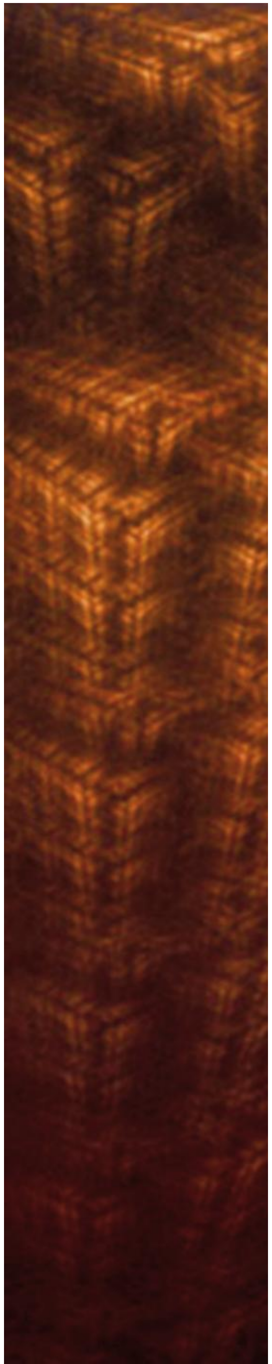

# *Neurite*: a finite difference continuum model of the electrophysiological-mechanical coupling in neurons under mechanical loading

*Advanced computing for science and engineering*


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Advisor: Prof. Jose Maria Peña
External advisor: Dr. Antoine Jerusalem


***Master thesis, UPM, CACI, Madrid, July 2012***

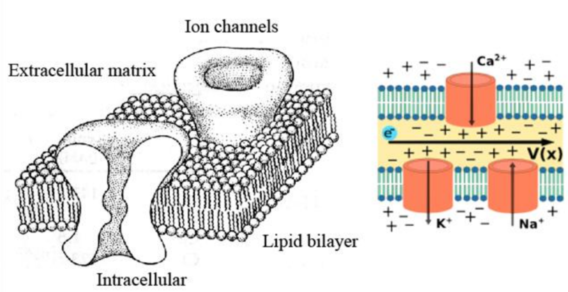
# Outline

1. Introduction and objectives
2. Model. *Neurite*
3. Model analysis
4. Conclusions and future work

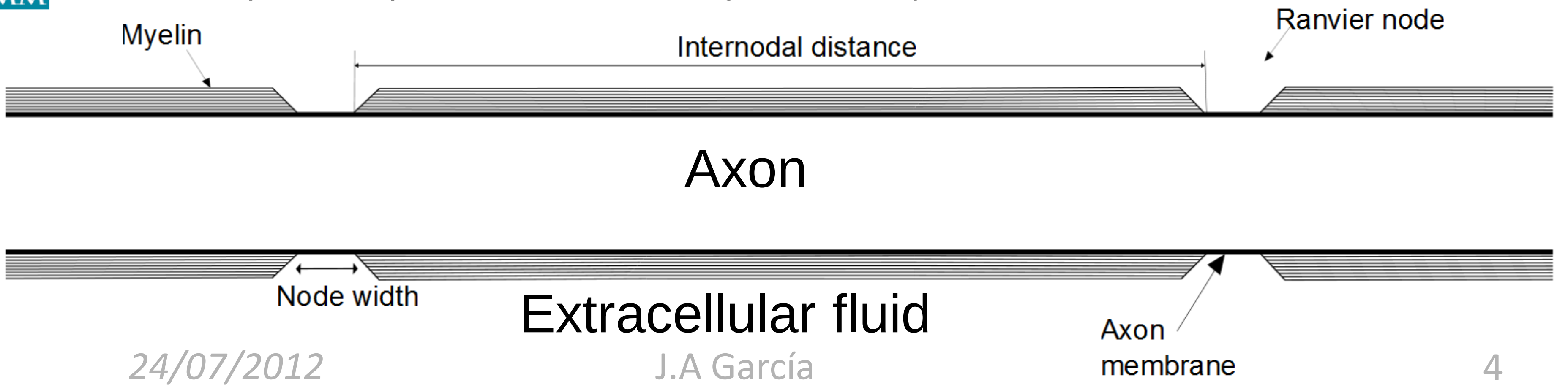
# 1. Introduction and objective

# Myelinated axons

- Neurons are excitable cells that transmit electrical and chemical signaling
- Axons are covered by layers of lipid and proteins (myelin)
- The myelin sheet is interrupted at regular intervals along axon by nodes (nodes of Ranvier)
- At nodes of Ranvier extracellular fluid gains direct access to the axonal membrane:
  - Regulate the flow of ions across membrane
  - Are responsible for action potential creation and propagation
  - Are described by Hodgkin Huxley model (sodium, potassium and leakage channels)

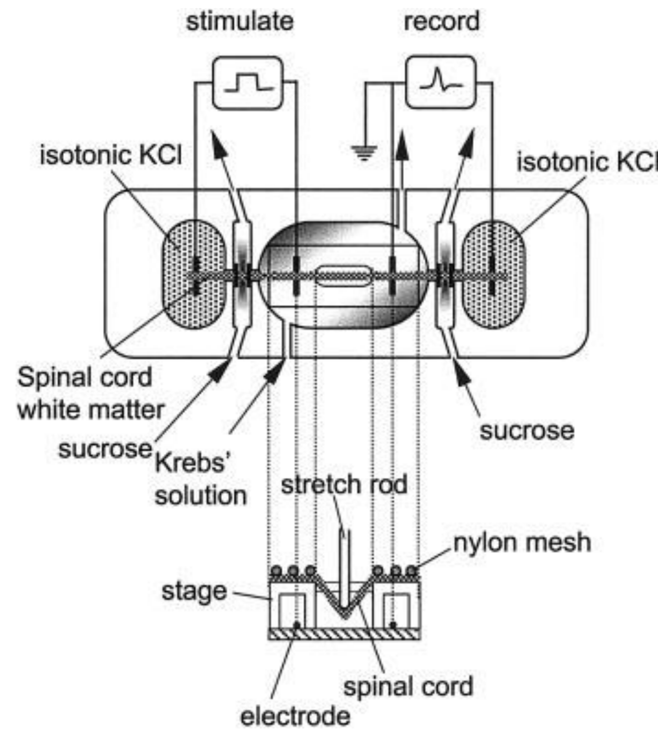



Adapted from Biophysics of computation. C. Kock. 1999



# Mechanical traumas

- Axonal injuries are one of the most common and devastating consequences of traumatic brain and spinal cord injury
  - These injuries are the results of mechanical stresses/strains at generally high stress/strain-rates (tension, compression, shearing, etc.)
  - Such damage can produce the disruption of axon functionalities, *e.g.* degradation of electrical properties
  - *Ex vivo* model of Shi and coworkers allows for quantification of axon electrical property loss after stretching and compression




J.M Jensen and R. Shi. Effects of 4-Aminopyridine on stretched mammalian spinal cord: the role of potassium channels in axonal conduction. Journal of Neurophysiology. 2003; 90: 2334-2340

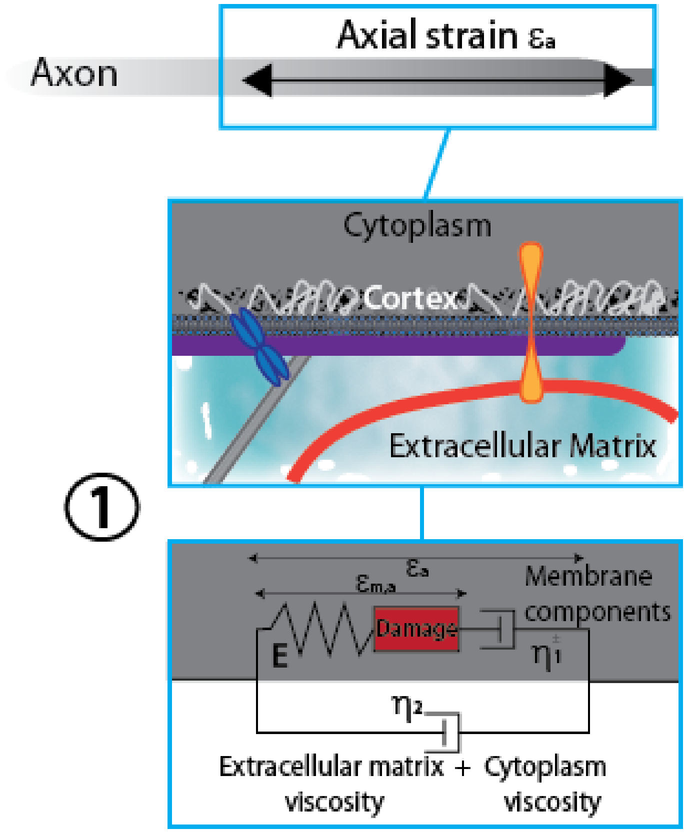
# Objective

**Develop an electro-mechanical model simulating the axonal electrical behavior during mechanical loading**

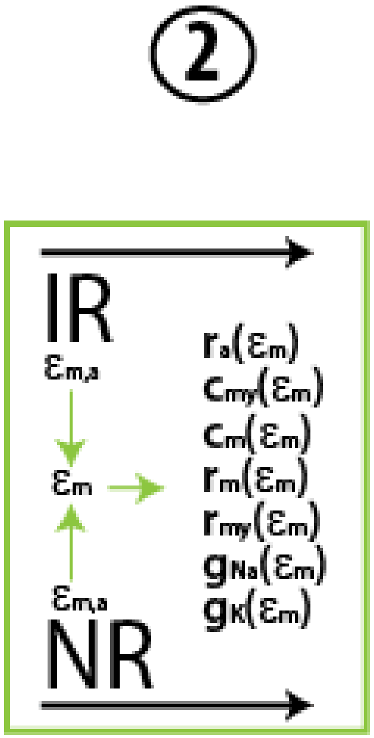
- Cable theory and Hodgkin Huxley model to describe electrical conduction along axon (myelinated and nodes of Ranvier, respectively)
- The mechanical model relates the electrical and mechanical properties
- In the application example, calibration and validation against experimental works of Shi and Whitebone (2006) and Ouyang *et al* (2010)

# 2. Model

# Mechanical and coupling models




Mechanical model




Coupling

Adapted from: A computational model coupling mechanics and electrophysiology in traumatic brain injury. *Journal of Neurotrauma,* 2012, Under review.

# Neurite

$$\begin{cases} r_a = \frac{4\rho_a(1+\epsilon_{m,a})}{\pi d_0}\Delta x \\ r_m = \frac{\rho_m h_0\sqrt{1+\epsilon_{m,a}}}{\pi d_0}\Delta x \\ r_{mm} = r_m + n_{my} r_{my} \\ c_m = \frac{C_m \pi d_0}{h_0\sqrt{1+\epsilon_{m,a}}}\Delta x \\ c_{mm} = \left(\frac{1}{c_m} + \frac{n_{my}}{c_{my}}\right)^{-1} \end{cases}$$

$$\Delta x^{IR} = \Delta x_0^{IR}(1+\epsilon_{m,a}^{IR})$$
$$\Delta x^{NR} = \Delta x_0^{NR}(1+\epsilon_{m,a}^{NR})$$

$$\begin{cases} g_{Na}(V) = \frac{\pi d_0 G_{Na}(V)}{h_0(1+\epsilon_{m,a})}\Delta x \\ g_K(V) = \frac{\pi d_0 G_K(V)}{h_0(1+\epsilon_{m,a})}\Delta x \end{cases}$$

Without myelin for the nodes of Ranvier

$$n_{my} = 0$$

Independent of the strain

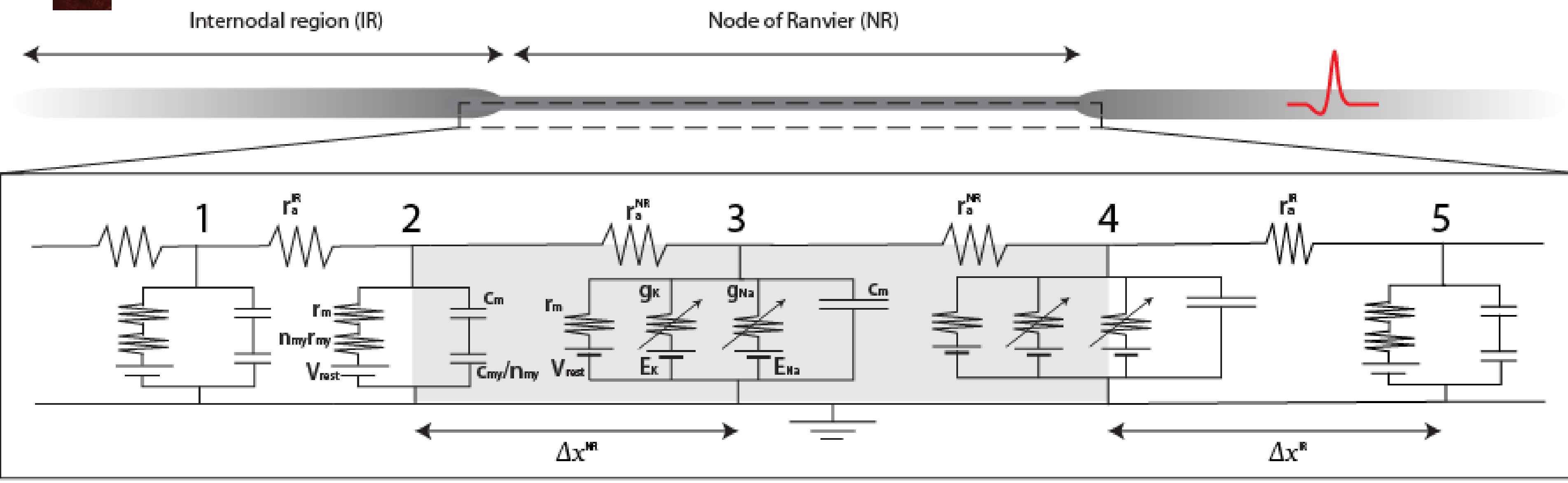
- Cable theory: $\frac{\Delta x^{IR^2}}{r_a^{IR}}\frac{\partial^2 V}{\partial x^2} - c_{mm}\frac{\partial V}{\partial t} - \frac{V}{r_{mm}} + \frac{V_{rest}}{r_{mm}} = 0$

- Hodgkin and Huxley:

$$\frac{\Delta x^{NR^2}}{r_a^{NR}}\frac{\partial^2 V}{\partial x^2} - c_m\frac{\partial V}{\partial t} - (g_{Na}+g_k+g_m)V + g_{Na}E_{Na} + g_k E_K + g_m E_m = 0$$

# Discretization

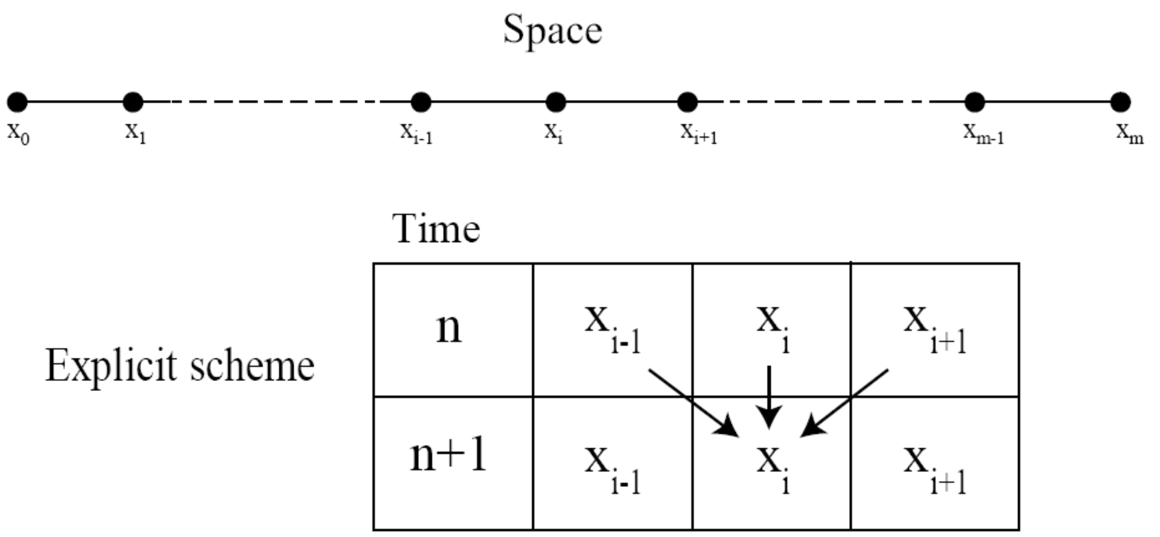
General scheme:




- Finite difference method (FDM)
- Spatial and temporal discretization
- Different type of elements

| i | i+1 | Name | Example |
|---|---|---|---|
| IR | IR | Pure IR | i=1 |
| NR | NR | Pure NR | i=3 |
| IR | NR | Paranodal IR-NR | i=2 |
| NR | IR | Paranodal NR-IR | i=4 |

# Explicit scheme (1/2)




- Relates the current state of a variable to its and its neighbors old states
- Forward difference in time for first order derivative
- Numerically stable for a time step small enough

# Explicit scheme (2/2)

Final set of equations for the explicit method:

IR-IR (pure IR):

$$V_i^{n+1} = V_i^n + \frac{\Delta t}{c_{mm}}\left(\frac{V_{i-1}^n - 2V_i^n + V_{i+1}^n}{r_a^{IR}\Delta x^{IR^2}} - \frac{V_i^n}{r_{mm}} + \frac{V_{rest}}{r_{mm}} + \frac{i_0}{\Delta x^{IR}}\right)$$

NR-NR (pure NR):

$$V_i^{n+1} = V_i^n + \frac{\Delta t}{c_m}\left(\frac{V_{i-1}^n - 2V_i^n + V_{i+1}^n}{r_a^{NR}\Delta x^{NR^2}} - (g_{Na} + g_K + g_m)V_i^n + g_{Na}E_{Na} + g_K E_K + g_m E_m + \frac{i_0}{\Delta x^{NR}}\right)$$

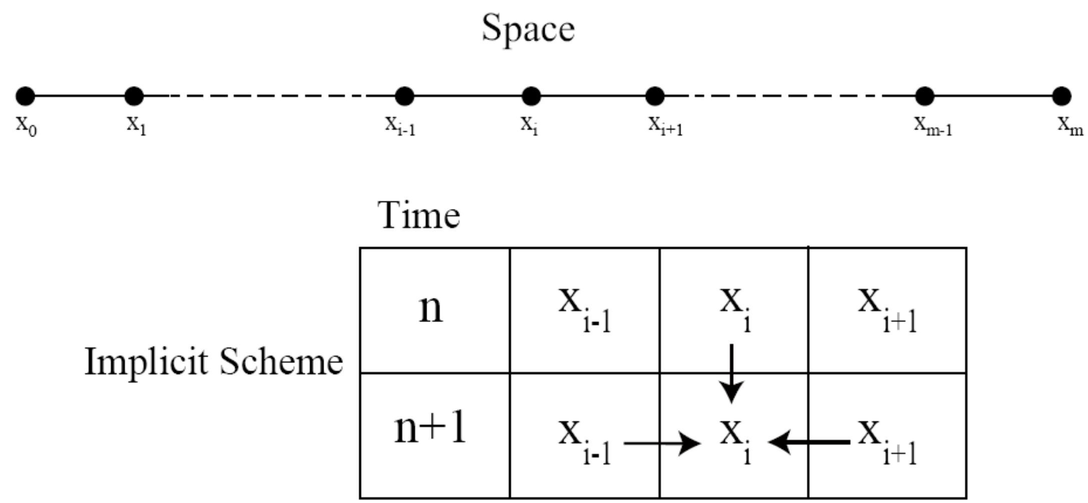
IR-NR paranodal:

$$V_i^{n+1} = V_i^n + \frac{\Delta t}{c_{mm}}\left(\frac{V_{i-1}^n - V_i^n}{r_a^{IR}\Delta x^{IR^2}} + \frac{V_{i+1}^n - V_i^n}{r_a^{NR}\Delta x^{NR}\Delta x^{IR}} - \frac{V_i^n}{r_{mm}} + \frac{V_{rest}}{r_{mm}} + \frac{i_0}{\Delta x^{IR}}\right)$$

NR-IR paranodal:

$$V_i^{n+1} = V_i^n + \frac{\Delta t}{c_m}\left(\frac{V_{i-1}^n - V_i^n}{r_a^{NR}\Delta x^{NR^2}} + \frac{V_{i+1}^n - V_i^n}{r_a^{IR}\Delta x^{IR}\Delta x^{NR}} - (g_{Na} + g_K + g_m)V_i^n + g_{Na}E_{Na} + g_K E_K + g_m E_m + \frac{i_0}{\Delta x^{NR}}\right)$$

# Implicit scheme (1/2)




Relates the old stat of the variable and its and its neighbors current states

$$\alpha V_{i+1}^{n+1} + \beta V_i^{n+1} + \gamma V_{i-1}^{n+1} = b_i(V_i^n)$$

$$\underbrace{\begin{pmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \alpha & \beta & \gamma & 0 & 0 & 0 & 0 & 0 \\ 0 & \alpha & \beta & \gamma & 0 & 0 & 0 & 0 \\ 0 & 0 & \alpha & \beta & \gamma & 0 & 0 & 0 \\ 0 & 0 & 0 & \alpha & \beta & \gamma & 0 & 0 \\ 0 & 0 & 0 & 0 & \alpha & \beta & \gamma & 0 \\ 0 & 0 & 0 & 0 & 0 & \alpha & \beta & \gamma \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix}}_{A} \begin{pmatrix} V_0^{n+1} \\ V_1^{n+1} \\ V_2^{n+1} \\ V_3^{n+1} \\ V_4^{n+1} \\ V_5^{n+1} \\ V_6^{n+1} \\ V_7^{n+1} \\ V_8^{n+1} \end{pmatrix} = \begin{pmatrix} b_0(V_0^n) \\ b_1(V_1^n) \\ b_2(V_2^n) \\ b_3(V_3^n) \\ b_4(V_4^n) \\ b_5(V_5^n) \\ b_6(V_6^n) \\ b_7(V_7^n) \\ b_8(V_8^n) \end{pmatrix}$$

A linear system of equations must be solved each time step

# Implicit scheme (1/2)

Final set of equations for the implicit method:

IR-IR (pure IR):

$$\begin{cases} \alpha = 1 \\ \beta = -2 - \frac{c_{mm} r_a^{IR} \Delta x^{IR^2}}{\Delta t} - \frac{r_a^{IR}}{r_{mm}} \Delta x^{IR^2} \\ \gamma = 1 \\ b_i = -\frac{c_{mm} r_a^{IR} \Delta x^{IR^2}}{\Delta t} V_i^n - \frac{r_a^{IR}}{r_{mm}} \Delta x^{IR^2} V_{rest} - \Delta x^{IR} r_a^{IR} i_0 \end{cases}$$

NR-NR (pure NR):

$$\begin{cases} \alpha = 1 \\ \beta = -2 - \frac{c_m r_a^{NR} \Delta x^{NR^2}}{\Delta t} - (g_{Na} + g_K + g_m) r_a^{NR} \Delta x^{NR^2} \\ \gamma = 1 \\ b_i = -\frac{c_m r_a^{NR} \Delta x^{NR^2}}{\Delta t} V_i^n - (g_{Na} E_{Na} + g_K E_K + g_m E_m) r_a^{NR} \Delta x^{NR^2} - \Delta x^{NR} r_a^{NR} i_0 \end{cases}$$

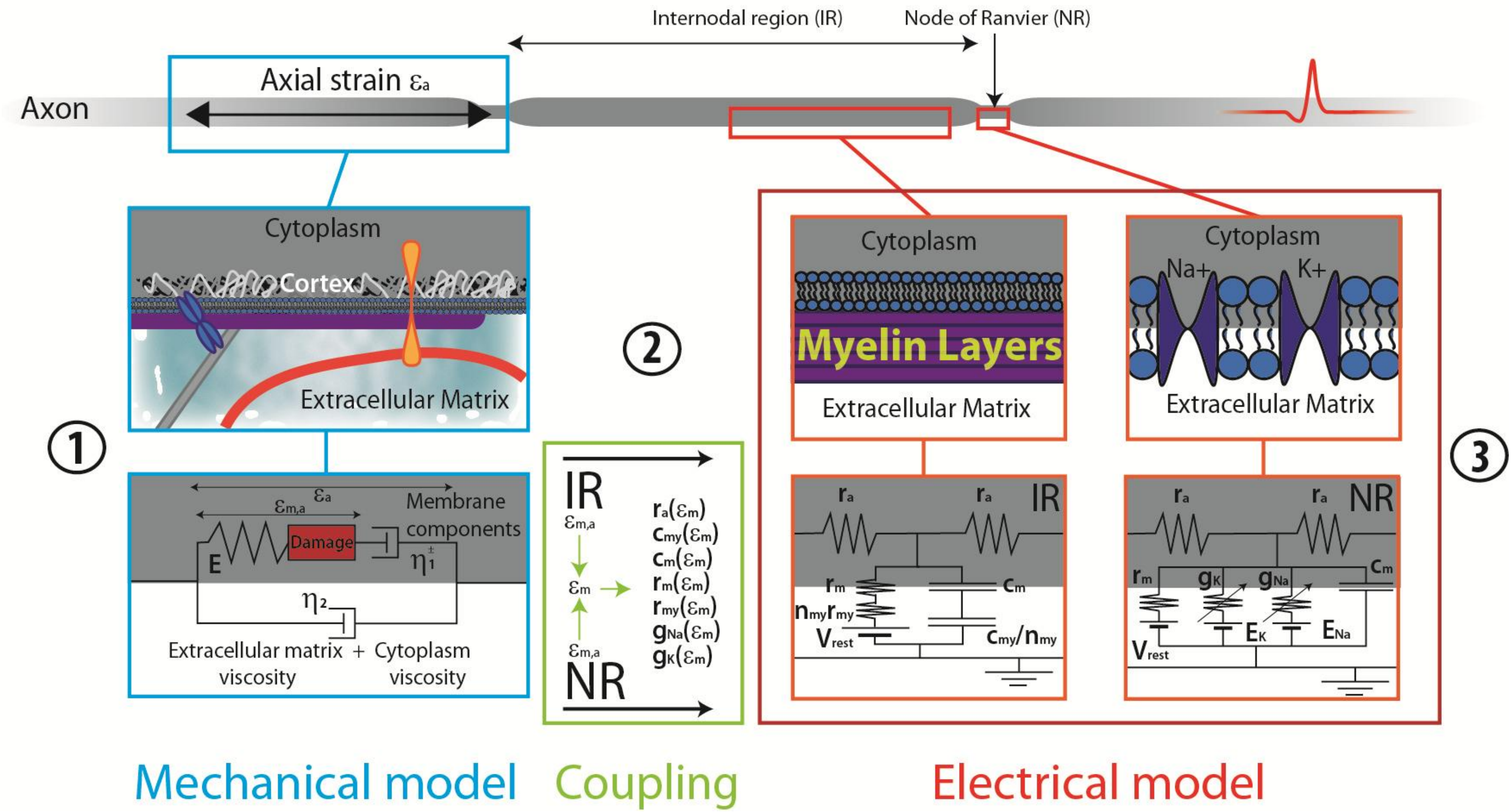
IR-NR paranodal:

$$\begin{cases} \alpha = \frac{1}{\Delta x^{IR} r_a^{IR}} \\ \beta = -\frac{1}{\Delta x^{IR} r_a^{IR}} - \frac{1}{\Delta x^{NR} r_a^{NR}} - \frac{c_{mm} \Delta x^{IR}}{\Delta t} - \frac{\Delta x^{IR}}{r_{mm}} \\ \gamma = \frac{1}{\Delta x^{NR} r_a^{NR}} \\ b_i = -\frac{c_{mm} \Delta x^{IR}}{\Delta t} V_i^n - \frac{\Delta x^{IR}}{r_{mm}} V_{rest} - i_0 \end{cases}$$

NR-IR paranodal:

$$\begin{cases} \alpha = \frac{1}{\Delta x^{NR} r_a^{NR}} \\ \beta = -\frac{1}{\Delta x^{IR} r_a^{IR}} - \frac{1}{\Delta x^{NR} r_a^{NR}} - \frac{c_m \Delta x^{NR}}{\Delta t} - (g_{Na} + g_K + g_m) \Delta x^{NR} \\ \gamma = \frac{1}{\Delta x^{IR} r_a^{IR}} \\ b_i = -\frac{c_m \Delta x^{NR}}{\Delta t} V_i^n - (g_{Na} E_{Na} + g_K E_K + g_m E_m) \Delta x^{NR} - i_0 \end{cases}$$

# Overall model




A computational model coupling mechanics and electrophysiology in traumatic brain injury. *Journal of Neurotrauma,* 2012, Under review.

# 4. Results and discussion

# Convergence = stability +consistency

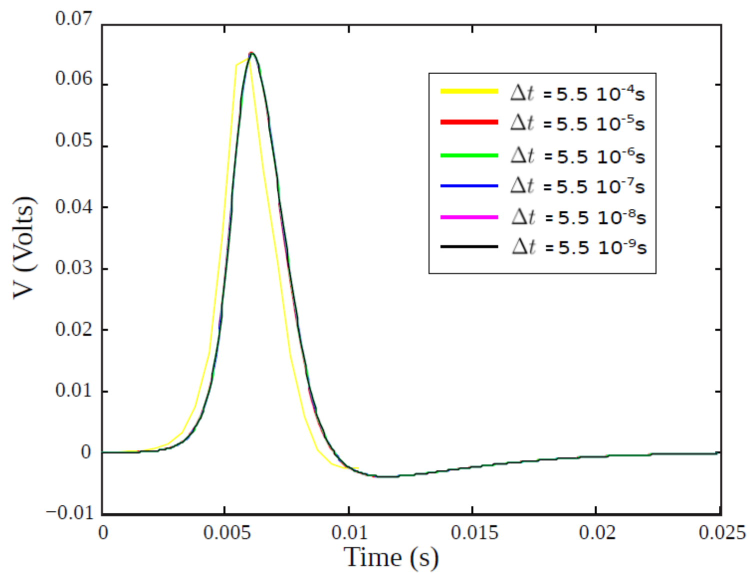
## Stability:

Expectral analysis
- Temporal
  - Explicit: $\Delta t_c = \min\left(\Delta t_c^{IR}, \Delta t_c^{NR}\right)$
  - Implicit: Unconditioned
- Spatial: Unconditioned

**Guaranteed!!!**

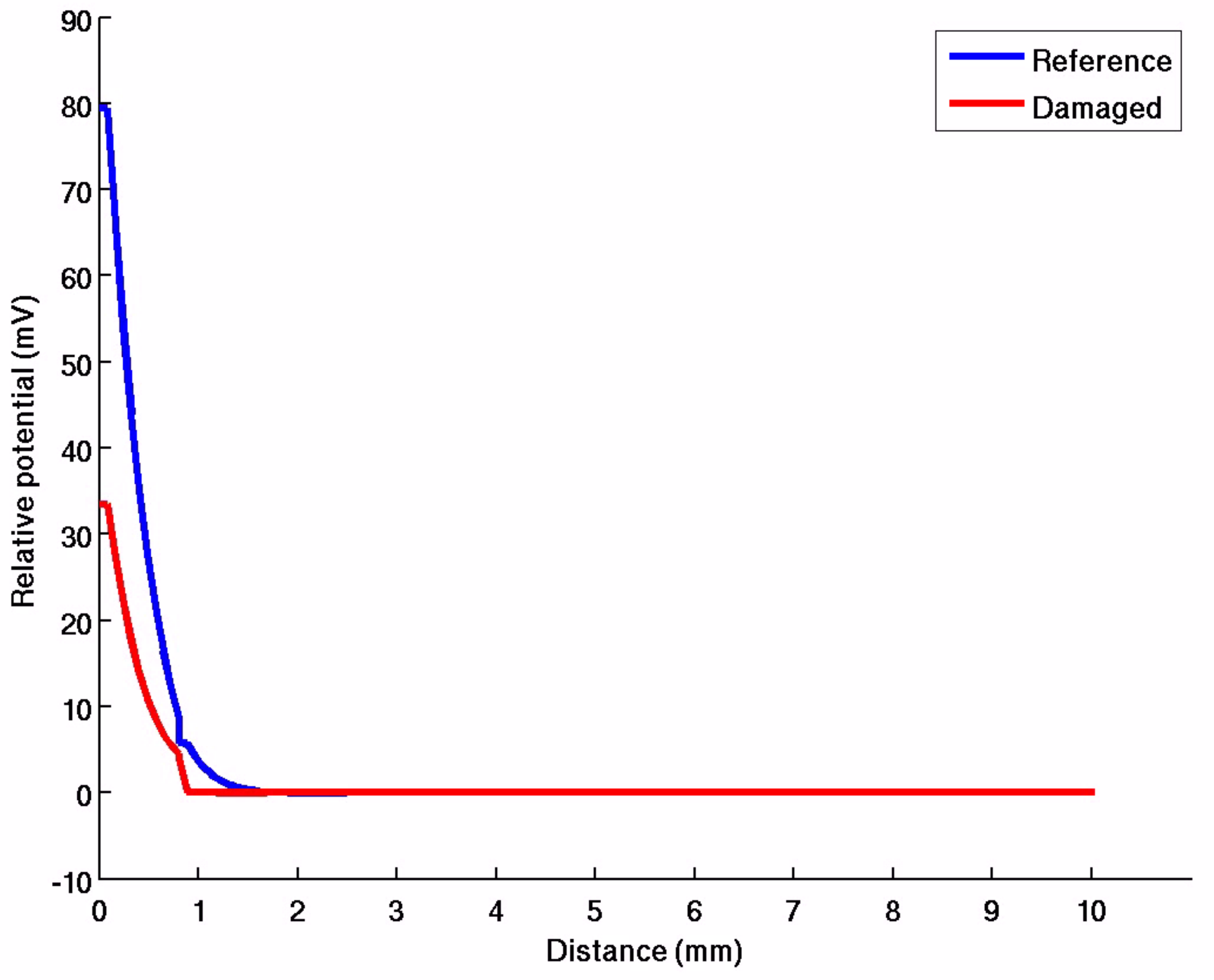
## Consistency: **Guaranteed!!!**

- Solutions calculated by the difference scheme at a given coordinate converge to its analytical PDE solution when the grid goes to zero ( $\Delta x^{IR}$, $\Delta x^{NR}$ and $\Delta t$ )
- Analytical solutions are unknown
- Consistency is assumed when the results do not change when the grid is decreased

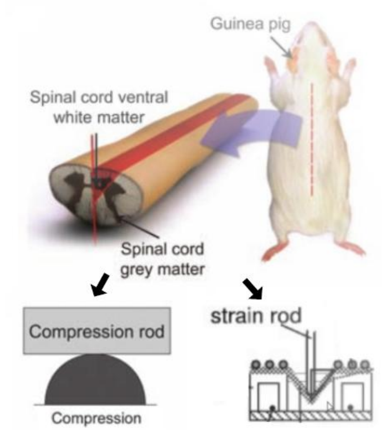



**Stability + consistency = convergence !!!**

# Electro-mechanical model

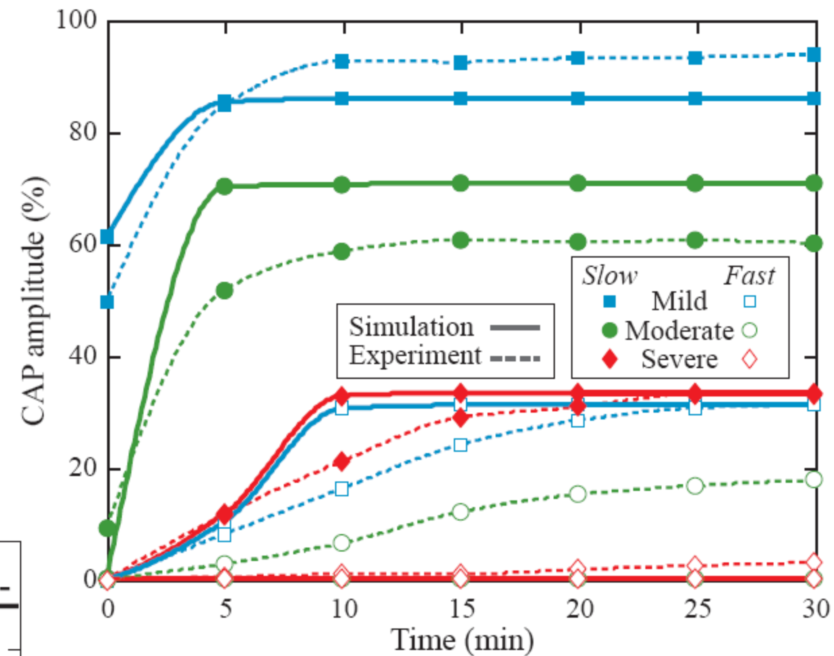


# Application example

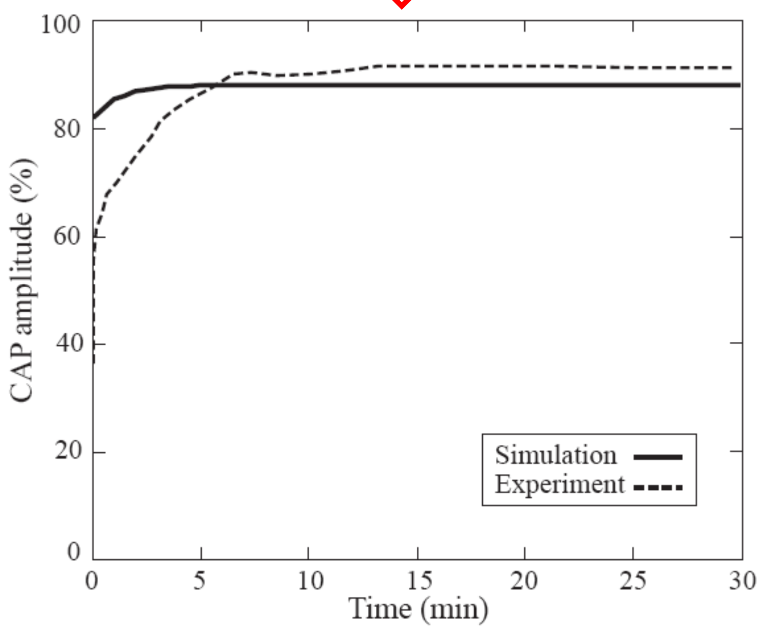



Adapted from Shi and coworkers (2010) and Ouyang *et al* (2006)

## Calibration




## Validation




| Parameter | Value |
|---|---|
| $\tau^{+}$ | 16.66 s |
| $\Sigma$ | $8.26 \times 10^{-2}$ |
| $\alpha$ | 7.50 |
| $\tau^{-}$ | 79.06 s |

from: A computational model coupling mechanics and electrophysiology in traumatic brain injury. *Journal of Neurotrauma,* 2012, Under review.

# 5. Conclusions and future work

# Conclusions and future work

**Conclusions**:

➢ Coupling *Neurite* to the mechanical model is a novelty in the field to simulate functional deficits produced by mechanical loading

➢ The development, testing and analysis of this new extension of *Neurite* is the main contribution of this work

➢ This thesis constitutes a first step in the direction of a fully integrated mechanical-electrical-chemical *in silico* simulation platform for neurites

**Future work**:

➢ The electrical part of *Neurite* will be implemented in GPU's (collaboration with DATSI department UPM).

➢ Application of *Neurite* to simulate action potential propagation in human nerves (Collaboration with Center of Biomedical Technology in UPM).

➢ Extent *Neurite* from FDM to FEM (3D)

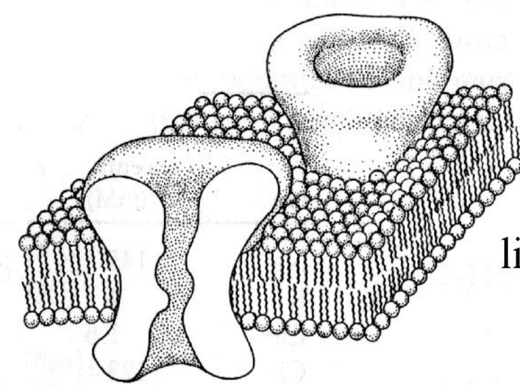
➢ Coupling both parts of *Neurite*: the growth model + electro-mechanical model

# Thanks

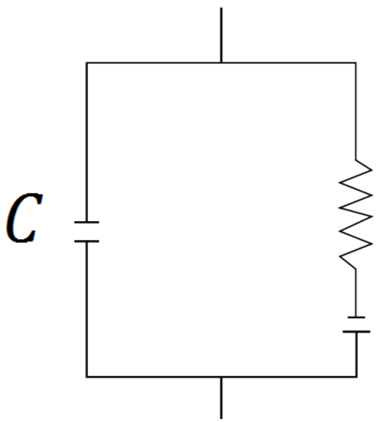
# Backup slides

# Neuronal membrane

- Neuronal membrane is composed of:
  - Lipid bilayer
  - Ion channels
- The membrane separates charges between inside and outside: acts as a capacitance *C*
- Current conductance along possible gates (passive ion channels, pores, etc.) is described by a resistance *R*
- $V_{rest}$ represents the membrane potential at rest

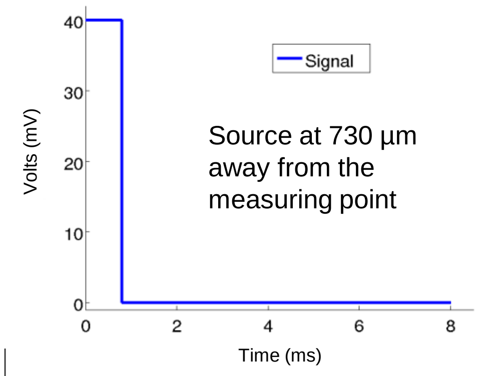


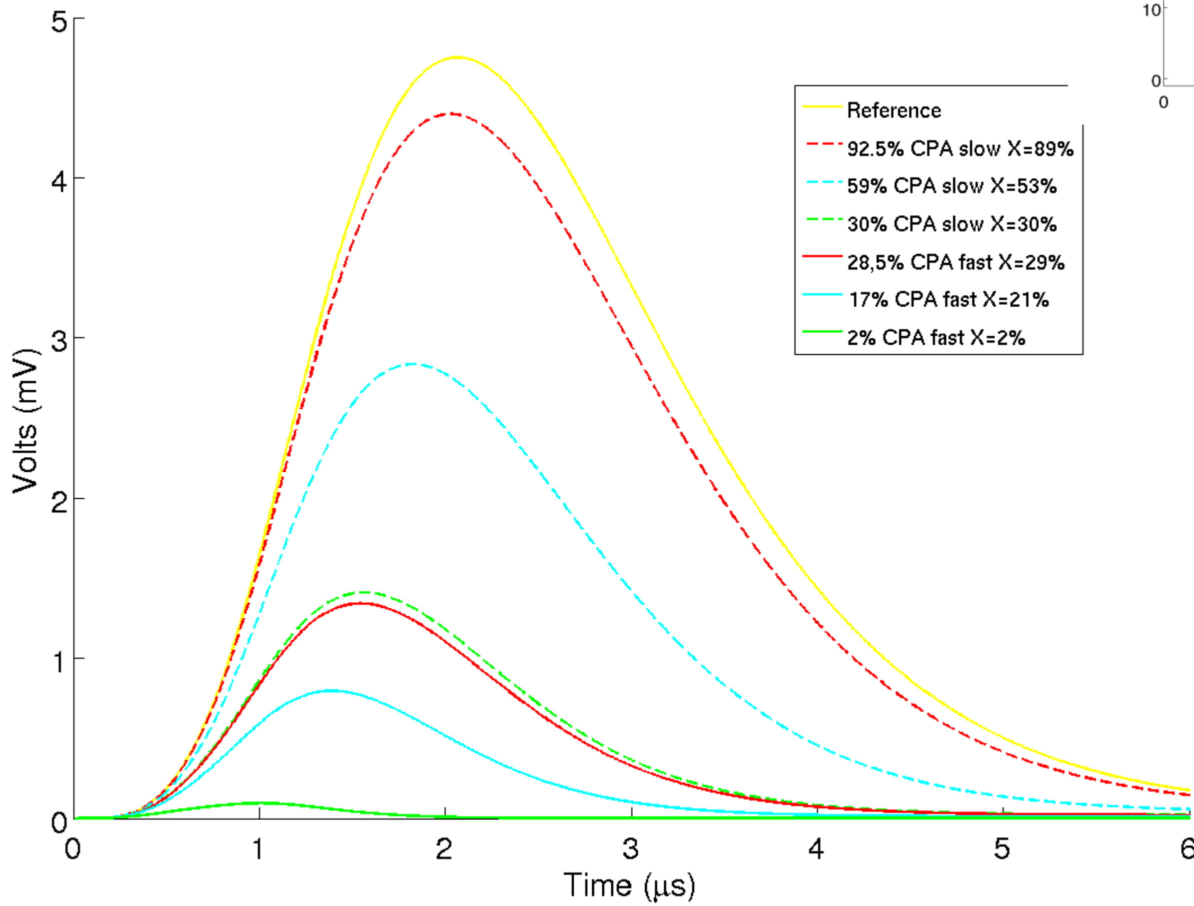

Biophysics of computation. C. Kock. 1999



# Calibration (2/2)

- Looking for damage necessary:

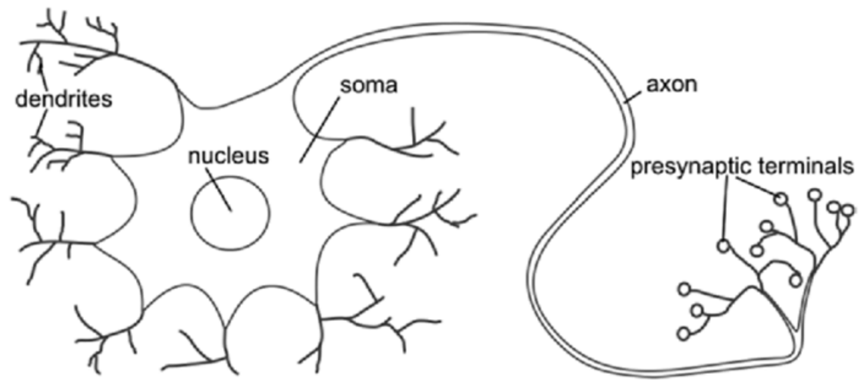


# Neurons

NEUROSCIENCE:

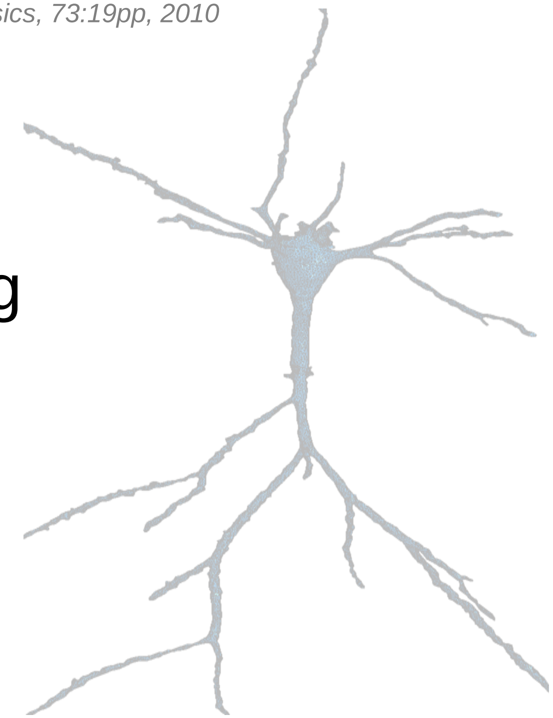
- Definition
- Computational neuroscience, Neuroinformatics, etc
- Applications




Franze and Guck. The biophysics of neuronal growth. *Reports on Progress in Physics, 73:19pp, 2010*

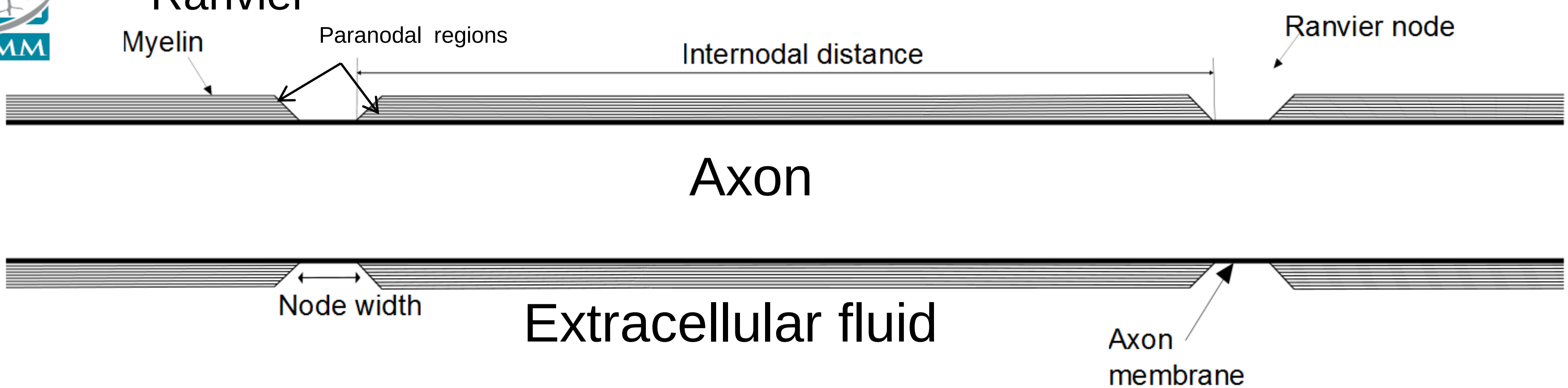
THE NEURON:

- Excitable cells
- Electrical and chemical signaling
- Axon and dendrites
- Networks
- Synapses



# Myelinated axons

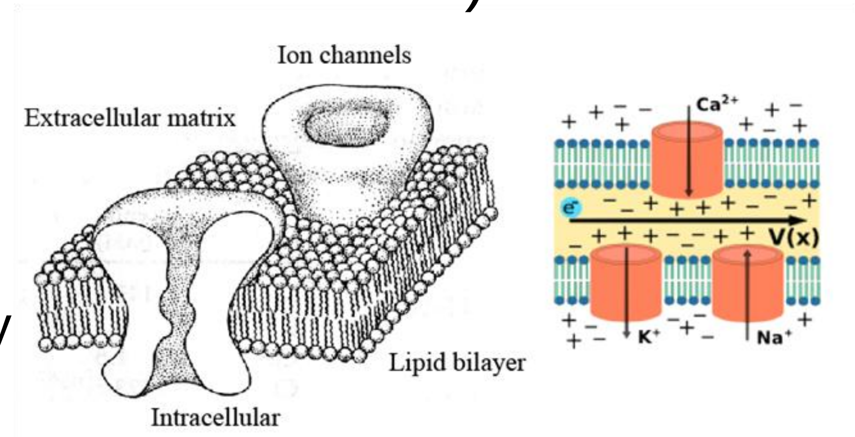
- Axons are covered by layers of lipid and proteins (myelin)
- Myelin layers insulate axon from extracellular fluid
- The myelin sheet is interrupted at regular intervals along axon by nodes (nodes of Ranvier)
- At nodes of Ranvier extracellular fluid gains direct access to the axonal membrane
- The region where internodal part transforms to node of Ranvier is called paranodal region
- Passive behavior for myelinated part and active for the nodes of Ranvier



# Membrane description

- Neuronal membrane is composed of:
  - Lipid bilayer
  - Ion channels
- Ion channels (uncovered at nodes of Ranvier):

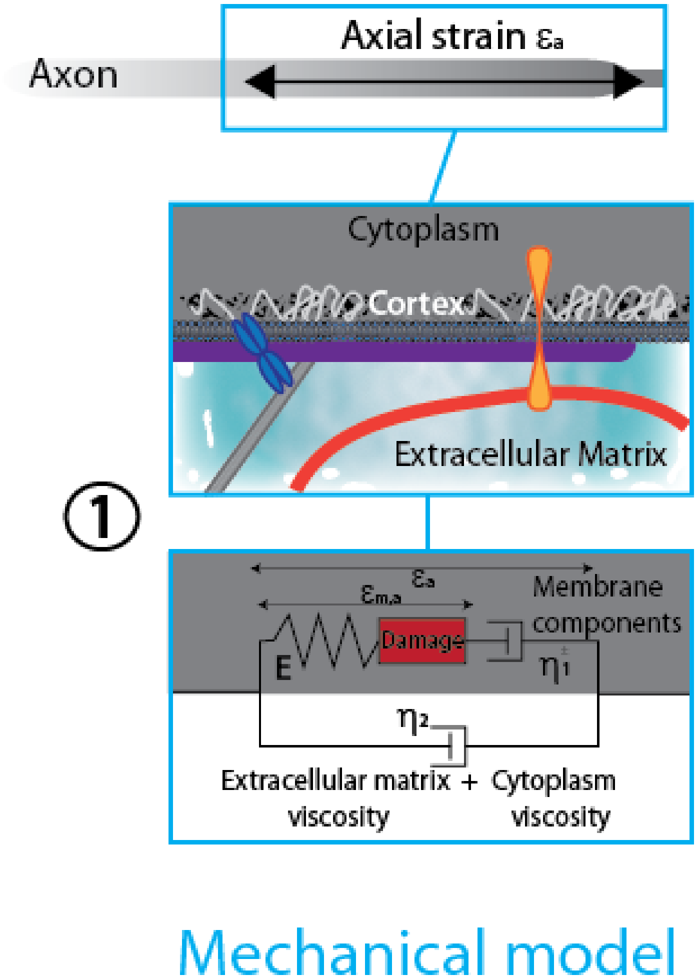
  - Regulate the flow of ions across membrane
  - Are responsible for action potential creation and propagation
  - Are described by Hodgkin Huxley model (sodium, potassium and leakage channels)




Adapted from Biophysics of computation. C. Kock. 1999

- Internodal part is described by cable theory

# Mechanical model




Adapted from: A computational model coupling mechanics and electrophysiology in traumatic brain injury. *Journal of Neurotrauma,* 2012, Under review.

$$
\begin{cases}
\sigma_1 = E(\epsilon_{m,a} - \epsilon_{D,a}) \\
\sigma_1 = \eta_1^{\pm}(\dot{\epsilon_a} - \dot{\epsilon}_{m,a}) \\
\sigma_2 = \eta_2 \dot{\epsilon}_a \\
\sigma = \sigma_1 + \sigma_2 \\
(\sigma_1 - \sigma_0 - k\epsilon_{D,a})\dot{\epsilon}_{D,a} = 0 \\
\quad \text{and } \sigma_1 \leq \sigma_0 + k\epsilon_{D,a}
\end{cases}
$$

Free parameters of the model:

$$
\begin{cases}
\tau^- = \eta_{eq}/E \\
\tau^+ = \eta_1^+/E \\
\Sigma = \sigma_0/E \\
\alpha = E/k
\end{cases}
$$

# Coupling model

- The bridge between the mechanical model and *Neurite*
- A new parameter $\nu \in [0,1]$ is proposed for distributing the strain along the axon

$$\begin{cases} \epsilon_{m,a}^{NR} = \dfrac{\nu L}{n_{NR} L_{NR}} \epsilon_{m,a} \\ \epsilon_{m,a}^{IR} = (1-\nu) \dfrac{L}{n_{IR} L_{IR}} \epsilon_{m,a} \end{cases}$$

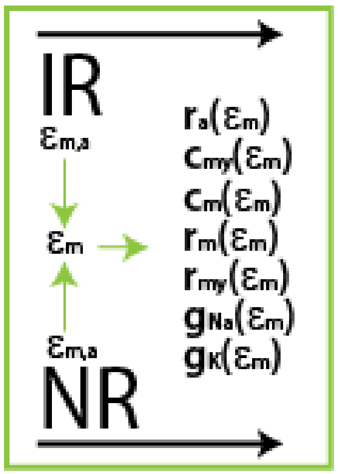
and assuming incompressibility:

$$1 + \epsilon_m = \sqrt{1 + \epsilon_{m,a}}$$

$$d = \frac{d_0}{\sqrt{1 + \epsilon_{m,a}}}$$

$$h = h_0.$$

Conductances for Hodgkin and Huxley model do not change under mechanical loading




Coupling

Adapted from: A computational model coupling mechanics and electrophysiology in traumatic brain injury. *Journal of Neurotrauma*, 2012, Under review.