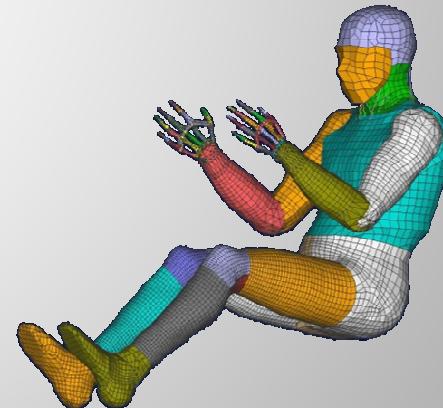
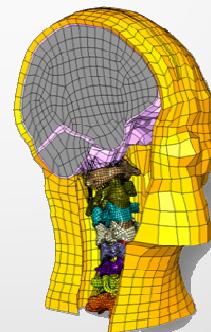
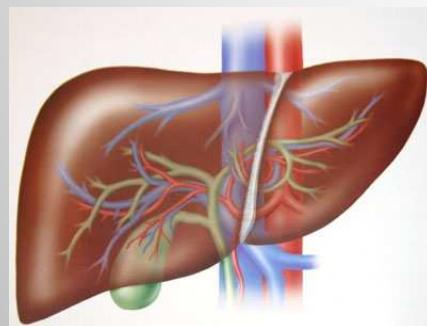


Caractérisation exérimentale et modélisation de tissus biologiques

remy.willinger@imfs.u-strasbg.fr

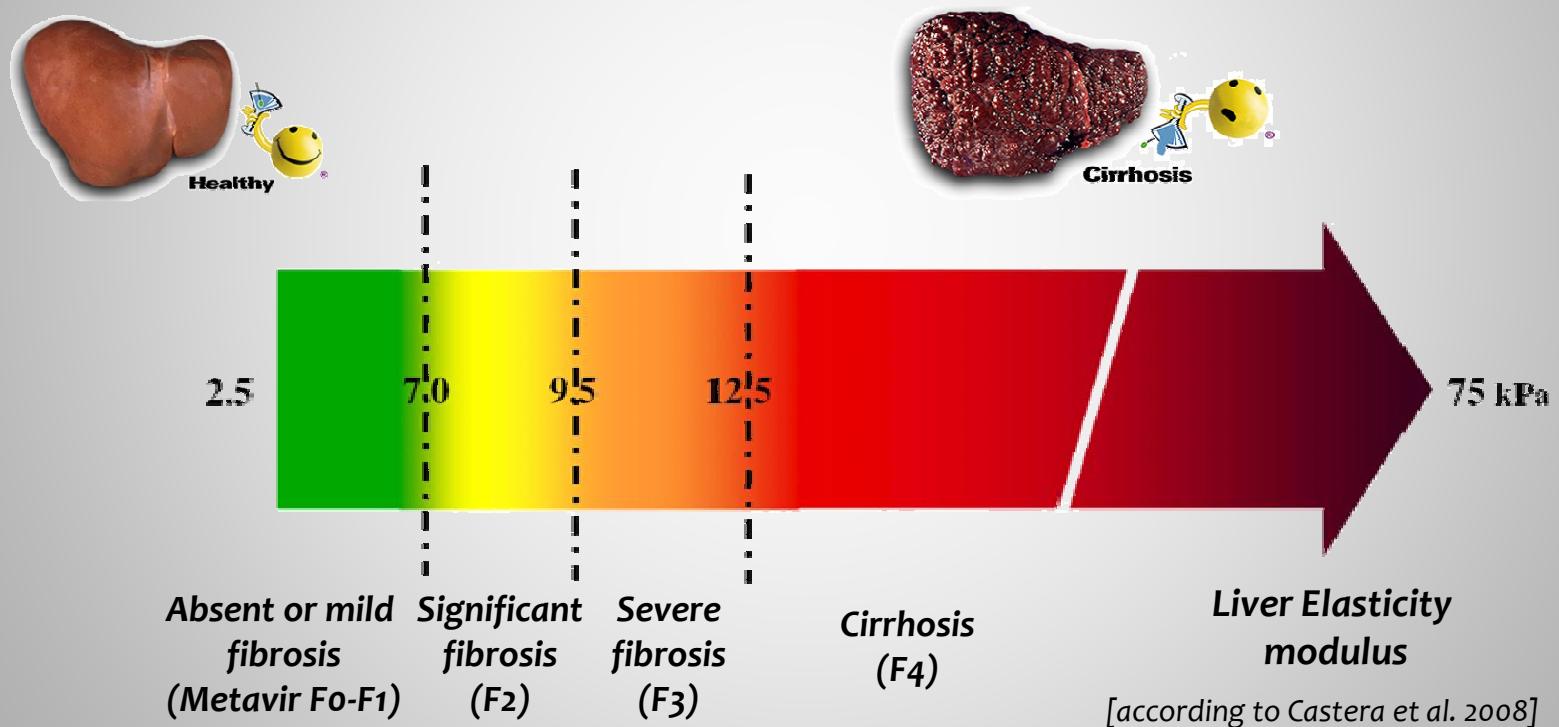


Rémy Willinger^a

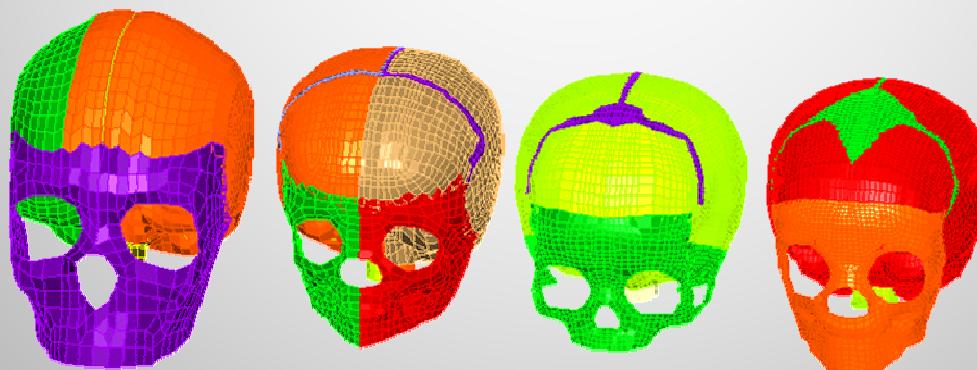
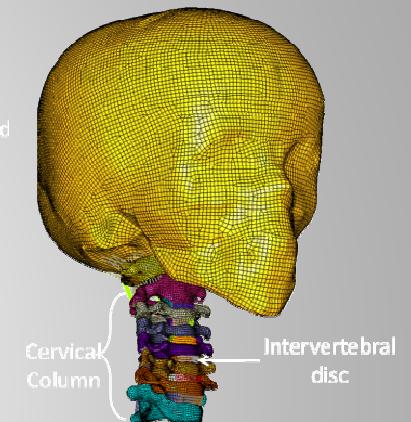
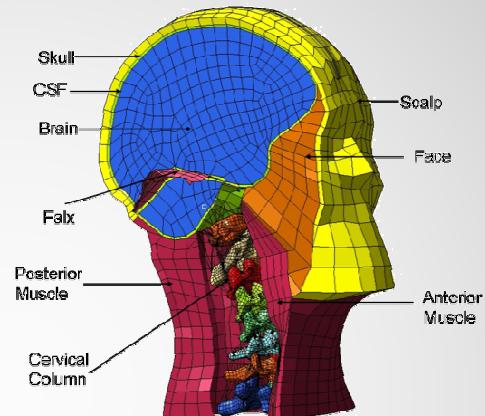
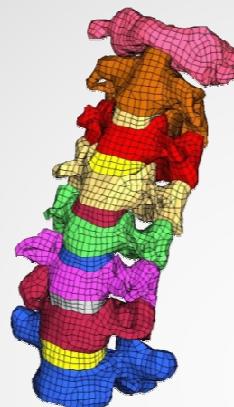
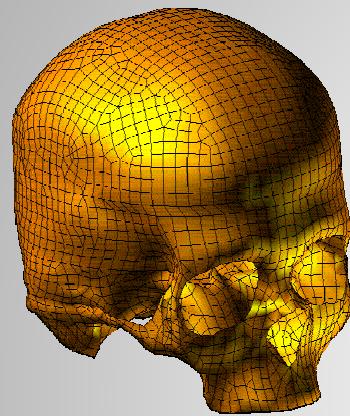
University of Strasbourg, IMFS-CNRS, Strasbourg, France

- Présentation générale des modèles
- *Méthodes expérimentales*
 - Rhéométrie
 - *Elastographie par RMN*
 - *Elastographie impulsionale*
- *Matière hépatique*
 - *In vivo*
 - *In vitro*
- *Matière cérébrale*
 - Caractérisation et modélisation
 - Limites de tolérance au choc
- Développements futurs

Correlation between liver mechanical characteristics and physiological functions



Biomécanique du traumatisme crânio-cérébral et cervical



Choix des modèles

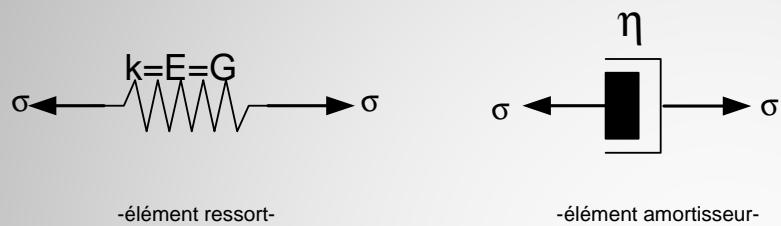


Fig.2-4: Les éléments de base d'un modèle mécanique.

$$\sigma = E\varepsilon$$

$$\sigma = G\gamma$$

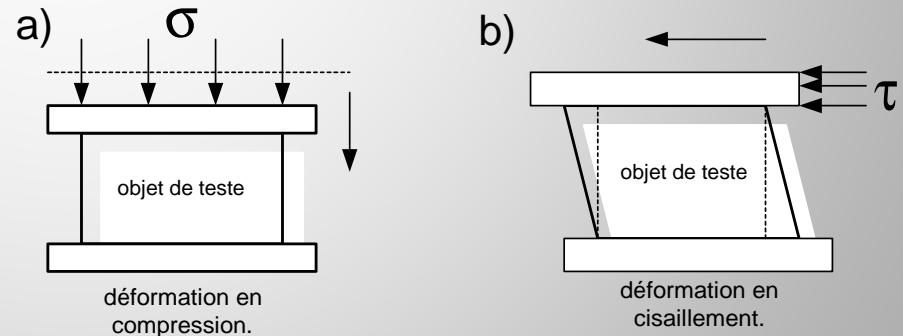


Fig. 2-2: les deux types de déformation de base .

Choix des modèles

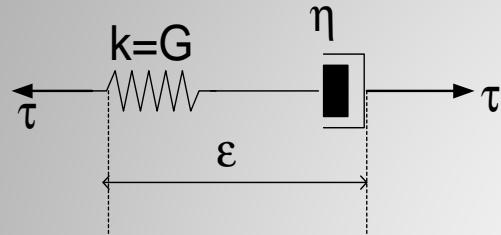


Fig.2-5: Le Modèle de Maxwell (M)

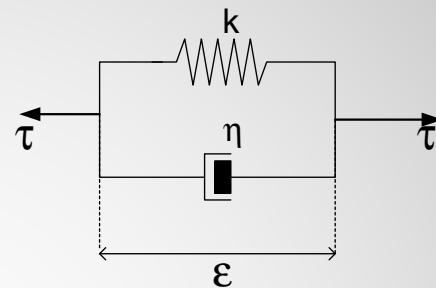


Fig.I-4: Modèle de Kelvin voight (K.V.).

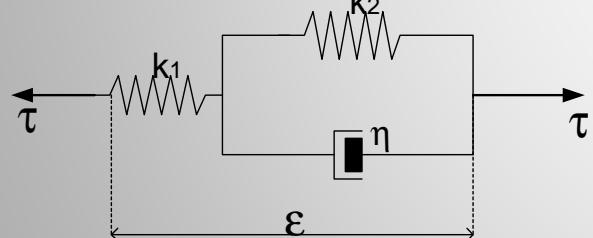


Fig.I-5: Modèle de Maxwell-Kelvin voight (M.KV).

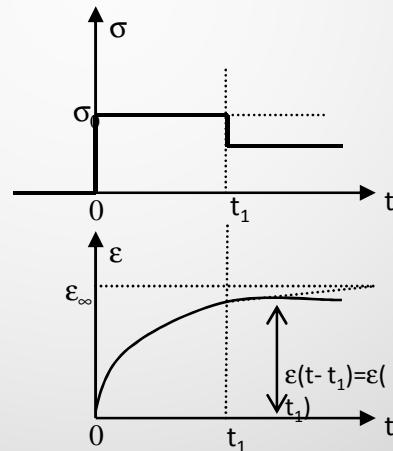


Fig.2-10 : la réponse en fluage du modèle de Kelvin-voight

Choix des modèles

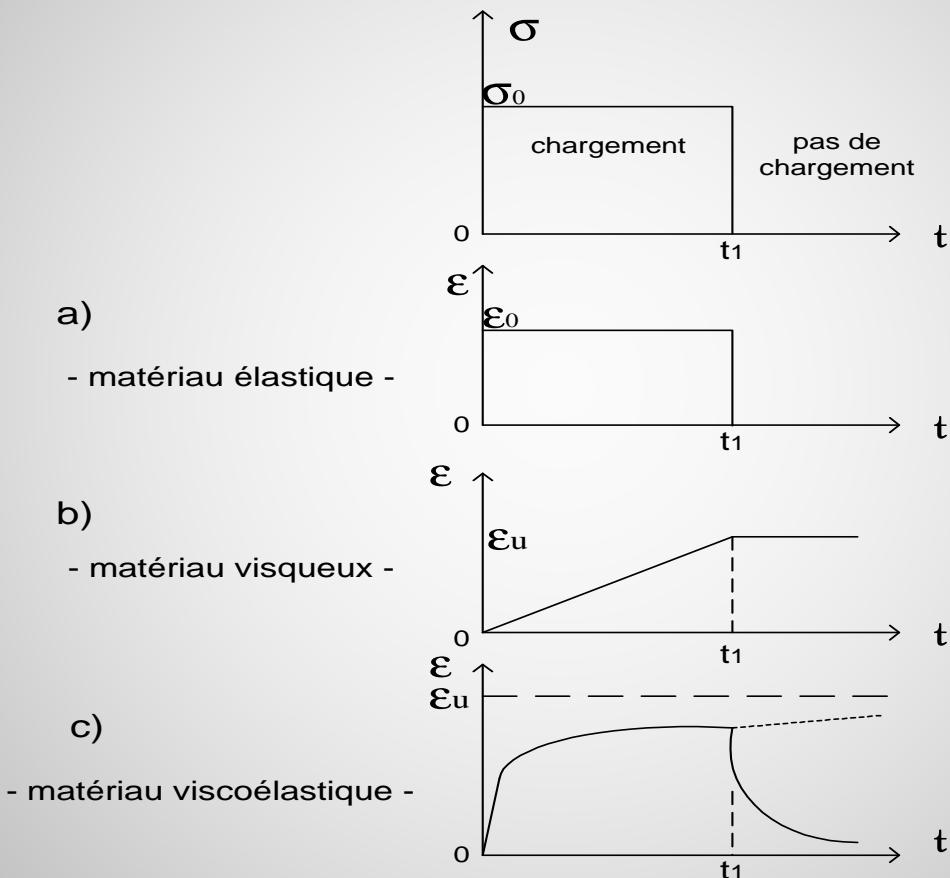
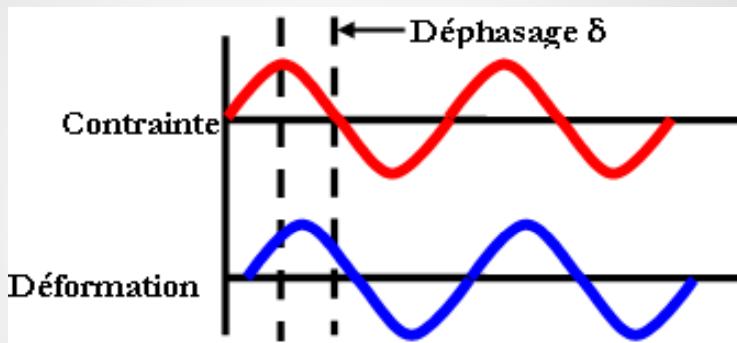


Fig. 2-1: les trois comportements(élastique, visqueux et viscoélastique) des matériaux.

Méthodes expérimentales

$$\sigma = \sigma_0 \exp(i\omega t + \delta)$$

$$\gamma = \gamma_0 \exp(i\omega t)$$

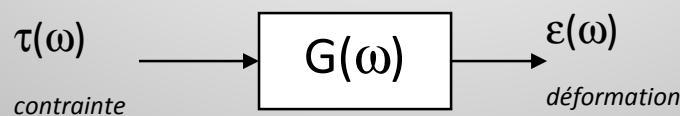


$$G^* = G' + iG''$$

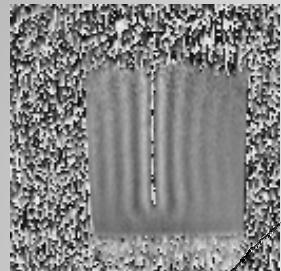
$$G' = \frac{\sigma_0}{\gamma_0} \cos \delta$$

$$G'' = \frac{\sigma_0}{\gamma_0} \sin \delta$$

$$\frac{G''}{G'} = \tan \delta$$



Existing Methodologies



***In vivo* - non-invasive technique**

Imaging
elastography

Indentation
tests

Magnetic Resonance
Elastography

Ultrasound-based
Transient Elastography



Rheometric
tests

***In vivo* - invasive technique**

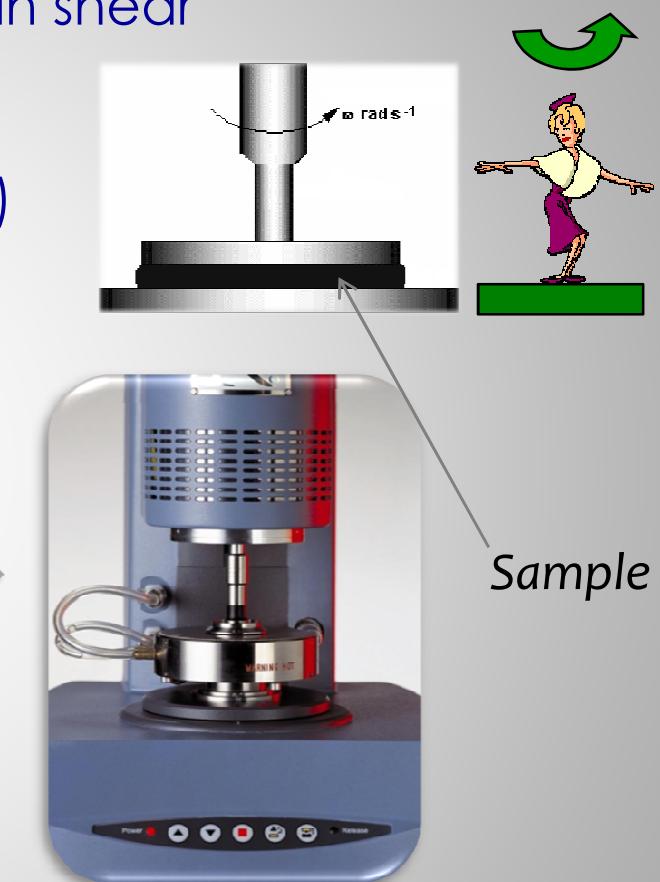
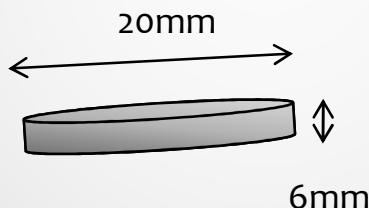
***In vitro* – Well known and validated method**

Rhéométrie classique (DMA)

- *In vitro* Dynamical Mechanical Analysis in shear
- G' & G'' (0.1Hz to 10Hz)
- Small deformations: 0.1% strain (linearity)



Cut samples



AR 2000 rheometer (TA-Instrument, New Castle, DE)

Synthèse

La rhéométrie : Le rhéomètre

AR 2000 : rhéomètre à contrainte contrôlée

Géométrie : plane

Hypothèses de travail : tissu étudié dans le domaine de viscoélasticité linéaire

(petites déformations)

Paramètres enregistrés : G' , G'' , raw phase

Lien entre les deux méthodes $G = \sqrt{G'^2 + G''^2}$

$$E = 3\rho V_s^2 = 3G \quad \text{Hypothèse d'un matériau purement élastique}$$



Elastographie par RMN

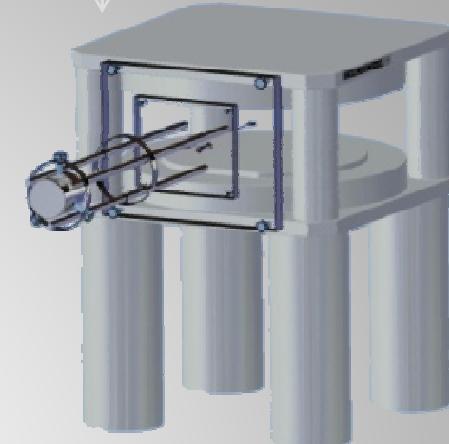
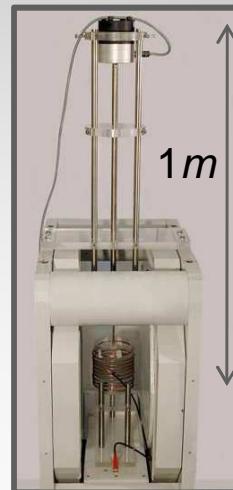
The Magnetic Resonance Elastography system

MRI
System
(0.1T magnets)

Mechanical
excitation

Vertical
excitation
(*in vitro* tests)

Horizontal
excitation
(*in vivo* tests)



Experimental device
with horizontal excitation

Experimental device
with vertical excitation

Wave equation inversion
2D-algorithm

Assumption of a purely
elastic medium

$$G = \rho \cdot \left(\frac{\omega}{k} \right)^2$$

ρ : density
 k : wavenumber
 ω : frequency
 λ : wavelength

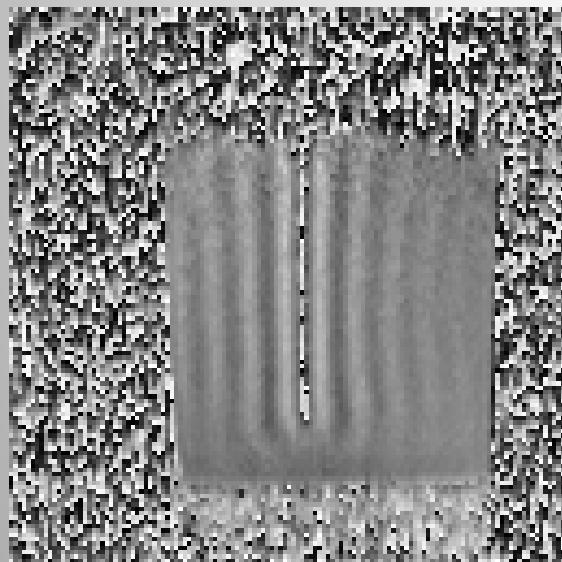
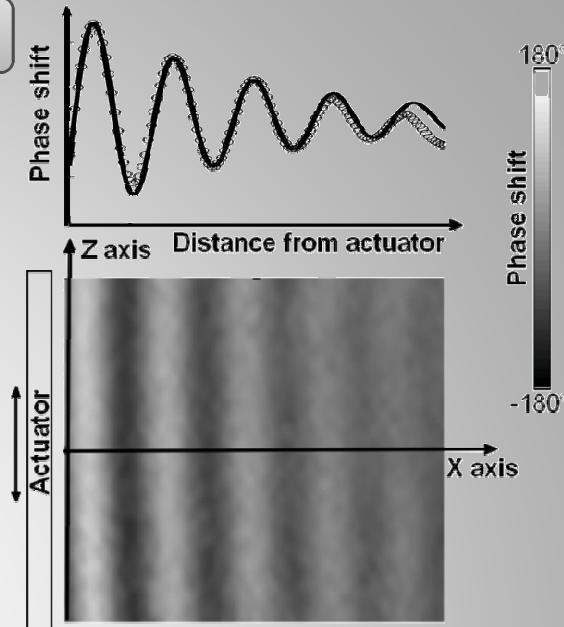
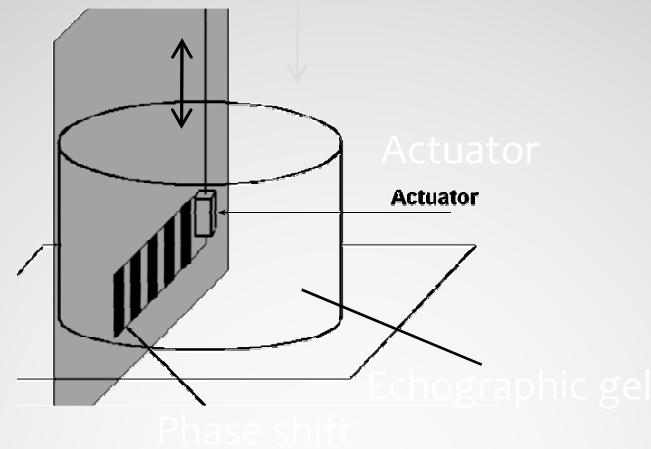
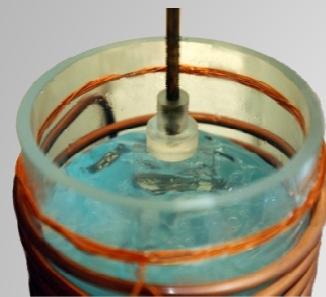
Assumption of a
viscoelastic medium

$$G' = \rho \omega^2 \frac{K'^2 - K''^2}{(K'^2 + K''^2)^2}$$

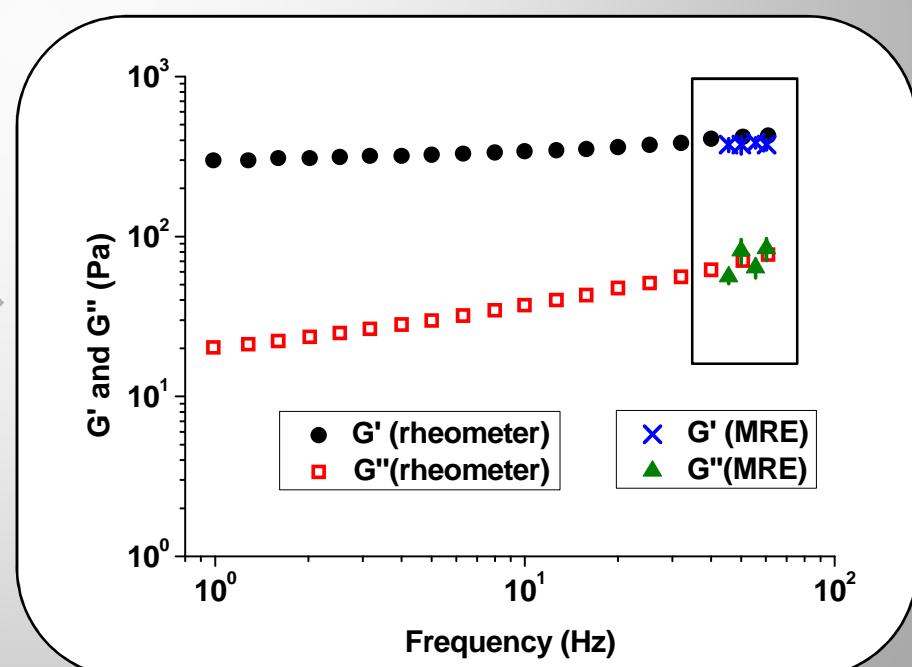
$$G'' = \rho \omega^2 \frac{K' K''}{(K'^2 + K''^2)^2}$$

In vitro tests : Validation on soft homogeneous gels

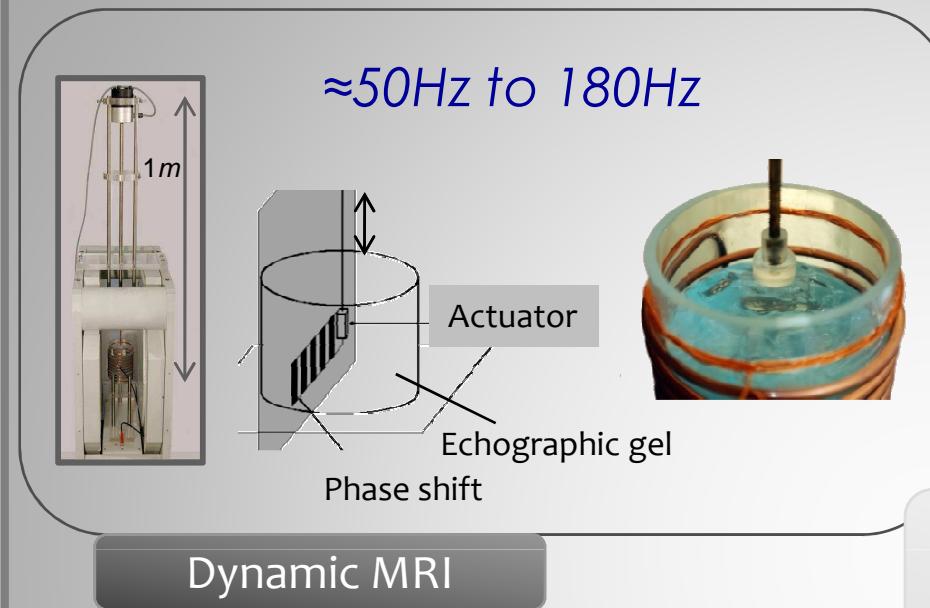
Vertical MRE Experimental device for echographic gel



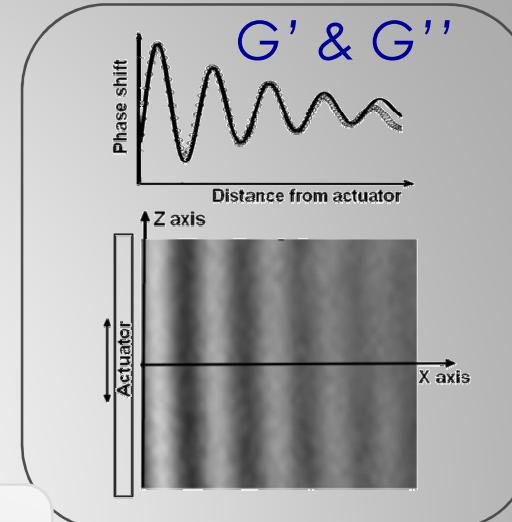
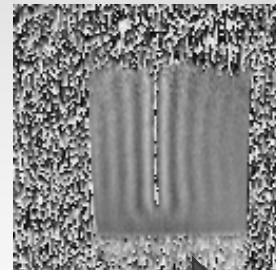
Shear wave propagation on echographic gel



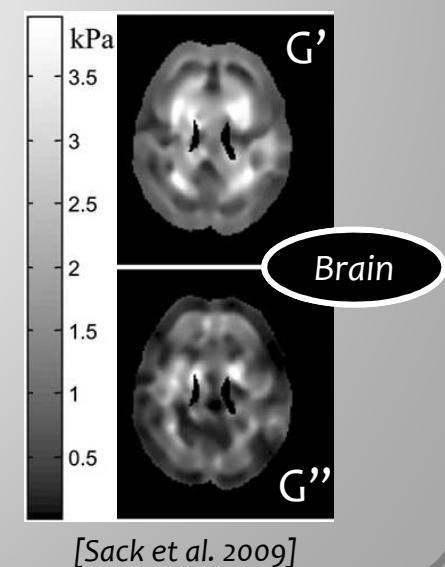
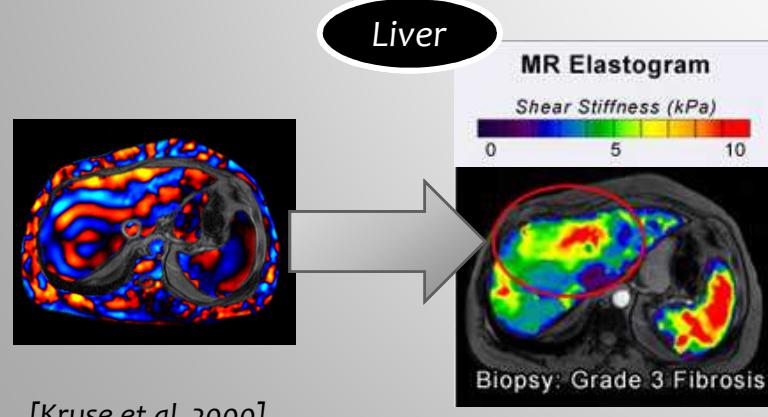
Magnetic Resonance Elastography (MRE)



[Vappou et al. 2007]



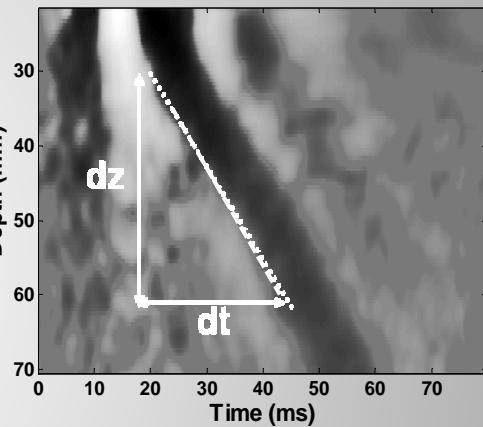
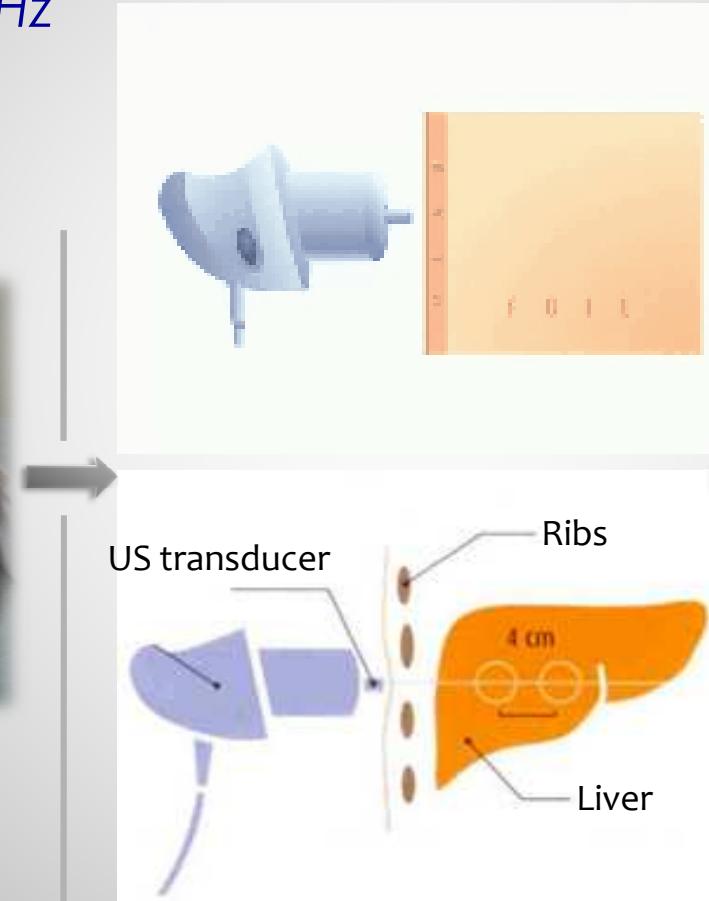
Wave propagation
inverse equations



Elastographie Impulsionnelle

Transient Elastography (TE)

- In vivo and ex vivo Transient Elastography
- Frequency: 50Hz
- Linearity



$$G = \rho V_s^2 = \rho \left(\frac{dz}{dt} \right)^2$$

Fibroscan (Echosens, Paris, France)

Synthèse

L'élastographie impulsionnelle : Le Fibroscan

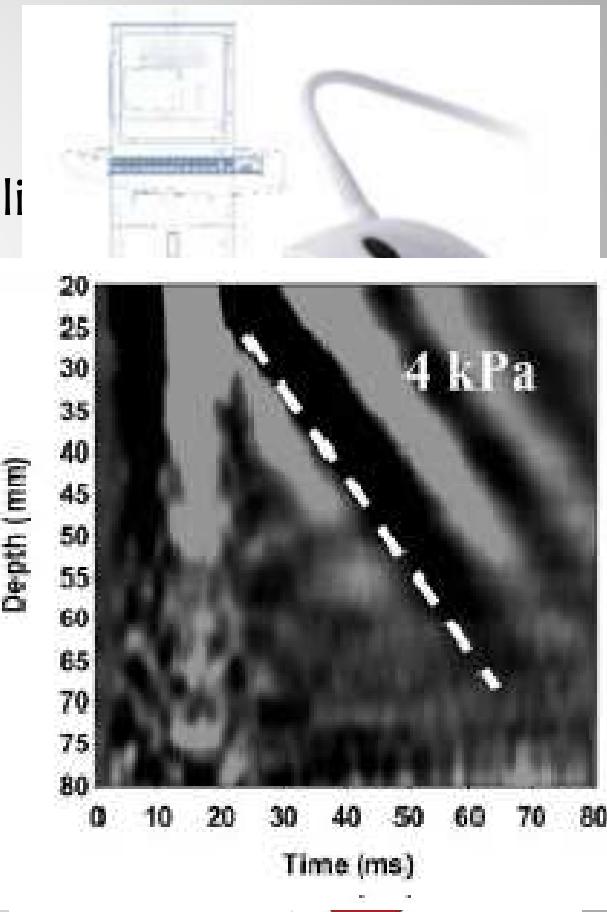
Fréquence de travail : 50 Hz

Hypothèses de travail : foie élastique, isotrope, li

$$E = 3\rho V_s^2$$

$$\rho = 1 \text{ g.cm}^{-3}$$

V_s Vitesse de propagation de l'onde
 de cisaillement



Matière hépatique

ETUDE BIBLIOGRAPHIQUE

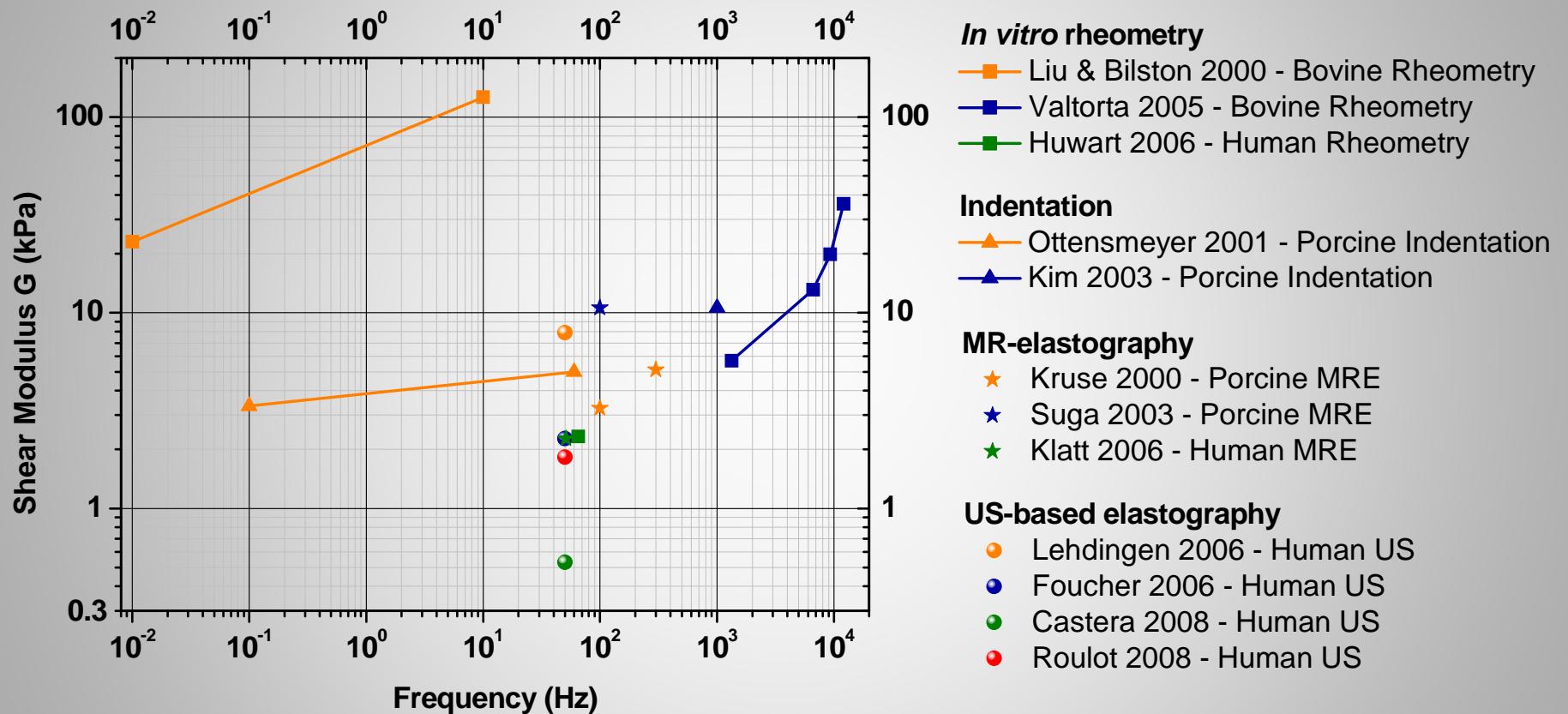
Les méthodes de caractérisation des propriétés mécaniques des tissus mous de la littérature (liste non exhaustive)

Auteur	Année	Méthode	Organe	Conditions	Type d'individu	Fréquence (Hz)	E (kPa)	G (kPa)
Brown	2003	ultrason	foie	in vivo	porc	1	80	
Chen	1996	ultrason	foie	in vitro	bovin	-	0,62 +/- 0,24	
Klatt	2006	MRE	foie	in vivo	homme malade	50 - 80		3 +/- 0,24
Kruse	2000	MRE	foie	in vitro	porc	100		2,5 – 4
Kruse	2000	MRE	foie	in vitro	porc	300		4 – 6,2
Carter	2001	indentation	foie	in vivo	homme sain	statique	270	
Carter	2001	indentation	foie	in vivo	homme malade	statique	740	
Kim	2003	indentation	foie	in vivo	porc	100	31,8	
Ottensmeyer	2001	indentation	foie	in vitro	porc	0,1 - 60	2,2	
Samur	2005	indentation	foie	in vitro	porc	statique	15	

ETUDE BIBLIOGRAPHIQUE

Auteur	Tissu	Conditions	Technique	E (en kPa)	G (en kPa)
Huwart	Foie homme	In vivo	MRE	7	
Klatt	Foie homme	In vivo	MRE		2,26 +/- 0,23
Ottensmeyer	Foie homme	In vivo	indentation	2,2	
Roulot	Foie homme	In vivo	Fibroscan	5,49 +/- 1,59	

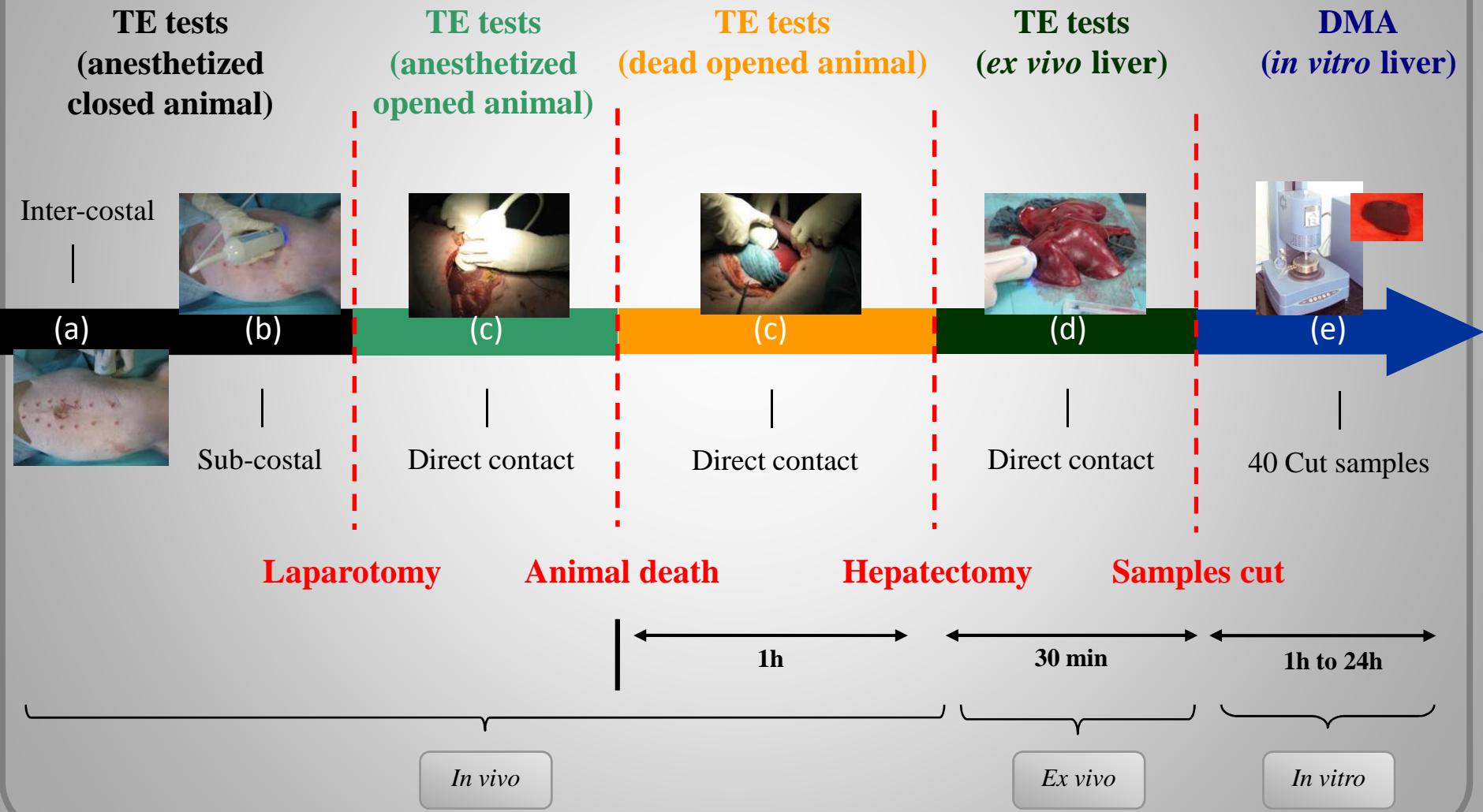
Shear Modulus G versus Frequency for Liver Tissue: a literature review



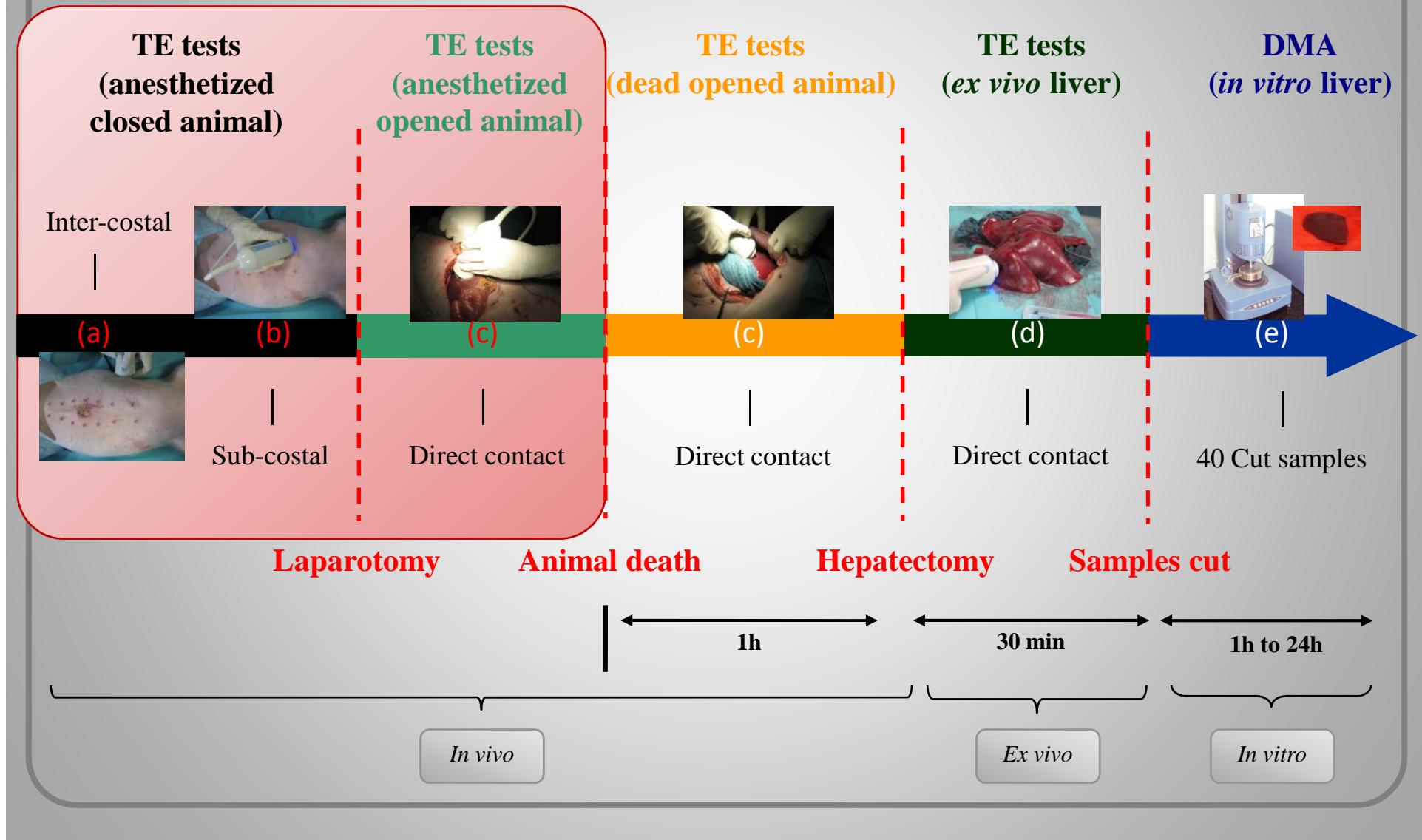
Difficulties to compare the results: inter-species variations,
protocols, frequency ranges, strain rates, ...

General experimental protocol

5 female pigs (25 to 35kg)



In vivo Transient Elastography tests



In vivo Transient Elastography tests



3 *in vivo* US-TE configurations:

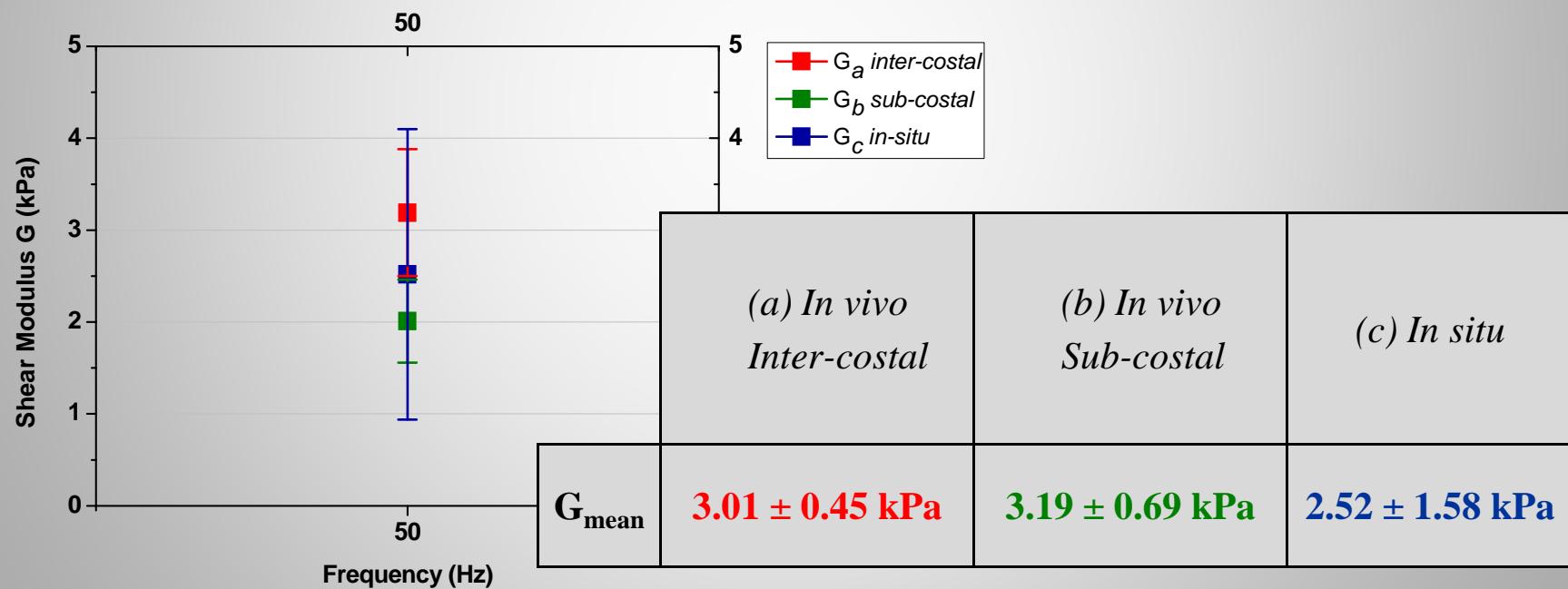
- (a) *In vivo* inter-costal (anesthetized closed animal)
- (b) *In vivo* sub-costal (anesthetized closed animal)
- (c) *In situ* (anesthetized or dead opened animal)

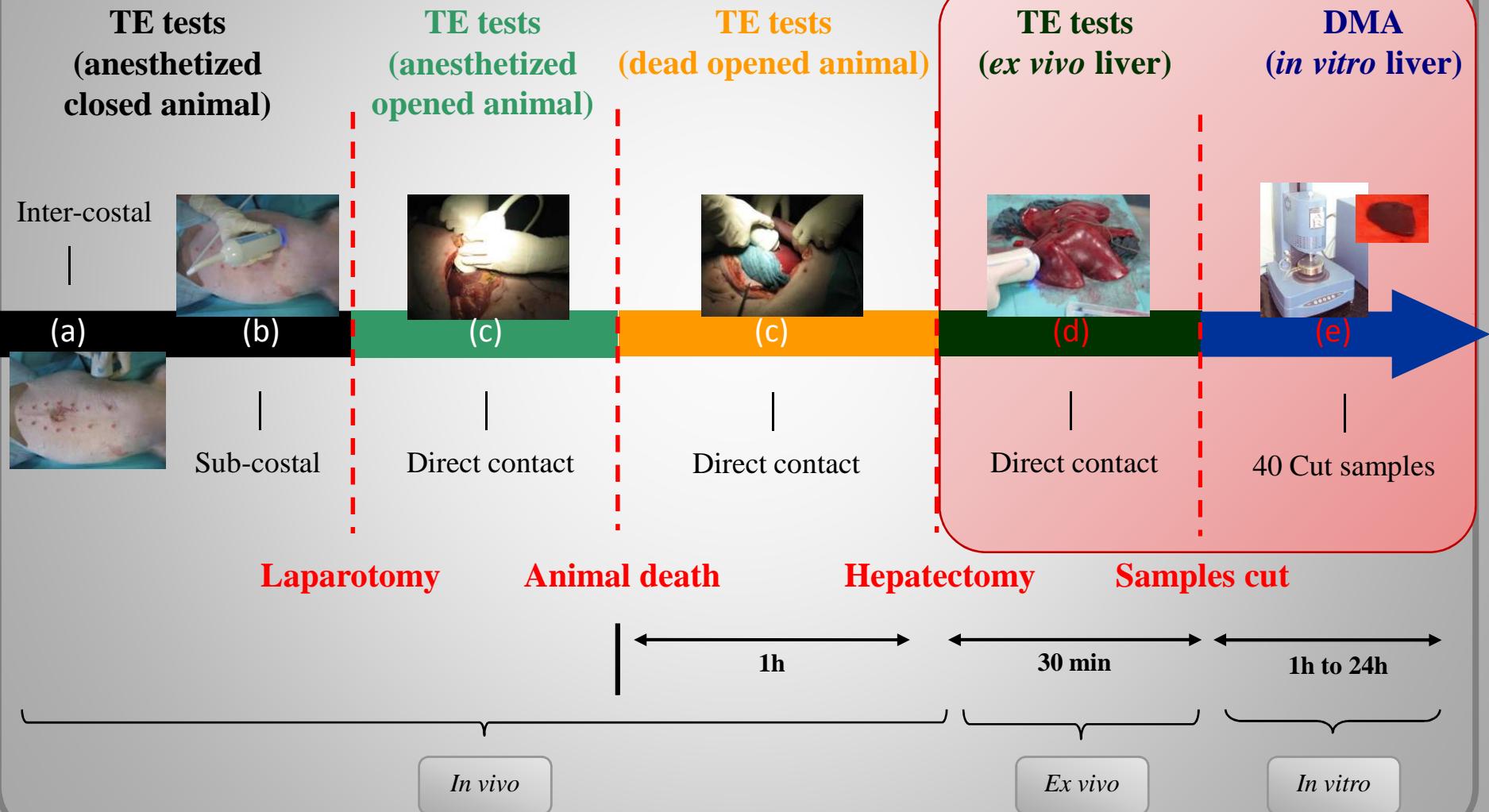
For each configuration:

5 pigs
10 measurements/pig

1 mean shear modulus value

In vivo Transient Elastography results





Ex vivo Transient Elastography tests



Ex vivo US-TE configuration (d):

- Ex vivo
(dead animal after hepatectomy)
- Clamped liver:
 maintained blood pressure
- Controlled temperature

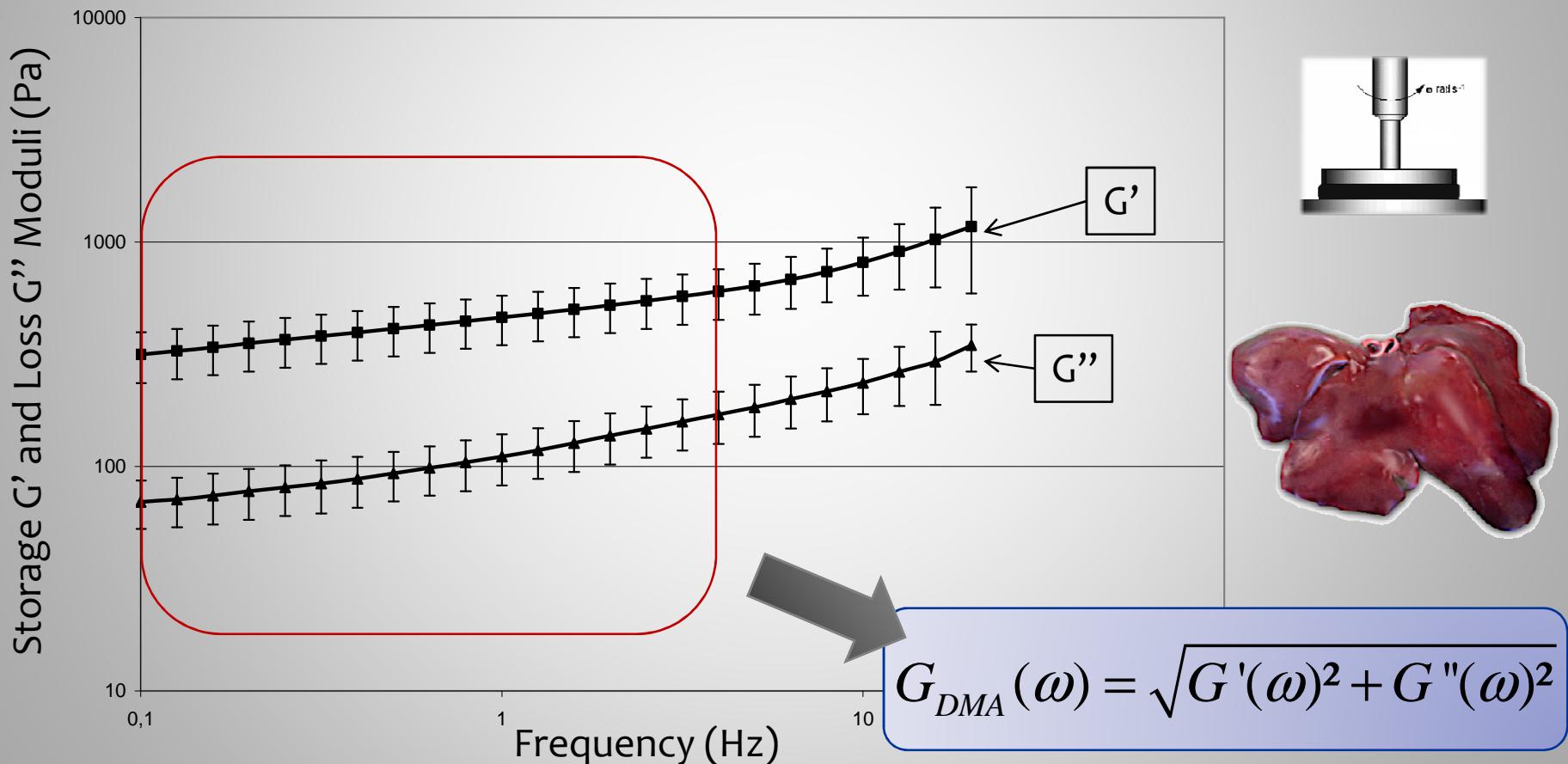


In vitro DMA tests (e):

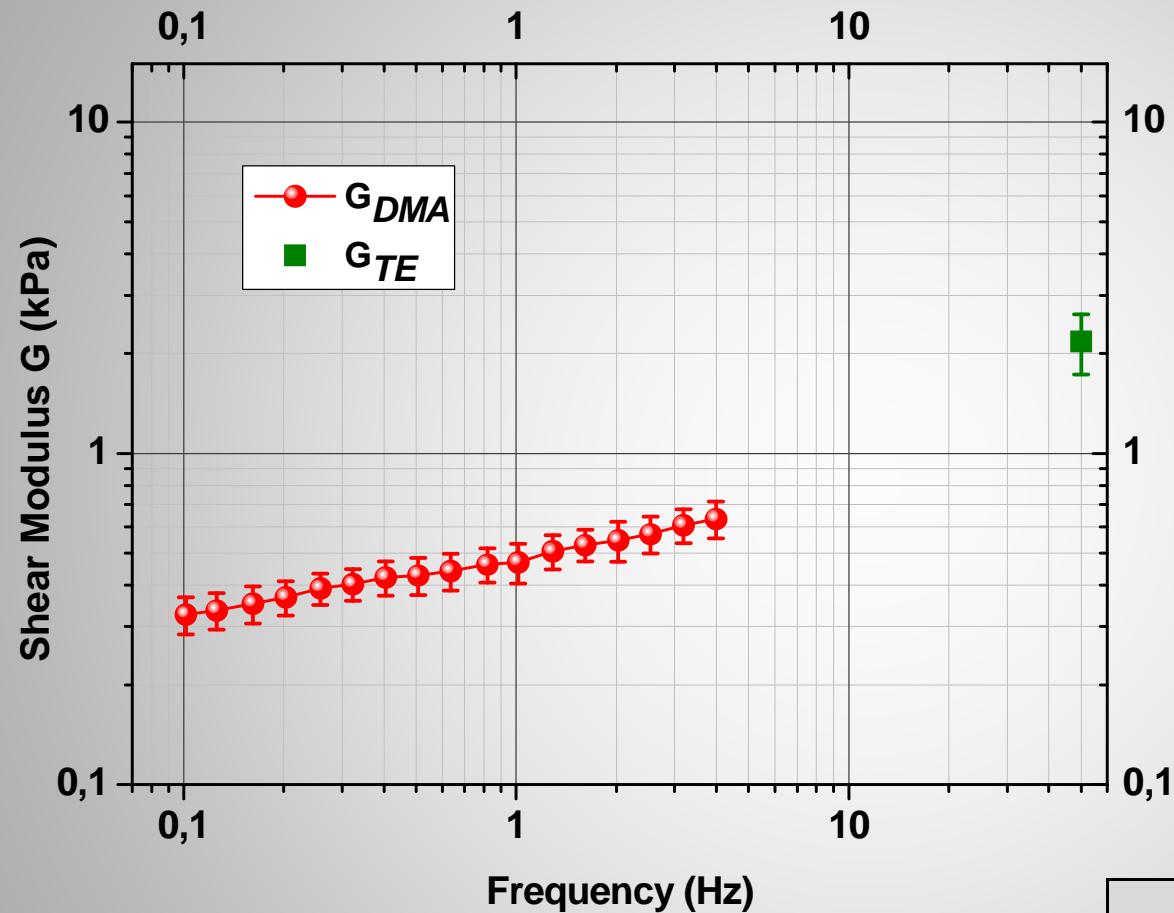
- Ex vivo
- Clamped liver:
 maintained blood pressure
- Temperature monitoring

Ex vivo results: TE versus DMA

Mean storage G' (square) and loss G'' (triangle) moduli obtained by Dynamic Mechanical Analysis on *in vitroporcine* hepatic tissue samples



Ex vivo results: TE versus DMA



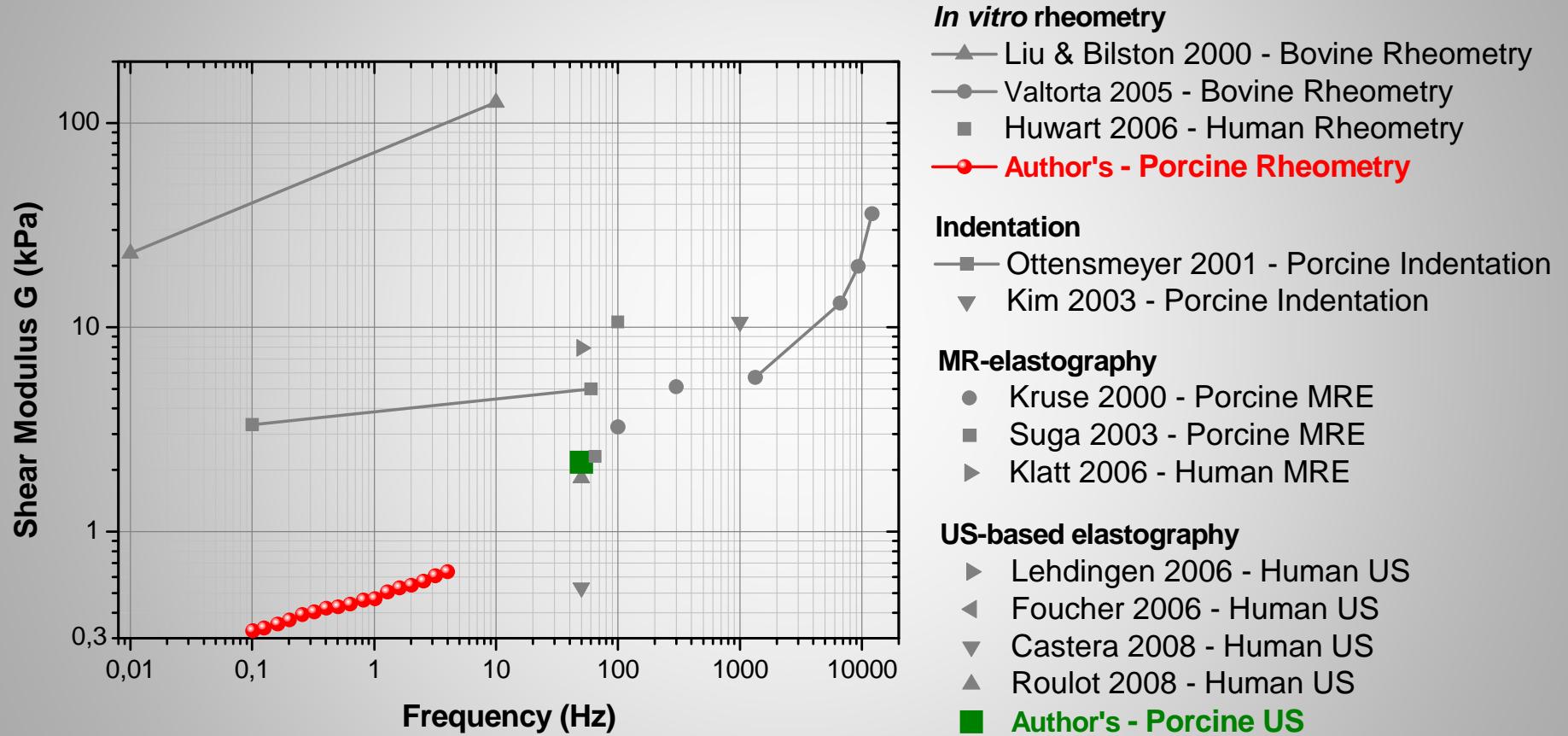
5 porcine livers
-
40 DMA samples
50 TE tests

(d) Ex vivo TE

G_{mean}

2.18 ± 0.45 kPa

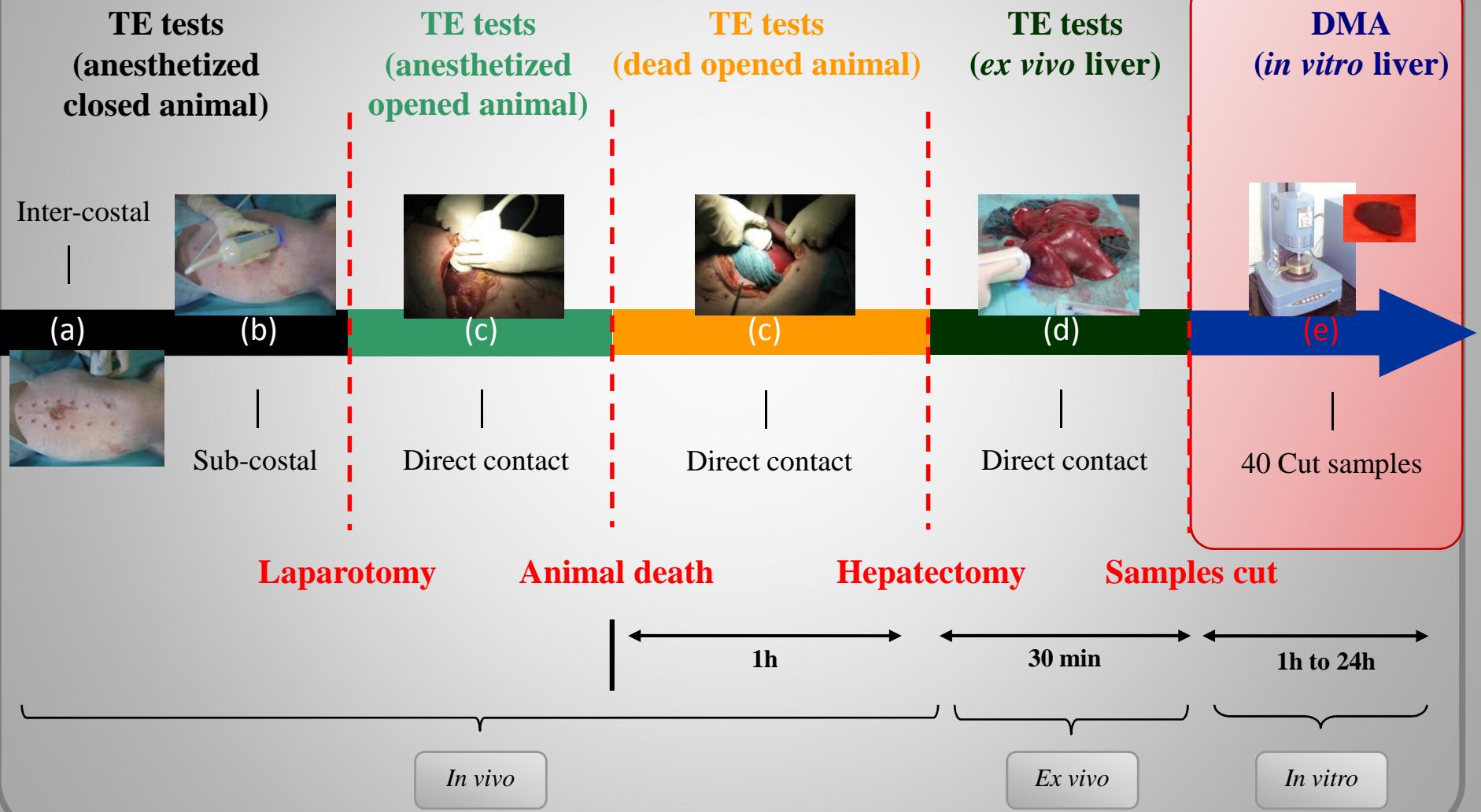
Shear Modulus G versus Frequency for Liver Tissue: comparison with the results from the literature



→ US-TE validated

Analyse in vitro et modélisation

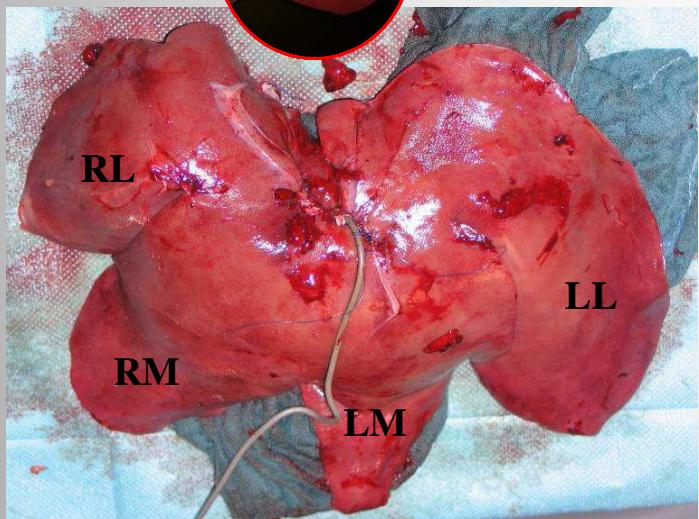
Ex vivo Hepatic tissue properties



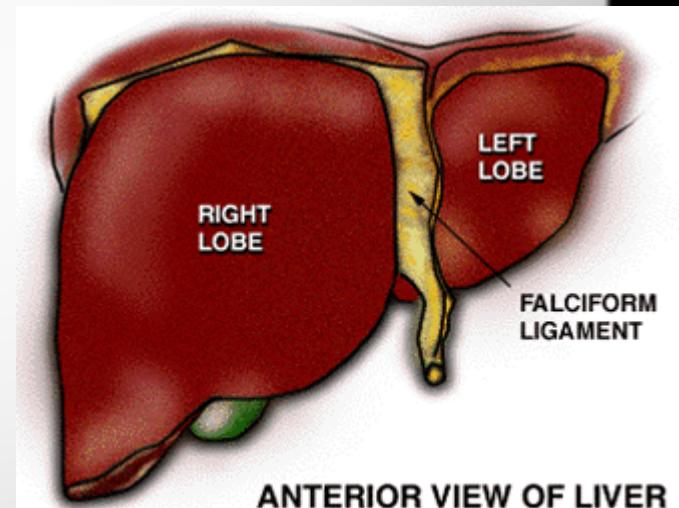
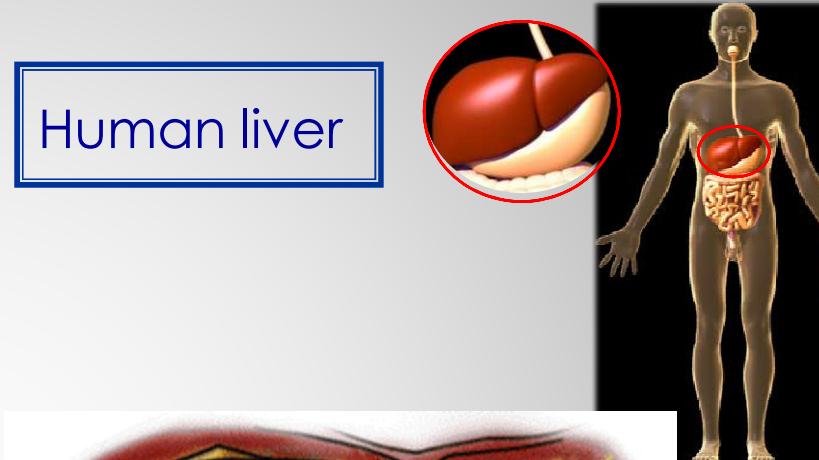
In vitro liver anisotropy investigation



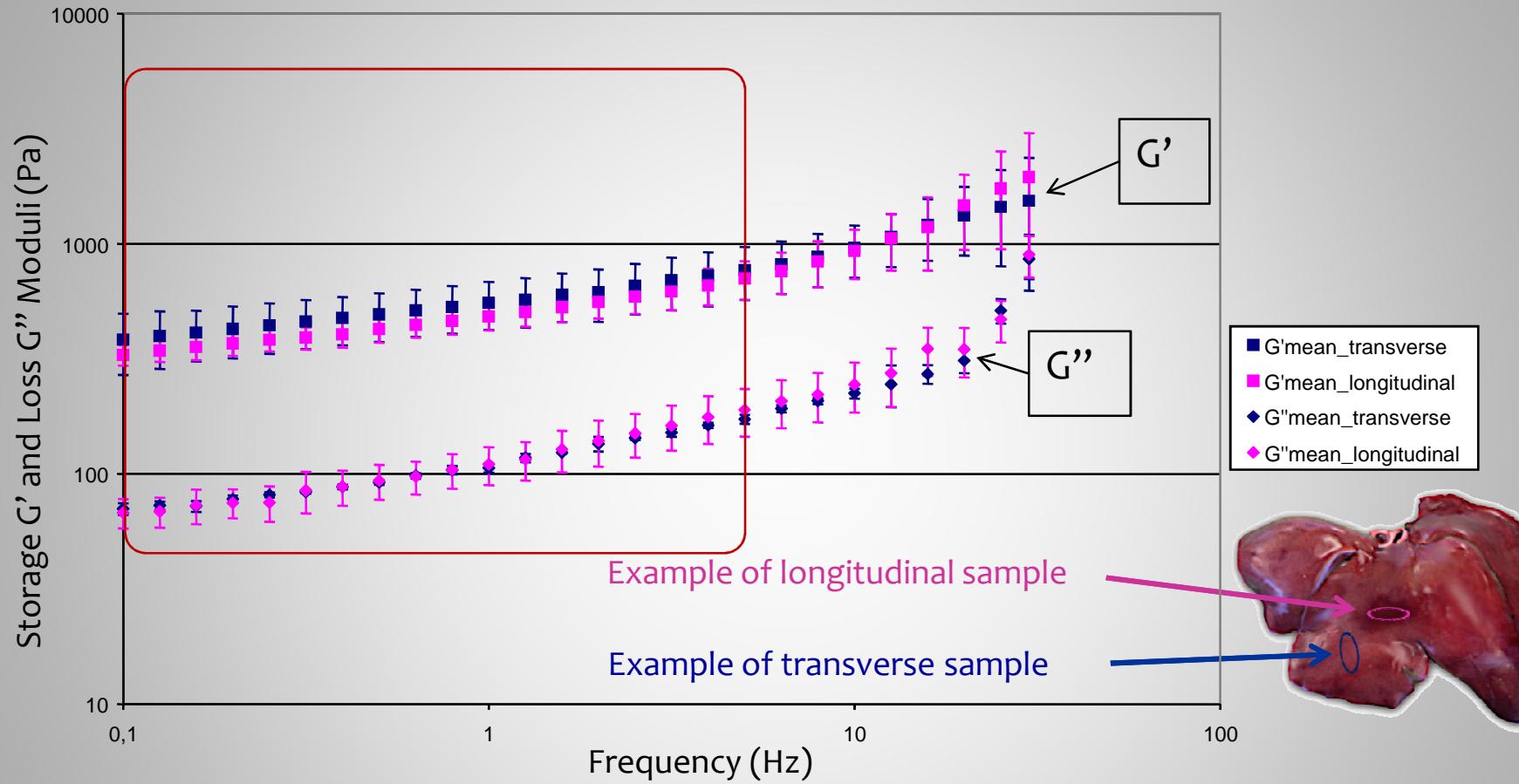
Porcine liver



Human liver

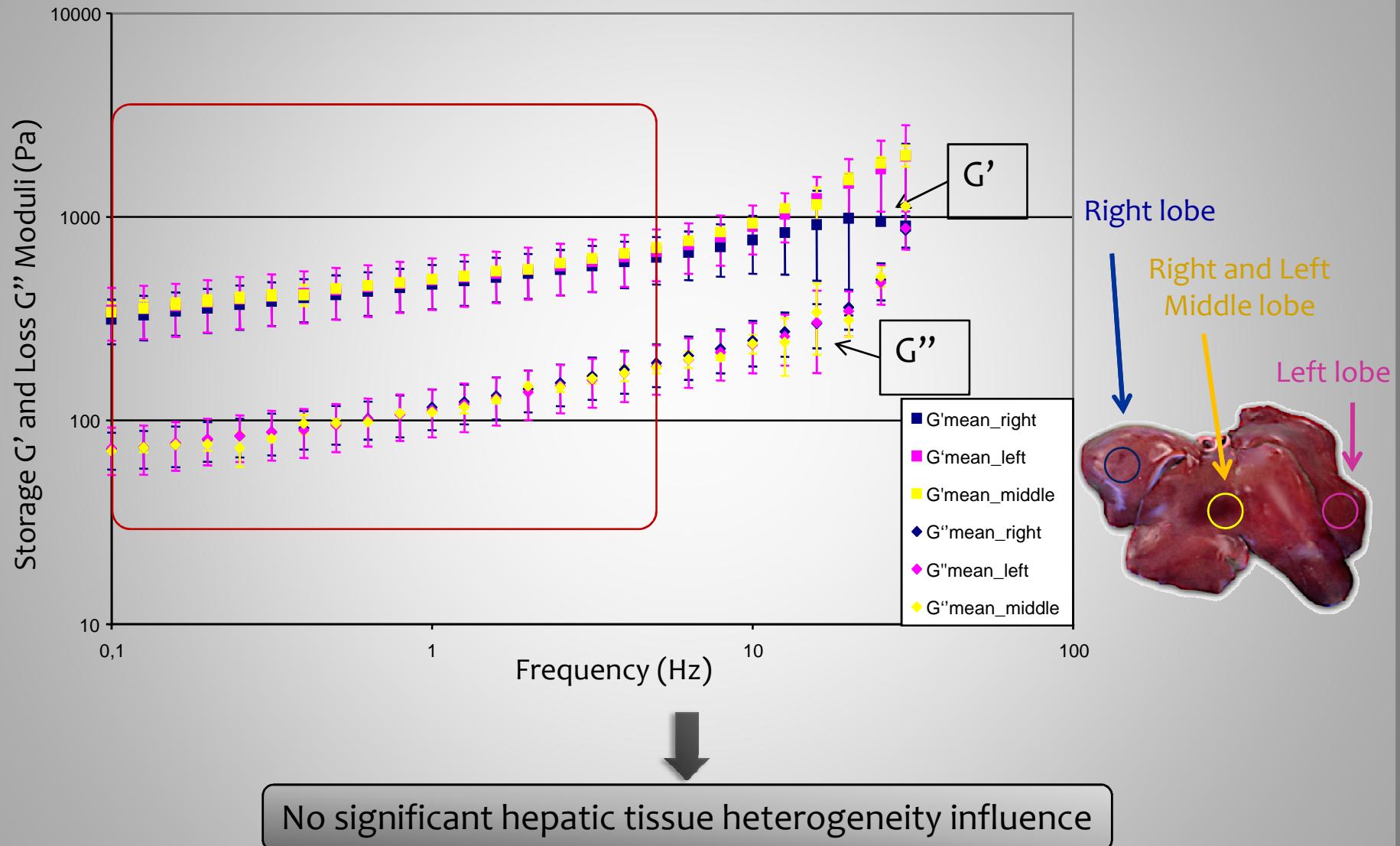


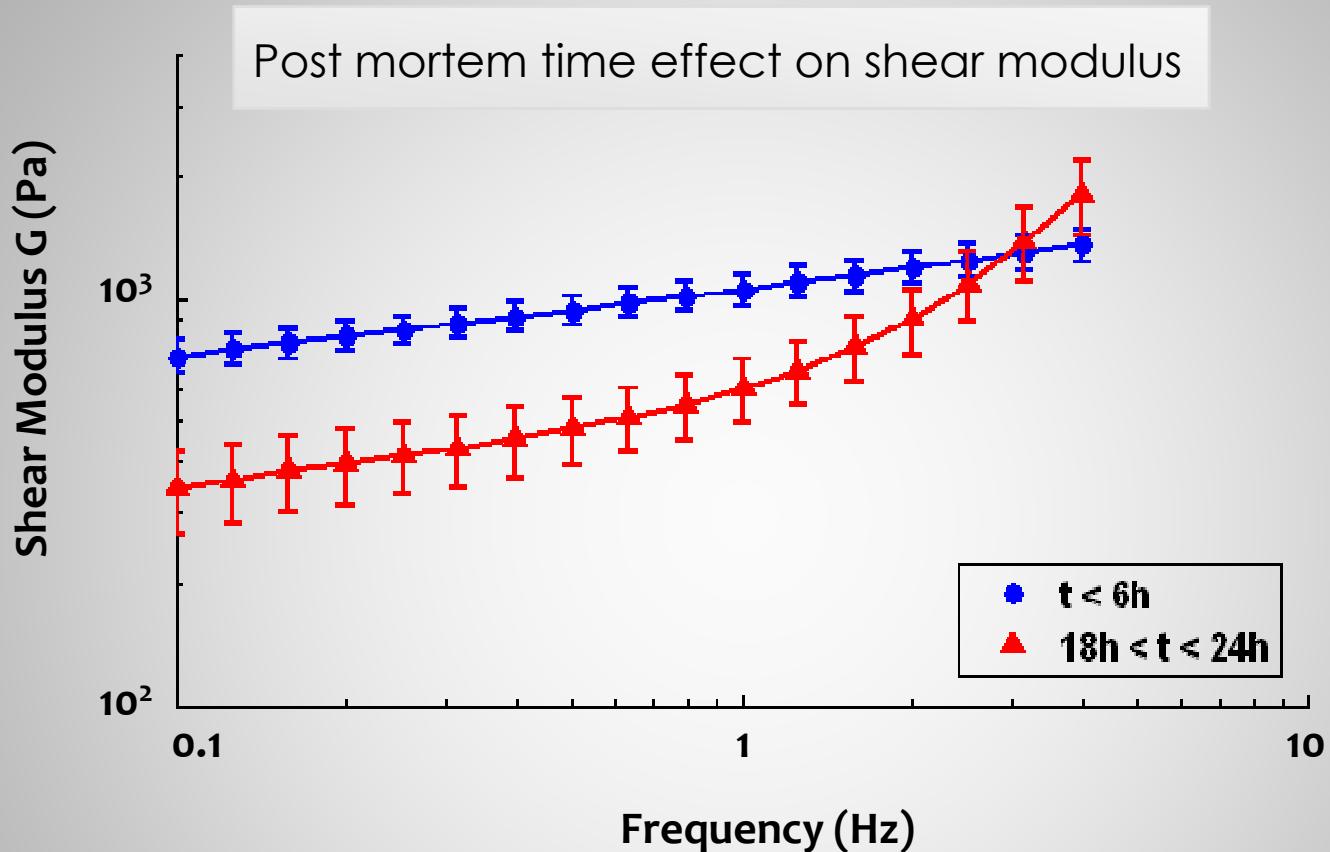
In vitro liver anisotropy investigation



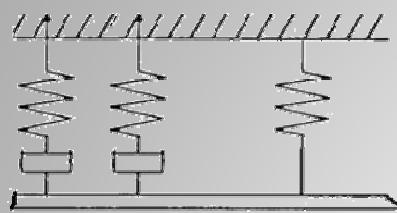
No significant hepatic tissue anisotropy influence

In vitro liver heterogeneity investigation



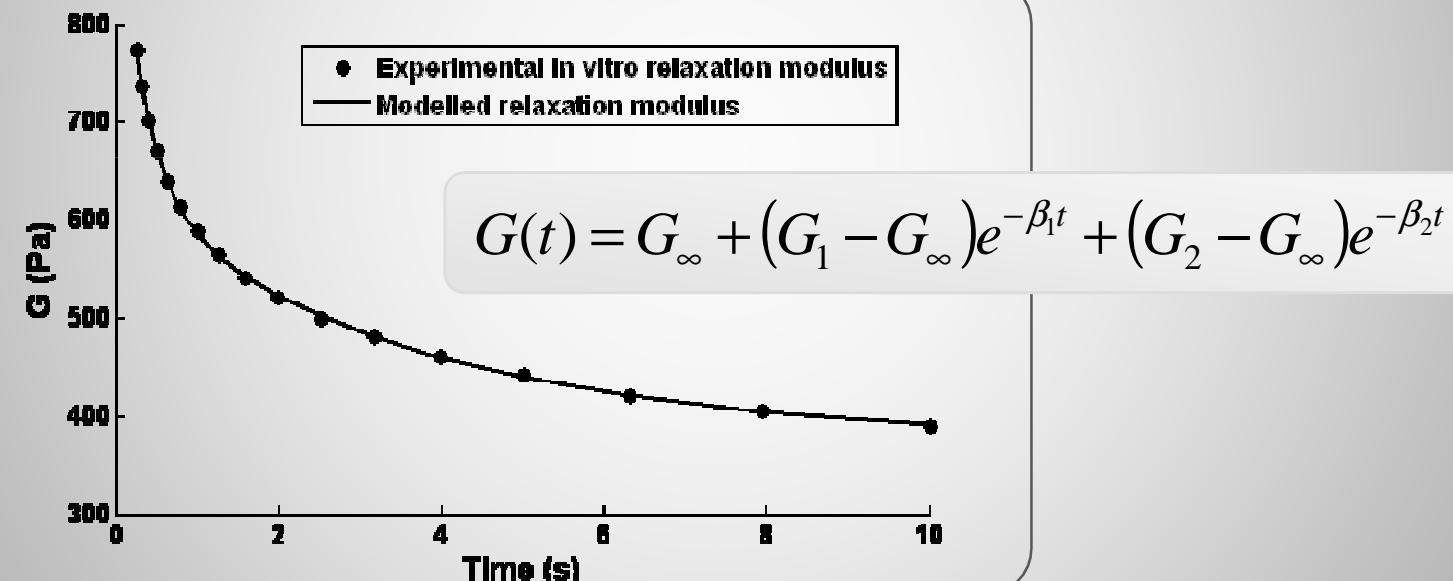


Post mortem time effect on the linear viscoelastic strain limit	Short time: γ_{lim}	$0.8 \pm 0.3 - 1.8 \pm 0.2$
	Long time: γ_{lim}	$5.6 \pm 2.4 - 6.3 \pm 0.0$



Generalized Maxwell model

- 2 relaxation modes
- Based on 0.1 to 10Hz DMA mean results



G_{∞} (Pa)	G_1 (Pa)	β_1 (s^{-1})	G_2 (Pa)	β_2 (s^{-1})
377	169	1	290	10

Conclusions

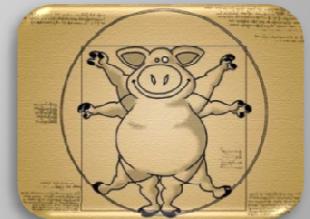
Conclusions

- All the tests on the same 5 porcine livers
 - 3 *in vivo* configurations comparison
 - *Ex vivo* US-TE / *In vitro* DMA
- Mean shear modulus value at 50Hz:
- Mean shear modulus value at 50Hz:
 - *In vivo*: $G = 2.0 \pm 0.5$ kPa
 - *In vitro*: $G = 1.2 \pm 0.4$ kPa
- Hepatic tissue characterization
 - Homogeneous
 - Isotropic
 - High post mortem time dependence



Perspectives and limits

- More significant number of animals
- Same protocol to characterize fibrosis
- No *in vivo* viscosity measurement, but elastic assumption validated



Matière Cérébrale

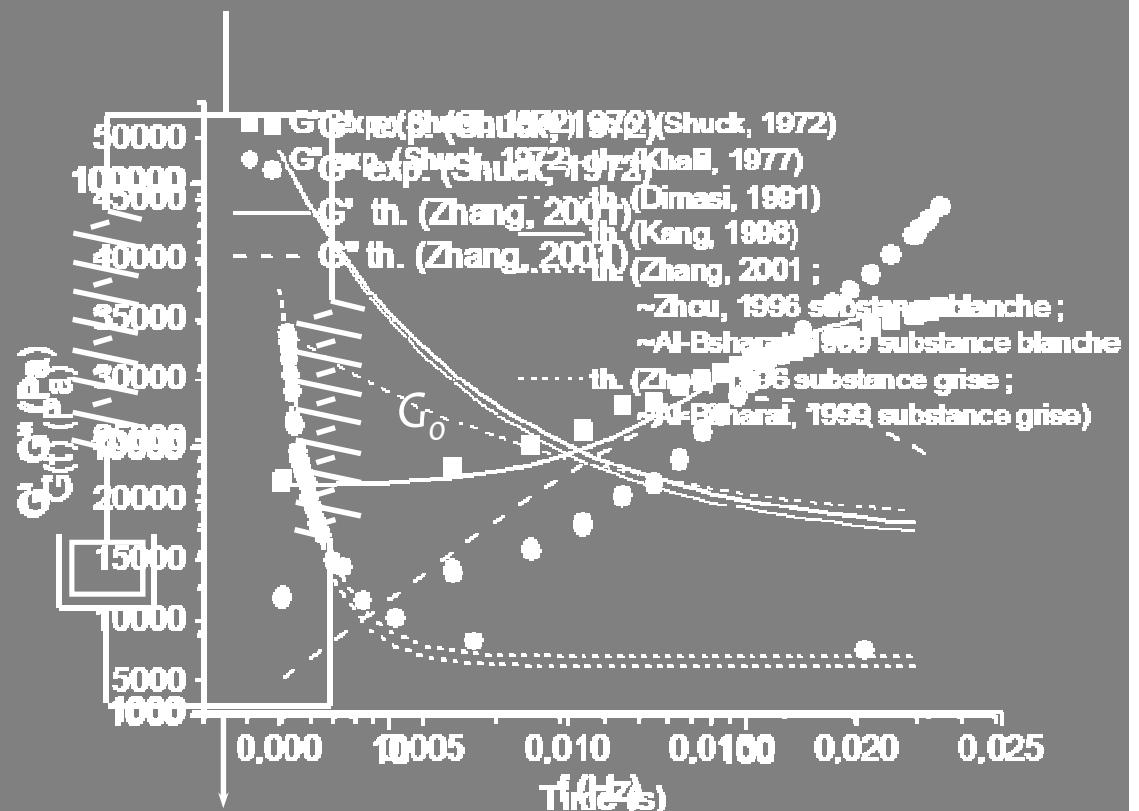
Modeling of Shear Linear Behavior (Commonly used in the literature)

$$G_0 - G_\infty$$

$$\eta = (G_0 - G_\infty)/\beta$$

Relaxation Modulus:

$$G(t) = G_\infty + (G_0 - G_\infty) e^{-\beta t}$$



Objectives

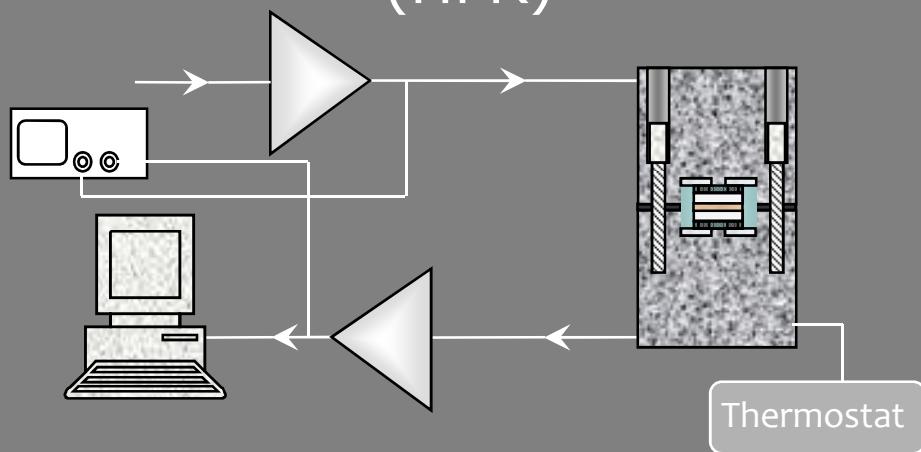
Enhance the Knowledge of the Shear Linear Behavior of Brain Tissue

Highlight the Effect of Experimental Conditions

Improve the Modeling of the Brain Tissue

Experimental Setups

"High Frequency Rheometer"
(HFR)



Use for translational shear tests:

- Small strains ($Disp_{max} = 50 \text{ \AA}$)
- Frequency sweep ($f < 10 \text{ kHz}$)

"Low Frequency Rheometer"
(LFR)



Use for torsional shear tests:

- Small and large strains
- Frequency sweep ($f < 150 \text{ Hz}$)
- Time sweep ($t > 0.01 \text{ s}$)

Samples Origin and Preparation

Human Brain

HFR (N = 9)

White Matter 

Thickness: 418 – 427 µm

Diameter: 10 mm

Sample Axis: Tr

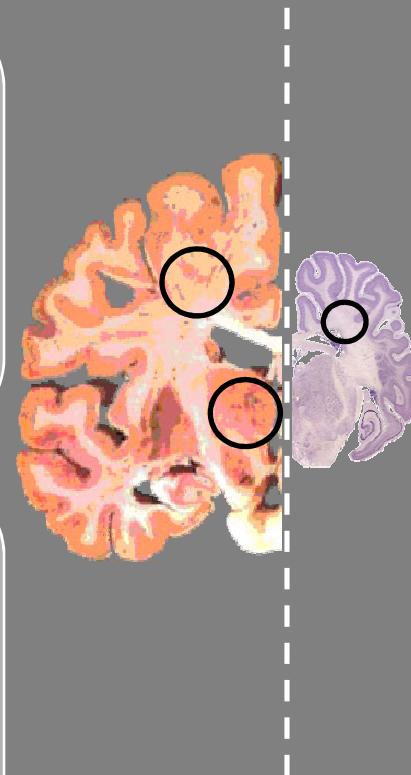
HFR (N = 2)

Gray Matter 

Thickness: 418 – 427 µm

Diameter: 10 mm

Sample Axis: Tr



Pig Brain

(N = 21) HFR

White Matter 

Thickness: 150 – 850 µm

Diameter: 10 mm

Sample Axis: Tr, A-P, S-I

(N = 7) LFR

White Matter 

Thickness: 2250 µm

Diameter: 20 mm

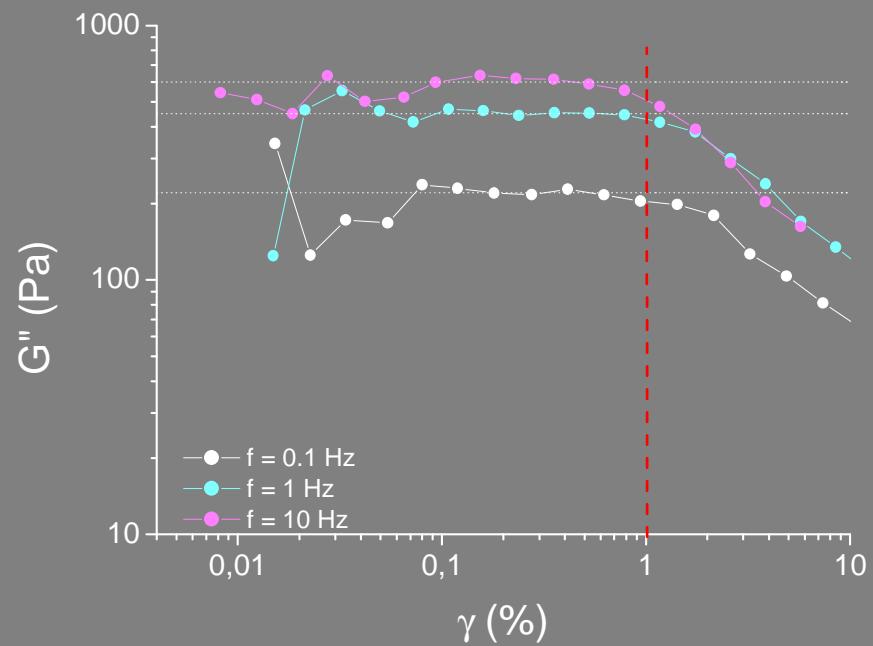
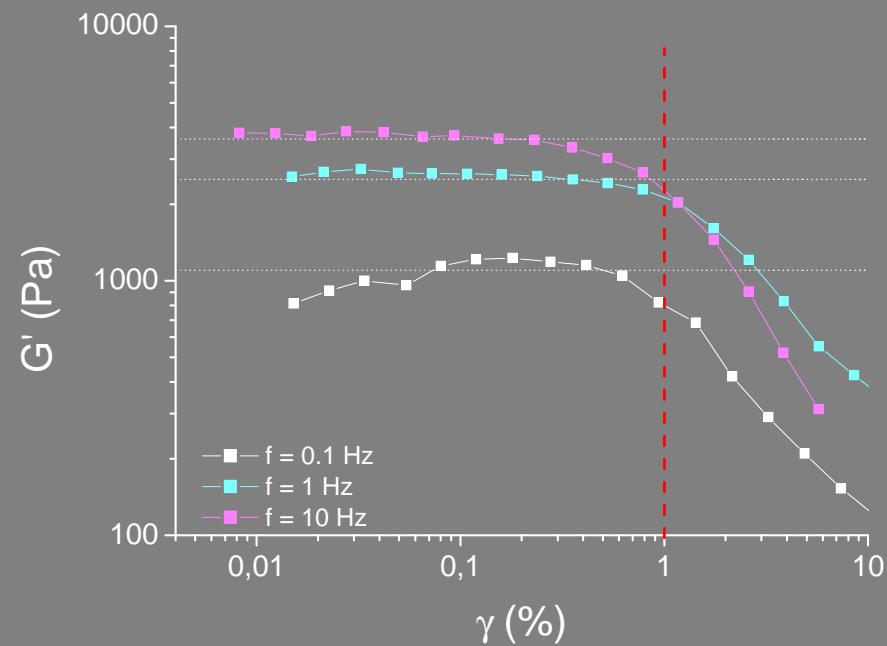
Sample Axis: Tr

Sequence of the Tests

Experimental Sequence Effects

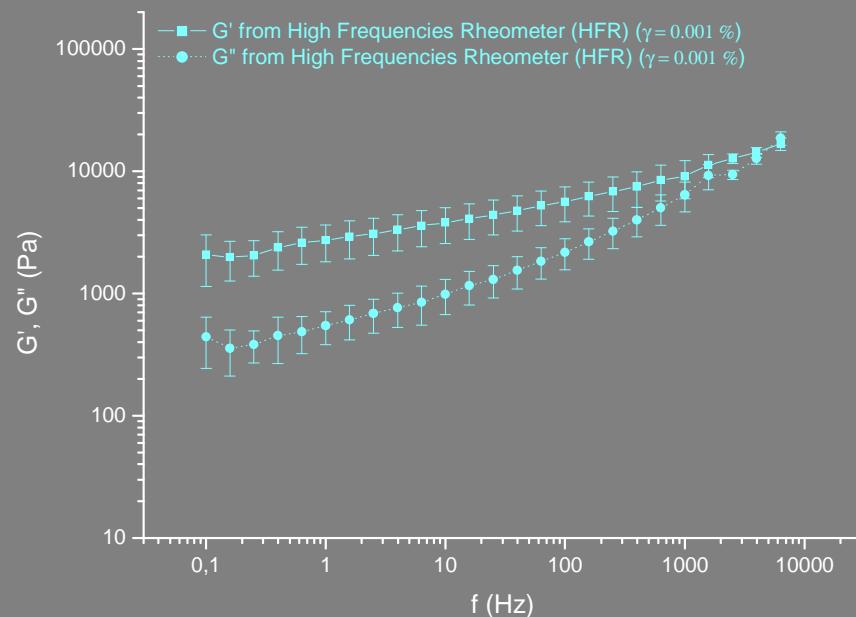
- Slipping Effect
- Interlayer Slipping Effect
- Linear Viscoelastic Effect
 - Wedge Effect
 - Anisotropy Effect
 - Elongation Strain Tissue
 - Strain Effect

Experimental Results: Linear Domain

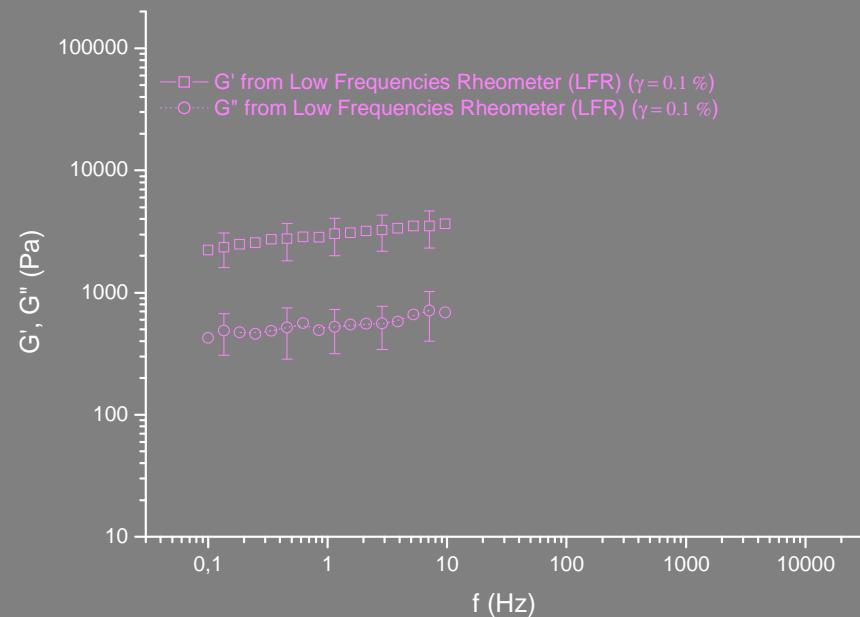


Linear Viscoelastic Limit: $\sim 1\%$

Experimental Results: Frequency Domain

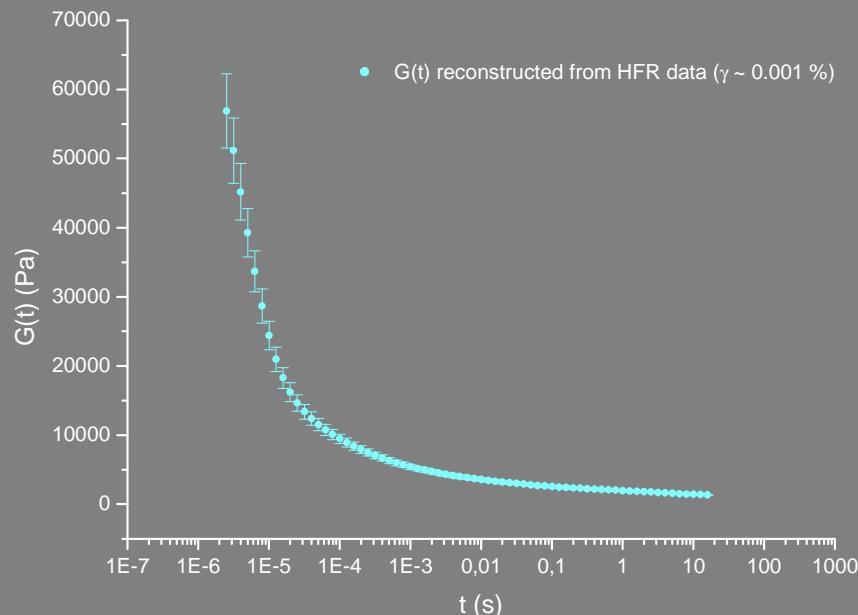


HFR Results
(N = 18)

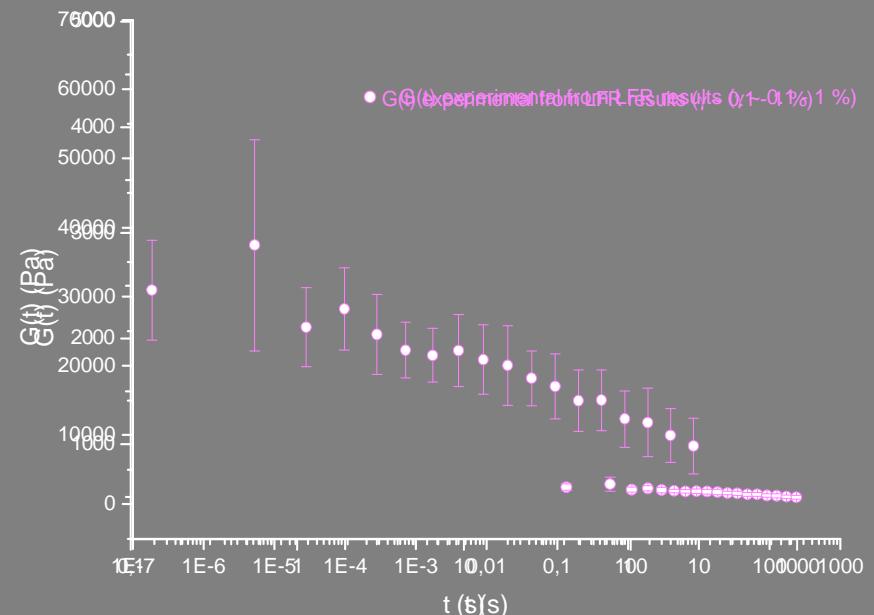


LFR Results
(N = 3)

Experimental Results: Time Domain

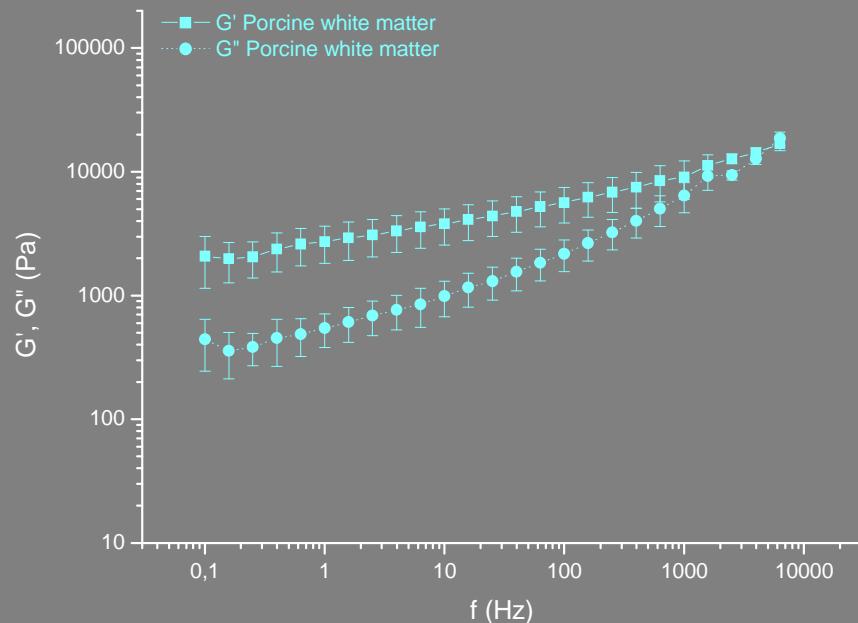


HFR Results ($N = 18$)
 $(G', G'')_{\text{exp}} \Rightarrow H(\tau) \Rightarrow G(t)$

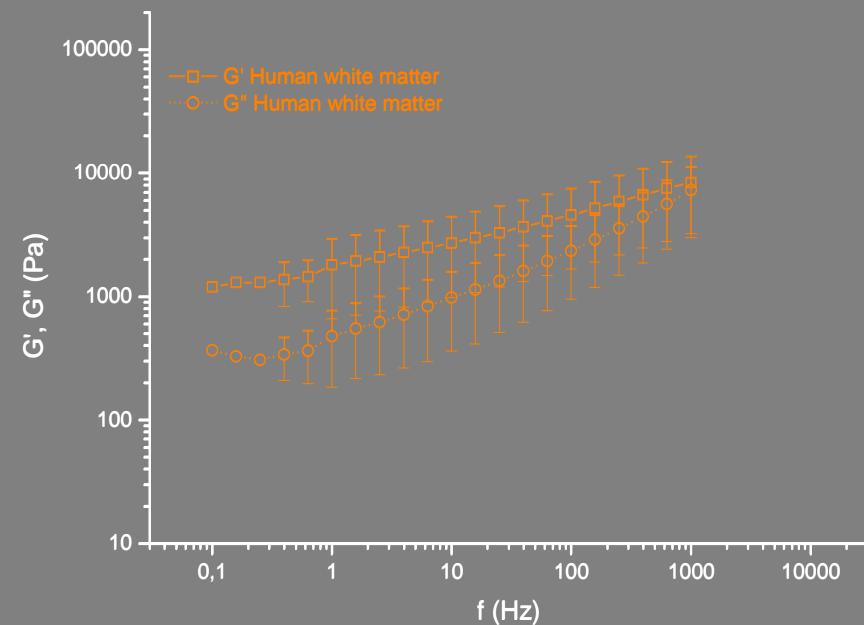


LFR Results ($N = 3$)
 $G(t)_{\text{exp}}$

Experimental Results: Inter-Species

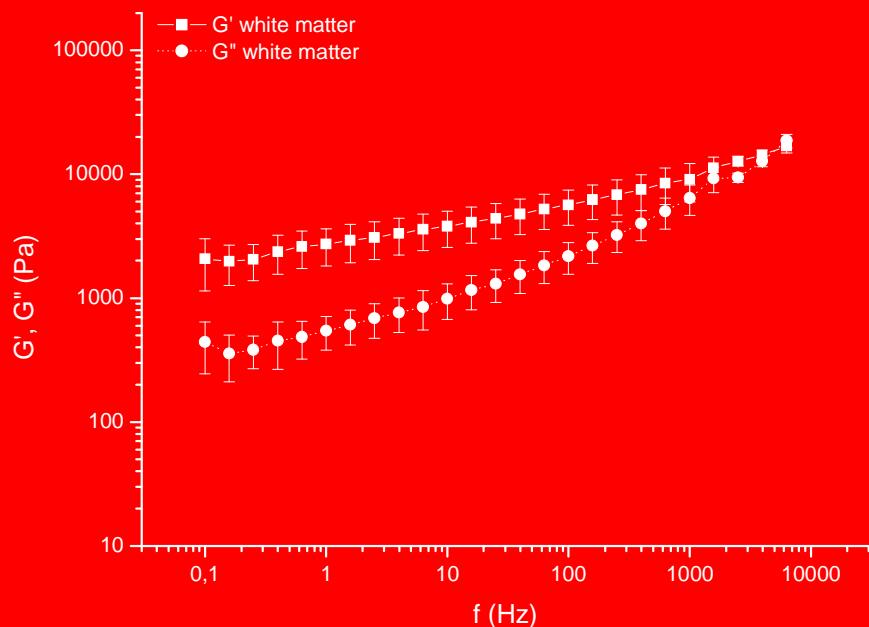


Porcine white matter
($N = 18$)

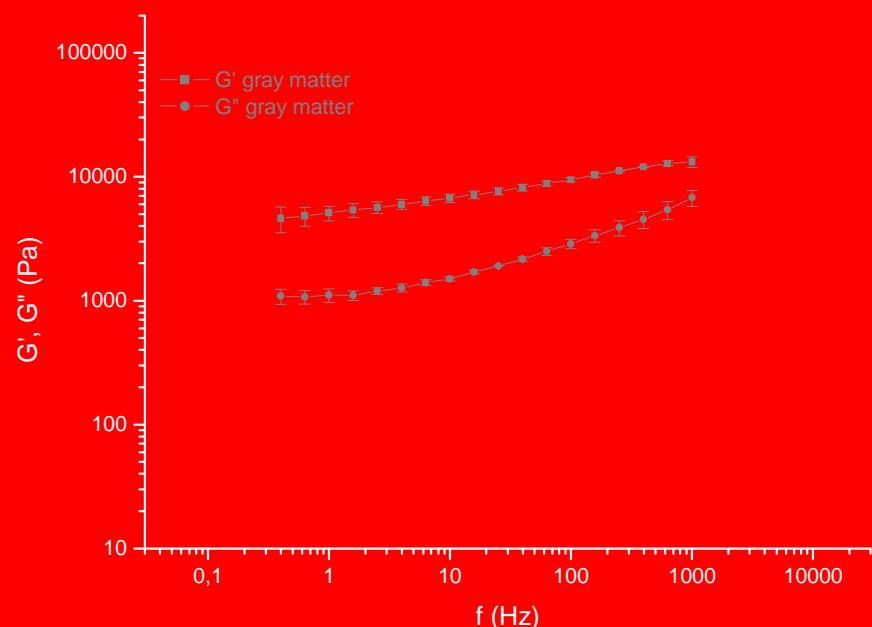


Human white matter
($N = 9$)

Experimental Results: Inter-Region

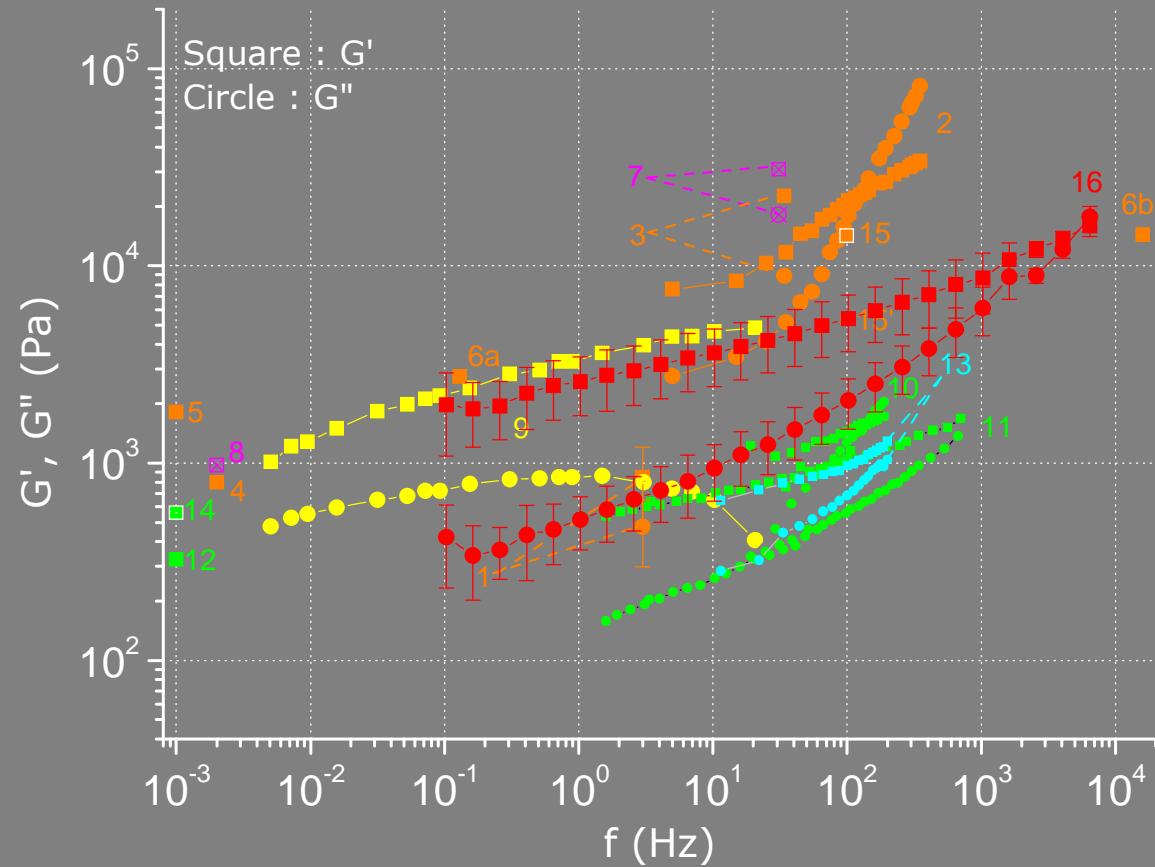


White Matter ($N = 9$)
(*Corona Radiata*)



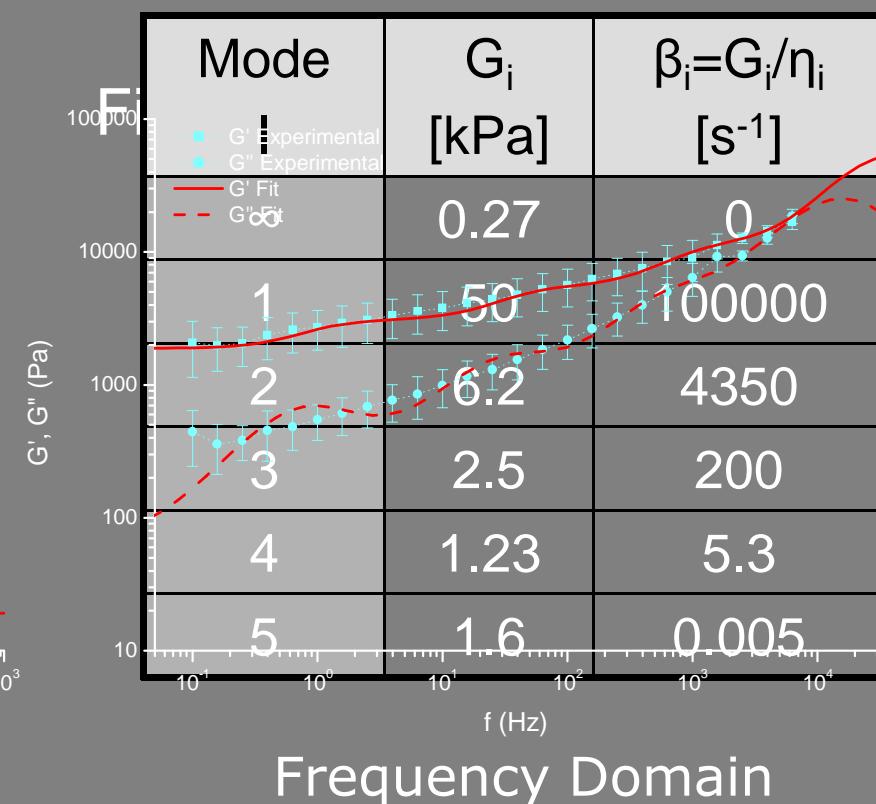
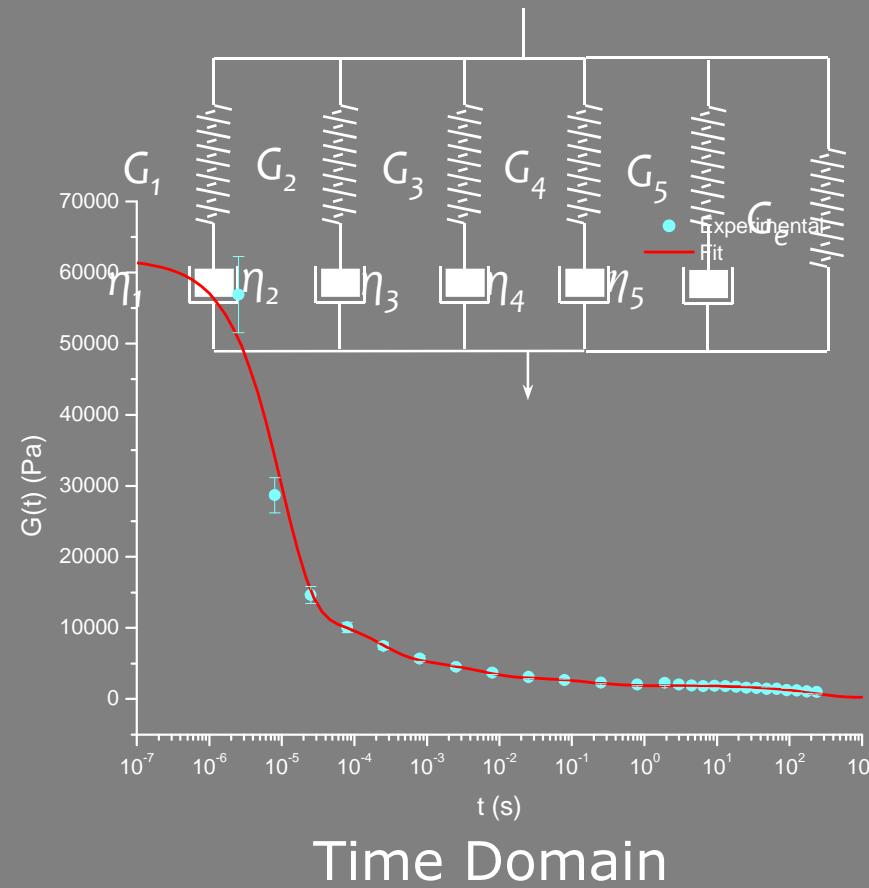
Gray Matter ($N = 2$)
(*Thalamic Nuclei*)

Experimental Results: Comparison with Literature

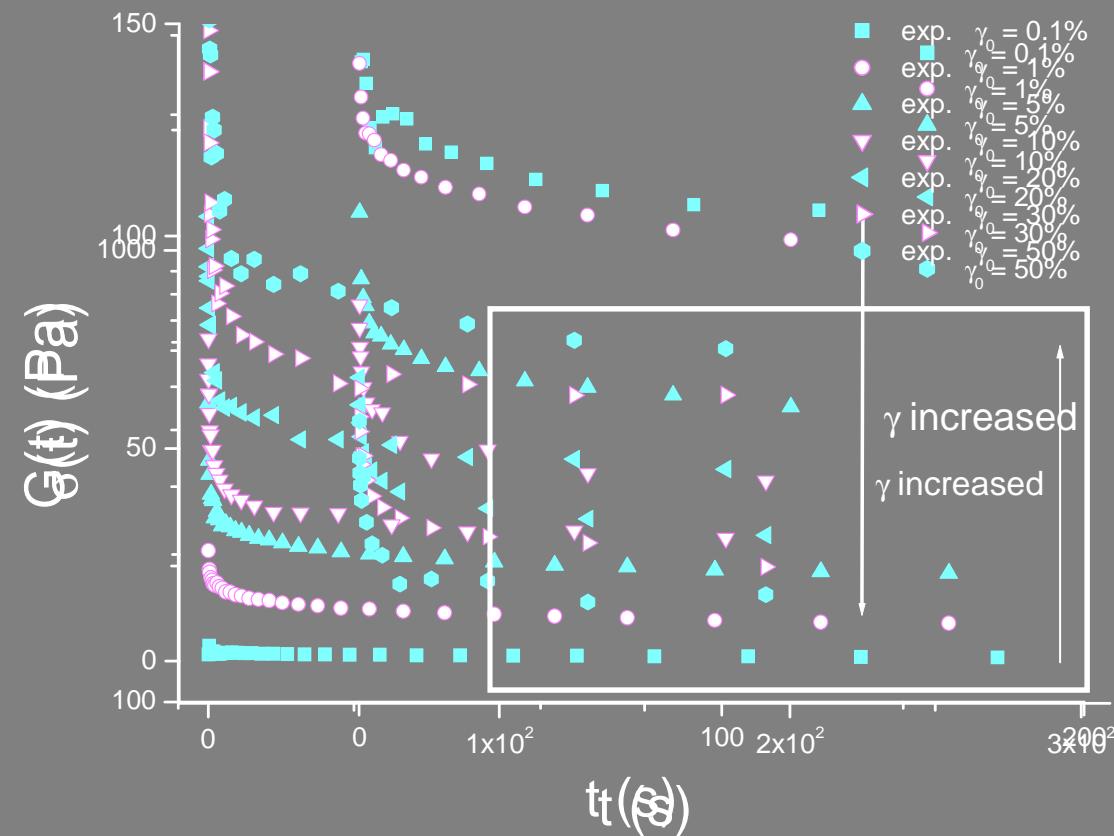


1. Human (Fallenstein, 1969)
2. Human (Shuck, 1972)
3. Human (Galford, 1970)
4. Human (Galford, 1970)
5. Human (Donnelly, 1997)
6. Human (Mendis, 1995)
7. Monkey (Galford, 1970)
8. Monkey (Galford, 1970)
9. Bovine (Bilston, 1997)
10. Porcine (Arbogast, 1997)
11. Porcine (Brands, 2002)
12. Porcine (Miller, 1997)
13. Infant pig (Thibault, 1998)
14. In vivo pig (Miller, 2000)
15. In vivo human (Manduca, 2001)
16. Human & Porcine (Author)

Modeling Results: Shear Linear Behavior



Analysis of the Shear Strain Softening of Brain Tissue



Hyperelastic Model

Hypothesis

- Reference State: Linear State
- Incompressibility: $G(\sim 1000 \text{ Pa}) \leq K(\sim 2.1 \text{ GPa})$
- Isotropy: Low degree of anisotropy of the *Corona Radiata*

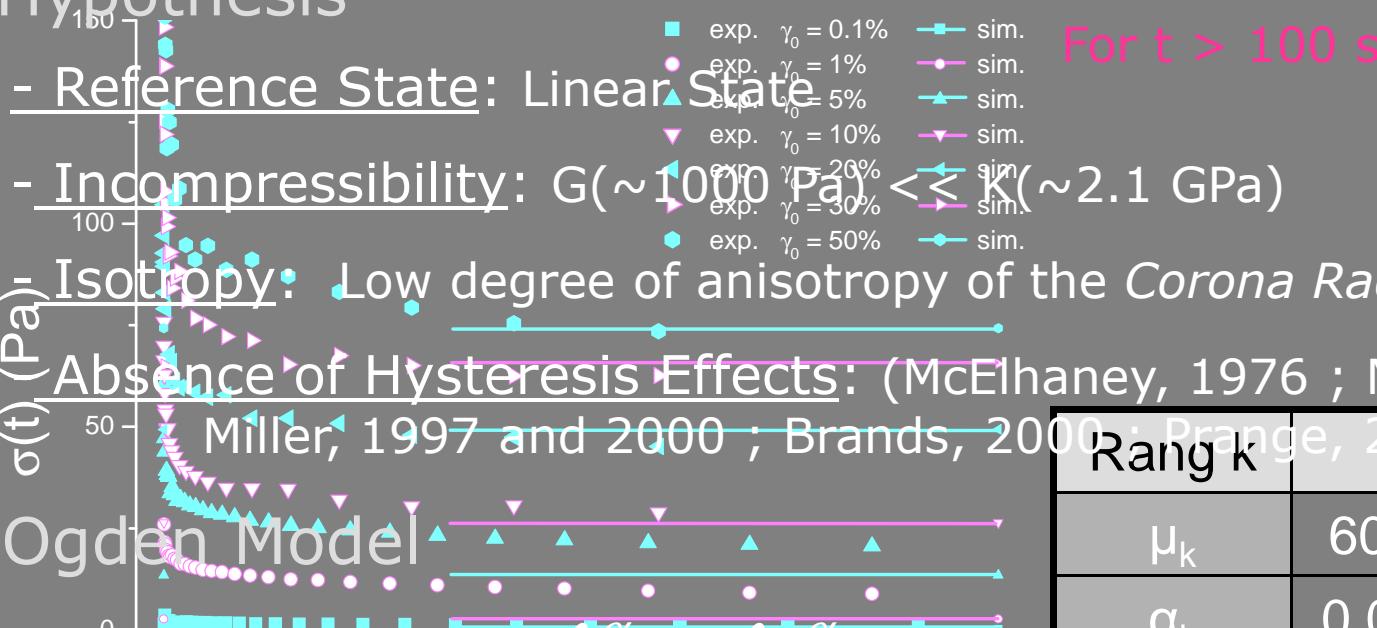
Absence of Hysteresis Effects: (McElhaney, 1976 ; Mendis, 1995 ; Miller, 1997 and 2000 ; Brands, 2000 ; Prange, 2000)

Ogden Model

$$\sigma^0(\lambda) = \sum_k^{10} \mu_k \frac{\lambda^{\alpha_k} - \lambda^{-\alpha_k}}{t(s\lambda + \lambda^{-1})}$$

Rang k	1	2	3
μ_k	60000	560	1.25
α_k	0.0451	-3.9	16.3

$$\text{Where } \lambda = \frac{\gamma}{2} + \sqrt{1 + \frac{\gamma^2}{4}}$$

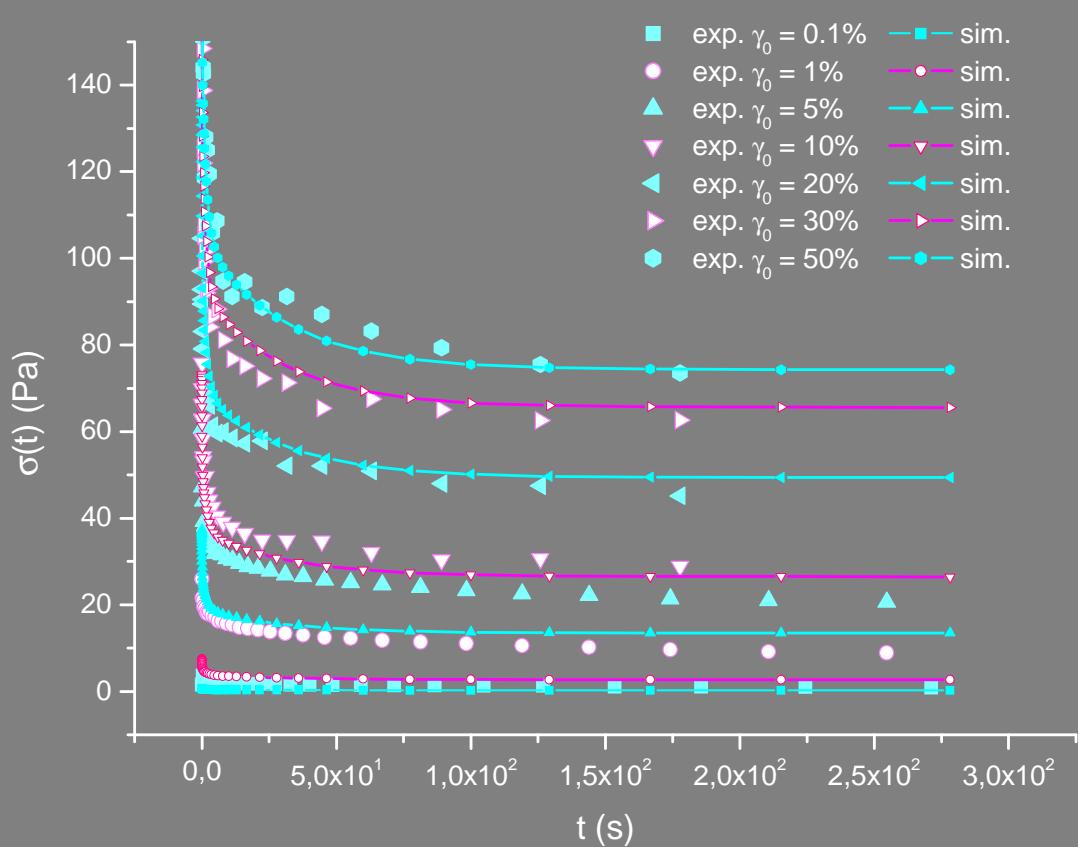


Towards a Visco-Hyperelastic Model

Hypothesis

- Time/Strain Factorization: Time-Dependant Behavior Is Independent of the Applied Strain
 - At Long Times: $\sigma(\lambda, t \rightarrow \infty) = \sum_k \mu_k^e \frac{\lambda^{\alpha_k} - \lambda^{-\alpha_k}}{\lambda + \lambda^{-1}}$
 - At Small Strain: Generalized Maxwell Model
- $\sigma(\lambda, t) = \sum_k \mu_k \left(1 + \sum_{j=1}^n C_j e^{-\gamma_j t} \right)^{-1}$
-
- | Mode i | 1 | 2 | 3 |
|----------|----------------|------|-----|
| C_j | 0.9 | 0.53 | 0.4 |
| τ_j | $0.13\alpha_k$ | 1.76 | 31 |

Towards a Visco-Hyperelastic Model



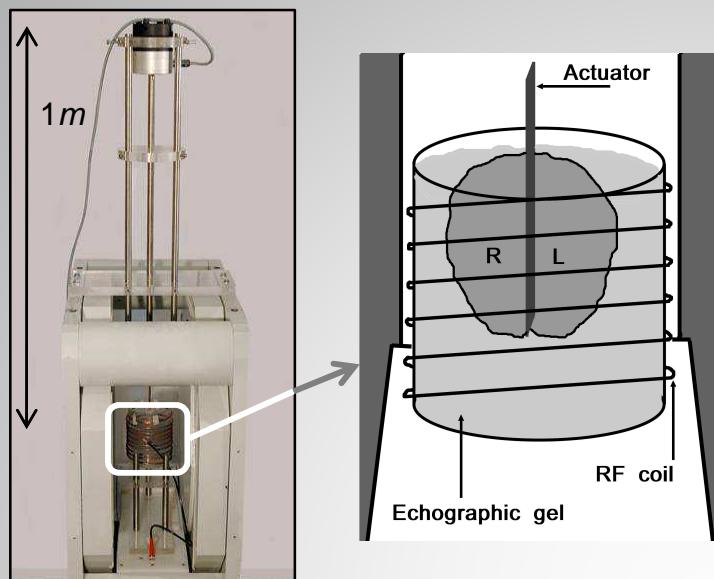
$$\sigma(\lambda, t) = \sum_k \mu_k \left(1 + \sum_{j=1}^n C_j e^{-t/\tau_j} \right) \frac{\lambda^{\alpha_k} - \lambda^{-\alpha_k}}{\lambda + \lambda^{-1}}$$

Rang k	1	2	3
μ_k	60000	560	1.25
α_k	0.0451	-3.9	16.3

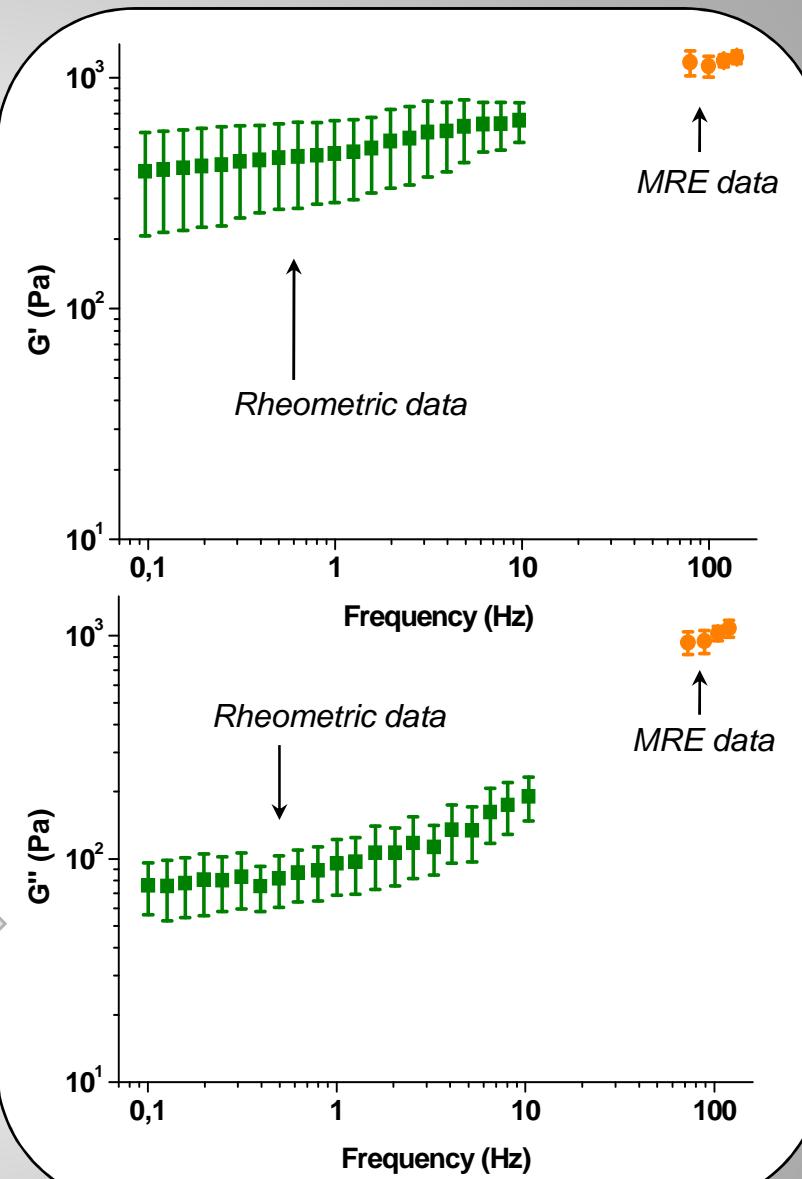
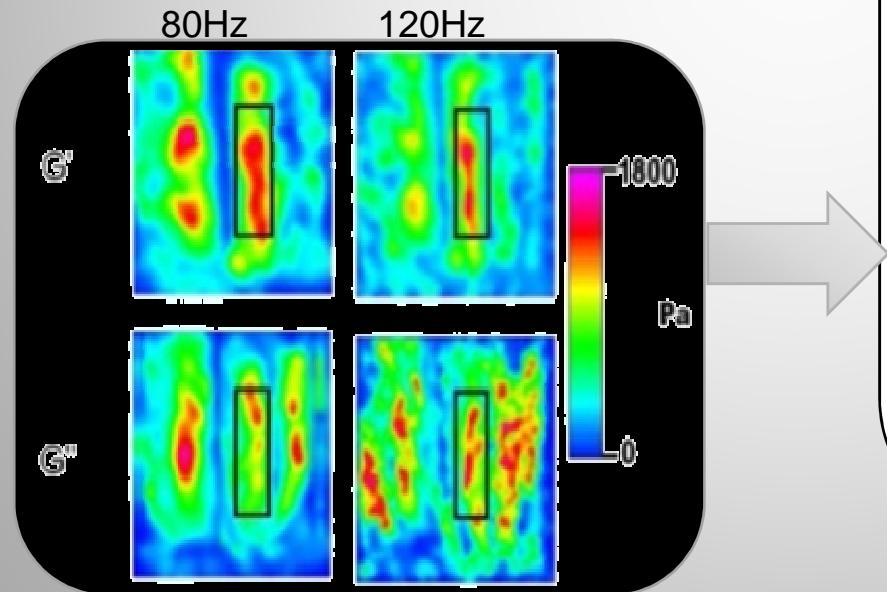
Mode i	1	2	3
C_j	0.9	0.53	0.4
τ_j	0.13	1.76	31

CARACTERISATION DU CERVEAU IN VIVO

In vitro tests : Validation on ex-vivo porcine brains

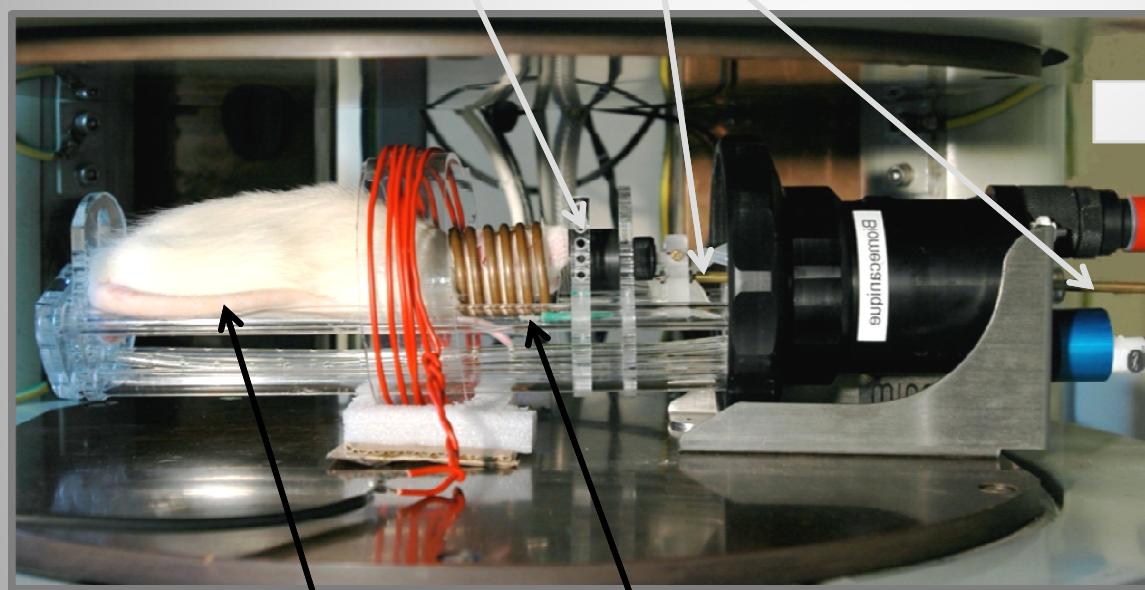
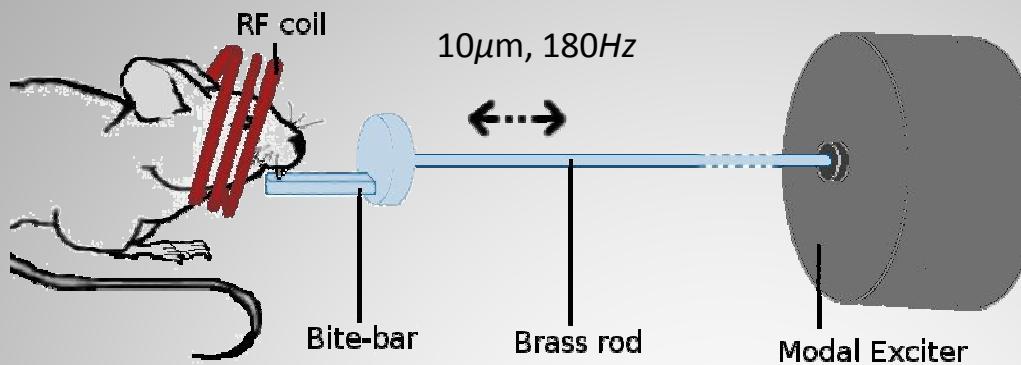


Vertical MRE Experimental device for ex vivo porcine brain



In vivo tests :

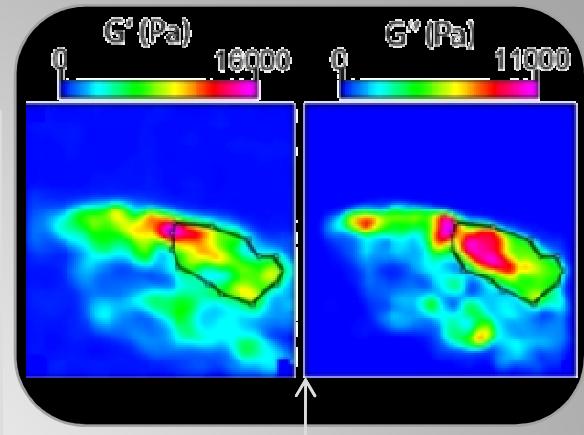
preliminary results on 7 rats



Sprague-Dawley
anesthetized male rat

RF coil

**Horizontal MRE Experimental device for in vivo
rat brain**



Rat brain distribution maps of G' and G'' with a manually selected region of interest

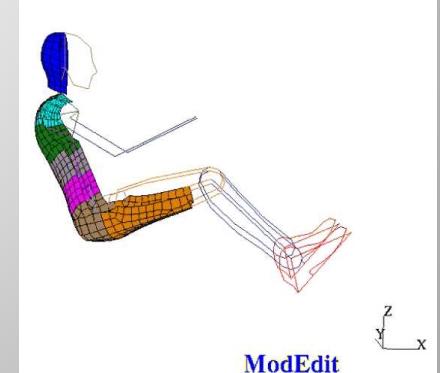
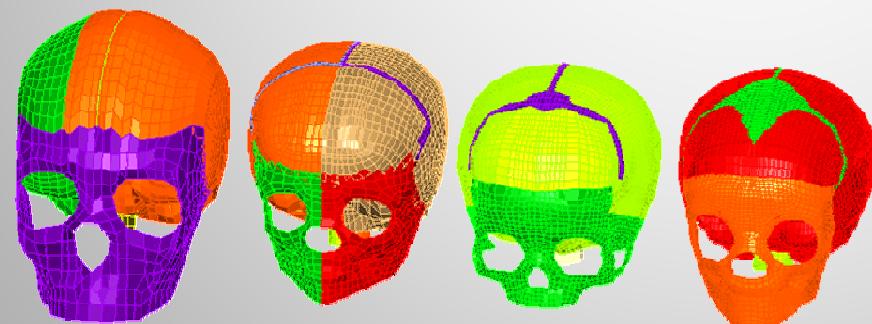
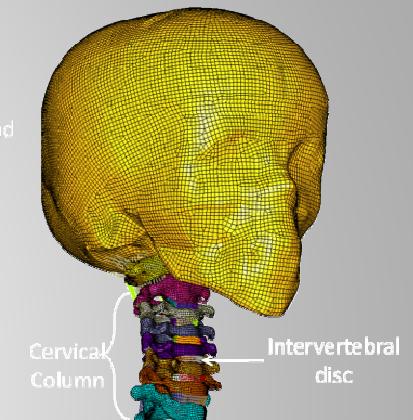
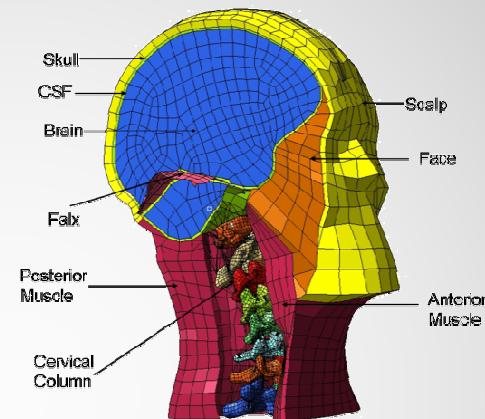
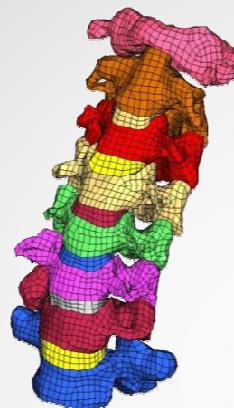
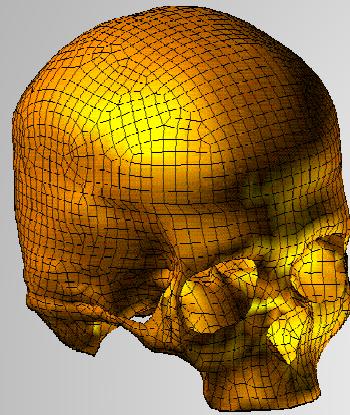
Mean shearing moduli at
180Hz for the 7 tested rats :

$$G' = 7600 \pm 650 \text{ Pa}$$

$$G'' = 7500 \pm 1600 \text{ Pa}$$

Limite de tolérance au choc

HUMAN SEGMENTS

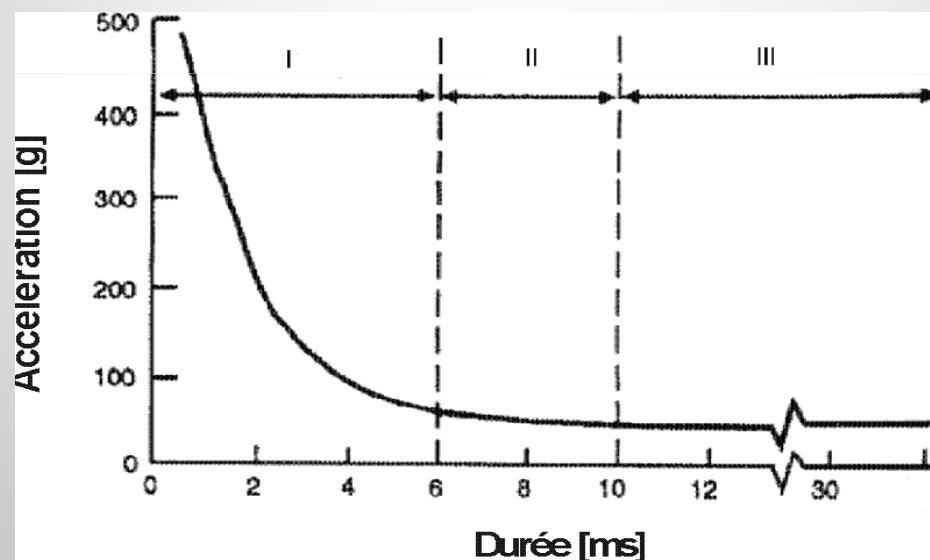


Biomécanique du Traumatisme Crânien

- Aspect historique
- Modélisation et validation du modèle de la tête
- Limites de tolérances spécifiques à un mécanisme

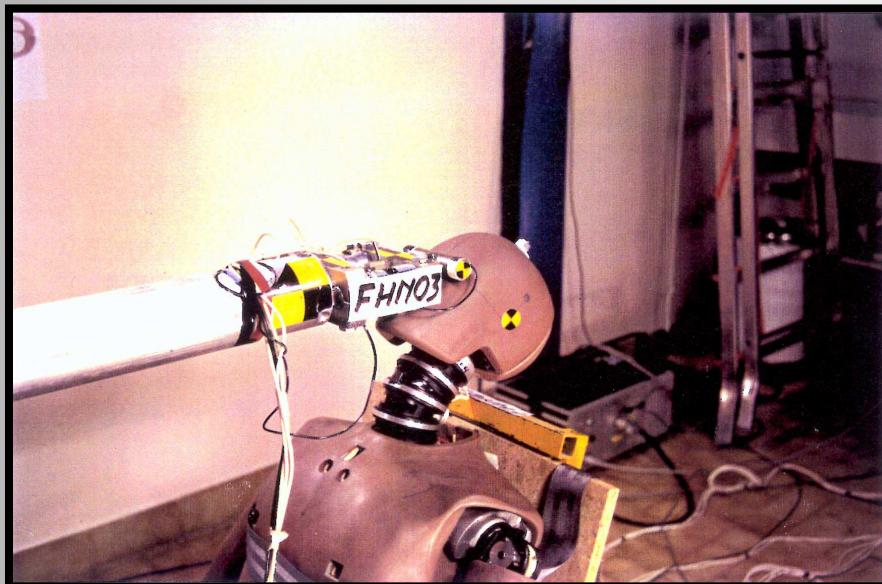
Existing Head Injury Criteria

- Head substitute: Headform mass of $M = 4.5$ to 4.8 kg
- Injury mechanism related to linear head acceleration
- Based on cadaver head tests(Wayne State University 1960)



Wayne State Tolerance Curve

Head Injury Criteria (HIC, 1972)



$M = 4.58 \text{ kg}$

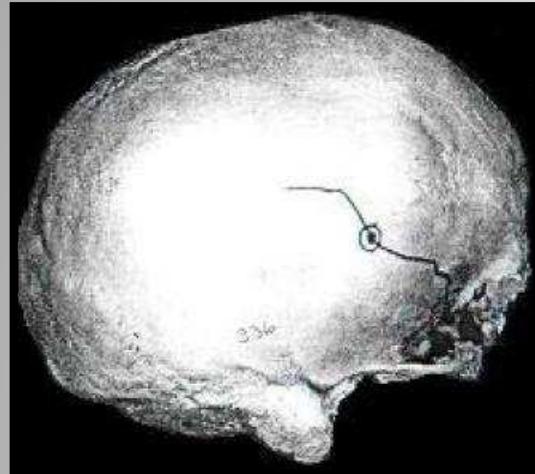
$$HIC = (t_2 - t_1) \left[\frac{1}{(t_2 - t_1)} \int_{t_1}^{t_2} adt \right]^{2.5}$$

$HIC = 1000$

Limites du HIC

- Non prise en compte de l'accélération rotatoire
- Non direction dépendant
- Ne tiens pas compte des mécanismes de lésion

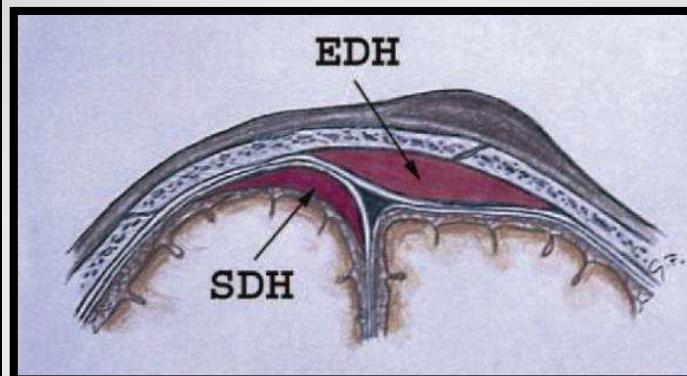
HEAD INJURY MECHANISMS AND RELATED PARAMETER



Skull fractures

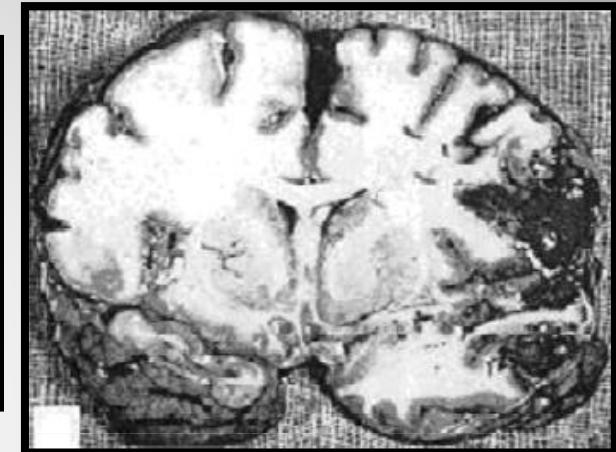


Skull deformation



**Subdural and
subarachnoidal
haematoma**

Relative motion between
the brain and the skull

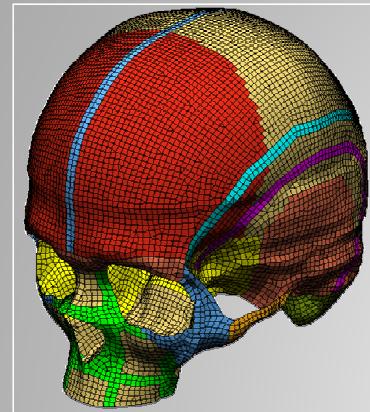


**Diffuse Axonal Injuries
(DAI)**

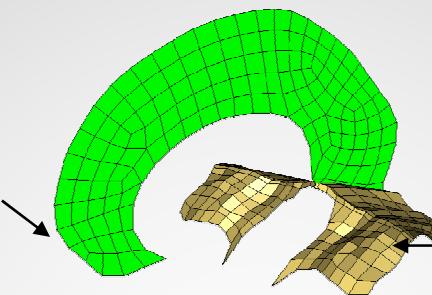


Intracerebral strains/stress

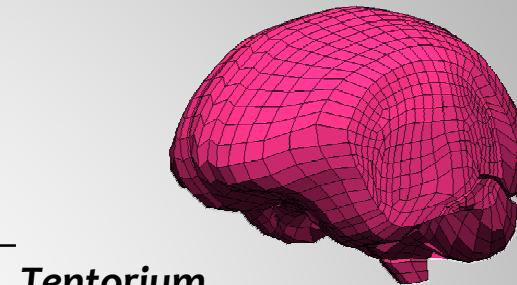
STRASBOURG UNIVERSITY FE HEAD MODEL



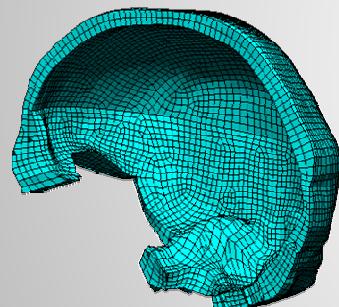
Outer table



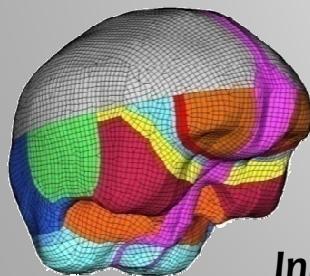
Falx



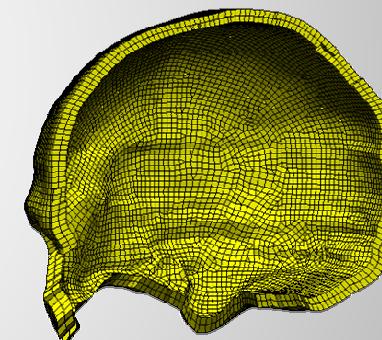
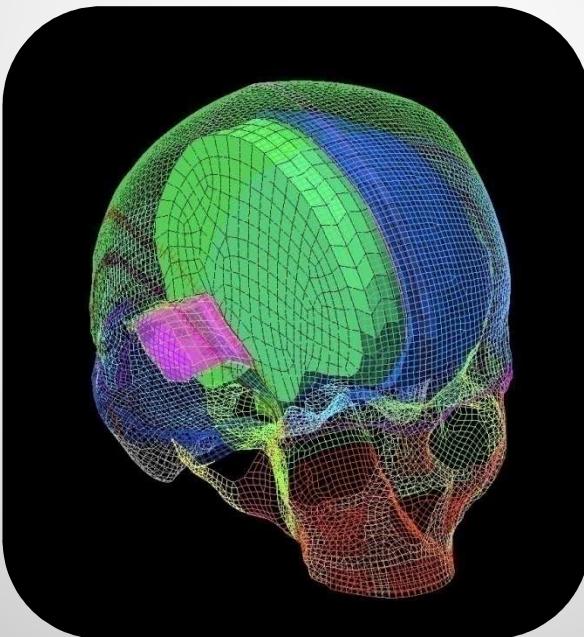
Brain



Diploë



Inner table



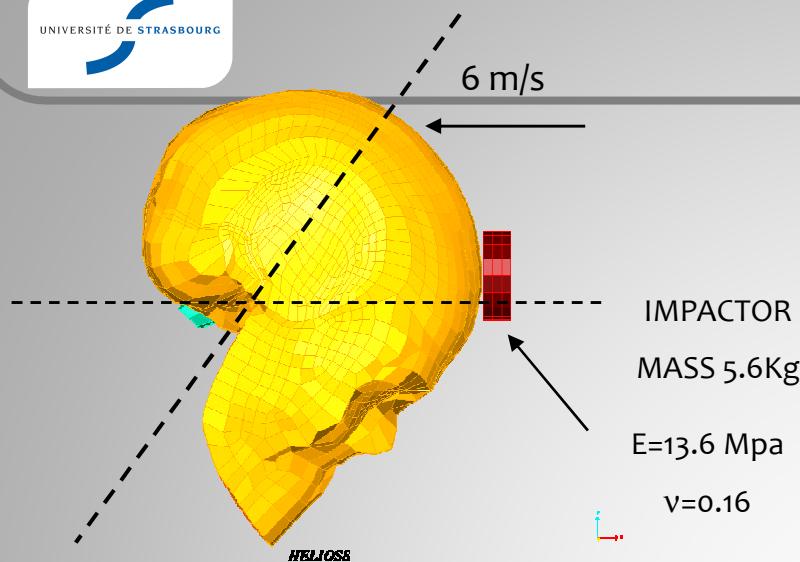
Scalp

48266 bricks

25977 shell

74243 elements

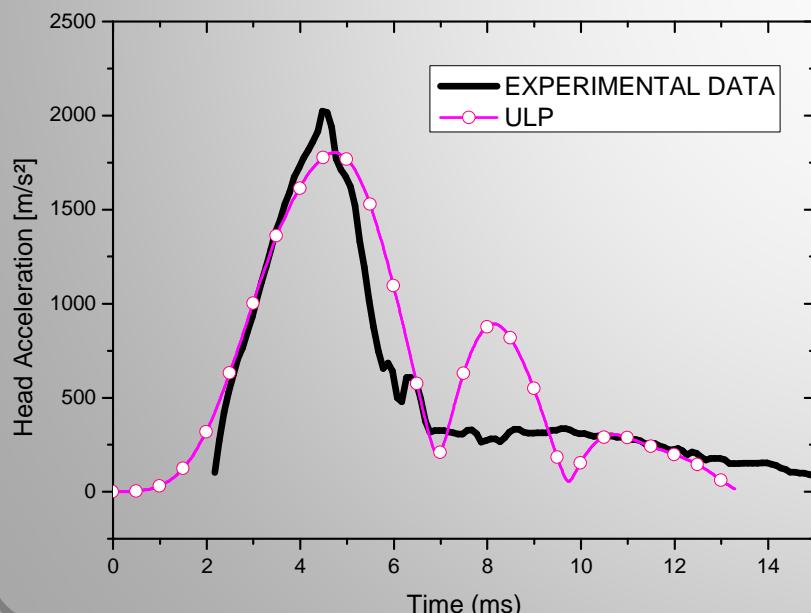




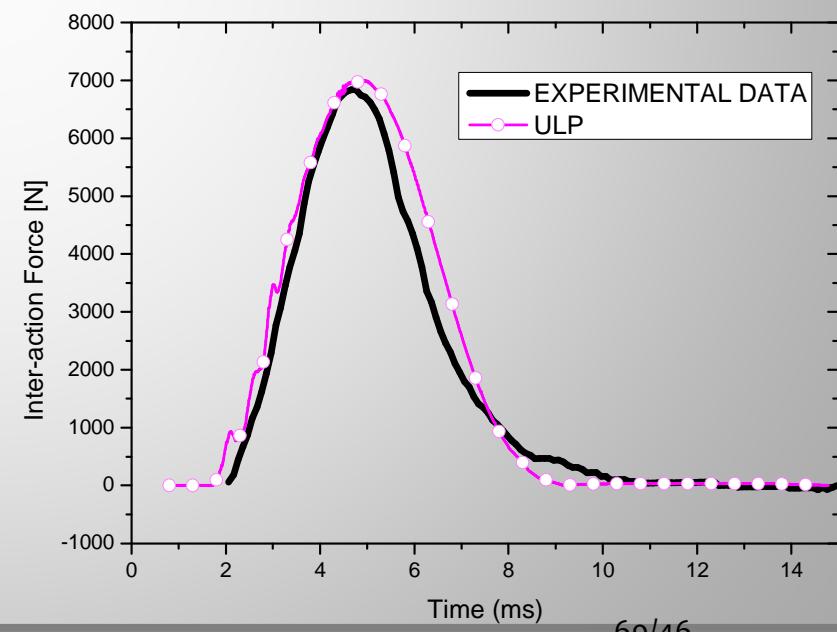
Validation parameters

- Impact force
- Linear Head acceleration
- Five intracranial-pressure

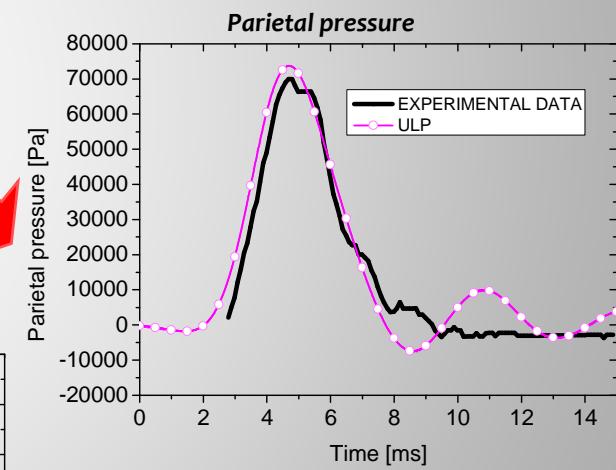
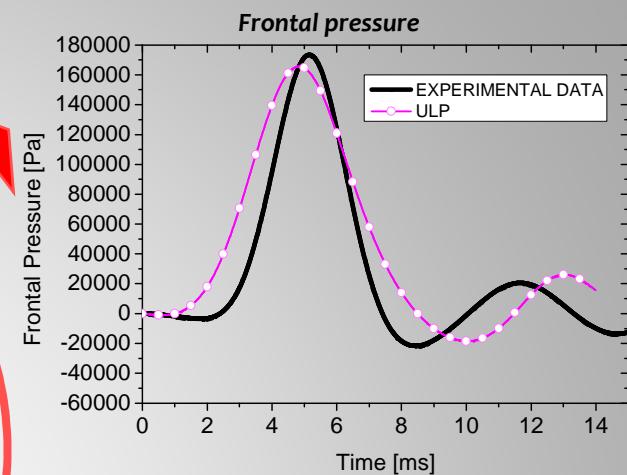
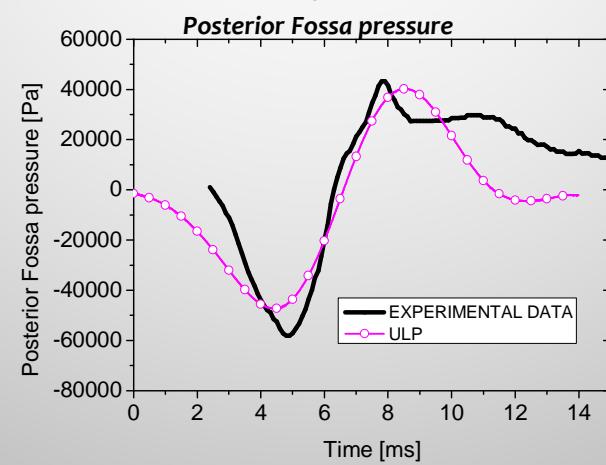
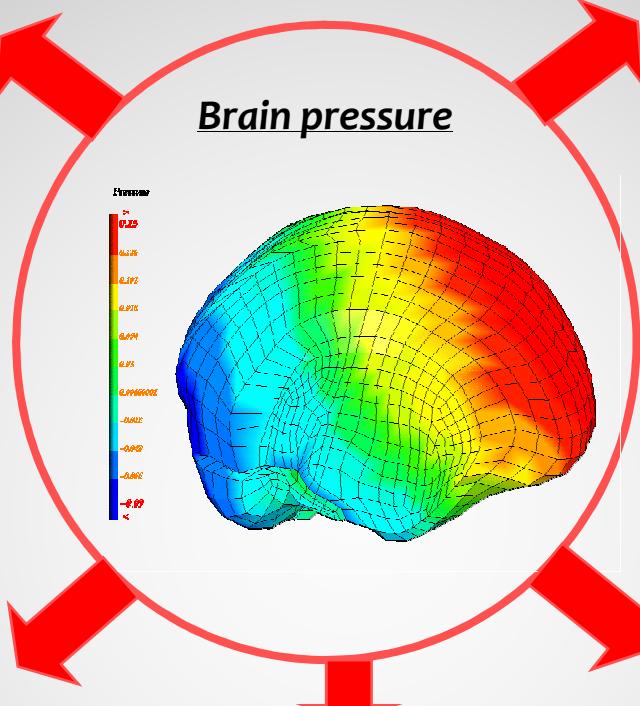
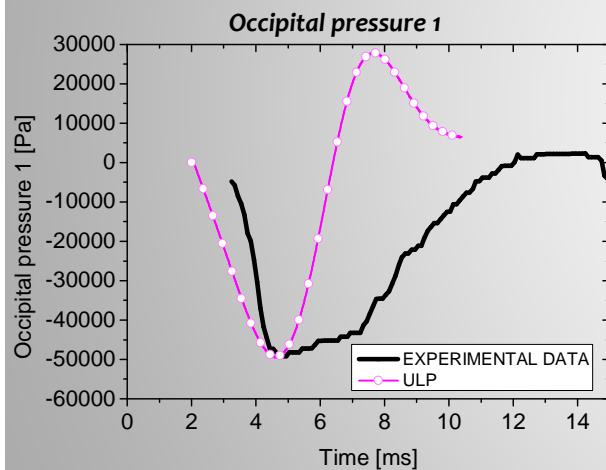
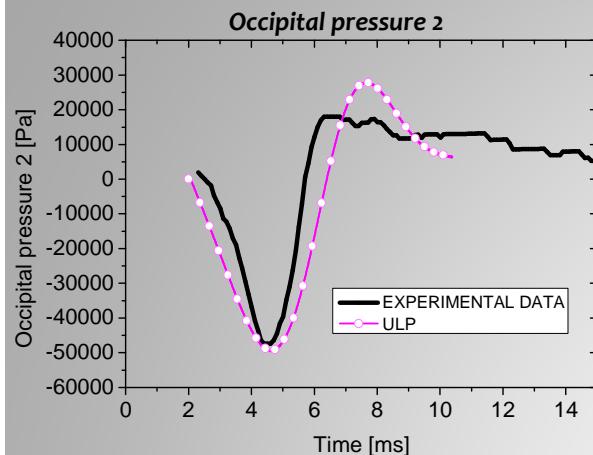
Head acceleration



Impact Force



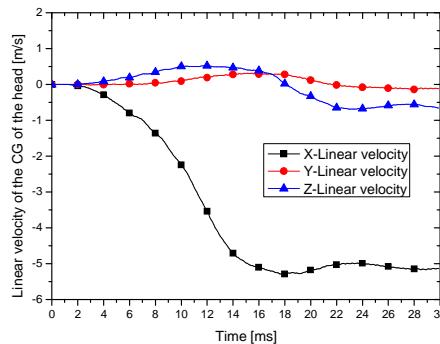
NAHUM (1977)



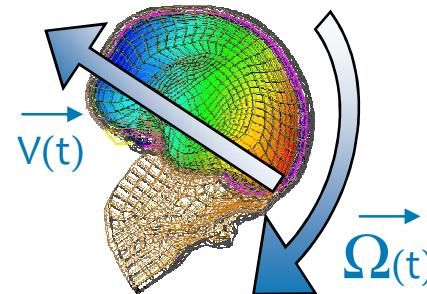
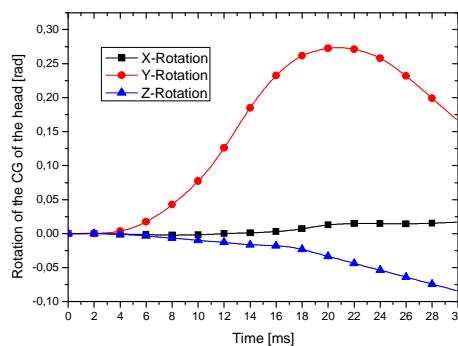
MS428-2 case

INPUT

Linear accelerations

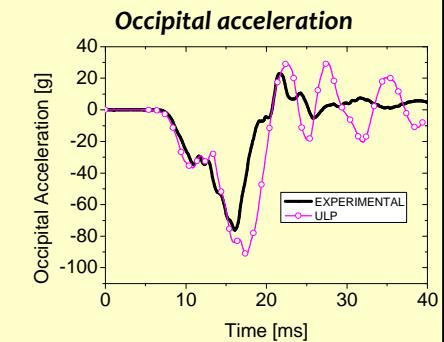
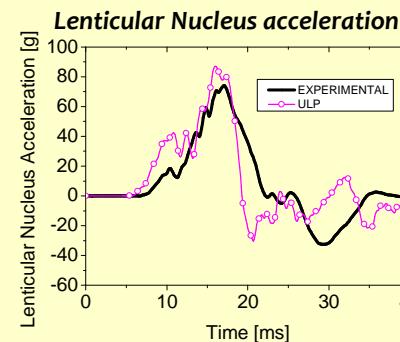
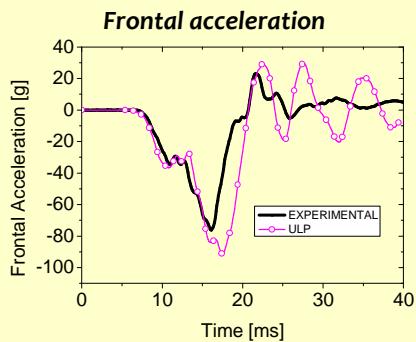


Rotational accelerations

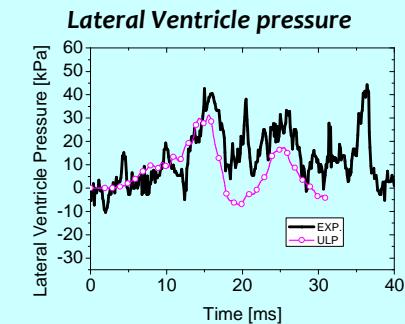
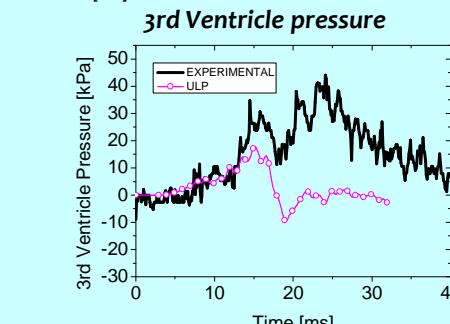
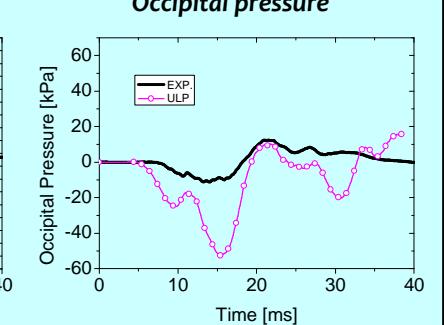
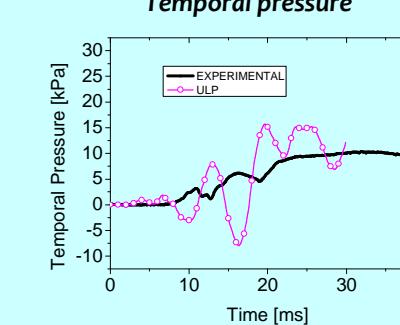
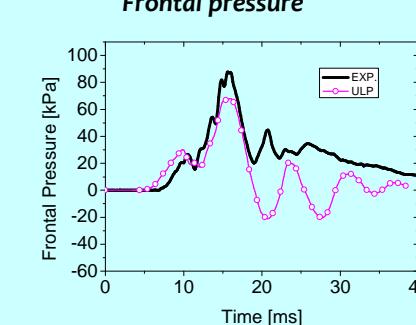


OUTPUT (3 accelerations, 5 pressures)

ACCELERATION



PRESSURE

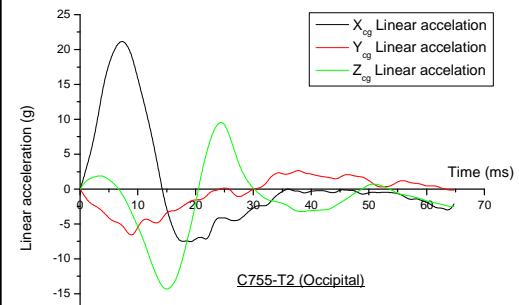


Occipital impact (C755-T2)

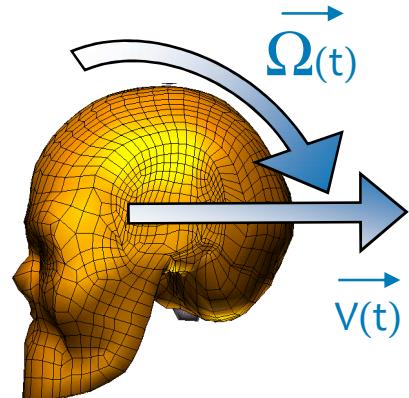
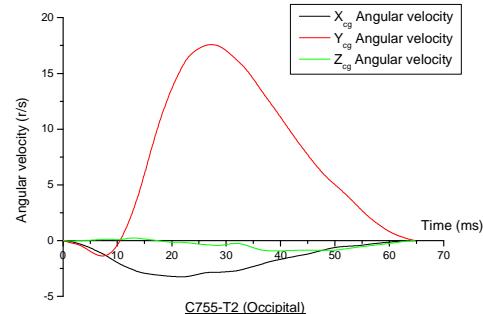
HARDY (2001)

INPUT

Linear accelerations

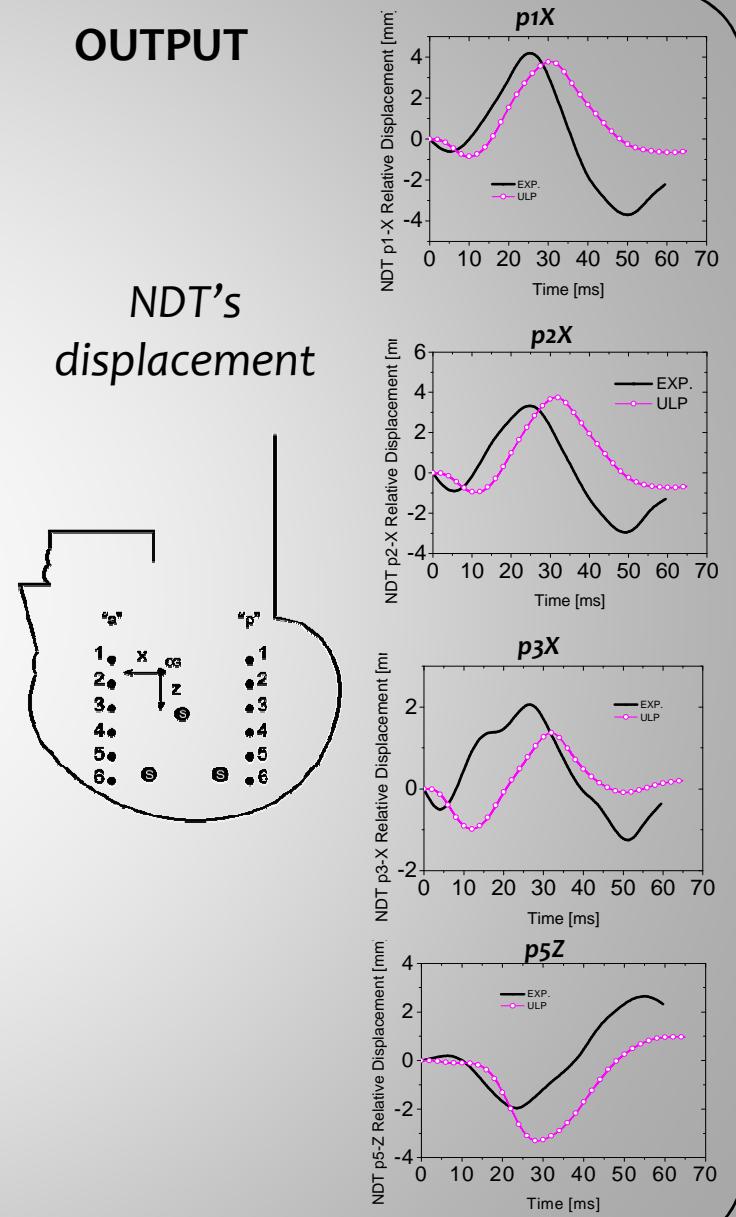
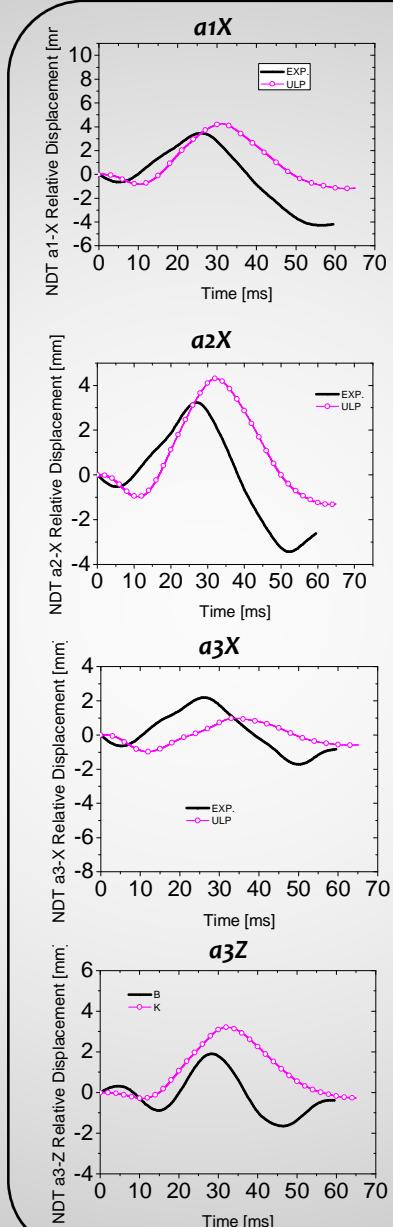


Rotational accelerations



OUTPUT

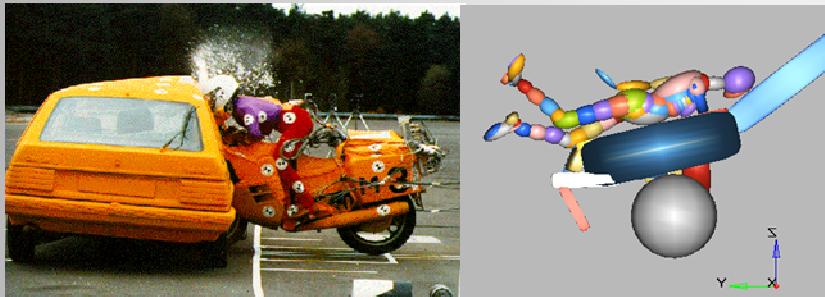
NDT's displacement



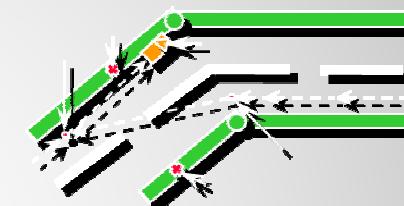
Simulation de Trauma Crâniens

MODEL BASED INJURY CRITERIA

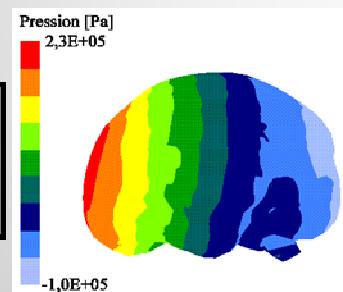
Experimental or analytical replication



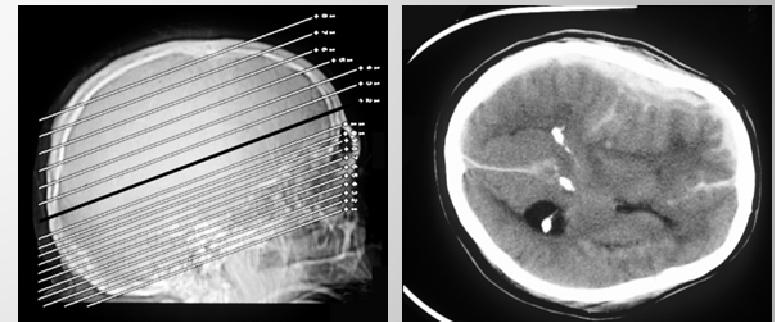
Real accidents



Numerical reconstruction

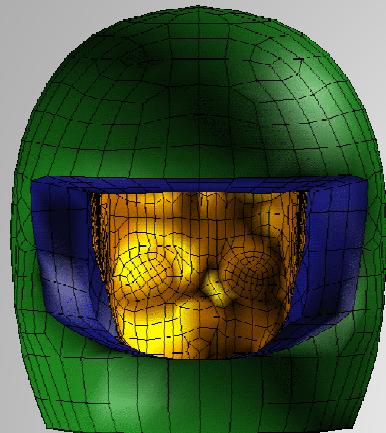


Detailed medical report

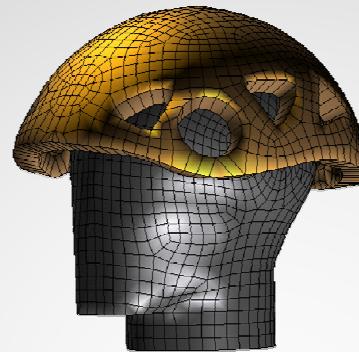


Injury mechanisms and tolerance limits

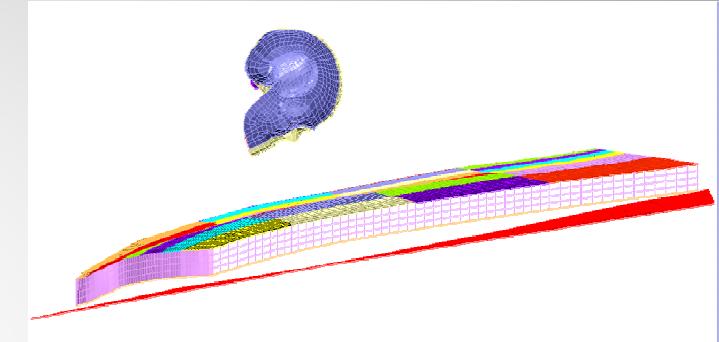
MODELLING OF THE PROTECTION SYSTEMS



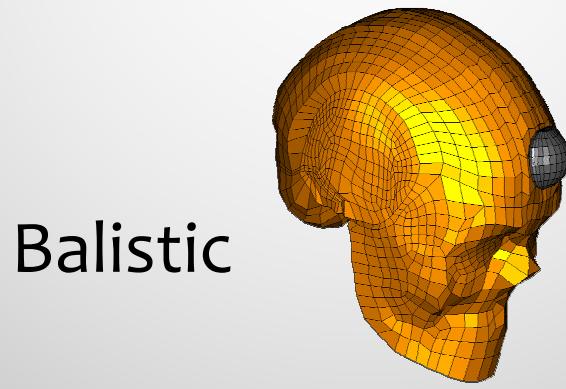
Motorcyclist



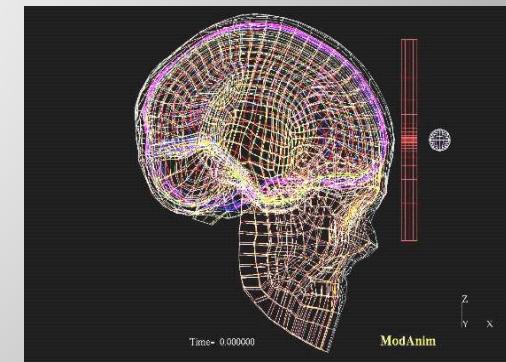
Cyclist



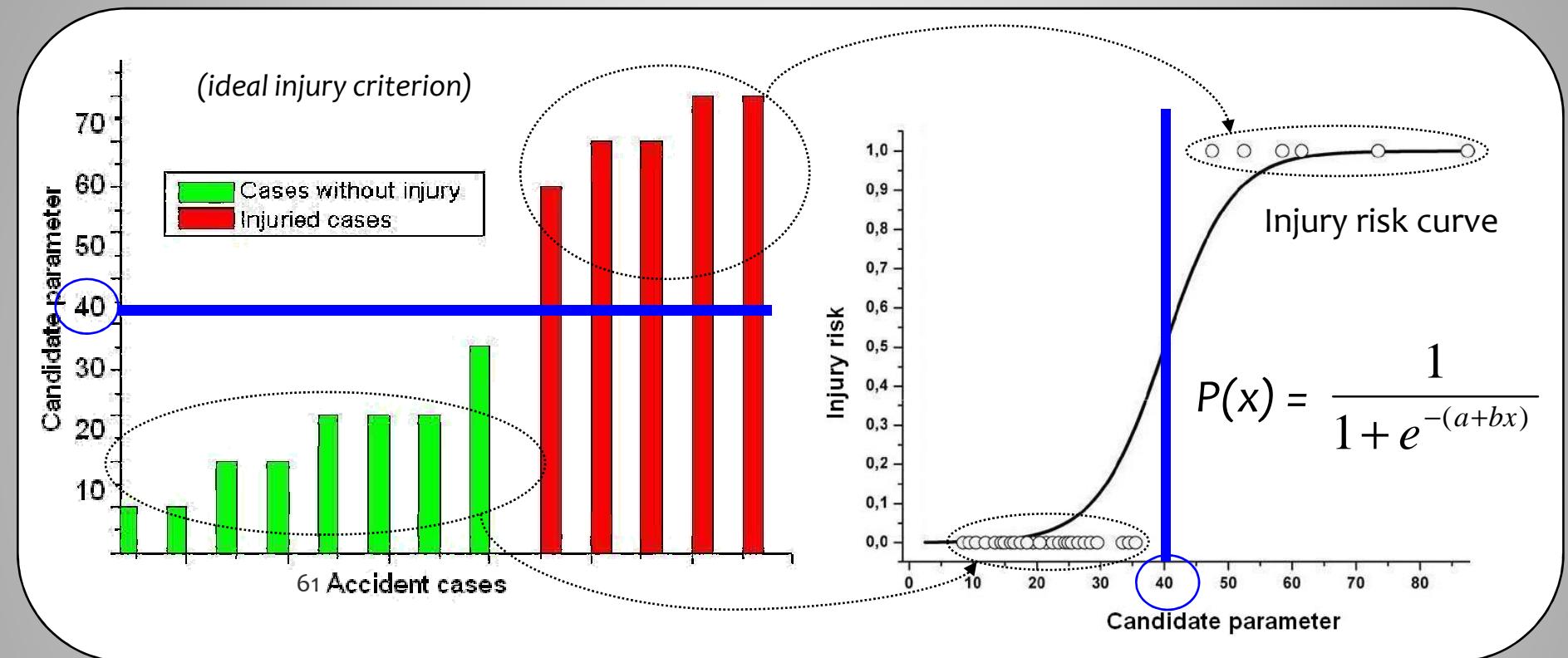
Pedes



Balistic



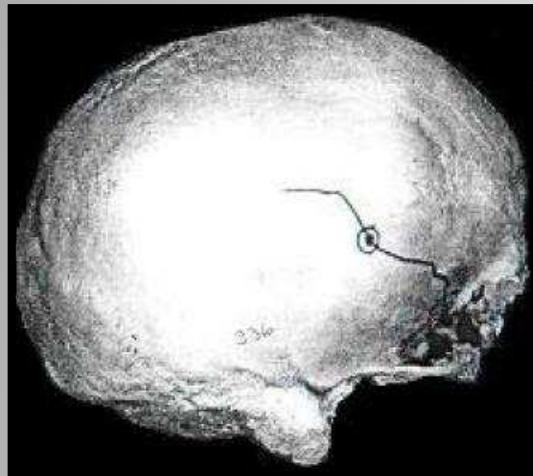
EXTRACTION OF CRITERIA



Binary logistic regression (SPSS v14.0)

Nagelkerke R-sq statistic

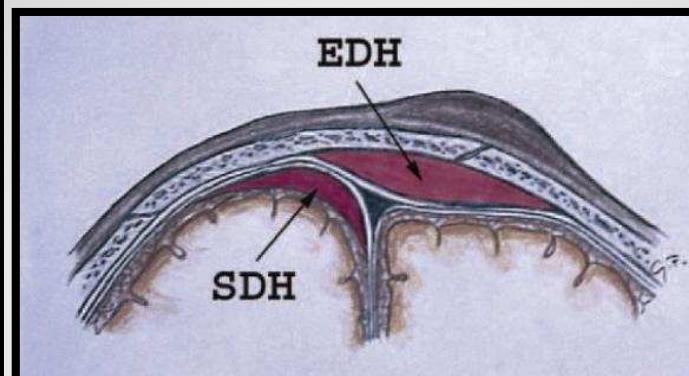
HEAD INJURY MECHANISMS AND RELATED PARAMETER



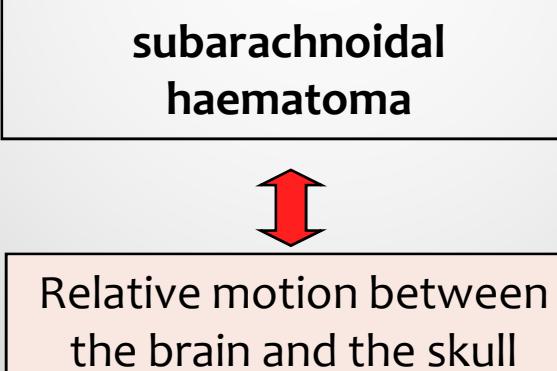
Skull fractures



Skull deformation



**Subdural and
subarachnoidal
haematoma**



Relative motion between
the brain and the skull

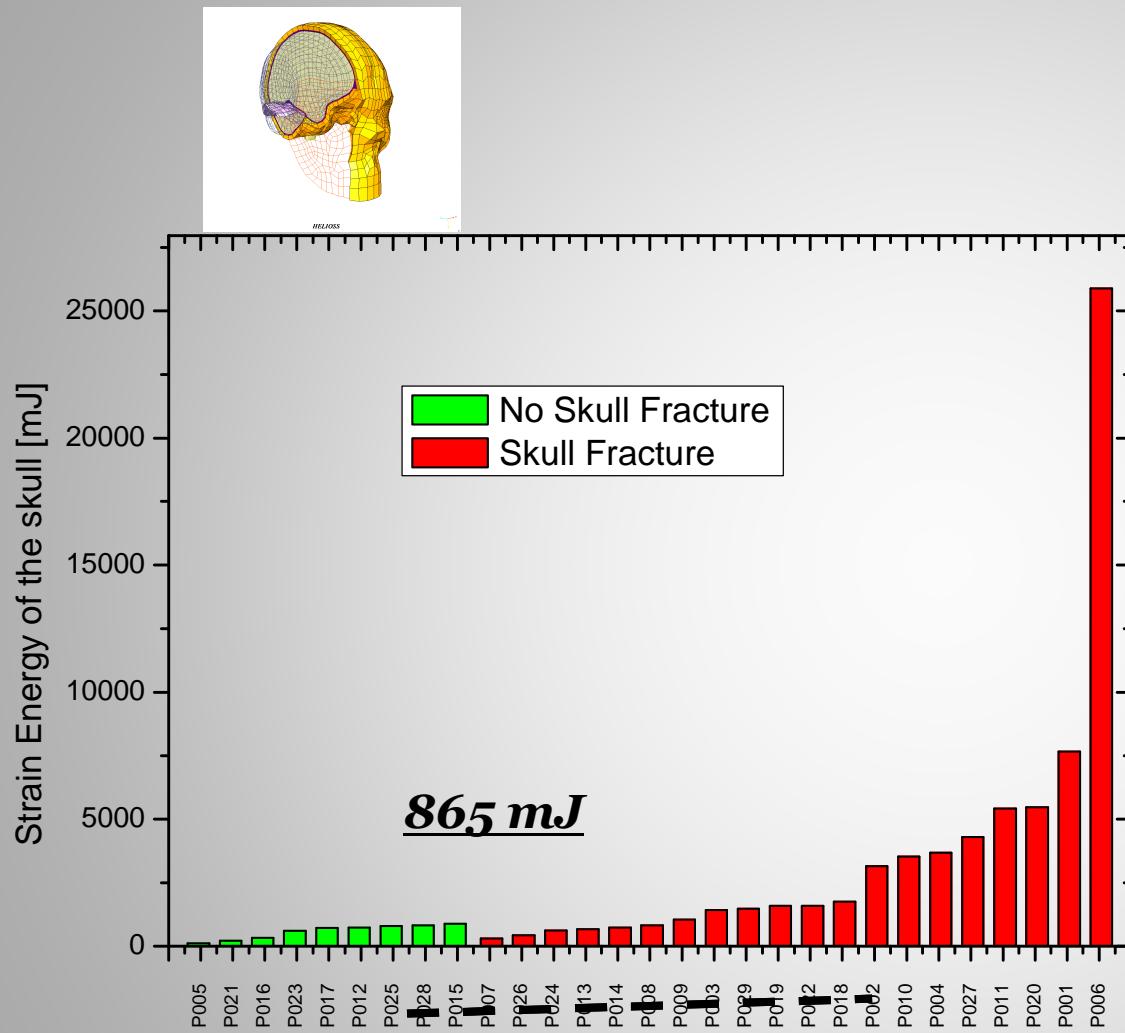


**Diffuse Axonal Injuries
(DAI)**

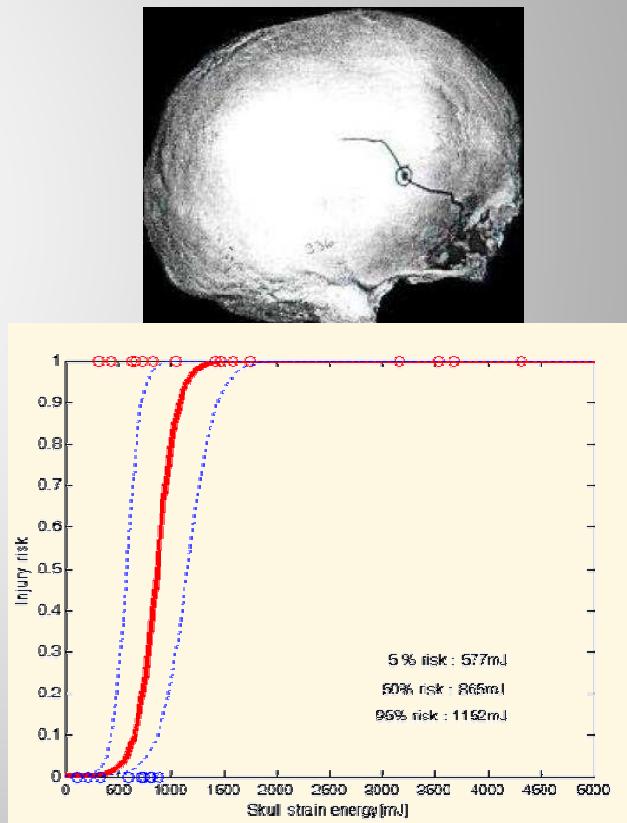


Intracerebral strains/stress

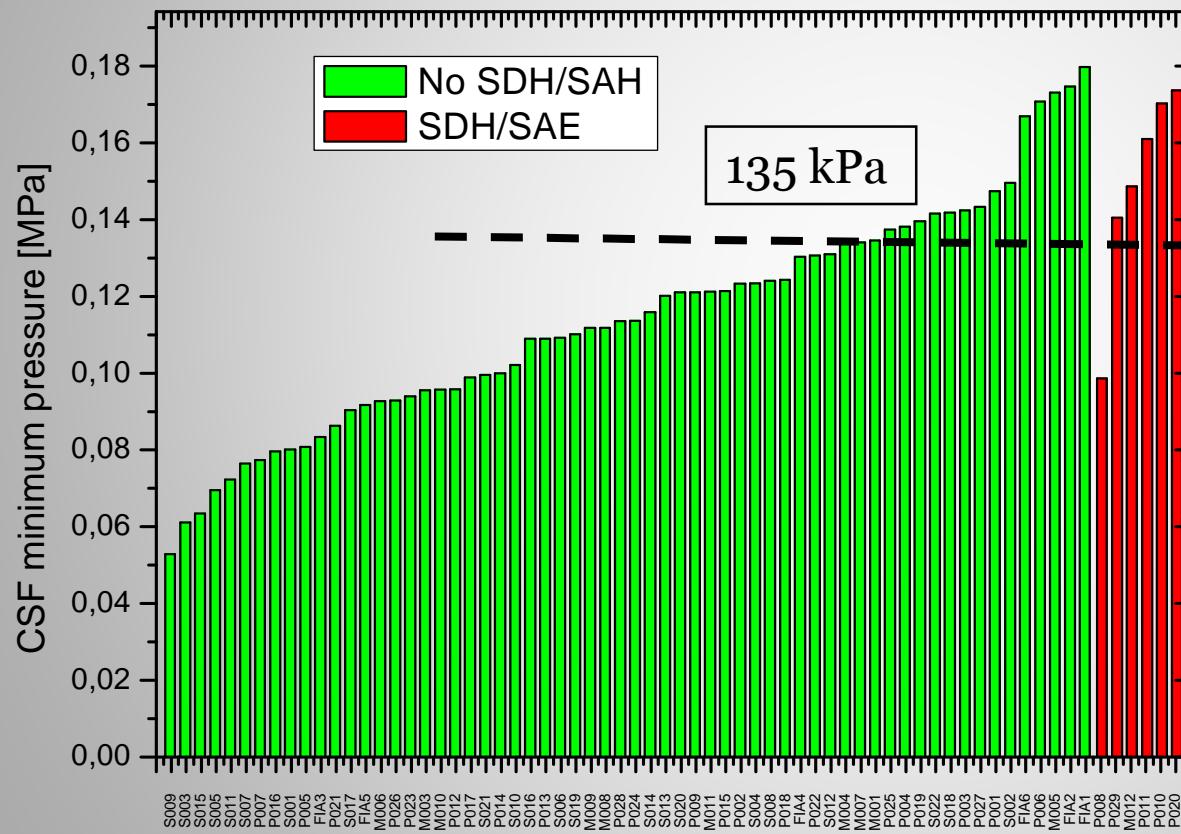
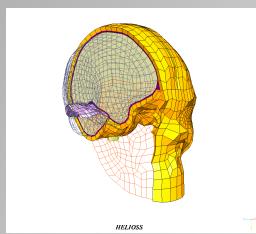
UdS TOLERANCE LIMIT TO SKULL FRACTURE



Bone injuries
Skull fracture

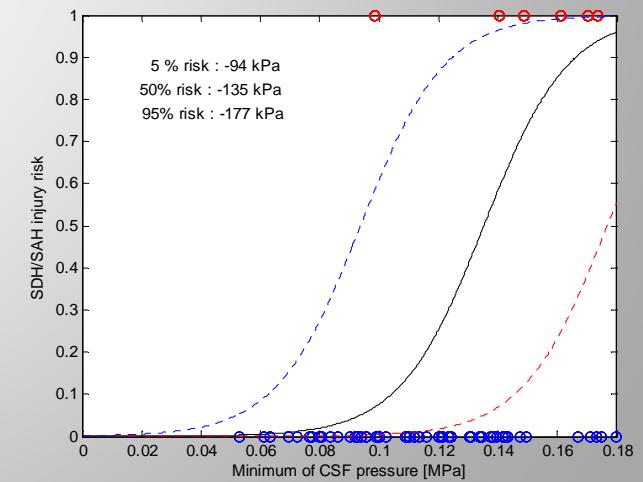
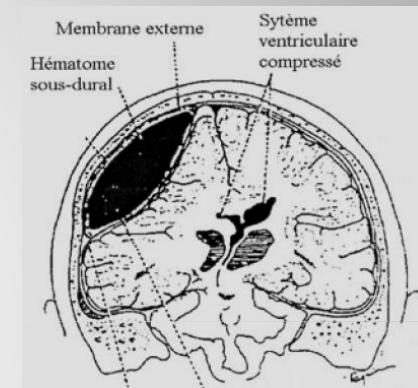


UdS TOLERANCE LIMIT TO SDH

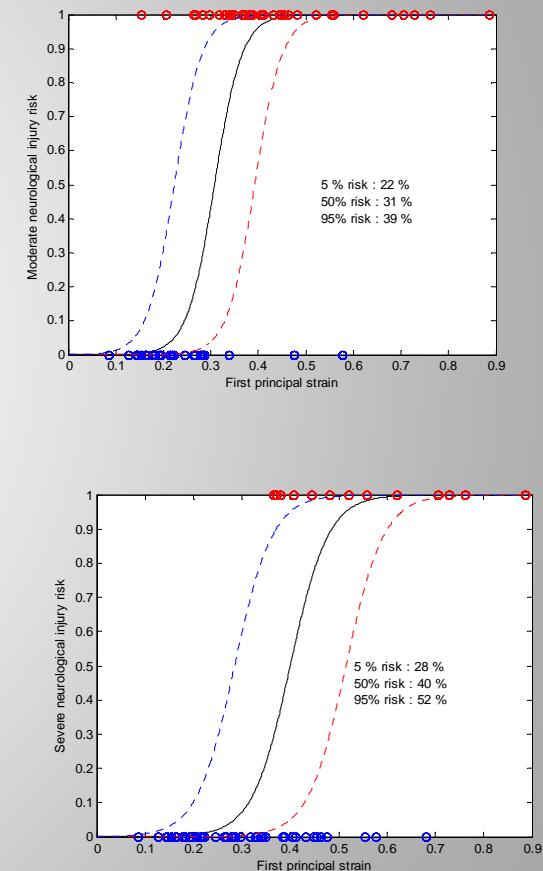
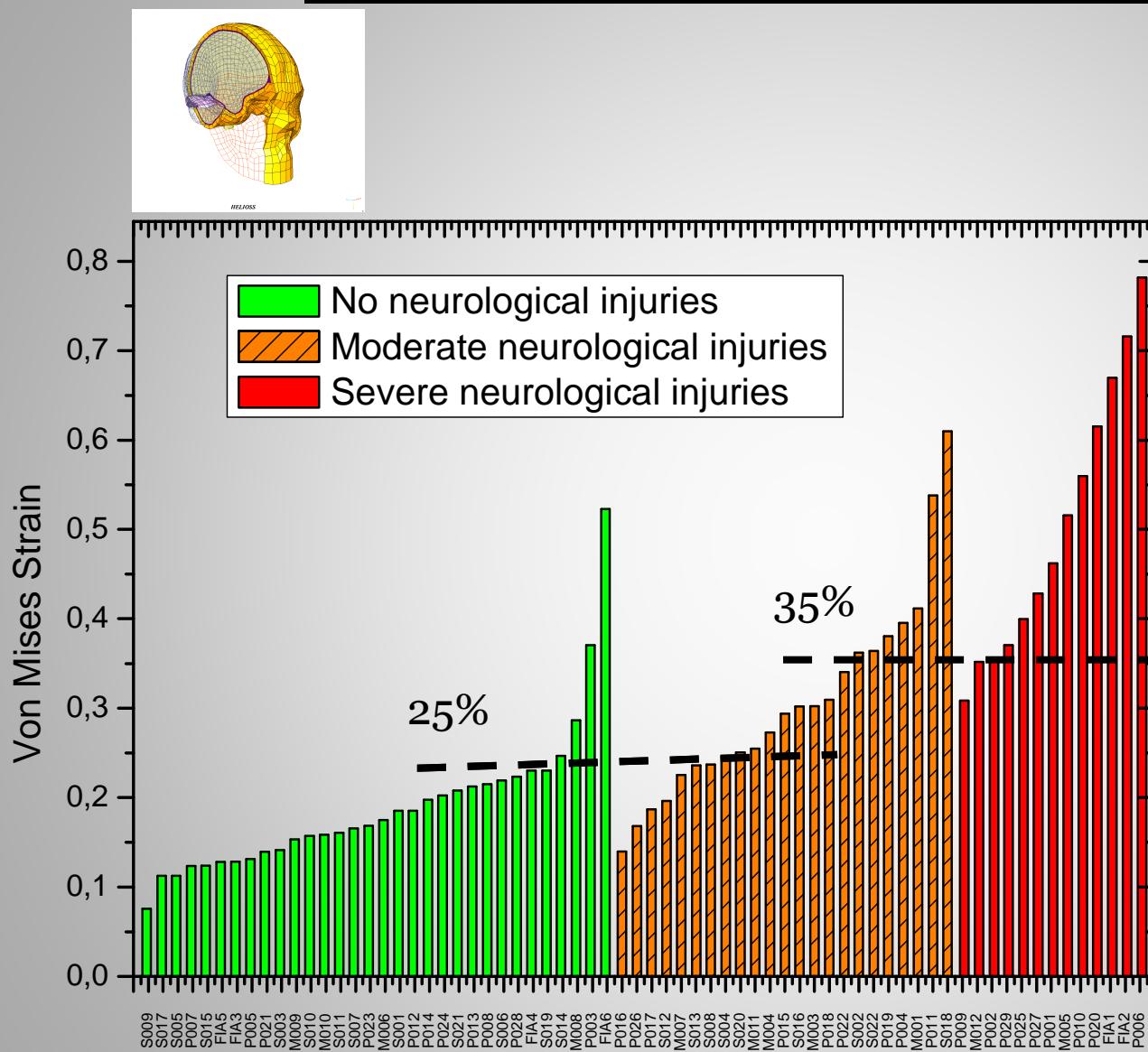


Vascular injuries

Subdural hematoma

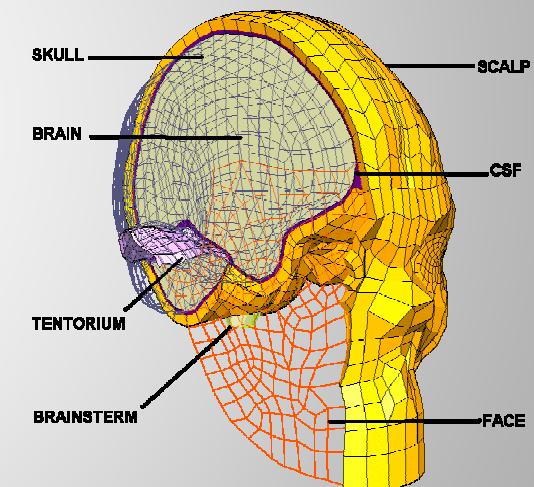


UdS TOLERANCE LIMIT TO DAI



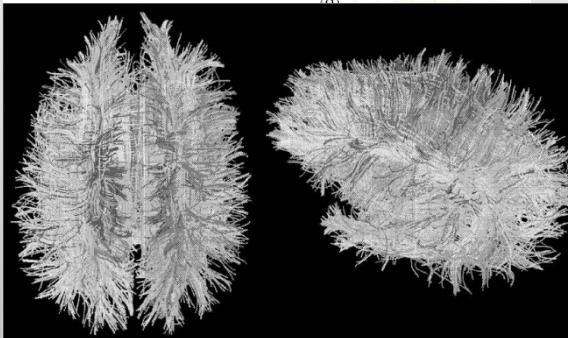
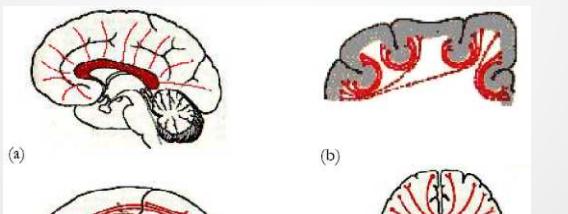
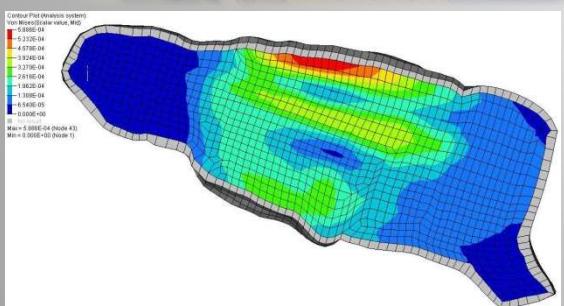
UdS HEAD INJURY CRITERIA

- Sub-arachnoidal haematoma (50% risk)
 - CSF Minimum pressure : 135 kPa
- Moderate neurological injuries (50% risk)
 - Intra-cerebral Von Mises stress > 26 kPa
 - Intra-cerebral Von Mises strain > 25 %
- Severe neurological injuries (50% risk)
 - Intra-cerebral Von Mises stress > 33 kPa
 - Intra-cerebral Von Mises strain > 35 %
- Skull fractures (50% risk)
 - Global strain energy of the skull > 0.865 J



Développements futurs

- Investigations in vivo (humain et animal)
- Caractérisation aux grandes déformations
- Anisotropie / hétérogénéité
- Effets des vaisseaux sanguins et pressurisation
- Limites de tolérance sur modèle animal



Remerciements

Chatelin S, Constantinesco A.,

Deck C., Kang H. Nicolle S.,

Oudry J, Soleur L., Vappou J

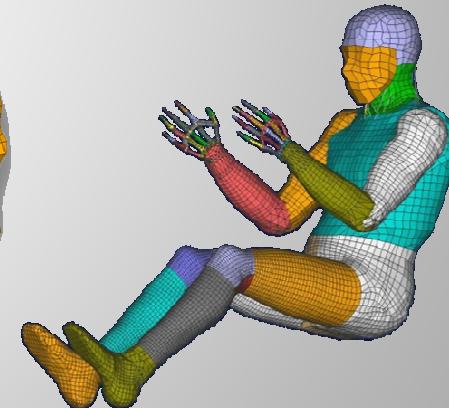
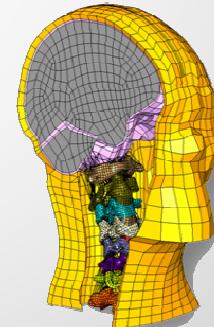
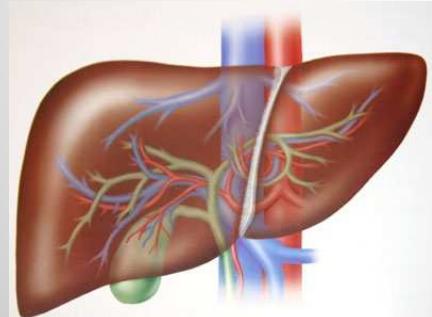
IRCAD, ENSPS

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Caractérisation expérimentale et modélisation de tissus biologiques

remy.willinger@imfs.u-strasbg.fr



Rémy Willinger^a

University of Strasbourg, IMFS-CNRS, Strasbourg, France