New Statistical Tools to Study Heritability of the Brain

(Great data ... new challenges)

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Quality of brain fibres can impact quality of life

White matter (WM) comprises long myelinated **axonal fibres** generally regarded as passive routes connecting several grey matter regions to permit flow of information across them (brain networks).

- Elucidation of the **genes involved in WM integrity** may clarify the relationship between WM development and atrophy (e.g., Leukoaraiosis), or between WM integrity and age-related decline and disease (e.g., Alzheimer [Teipel et al., 2014]).
- This may help to suggest novel **preventative** (modification of environmental factors, if no genes are involved) or **treatment** (gene therapy) strategies for WM degeneration [Kanchibhotla et al., 2013].

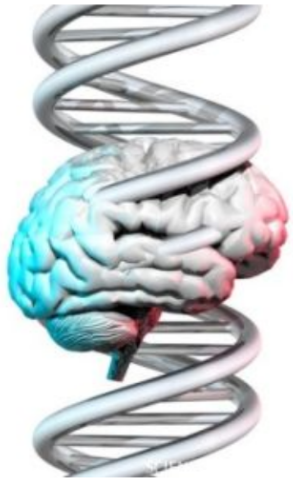
OATS study

We will use the **O**ld **A**ustralian **T**win **S**tudy (OATS) [Sachdev et al., 2009] data set, that was built by members of the **C**entre for **H**ealthy **B**rain **A**geing (CHeBA), here in Sydney : `http://cheba.unsw.edu.au`.

The OATS cohort was aged 65–88 at baseline (now has 3 waves of data over 4 years). The variables measured on the **twins** are : **Zygosity**, Age, Sex, Scanner information, **MRI measures**, **genetic information**, etc.

We want to rely the **genetic information** to some **brain charactetistics**.

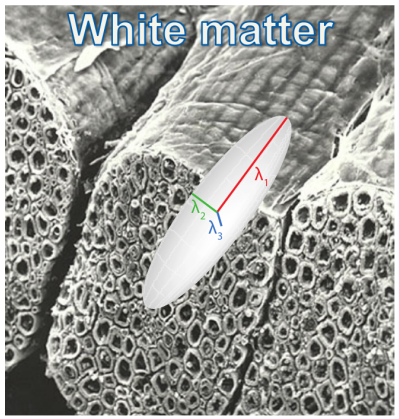
New hot field of NeuroImaging Genetics !



Let us first start by introducing a few neuroimaging concepts !

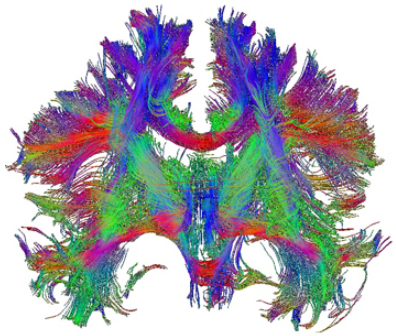
Diffusion MRI or Diffusion Tensor Imaging (DTI)

Water molecular diffusion in white matter in the brain is not free due to obstacles (fibres = neural axons). Water will diffuse more rapidly in the direction aligned with the internal structure, and more slowly as it moves perpendicular to the preferred direction.



In the diffusion tensor model, the (random vector of) water molecules' displacement (diffusion) $\mathbf{x} \in \mathbb{R}^3$ at voxel k (with center $\boldsymbol{\mu}_k$) follows a $\mathcal{N}_3(\boldsymbol{\mu}_k, \boldsymbol{\Sigma}_k)$ law. The convention is to call $D = \boldsymbol{\Sigma}/2$ the **diffusion tensor**, which is estimated at each voxel in the image from the available MR images.

The principal direction of the diffusion tensor (first eigenvector of D) can be used to infer the **white-matter connectivity** of the brain (i.e., tractography = fibre tracking).



Fractional Anisotropy (FA)

In diffusion tensor imaging a **strongly anisotropic diffusion** tensor indicates a **strong direction** of white matter fibre tracts.

A measure that is very commonly used in diffusion tensor imaging is **Fractional Anisotropy** :

$$\textbf{FA} = \left\{ \frac{1}{2} \frac{(\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_3 - \lambda_1)^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2} \right\}^{1/2} = \left\{ \frac{3}{2} \sum_{i=1}^{3} (\lambda_i - \overline{\lambda})^2 \Big/ \sum_{i=1}^{3} \lambda_i^2 \right\}^{1/2}$$

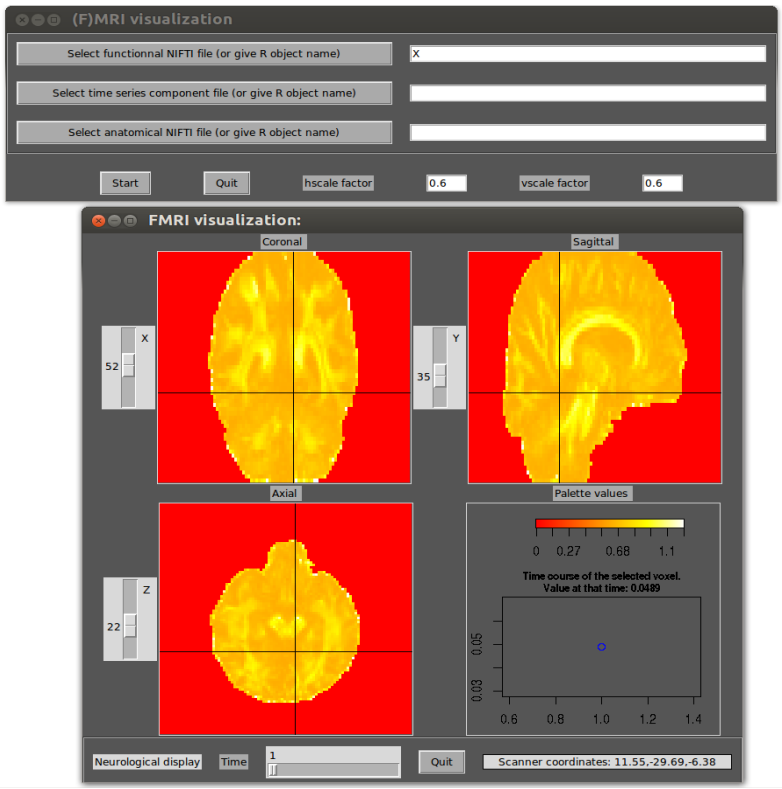
where $0 \leq FA \leq 1$ and λ_i are the eigenvalues of the diffusion tensor matrix.

Note that $FA \approx 1$ if $\lambda_1 >> \lambda_i \approx 0, i > 1$ (very strong principal axis) and $FA = 0$ for isotropy. See [Dryden et al., 2009] for other measures of anisotropy. This measure **characterizes WM integrity**.

External link : `http://brainimaging.waisman.wisc.edu/~tromp/DTI_101.pdf`

3D map of FA values

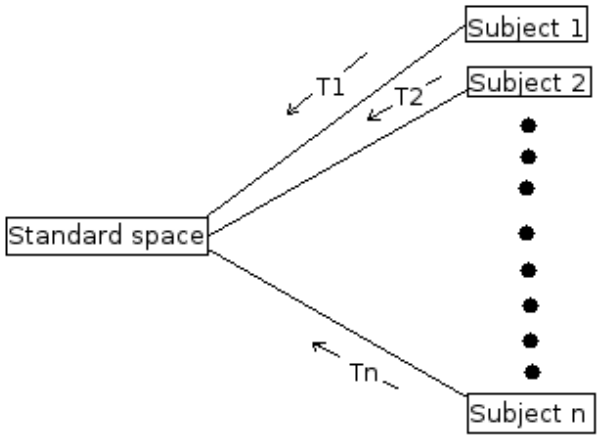
For each one of n subjects, we have a 3D map (voxels) of FA values stored in the NIFTI format that can be read using the `AnalyzeFMRI` **R** package v. 1.7 [Bordier et al., 2011].




```
require("AnalyzeFMRI")
X <- f.read.volume("11001_FA_Na.nii")
hdr <- f.read.header("11001_FA_Na.nii")
flip.fonc <- 1 ; f.plot.volume.gui(X,hdr)
```

Affine transformations : make several brains comparable

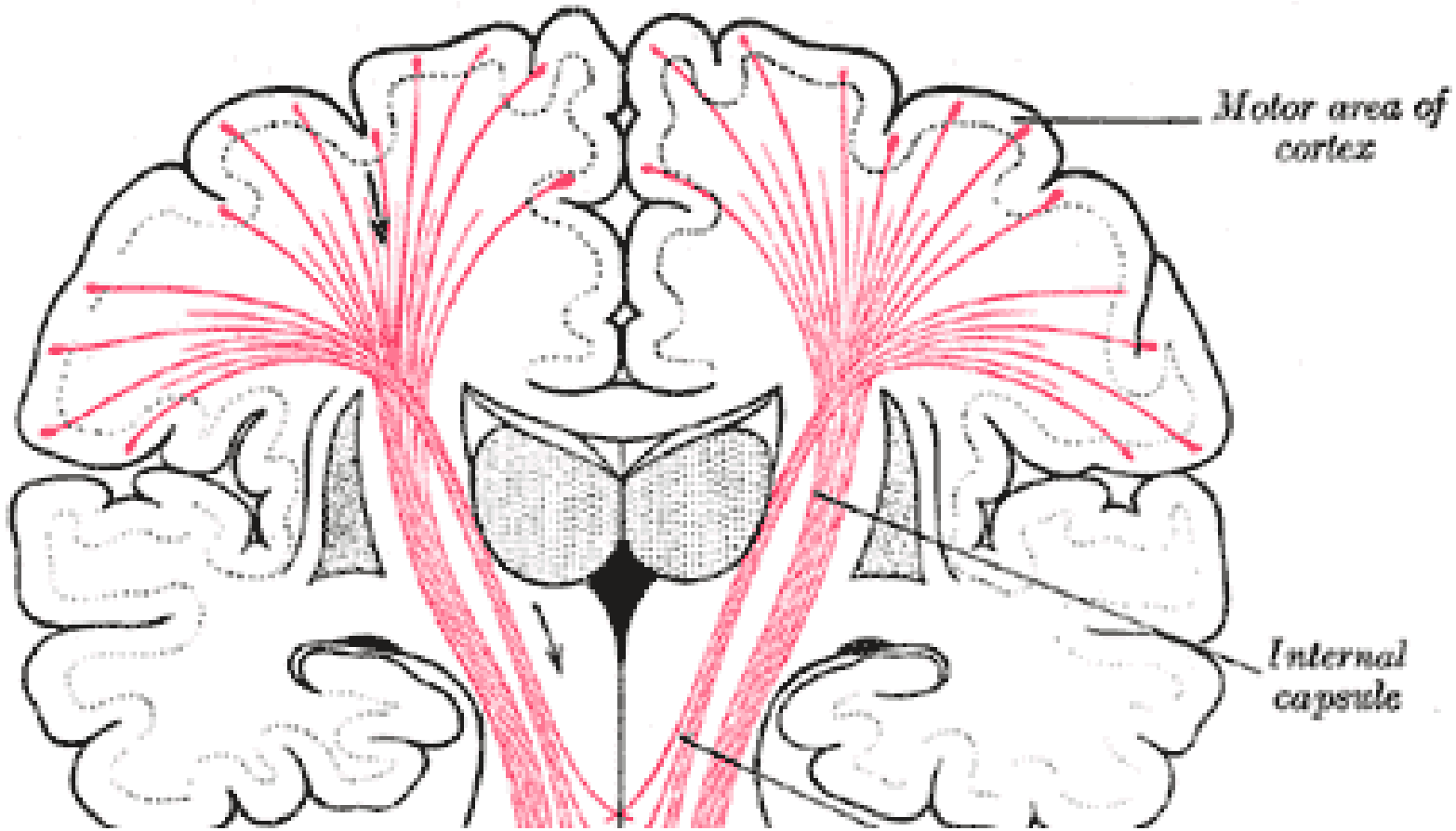
Inversible affine transformations T_i can be applied to place the brain of all the subjects into the same **Standard Space** (St.).



$$\begin{pmatrix} x \\ y \\ z \\ 1 \end{pmatrix}_{St.} = T \begin{pmatrix} x \\ y \\ z \\ 1 \end{pmatrix}_{Na.}$$

Transformation T_i, which is represented by a 4×4 affine transformation matrix (composition of Translation, Scale, Shear and Rotation), can be used to **map** any given voxel (x, y, z) in the brain of subject i (called the **Native Space** (Na.) of subject i) to the corresponding voxel in the common Standard Space, and back (using the inverse transform T_i^{-1}).

Studying the heritability of the CerebroSpinal Tract (CST)

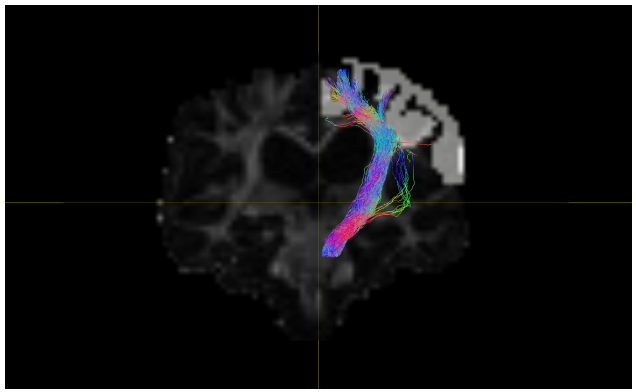


Main fibre tract of the brain (from brainstem to motor cortex).

Fibre tracking

In the Standard Space, we select, with masks, a (small = 2mm) **source region** $R_S^{St.}$ (located in the brainstem) and a (large) **target region** $R_T^{St.}$ (located in the motor cortex). These regions can be mapped back to corresponding regions $R_S^{Na.}(i)$ and $R_T^{Na.}(i)$ in each native space.

We then use the `streamtrack` function from `MRtrix` software (`http://www.brain.org.au/software/mrtrix`) to obtain, for each subject i, **a set of N_i fibres** $\mathcal{F}_i = \{f_{i,1}, \ldots, f_{i,N_i}\}$ that go from $R_S^{Na.}(i)$ to $R_T^{Na.}(i)$ (in their native space).



Note : we have two such sets for each subject (left and right hemisphere).

Data on fibres

Each fibre has two extremities, called the *origin* and *destination*.

The jth fibre $f_{i,j}$ $(j = 1, \ldots, N_i)$ of subject i is given as the (ordered, from the lower extremity to the uper extremity) set of points

$$\{P_{h,j} \equiv (x_{(h),j}, y_{(h),j}, z_{(h),j}); h = 1, \ldots, n_{f_j}\}_i.$$

This information is stored in `*.txt` files having a relatively complex structure. We have created several **R** codes to read these files and extract geometric properties of the fibres (see the `DTI.R` script).

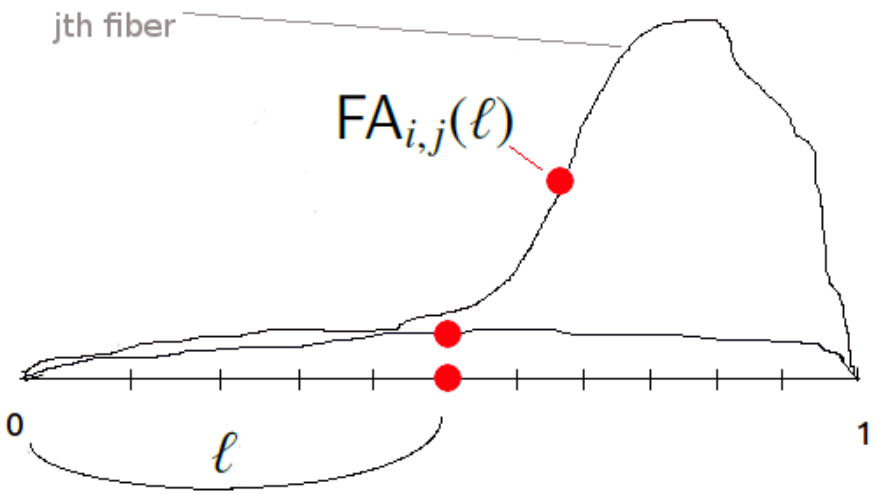
Length of fibre $f_{i,j}$ can be computed as follows :

$$L_{i,j} \equiv \sum_{h=1}^{n_f-1} d_h \equiv \sum_{h=1}^{n_f-1} \sqrt{(x_h - x_{h+1})^2 + (y_h - y_{h+1})^2 + (z_h - z_{h+1})^2}.$$

Sampling FA values along the fibres

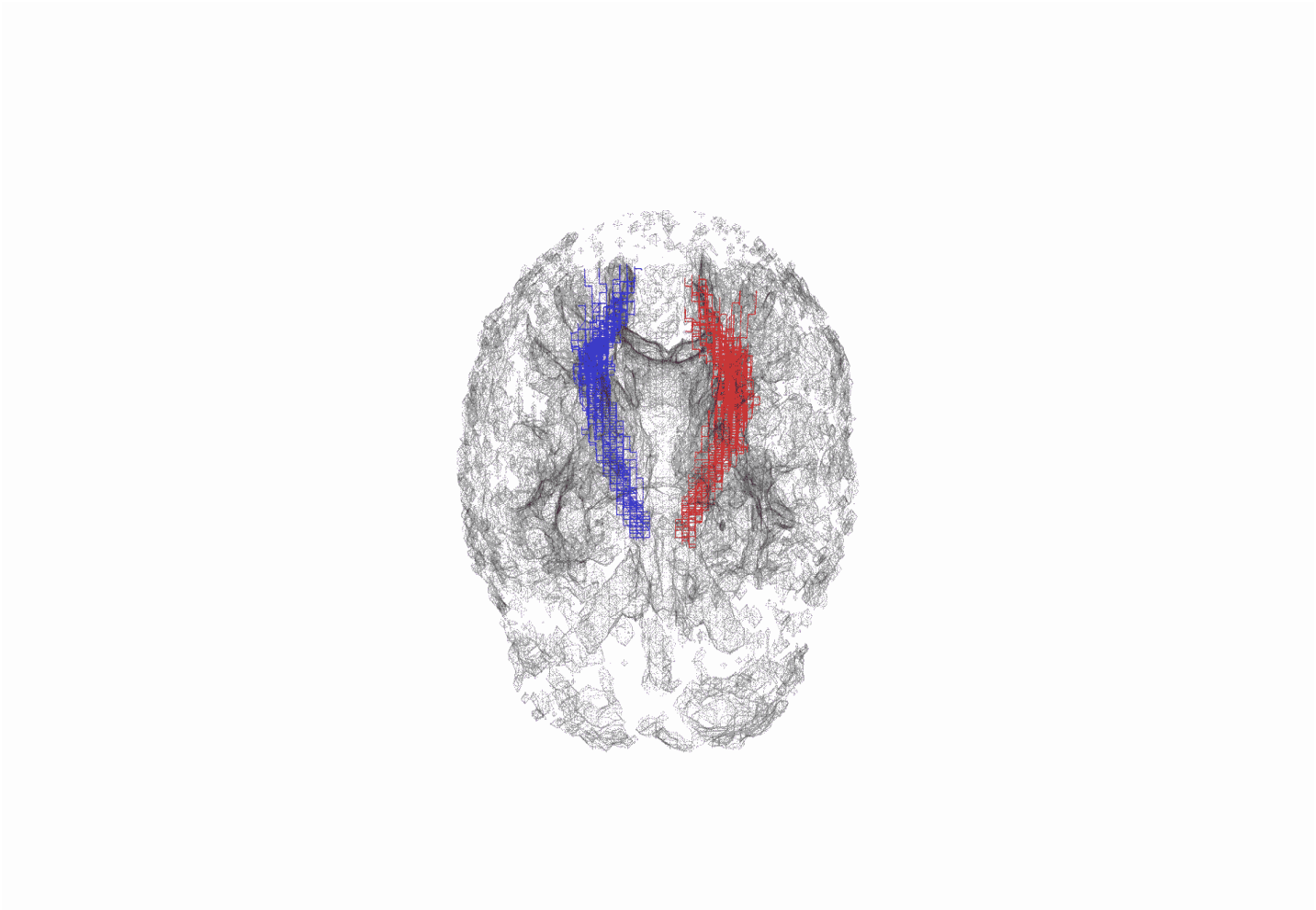
Because the fibres are not of equal length, we map each fibre to a (oriented) straight segment of length 1, divided into $q-1$ equal-length portions.

We note $\mathrm{FA}_{i,j}(\ell)$ the FA value (obtained from the 3D map) at length $\ell L_{i,j}$ on fibre $f_{i,j}$, corresponding to length ℓ $(0 \leq \ell \leq 1)$ on this $[0,1]$ segment.



Visualization of fibres geometry

Our script `rgl-fibres.R` produces the following visualization :



Note : some fibres can be thought to be outliers.

Using architecture of the fibres to remove outliers

Given a subject i :

Step 0 : Set $h = 1$ and consider the set of points $\mathcal{P}_h = \{P_{1,j}; j = 1, \ldots, N_i\}$.

Step 1 : Compute the projection median M_h [Basu et al., 2012] (or the trimmed centroid) of the set of points $\mathcal{P}_h$.

Step 2 : Find the nearest point to M_h among $\{P_{h,j}; j = 1, \ldots, N_i\}$ and call it $P_{h,k}$.

Step 3 : If ($P_{h+1,k}$ exists) Then {Consider the vector $\overrightarrow{P_{h,k}P_{h+1,k}}$ and find the orthogonal plane to this vector that goes through $P_{h+1,k}$} Else Stop.

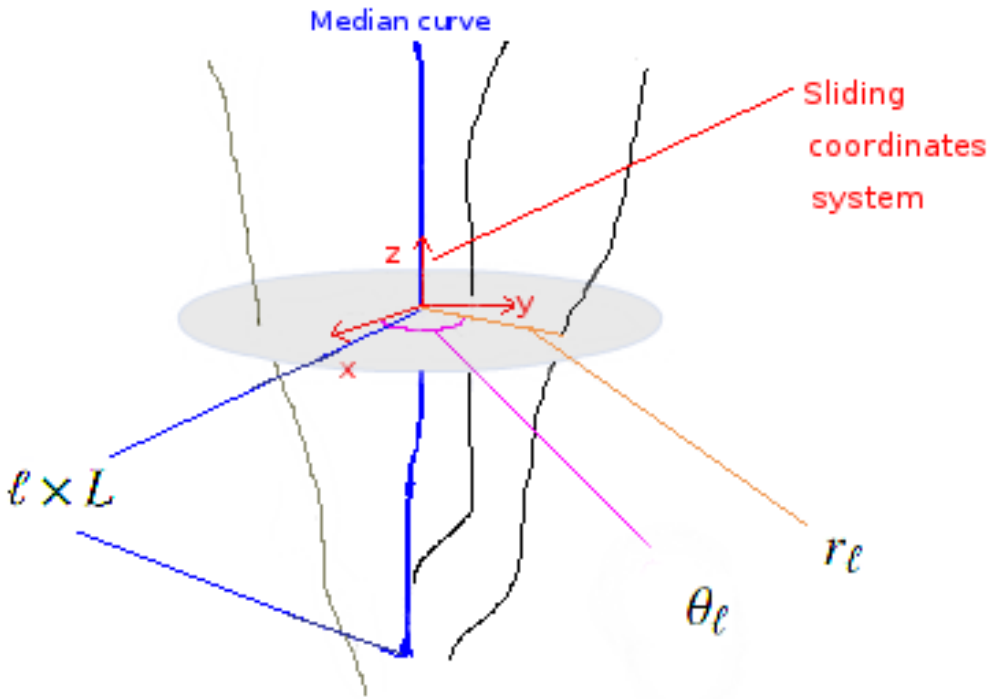
Step 4 : Find one point on each one of the N_i (discretized) fibres that is closest to this plane. Call $\mathcal{P}_{h+1}$ this new set of N_i points.

Step 5 : If ($\mathcal{P}_{h+1} \neq \mathcal{P}_h$) Then {$h \leftarrow h + 1$ and goto **Step 1**} Else Stop.

The "curve" built using these values $\{M_h; h \geq 1\}$ will be called the **Median curve of the bundle** (3D spatial median of the N_i fibres).
We can then remove the fibres too far apart from this Median curve.

Characterizing the geometry of the fibres

We can also parameterize each fibre with respect to this median curve using three "polar coordinates" : $(\ell, r_\ell, \theta_\ell)$ where $\ell \times L$ is the position (arc length) along the median curve (of length L), r_ℓ is the distance from the fibre to the median curve at position ℓ and θ_ℓ is the angle, using a sliding coordinates system (z axis is aligned with the median curve), $\ell \in [0, 1]$.



Complete characterization of the bundle

For each subject i $(i = 1, \ldots, n)$, we observe N_i fibres $f_{i,j}$ $(j = 1, \ldots, N_i)$. The jth fibre is characterized by the set of triplet values :

$$f_{i,j} = \left\{ (FA_{i,j}(\ell), \theta_{i,j}(\ell), r_{i,j}(\ell)); \ell = \frac{0}{q-1}, \frac{1}{q-1}, \ldots, \frac{q-1}{q-1} \right\}.$$

More formally, we can consider that the whole CST bundle of a subject is characterized by a trivariate stochastic process

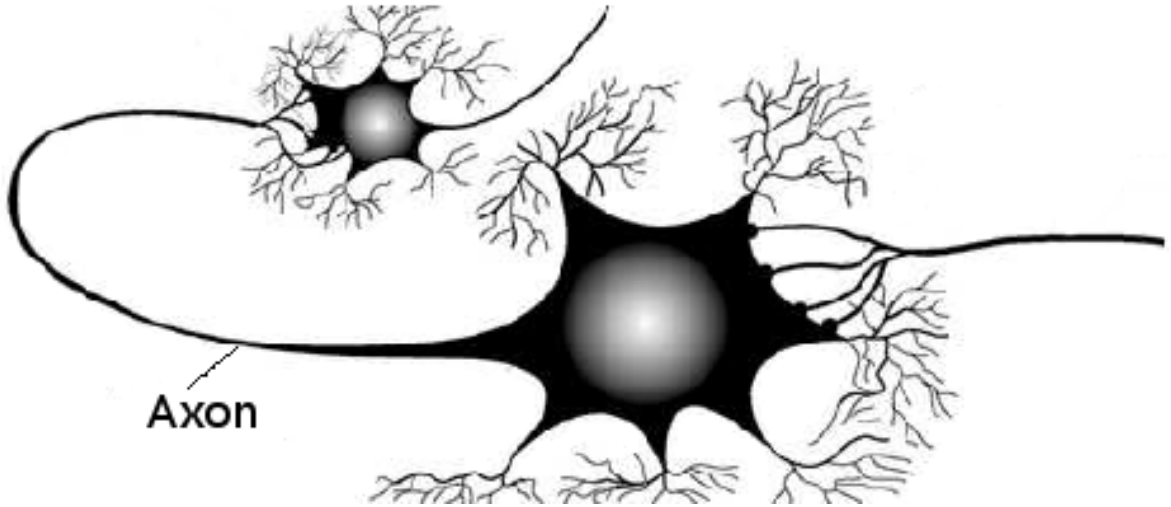
$$\{\mathbf{Y}_\ell\}_{\ell \in [0,1]} \equiv \{\mathbf{Y}_\ell = (FA(\ell), \theta(\ell), r(\ell)); \ell \in [0,1]\}.$$

For a given subject i and a given value of $\ell \in [0,1]$, we have several (i.e., N_i repeated) observations of $\mathbf{Y}_{i,\ell}$.

We can also apprehend this problem by working with functional data on the space of 3D parameterized curves (of parameter ℓ).

Scientific aim : explore heritability of the fibre bundle

- The objective is to explore what is called the **heritability of the fibre bundle**.
- We want to examine whether a white matter bundle of fibres has a **uniform genetic control** over its entire length of axons.
- If some heritability is found, this will be a hint to further try to find which SNPs (or genes) are involved in the observed phenotype (e.g., FA here).



Some papers on this topic : [Chiang et al., 2008, Chiang et al., 2012], [Prasad et al., 2014], [Kochunov et al., 2010], [de Zubicaray et al., 2008]

Heritability

- **Heritability** h^2 measures the fraction of **phenotype variability** that can be attributed to **genetic variation**.
- Heritability is measured by estimating the relative contributions of genetic and non-genetic differences to the total phenotypic variation in a population.

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Any particular phenotype (trait) can be modeled as the sum of genetic effects, environmental effects and residual effects

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A particularly important component of the genetic variance is the **additive variance**, $\mathbb{V}\text{ar}(A)$, which is the variance due to the average effects (**additive effects**) of the alleles. The additive genetic portion of the phenotypic variance is known as Narrow-sense heritability :

$$h^2 = \frac{\mathbb{V}\text{ar}(A)}{\mathbb{V}\text{ar}(P)}$$

ACE model for the Fractional Anisotropy

$$FA_{sf} = \mu + A_{s,f} + C_{s,f} + E_{s,f}, \qquad s\text{=subject}, \quad f = \text{family}$$

$A_{s,f} \sim \mathcal{N}(0, \sigma_A^2)$ is an additive genetic component, $C_{s,f} \sim \mathcal{N}(0, \sigma_C^2)$ a common environment component and $E_{s,f} \sim \mathcal{N}(0, \sigma_E^2)$ a unique environment component (components are assumed to be mutually independent).

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The total variance of the Fractional Anisotropy is :

$$\mathbb{V}\text{ar}(FA_{s,f}) = \sigma_A^2 + \sigma_C^2 + \sigma_E^2.$$

Heritability is then defined as :

$$h^2 = \frac{\sigma_A^2}{\sigma_A^2 + \sigma_C^2 + \sigma_E^2}.$$

ACE model for Twin Data

Monozygotic twins (MZ) share all their genes while **Dizygotic** twins (DZ) share half of their genes. Consider two unrelated twin pairs $f = 1, 2$ with twins $s = 1, 2$ in each pair (first pair is (MZ,MZ) and second (DZ,DZ)).

$$\mathbb{V}\mathrm{ar}\begin{pmatrix} A_{1,1} \\ A_{2,1} \\ A_{1,2} \\ A_{2,2} \end{pmatrix} = \sigma_A^2 \begin{bmatrix} 1 & 1 & 0 & 0 \\ 1 & 1 & 0 & 0 \\ 0 & 0 & 1 & 1/2 \\ 0 & 0 & 1/2 & 1 \end{bmatrix} ; \quad \mathbb{V}\mathrm{ar}\begin{pmatrix} C_{1,1} \\ C_{2,1} \\ C_{1,2} \\ C_{2,2} \end{pmatrix} = \sigma_C^2 \begin{bmatrix} 1 & 1 & 0 & 0 \\ 1 & 1 & 0 & 0 \\ 0 & 0 & 1 & 1 \\ 0 & 0 & 1 & 1 \end{bmatrix}$$

$$\mathbb{V}\mathrm{ar}\begin{pmatrix} E_{1,1} \\ E_{2,1} \\ E_{1,2} \\ E_{2,2} \end{pmatrix} = \sigma_E^2 \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}.$$

This model is usually fitted using the OpenMX software (`http://openmx.psyc.virginia.edu`) that performs Structural Equation Modelling (SEM). There is also the function `twinlm()` in the **R** package `mets`. And also the software SOLAR (`http://solar.txbiomedgenetics.org`).

Reparameterization of an ACE model

$$FA_{s,f} = \mu + \pi_f^{Pair} + \eta_{s,f}\pi_f^M + (1 - \eta_{s,f})\pi_{s,f}^M + \epsilon_{s,f}.$$

See [Visscher et al., 2004, Rabe-Hesketh et al., 2008].

- $\pi_f^{Pair} \sim \mathcal{N}(0, \sigma^2_{Pair})$: random effects shared by all twins from the same family f.
- $\eta_{s,f}$ is an indicator variable with 1 for MZ and 0 for DZ.
- $\pi_f^M \sim \mathcal{N}(0, \sigma^2_M)$: random effects shared by only monozygotic twins from the same family.
- $\pi_{s,f}^M \sim \mathcal{N}(0, \sigma^2_M)$: random effects that concern only dizygotic twins but are different for each twin from the same family.

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	Covariance	
Twins	ACE	Reparameterization
MZ	$\sigma^2_A + \sigma^2_C$	$\sigma^2_{Pair} + \sigma^2_M$
DZ	$\frac{1}{2}\sigma^2_A + \sigma^2_C$	σ^2_{Pair}

$\hookrightarrow \sigma^2_A = 2 \times \sigma^2_M$ and $\sigma^2_C = \sigma^2_{Pair} - \sigma^2_M$.

Organization of data

Subject	Family	zyg(1=MZ ;0=DZ)	Pair	M	FA
1	1	1	P1	M1	Y1
2	1	1	P1	M1	Y2
3	2	0	P2	M2	Y3
4	2	0	P2	M3	Y4
5	3	0	P3	M4	Y5
6	3	0	P3	M5	Y6
7	4	1	P4	M6	Y7
8	4	1	P4	M6	Y8

Estimation using the R software

```
require("lme4")
model <- lmer(FA~1+(1|Pair)+(1|M),REML=FALSE)
res <- summary(model)
sig2E.es <- res$sigma**2
sig2A.es <- 2*res$varcor[1]$M[1]
sig2C.es <- res$varcor[2]$Pair[1]-res$varcor[1]$M[1]
(h2.es <- sig2A.es/(sig2A.es+sig2C.es+sig2E.es))
```

Equivalently, one can use :

```
require("nlme")
model.lme <- lme(FA~1,random=list(Pair=~1,M=~1),data=DataM,method="ML") # or equivalently:
model.lme <- lme(FA~1,random=list(Pair=pdDiag(~1),M=pdDiag(~1)),data=DataM,method="ML")
res.lme <- summary(model.lme)
sig2E.es <- res.lme$sigma**2
tmp <- as.numeric(VarCorr(res.lme)[4])
sig2A.es <- 2 * tmp[4]
sig2C.es <- tmp[2] - tmp[4]
(h2.es <- sig2A.es/(sig2A.es+sig2C.es+sig2E.es))
```

Note : For SAS, see [Feng et al., 2009, Wang et al., 2011].

Presence of heritability

We want to confront (test) the hypotheses :

$$\mathcal{H}_0 : h^2 = 0 \Leftrightarrow \sigma_A^2 = 0 \quad \textit{versus} \quad \mathcal{H}_1 : h^2 > 0 \Leftrightarrow \sigma_A^2 > 0.$$

Likelihood ratio test (LRT) is given by comparing the full model to the following restricted one :

$$FA_{s,f} = \mu + \pi_f^{Pair} + \epsilon_{s,f}.$$

Note that the distribution of the LRT statistic is a mixture $(1/2)\chi_0^2 + (1/2)\chi_1^2$ (see [Guo and Wang, 2002]). This necessitates to halve the p-value (see [Dominicus et al., 2006]).

Estimation using the R software

```
require("lme4")
model0 <- lmer(FA~1+(1|Pair),REML=FALSE)
test <- anova(model,model0)
(pvalue <- test$Pr[2]/2)
```

Equivalently, one can use :

```
require("nlme")
model.lme.0 <- lme(FA~1,random=list(Pair=~1),
                   data=DataM,method="ML")
test <- anova(model.lme,model.lme.0)
(pvalue <- test.lme$"p-value"[2]/2)
```

Application on real data

For each subject, one global FA mean value is computed for the bundle (from FA values over all positions and all fibres). Then heritability is obtained using the **R** script `heritability-total-mean.R`.

```
> Left.h2
[1] 0.4923544
> Right.h2
[1] 0
> Left.pval
[1] 0.04894947
> Right.pval
[1] 0.5
```

Application on real data (following)

We now take into account the position along the bundle, by dividing it into 2 then 4 portions. Heritability (and p-value) is then computed for each portion using the **R** script `heritability-portions.R`.

Left hemisphere

2 portions			
0.54 (0.022)		0.55 (0.027)	
4 portions			
0.74 (9.93e-05)	3.97e-16 (0.49)	0.43 (0.044)	0.63 (0.0069)

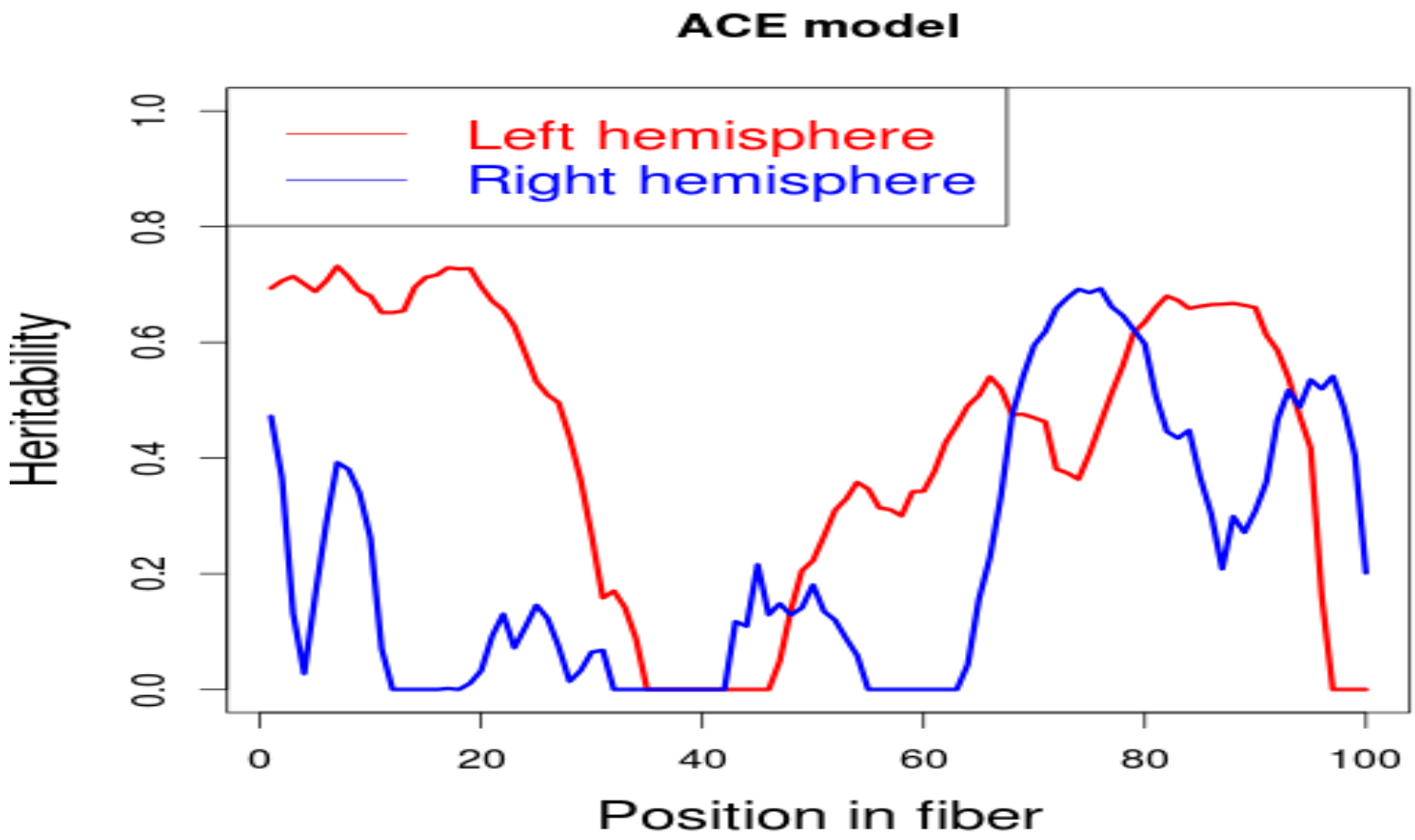
Right hemisphere

2 portions			
0 (0.5)		0.42 (0.094)	
4 portions			
0 (0.5)	1.85e-14 (0.49)	0.29 (0.18)	0.54 (0.04)

Numbers between brackets are p-values.

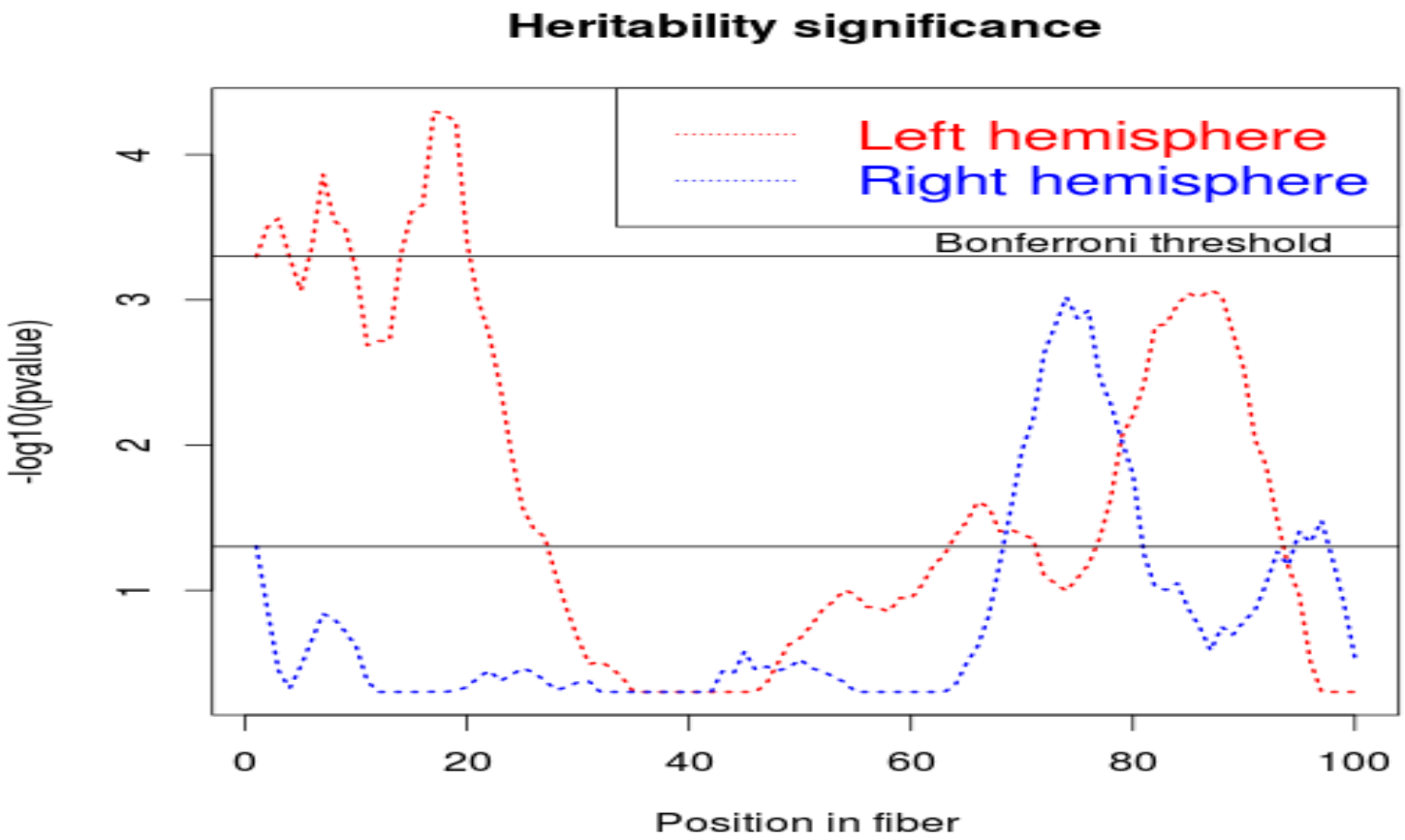
Application on real data (following)

We now divide the bundle into 99 portions and compute the heritability ...



Application on real data (following)

... and the associated p-values, using the **R** script `heritability.R`.



Repeated measures ACE model for twin data

Using the Linear Mixed Model Approach, we can define a repeated measures ACE model for twin data :

$$FA_{s,f,t} = \mu + \pi_s^W + \pi_f^{Pair} + \eta_{s,f}\pi_f^M + (1-\eta_{s,f})\pi_{s,f}^M + \epsilon_{s,f,t}, \qquad t = 1, \ldots, n_s$$

where n_s is the number of fibres for subject s and $\pi_s^W \sim \mathcal{N}(0, \sigma_W^2)$ is the random effect which enables to take into account the repeated fibres for each subject s.

```
modelR <- lmer(FA~1+(1|subject)+(1|Pair)+(1|M),REML=FALSE)
```

Multivariate ACE model

- We need to define a multivariate ACE model to modelize (FA, θ, r) and not only FA : this should not be too difficult using the *Multivariate Linear Mixed Models* approach.
- We will also need a new definition of heritability in this context : for example using a ratio of the determinants of the appropriate variance-covariance matrices ?

Multiplicity correction along a bundle

Given a sequence of correlated test statistics observed along the bundle, we need to be able to **correct for multiplicity** to test for the presence of heritability.

[Efron, 1997] has proposed a tool that could be applied in this context but in his paper, the test statistics are supposed to follow a $\mathcal{N}(0,1)$ distribution. This would have to be adapated to the case of a mixture $(1/2)\chi^2_0 + (1/2)\chi^2_1$, if possible.

Perspectives for this neuroscience research

- Fit an AE model to the data (using Linear Mixed Effect Models) and see if this is better than the ACE model.
- Identify the SNPs involved in the WM development/integrity, for example using Bayesian variable selection with the R2GUESS **R** package.
- Study heritability of all bundles in the brain (heavy computations).

Thank you for your attention ! !

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