

Validation and reproducibility in quantitative imaging of myelin microstructure

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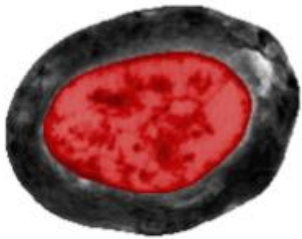
OHBM 2026 DISCLOSURES

I have no conflicts of interest in relation to this presentation to disclose.

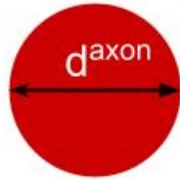
Measurements for g-ratio quantification

Histology

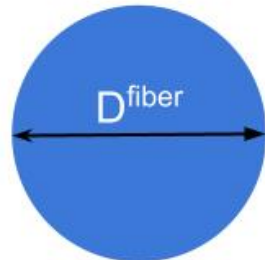
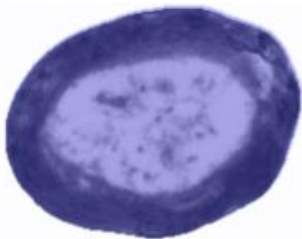
axon area



equivalent
circles

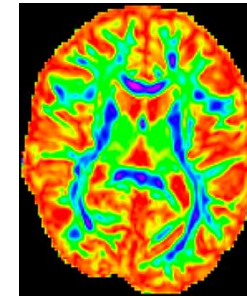


fiber area

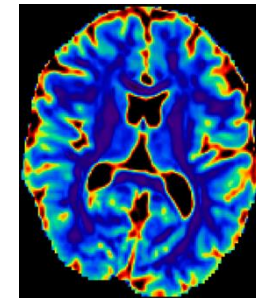


MRI

sensitive to **axon volume fraction**

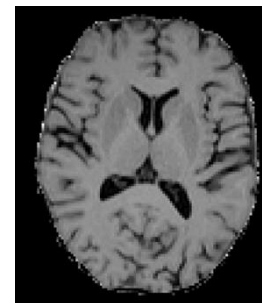


Fractional
anisotropy

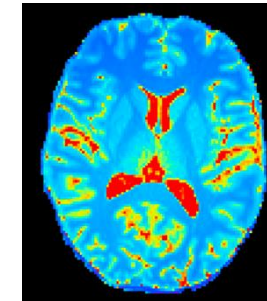


Radial
Diffusivity

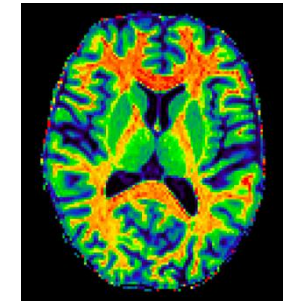
sensitive to **myelin volume fraction**



MTR



T₁



MTsat

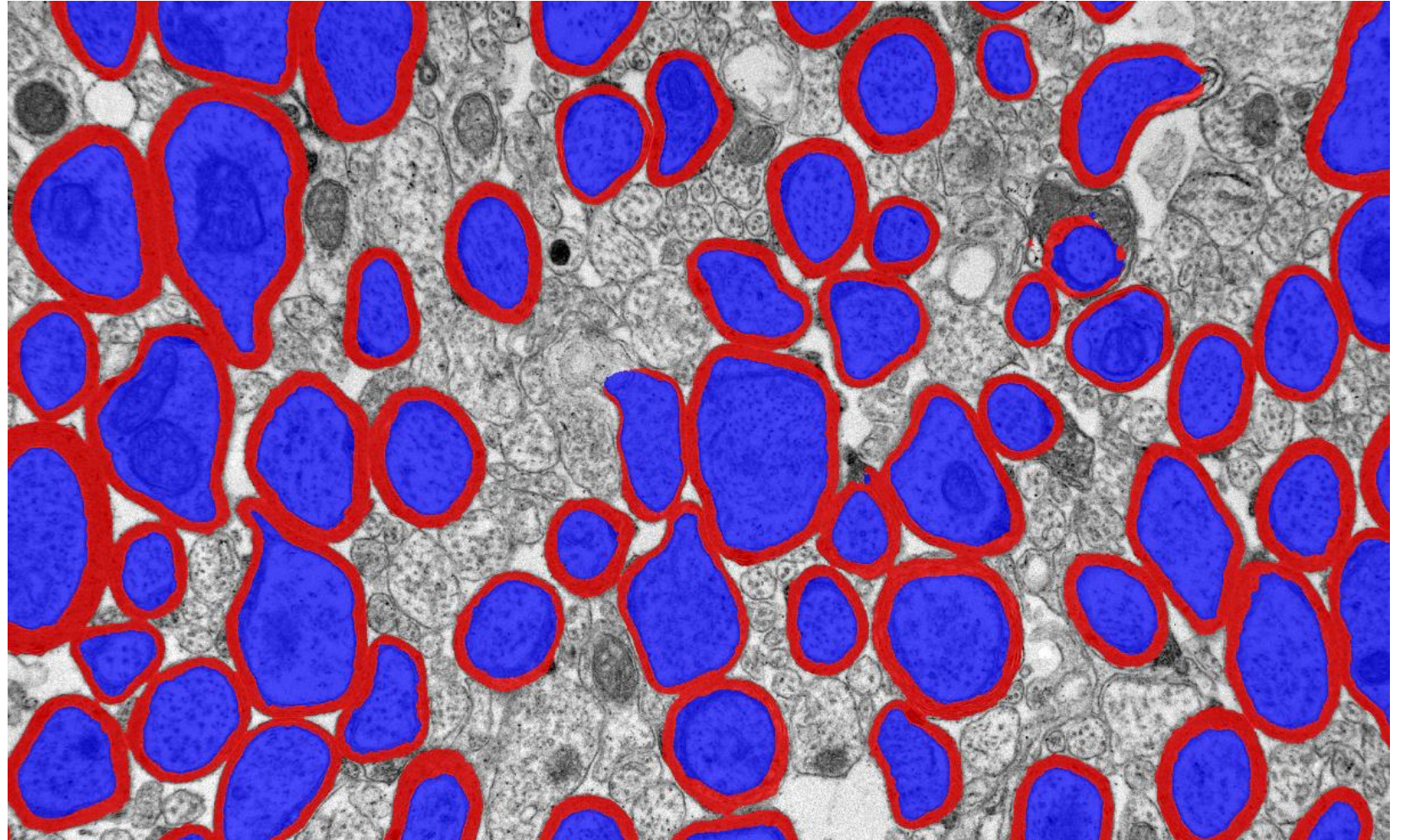
Histology

Fixation

Staining

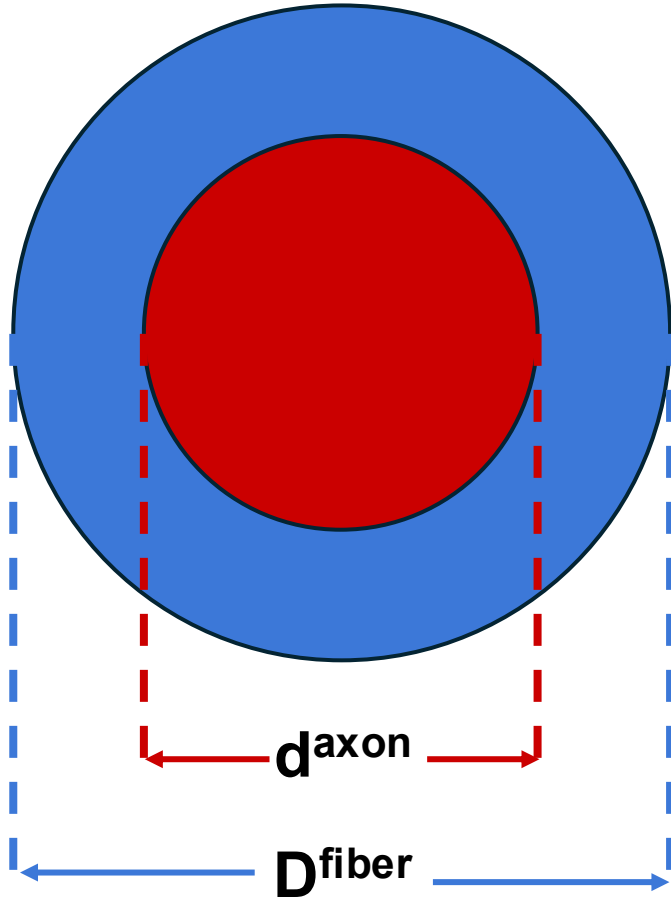
Microscopy

1 to 1000's of axons



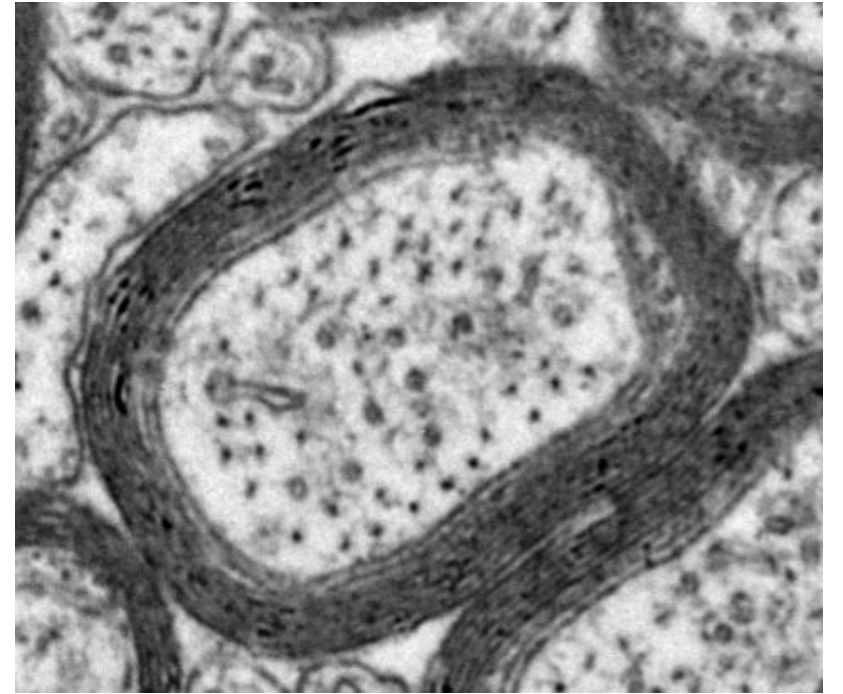
g-ratio: model vs reality

Idealized axon



$$\text{g-ratio} = \frac{d^{\text{axon}}}{D^{\text{fiber}}}$$

Real axon

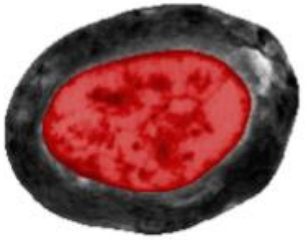


$$d^{\text{axon}} = ? \quad D^{\text{fiber}} = ?$$

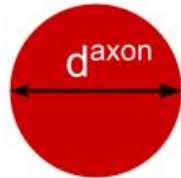
g-ratio: measurement options

Area-based

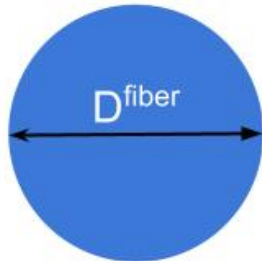
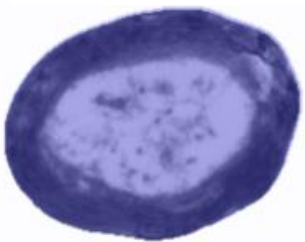
axon area



equivalent
circles

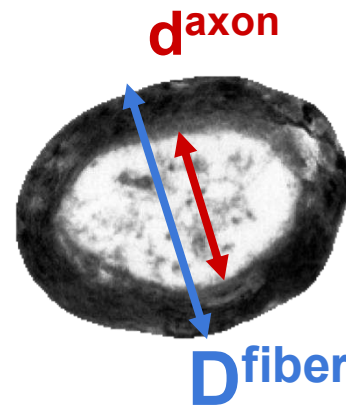


fiber area

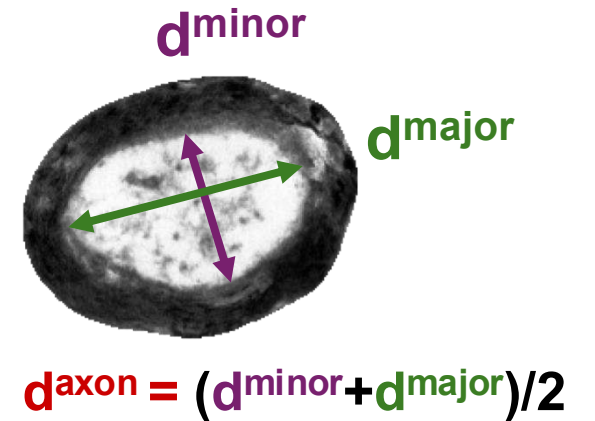


Line-based

Single-line

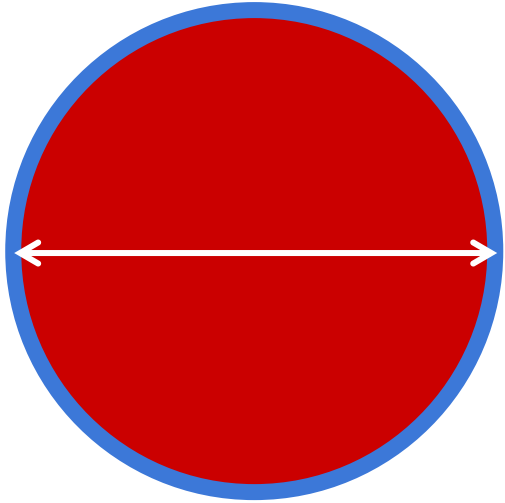


Multi-line



Not all g-ratio measures are equal

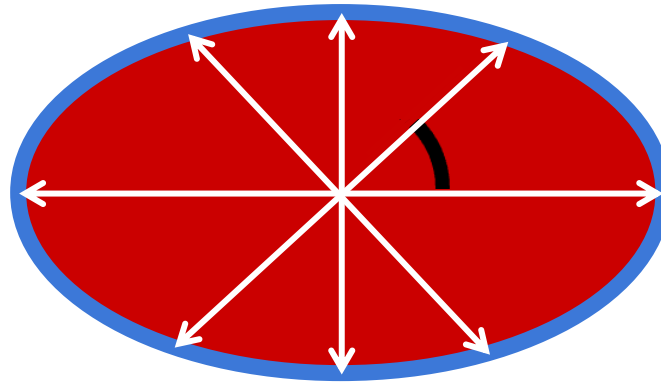
Circle



diameter = $10\text{ }\mu\text{m}$

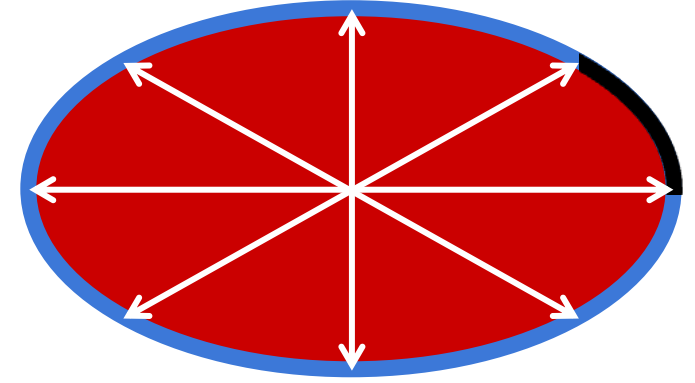
Ellipse

Equal angles



line_{avg} = $6.32\text{ }\mu\text{m}$

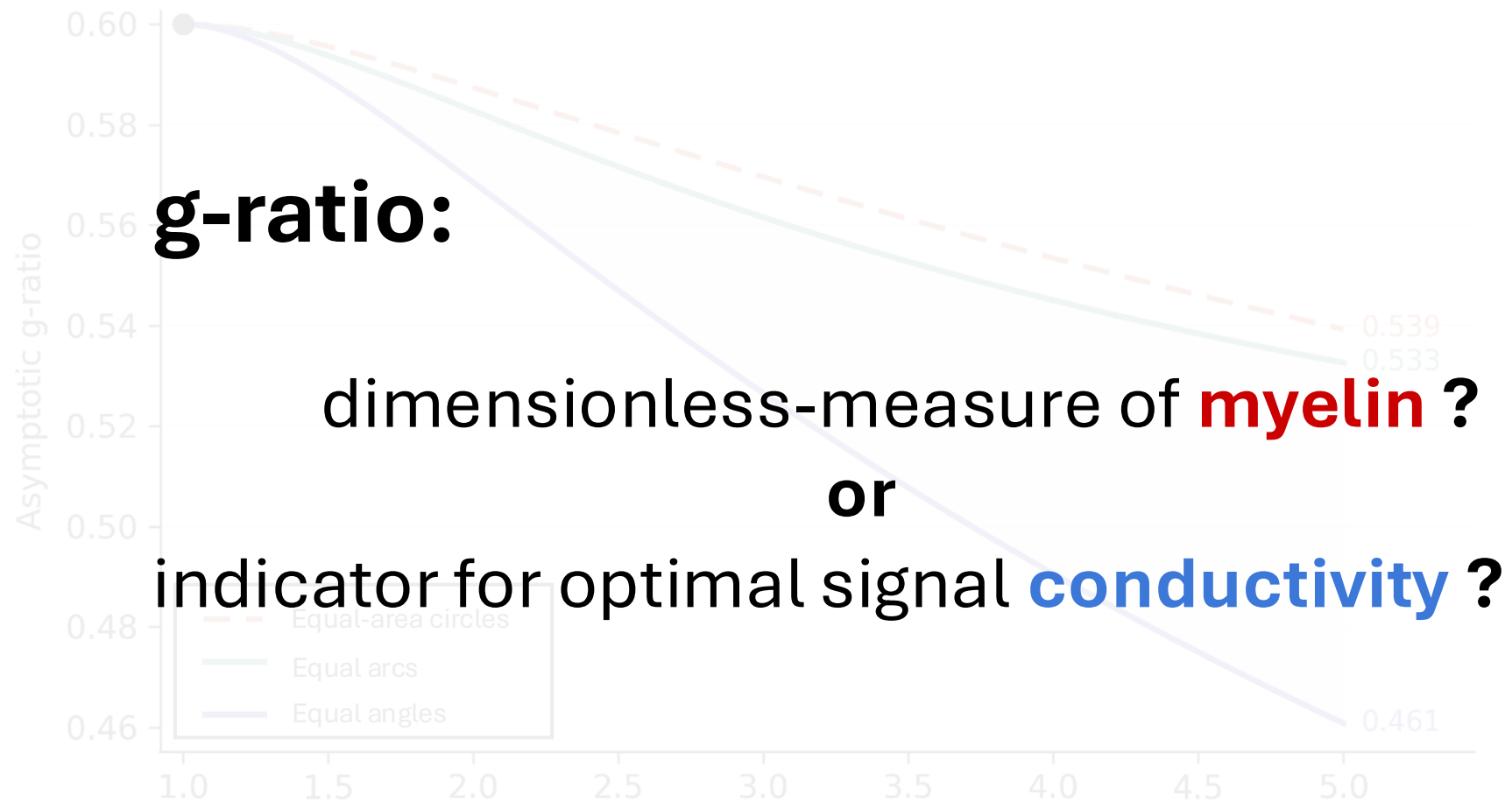
Equal arcs



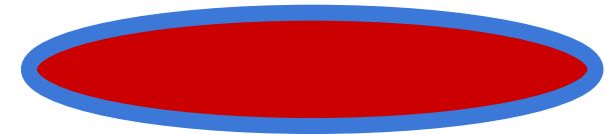
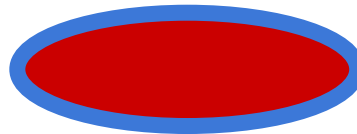
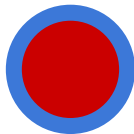
line_{avg} = $6.77\text{ }\mu\text{m}$

Bertrand's Paradox (Probability)

g-ratio: less circular $\rightarrow$ greater variation



For equivalent measured g-ratios, do these geometries produce equivalent conductivity?



Working group for the myelin g-ratio consortium

Group consensus manuscript in development

Delphi survey

Topics for open consensus

- Suitable **microscopy modalities**
- Recommended practices for:
 - **manual** measurements
 - **automated** tools
- Handling artefacts, oblique sections
- **Quality assurance**, reporting



Project Lead: **Armand Collin**



Senior PI: **Julien Cohen-Adad**

MRI

Histology defines the **g-ratio**

But are **aggregate g-ratio** measures
reproducible and **accurate**?

On validation and reproducibility of qMRI measures

Received: 17 October 2023 | Revised: 21 March 2024 | Accepted: 23 March 2024

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TECHNICAL NOTE

Magnetic Resonance in Medicine

Repeat it without me: Crowdsourcing the T₁ mapping common ground via the ISMRM reproducibility challenge

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Ecem Bozkurt⁶ | Madeline Carr^{7,8} | Marco Castellaro⁹ | Luis Concha¹⁰ |
Mariya Doneva¹¹ | Seraina A. Dual¹² | Alex Ensworth^{13,14} | Alexandru Foias¹ |
Véronique Fortier^{15,16} | Refaat E. Gabr¹⁷ | Guillaume Gilbert¹⁸ |
Carri K. Glide-Hurst¹⁹ | Matthew Grech-Sollars^{20,21} | Siyuan Hu²² |
Oscar Jalnefjord^{23,24} | Jorge Jovicich²⁵ | Kübra Keskin⁶ | Peter Koken¹¹ |
Anastasia Kolokotronis^{13,26} | Simran Kukran^{27,28} | Nam G. Lee⁶ | Ives R. Levesque^{13,29} |
Bochao Li⁶ | Dan Ma²² | Burkhard Mädler³⁰ | Nyasha G. Maforo^{31,32} |
Jamie Near^{33,34} | Erick Pasaye¹⁰ | Alonso Ramirez-Manzanares³⁵ | Ben Statton³⁶ |
Christian Stehning³⁰ | Stefano Tambalo²⁵ | Ye Tian⁶ | Chenyang Wang³⁷ |
Kilian Weiss³⁰ | Niloufar Zakariaei³⁸ | Shuo Zhang³⁰ | Ziwei Zhao⁶ |
Nikola Stikov^{1,2,39} | on behalf of the ISMRM Reproducible Research Study Group and
the ISMRM Quantitative MR Study Group



Research Article



Longitudinal reproducibility of brain and spinal cord quantitative MRI biomarkers

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Independent implementations

Controlled implementations

T₁ challenge: validating accuracy (phantom)

NIST phantom

→ known T₁ (**ground truth**)

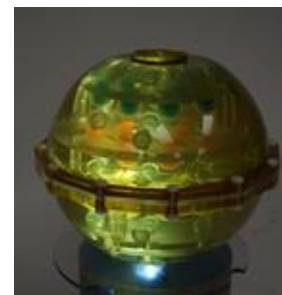
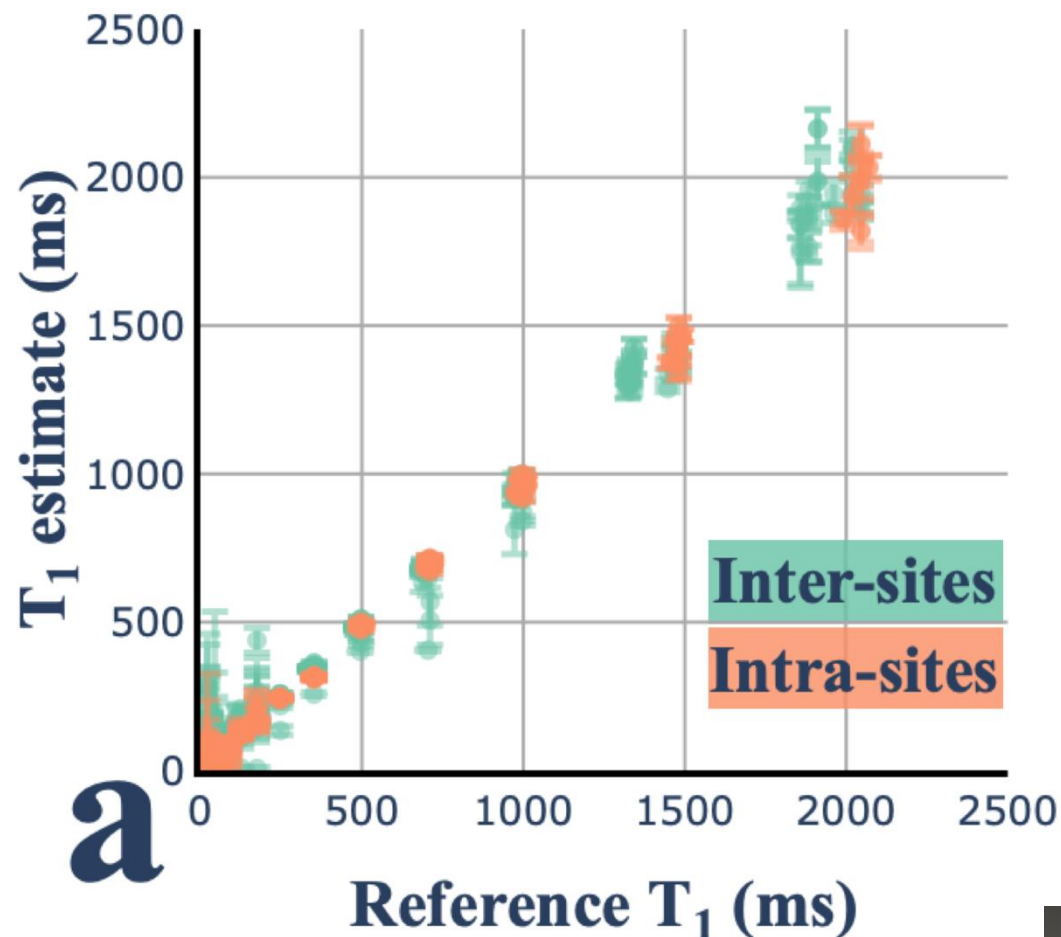
Healthy brain T₁ range at 3T

→ 700 ms to 1500 ms

Measured vs. reference

→ Removes **biological variability**

→ **Tests accuracy**, not spread



T₁ challenge: testing reproducibility (in vivo)

Real brains

→ No **ground truth**

→ Tests **reproducibility**

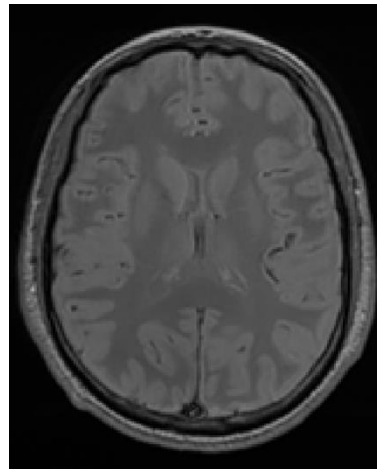
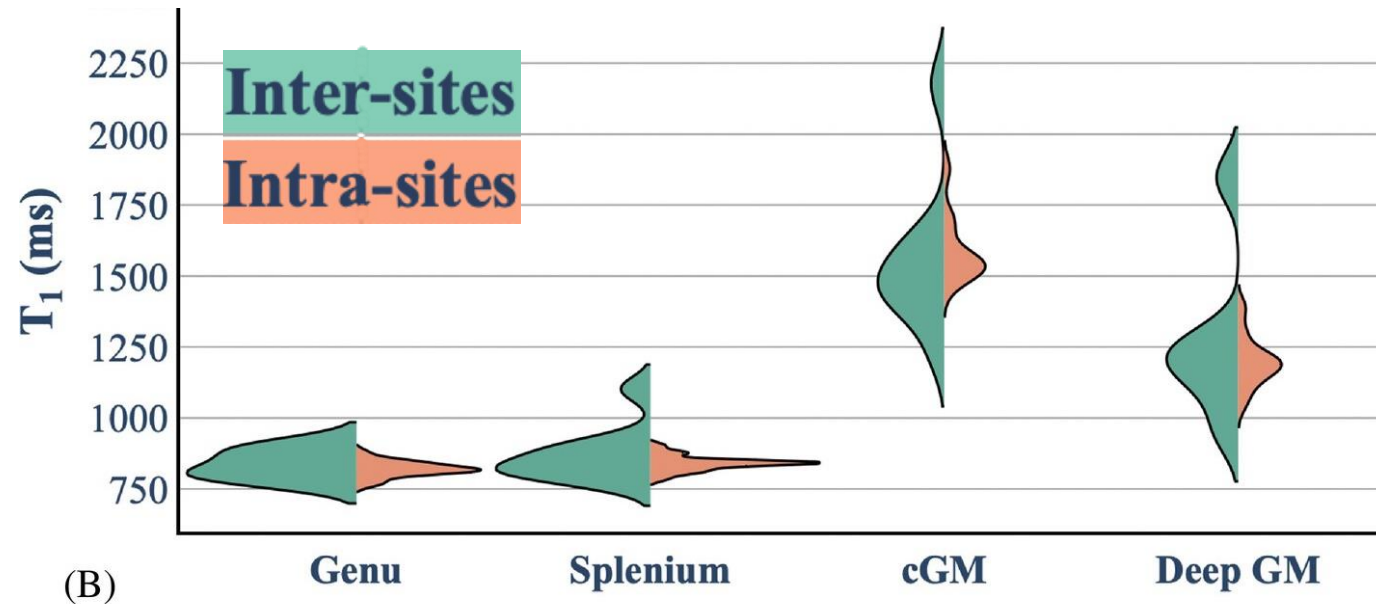
Independent vs. coordinated sites

→ Inter-sites: 2x variability

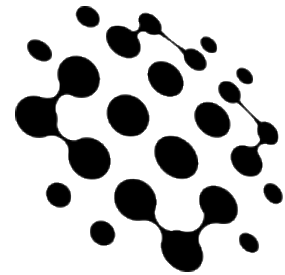
A paper is not enough

→ **Matched protocol** files (per vendor)

→ **Vendor-neutral** sequences (across vendors)



CNeuroMod: single-scanner longitudinal design

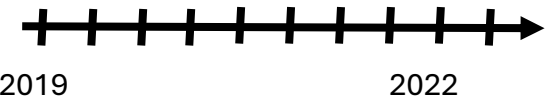


NEUROMOD

THE COURTOIS PROJECT
ON NEURONAL MODELLING



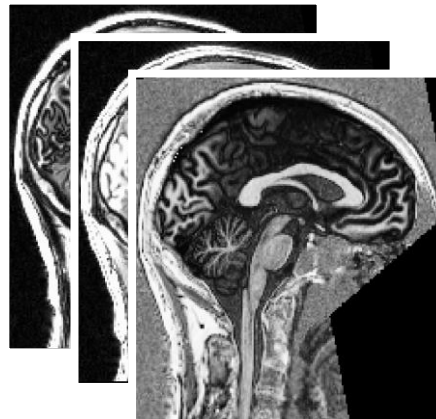
10 time points



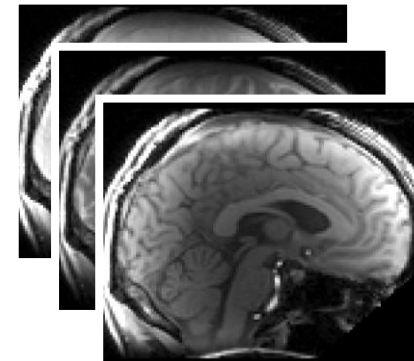
T1w (0.8mm)
Morphometry



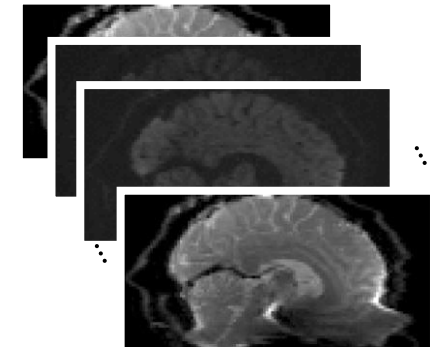
T2w (0.8mm)
Morphometry



MP2RAGE (1mm)
Demyelination



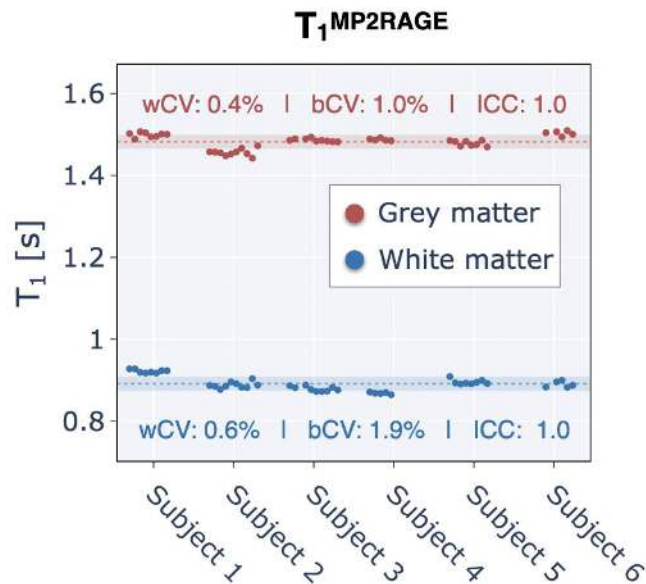
MT saturation (1.5mm)
Demyelination



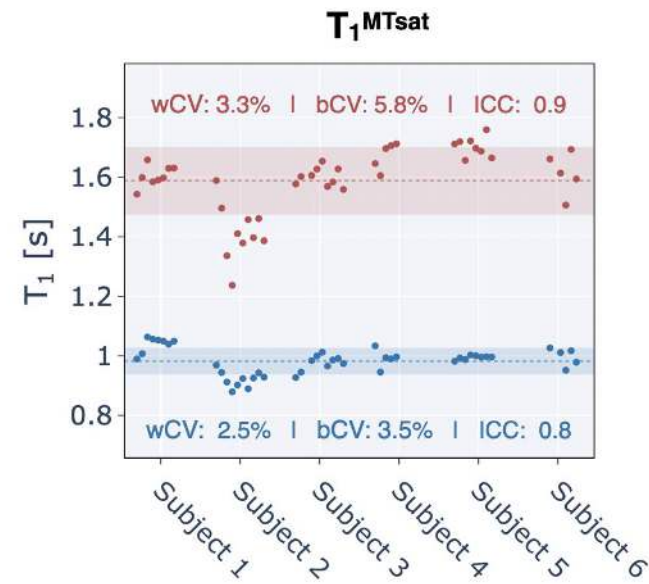
Diffusion (2mm)
Demyelination in WM
Axon degeneration

CNeuroMod: pushing reproducibility to its limit ([myelin](#))

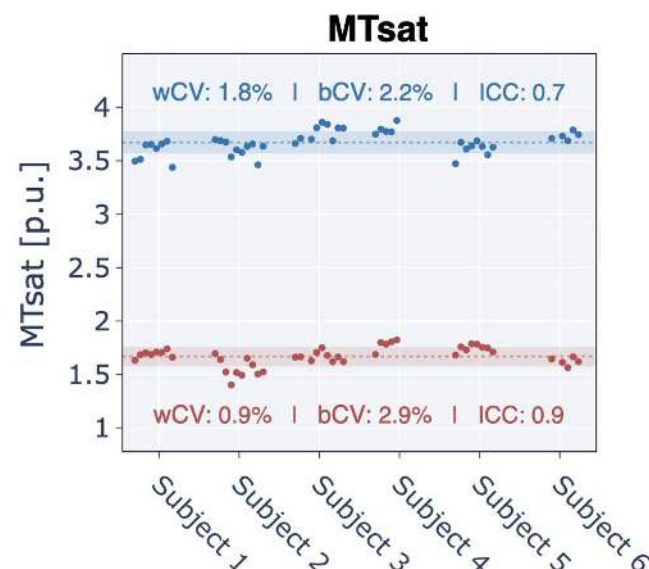
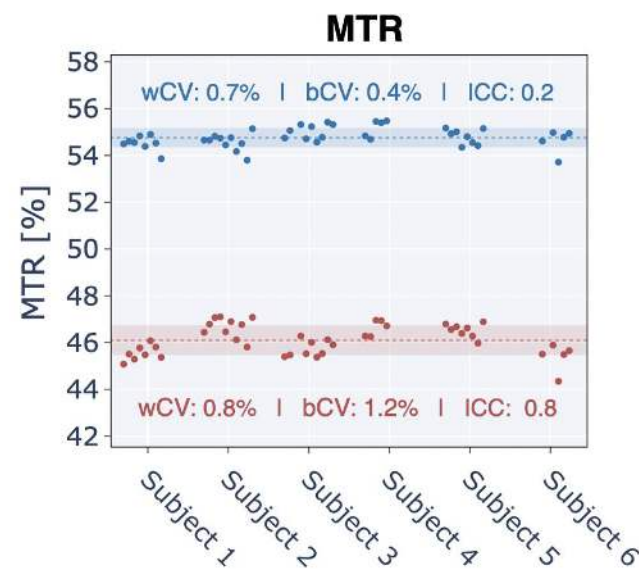
T_1^{MP2RAGE} : **reproducible** and **sensitive**



MTsat: **reproducible** and **sensitive**



MTR: **reproducible** but **not**

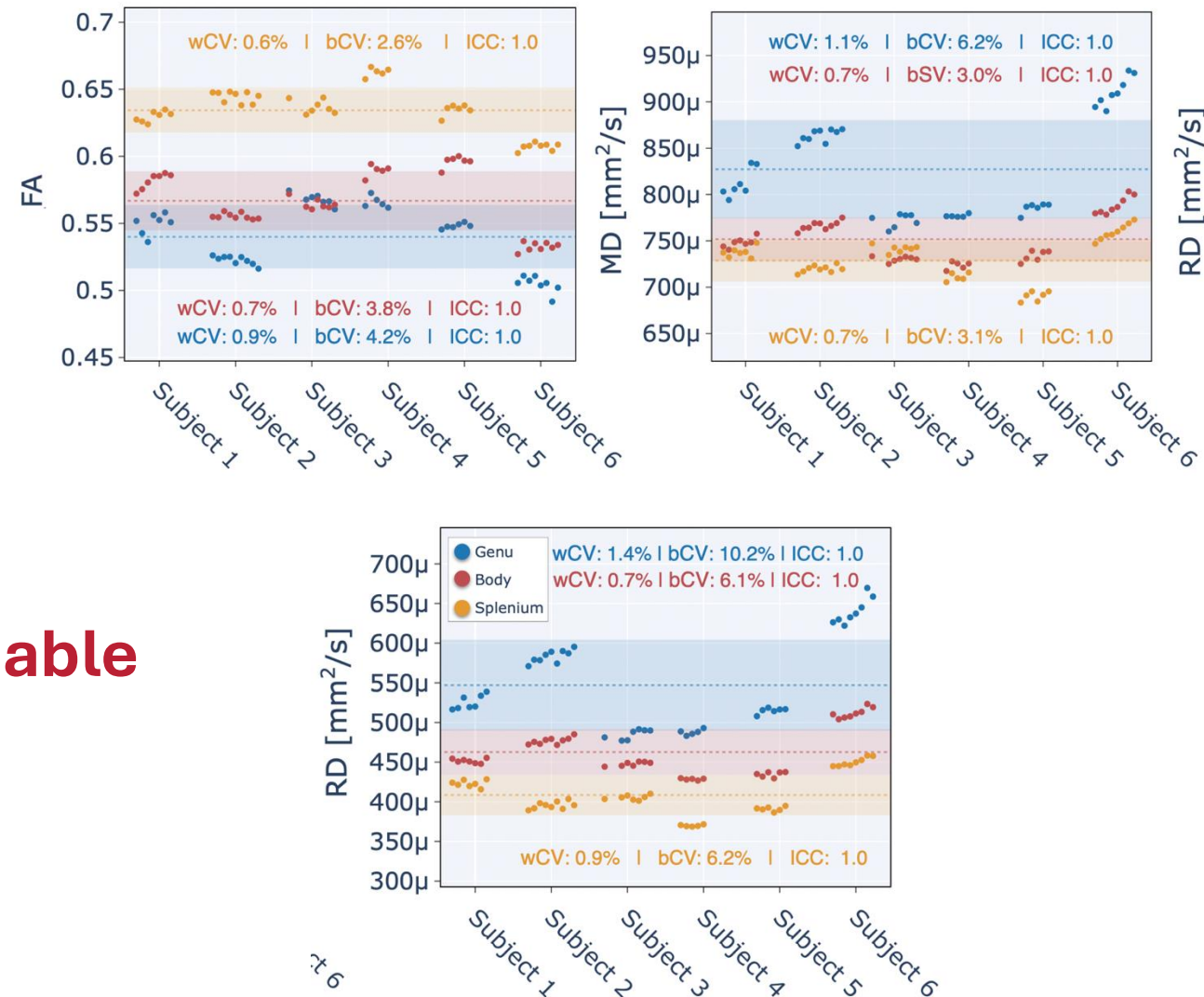


CNeuroMod: pushing reproducibility to its limit (**axon**)

FA, MD, RD: all **reproducible**

All **sensitive**: detectable subject variability

→ axon biomarkers: longitudinally **stable**



Concluding remarks

Quantitative MRI: can be reproducible and accurate

Aggregate g-ratio validation **needs histology**

→ but **no consensus** yet on how to measure it

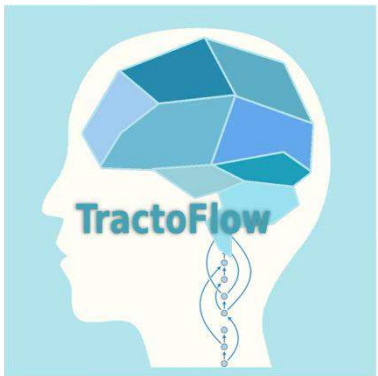
Open-source tools

MRI

hMRI



Quantitative MRI. Under one umbrella.



Pipeline managed by Nextflow
and mediated Docker



Histology



MyelTracer

Acknowledgments

ISMRM T₁ Challenge

Ecem Bozkurt	Siyuan Hu	Jamie Near
Madeline Carr	Oscar Jalnefjord	Erick Pasaye
Marco Castellaro	Jorge Jovicich	Alonso Ramirez-
Julien Cohen-Adad	Agah Karakuzu	Manzanares
Luis Concha	Kübra Keskin	Ben Statton
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Carri K. Glide-Hurst	Burkhard Mädler	Shuo Zhang
Matthew Grech-Sollars	Nyasha G. Maforo	Ziwei Zhao

Myelin g-ratio consortium

Intakhar Ahmad	Robert D Fields	Pablo Paez
Chidozie Anyaegbu	Melinda Fitzgerald	Alan Peterson
Petra M Bartmeyer	Victor Friedrich	Brian Popko
Anne Boullerne	Alexander Gow	James Salzer
Mary Bunge	Leif Havton	Alejandra Sierra
Arthur Butt	Ragnhildur	Nikola Stikov
Julien Cohen-Adad	Thóra Káradóttir	Peter Stys
Armand Collin	Grahame Kidd	Sebastian Timmler
Daniel Côté	Maarten Kole	Bruce Trapp
Ian Duncan	Taras Kotyk	Stephen Waxman
Jeffrey Dupree	Lin Mei	Brad Zuchero
Douglas Feinstein	Wiebke Möbius	
Guoping Feng	Siawoosh Mohammadi	

