMIT

Synthetic phantom [Caruyer et al. 2013]

- Geometry mimicking a real brain
 - 27 bundles
 - Various configurations of *crossing*, *bending* and *fanning* fibers
 - CSF contamination

Known ground-truth



True Positives (**TP**)



False Positives (FP)







False positives identification with COMMIT v2

Streamline det tracking



TP=27 (sensitivity=100%)

FP=235 (specificity=31.3%)

False positives identification with COMMIT v2



False positives identification with COMMIT v2



More anatomical priors to reduce invalid connections

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Tract selection with atlases, ROIs & anatomical knowledge



Atlas of Human Brain Connections

Marco Catari = Michel Thebaut de Schotten



 Tractometer reveals that they reduce invalid connections but at the price of removing some valid connections

Position bias: hard to track bundles

Bundle-Specific Tractography (BST)

Prior knowledge and bundle-specific parameters



[Chamberland et al 2014] [Chamberland et al HBM 2016]



[Rheault et al CDMRI 2017]

Bundle-specific tractography

Reducing position bias

- Use streamlines to create prior masks for seeding / masking
- Create orientational distribution priors































High resolution (300 um) High angular (192 dirs) Multi b-value (4 b's)

b=0

b=2000

b=4000

b=6000

[Theaud etal. ISMRM18]

V1-V2 binary connectome



1. 1.4 1.4

10.34.15

V1-V2 binary connectome





Can machine learning help tractography?

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Learn to track: Deep learning for tractography

- RNN learns the complicated and complex local/global streamline configurations not to get lost into them
- Learn to avoid invalid connections/bundles
- Notion of history & neighbouring streamlines





[Poulin et al. MICCAI 2017]








Open data challenge!

- Need more labeled data for learning!
 - Valid bundles / valid connections
 - Invalid bundles / invalid connections
 - Density maps



CST

Diffusion microstructure? *Can it reduce invalid connections*?



Diffusion measurements can be sensitive to different axon calibers



Diffusion propagator visualization [Girard et al IPMI 2015]

AxTract: Microstructureinformed tractography

- Add microstructure information from the propagator or ActiveAx-like fast solution with AMICO
- Reduce the number of false positives (by reducing the amount of bad turns taken)

Research Article

AxTract: Toward microstructure informed tractography

Gabriel Girard 🖾, Alessandro Daducci, Laurent Petit, Jean-Philippe Thiran, Kevin Whittingstall, Rachid Deriche, Demian Wassermann, Maxime Descoteaux

BRAIN MAPPIN

First published: 2 August 2017 Full publication history



[Gabriel Girard]

Explore this journal >

Deterministic HARDI Tractography - Tractometer



Kissing phantom

Deterministic HARDI Tractography - Tractometer



Kissing phantom

SNR:20 Valid connections: 53%

Invalid connections: 47%

00000 ////// 6.88µm 2.44µm **Geometry : Phantomas** [Caruyer et al., ISMRM, 2014] 114414411 · · · · × × × × / / / / DWI Signal : Camino [Hall and Alexander, TMI, 2009] 11111111 111111 1 1 1 1 1 1

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2.44µm

6.88µm

Geometry: Phantomas [Caruyer et al., ISMRM, 2014]

DWI Signal : Camino [Hall and Alexander, TMI, 2009]

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2.44µm



Geometry: Phantomas [Caruyer et al., ISMRM, 2014]

DWI Signal : Camino [Hall and Alexander, TMI, 2009]





2.44µm 6.88µm



2.44µm 6.88µm **SNR:20** Valid connections: 87% Invalid connections: 13%



6.88µm

HCP MGH data: 34 subjects - 5 shells b1000-10000



Average occurrence map where local directions was picked differently than standard tractography





Uncinate Fasciculus



Inferior Fronto-Occipital Fasciculus

Can functional imaging help tractography?

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Fibre directionality and information flow through the white matter: Preliminary results on the fusion of diffusion MRI and EEG

Samuel Deslauriers-Gauthier, Jean-Marc Lina, Russell Butler, Kevin Whittingstall, Pierre-Michel Bernier, Maxime Descoteaux

 Exploiting time delay from EEG data

[Deslauriers *et al. ISMRM* 2016] [Deslauriers *et al. MICCAI* 2017]



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Conclusion

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Towards quantitative connectomics

Connectomics

Tractography Tractometry Connectomics



Tissue properties local modelling microstructure (axon diameter, g-ratio, intra-extra axonal)





obabilistic V1-A

[Daducci, Descoteaux et al. Frontiers 2016]

Improving connectivity

- Adaptive tractography (position bias)
- Notion of neighbours (hybrid/global tracking)
- Need for advanced filtering (no space for everyone)
- Notion of anatomy (priors) & microstructure (AxTract)
- Validation and reproducibility (simulations and work on real data with tract-tracing/PLI/others)
- Bring multi-modal imaging in the picture (myelin & functional)

Diffusion in DIPY (Diffusion in Python)

- Pre-processing, registration, denoising & data quality
- Reconstruction of the local diffusion phenomena
- Tractography with anatomical priors
- Bundle analysis & streamlines post-processing
- Connectomics
- Visualization

DIPY www.dipy.org



Thank you!



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UNIVERSITÉ DE SHERBROOKE HE Dipy **Diffusion Imaging in Python**