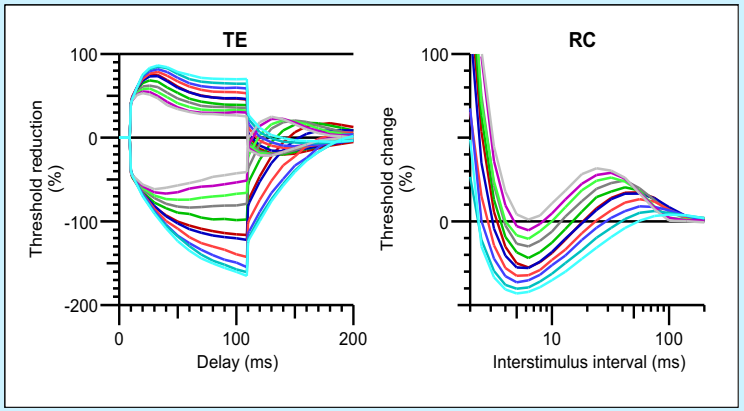
Annual Congress of the RBSPRM

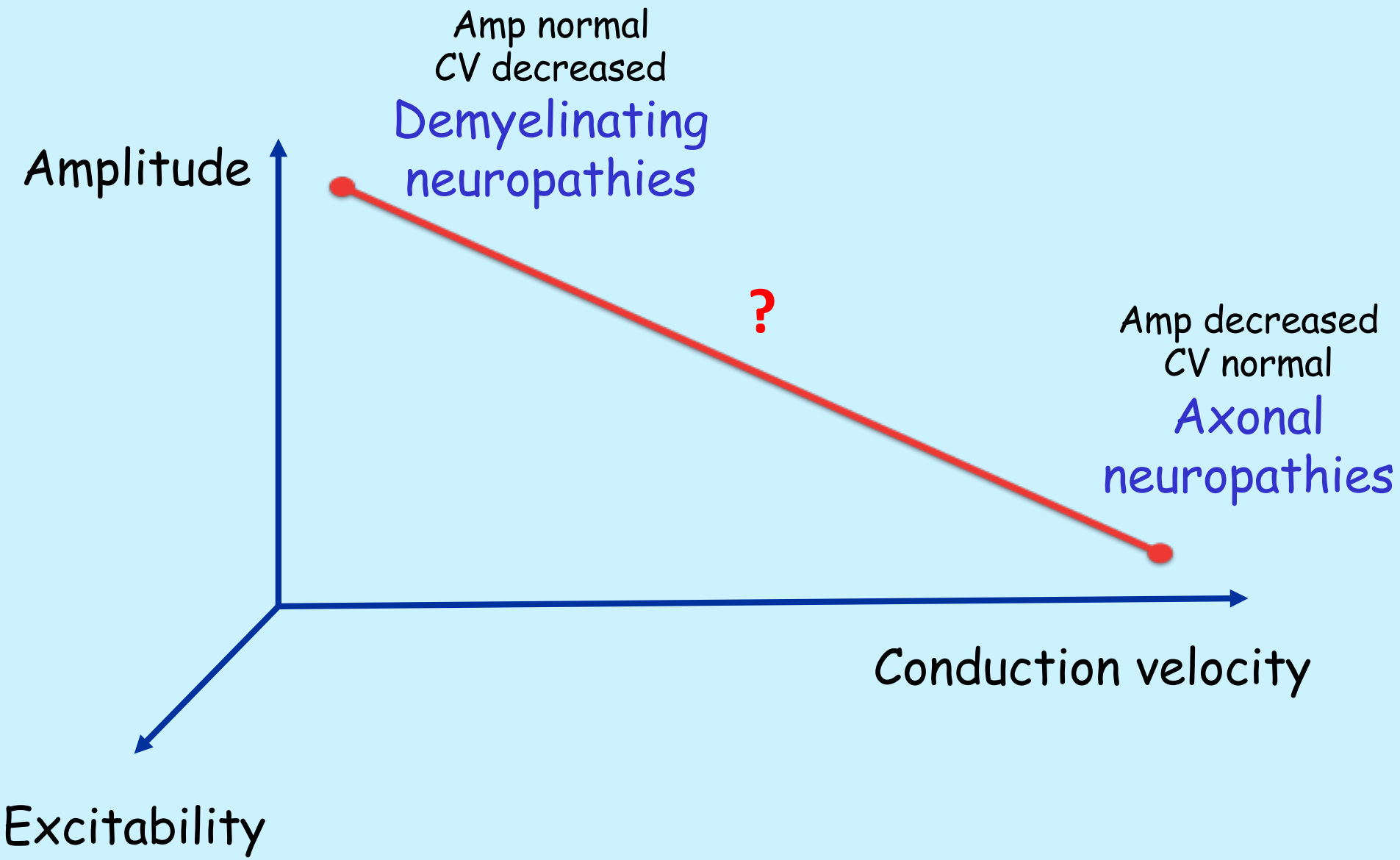
NERVOUS EXCITABILITY STUDY



Maëlle Tyberghein
François Wang

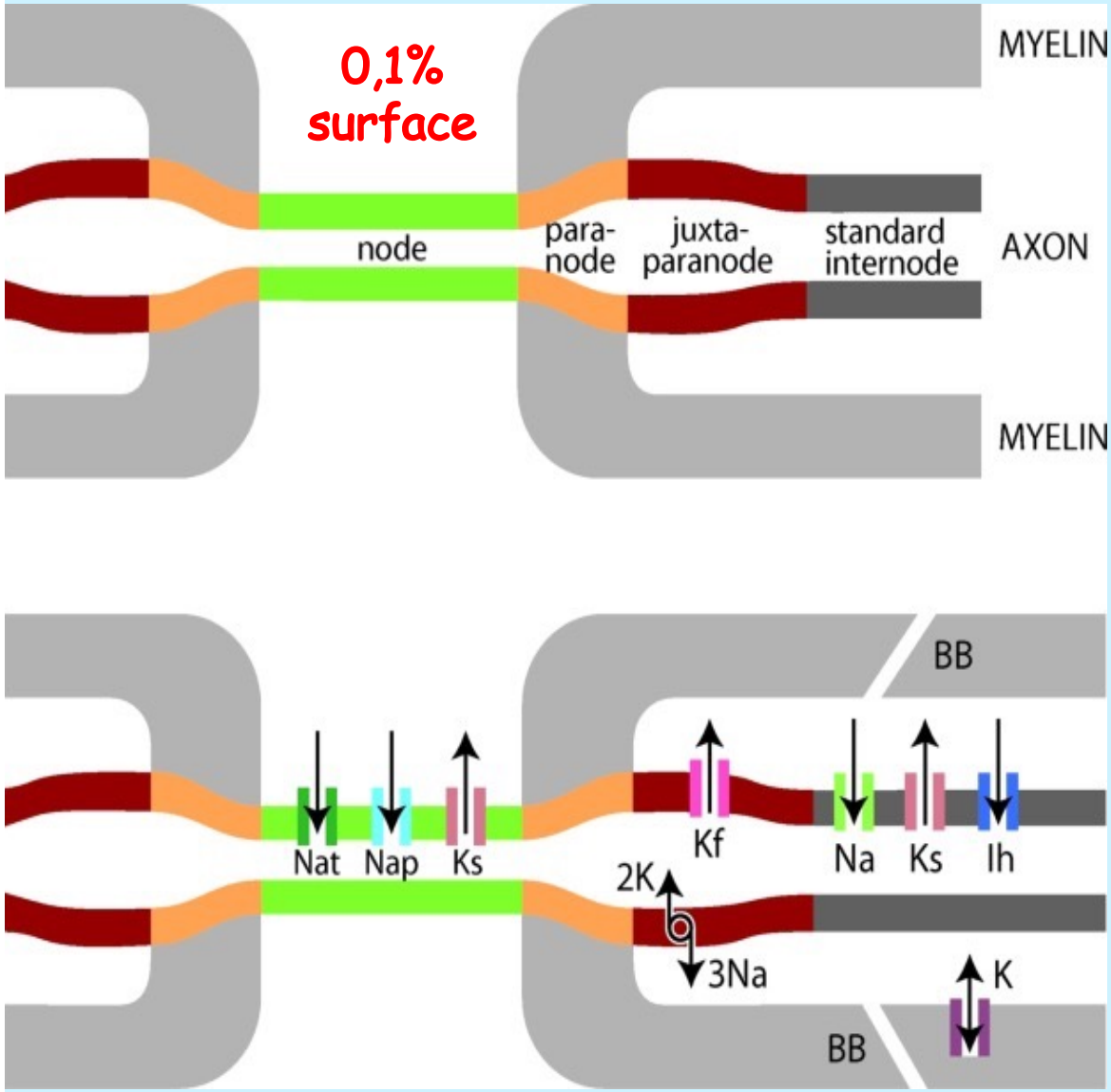
Clinical neurophysiology department
CHU, Liège

Why study axonal excitability?



Basic principles

Excitability actors



Node

Myelin

Na_t Channels
=> action potential

K_s and K_f Channels
$\Rightarrow$ restrict axonal depolarisation

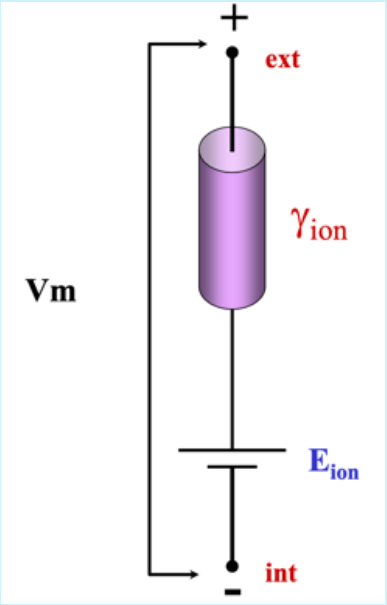
HCN Channels (Ih current)
=> restrict axonal hyperpolarisation

Nap Channels

Na-K Pump (ATPase)

Basic principles

Neuron = parallel RC circuit



Membrane = capacity (**C**)

Capacitance = capacity to stock electric charges (depends on membrane surface)
- node : low capacitance (quick charge)
- internode : large capacitance (slow charge)

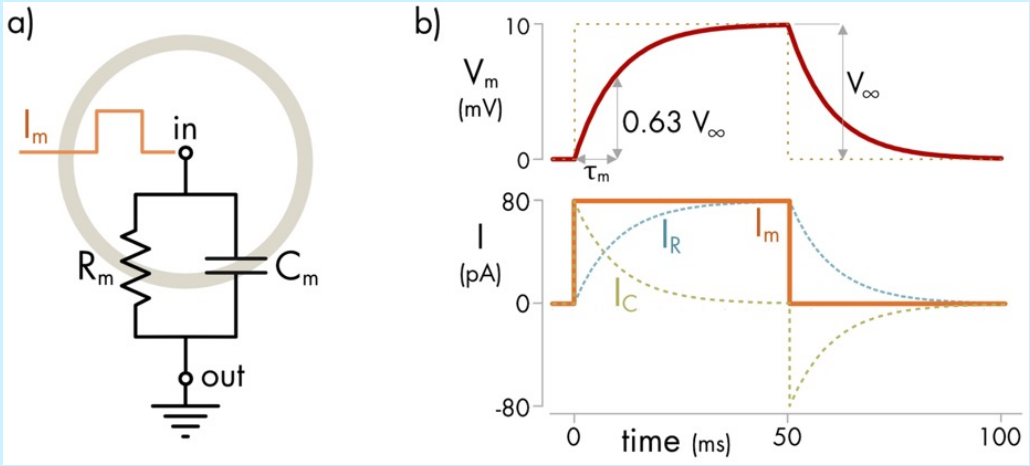
Ion channels = resistance (R)

Resistance variable :
- open channels : low resistance
- closed channels : high resistance

Nodal membrane potential increase and decrease depending on exponential kinetics characterized by time of constant = **RC**

= τ_m (time to change the potential of 63% of it's final value)

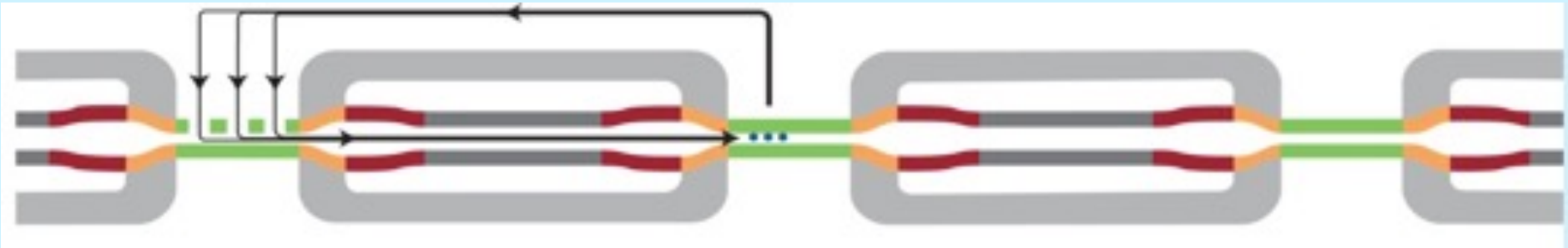
≃ chronaxie



Basic principles

The action potential

- Opening of Na nodal channels
  -> intrance of positives charges in the axone
  = **incoming ionic current** (Na^+)
- **Longitudinal axonal ionic current** (K^+, Cl^-, Na^+)
- **Outgoing capacitative current** in nodes where Na channels are closed -> node depolarization -> opening of nodal sodium channels



How to study axonal excitability?

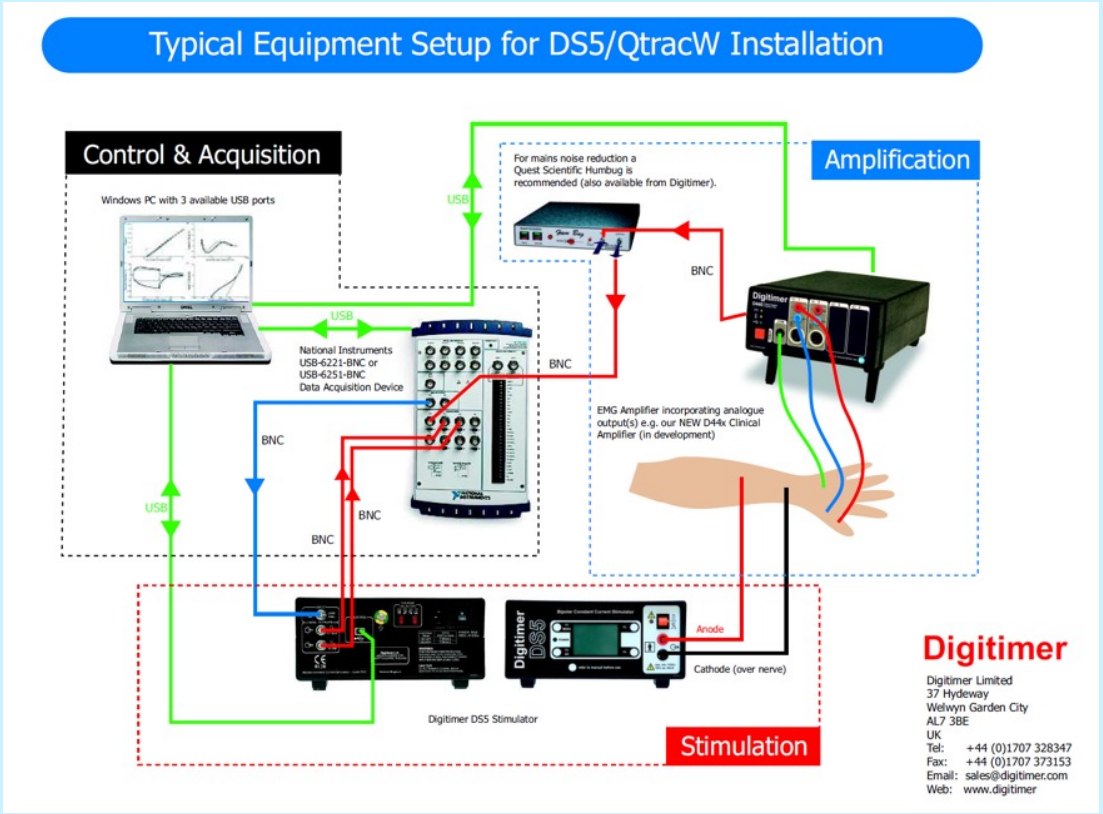
1. Strentgh-duration curves
2. Axonal excitability recovery cycle
3. Stimulus-response curves

=> Node excitability

4. Threshold tracking

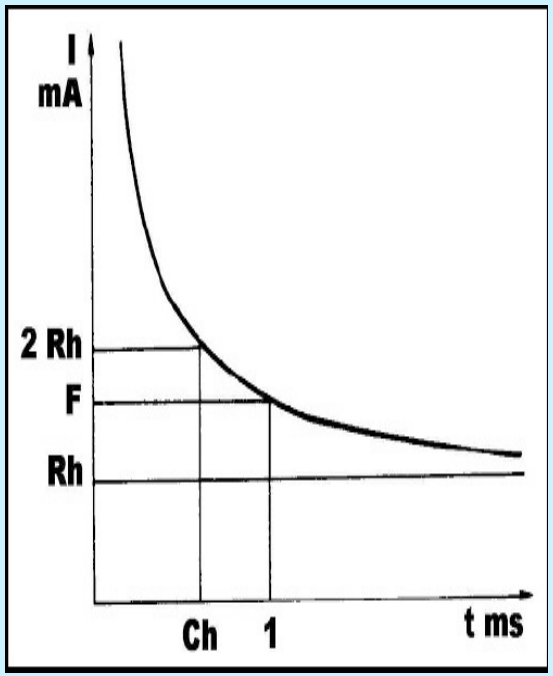
=> Internodal accomodation

How to study axonal excitability?



1. Strentgh-duration curves

Louis Lapicque
1866 – 1952
Sorbonne, Paris



In 1909, Lapicque defines:

Rheobase = estimated threshold current for a stimulus of infinitely long duration

Chronaxie = minimum stimulus duration for a current twice rheobase to stimulate a muscle.

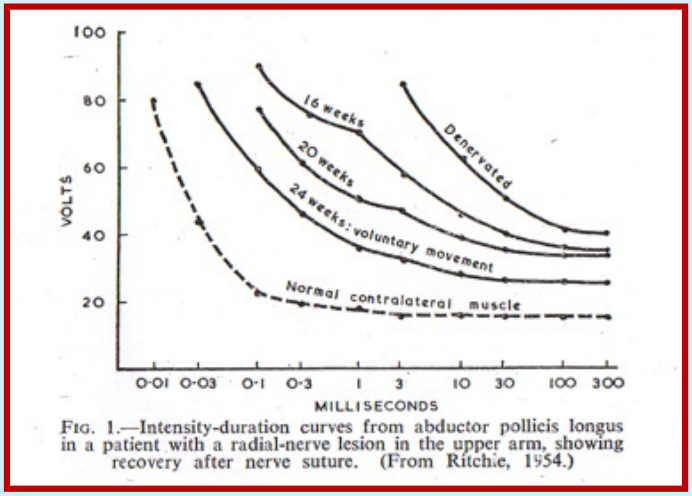
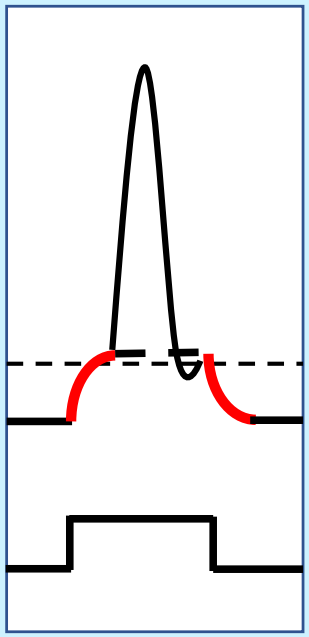


FIG. 1.—Intensity-duration curves from abductor pollicis longus in a patient with a radial-nerve lesion in the upper arm, showing recovery after nerve suture. (From Ritchie, 1954.)

1. Strentgh-duration curves

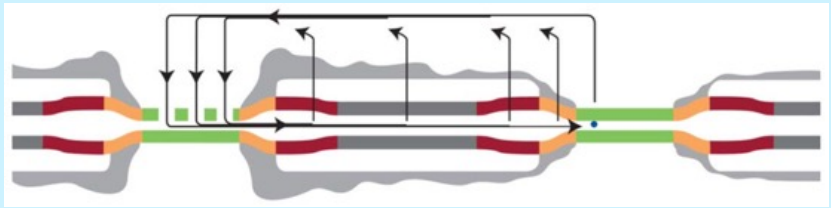


Chronaxie (τ) = time of constant = time it takes for the change in potential to reach 63% of its final value

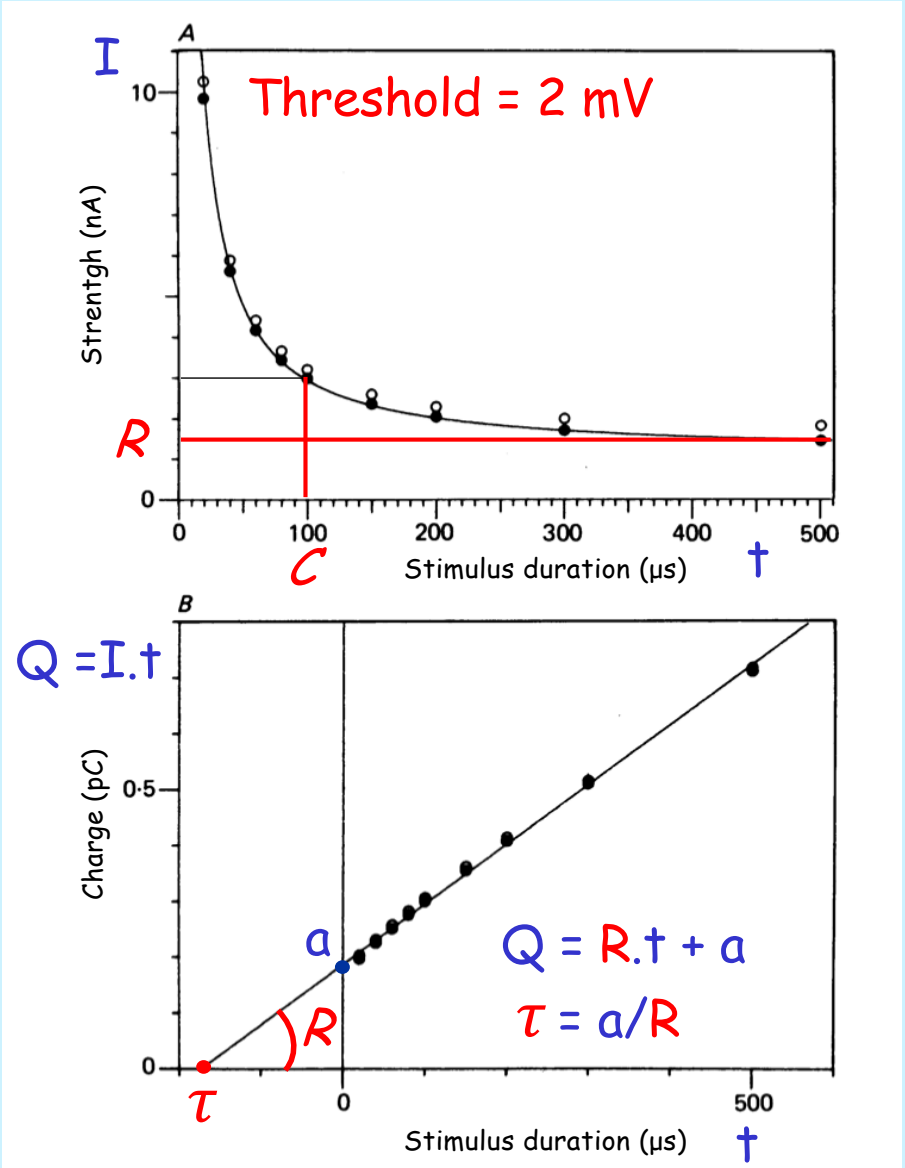
- Passive composant : 50 µs
  Node surface
- Active composant : 300-400 µs
  Leak Channels open at resting membrane potential Na_p

Rhéobase :

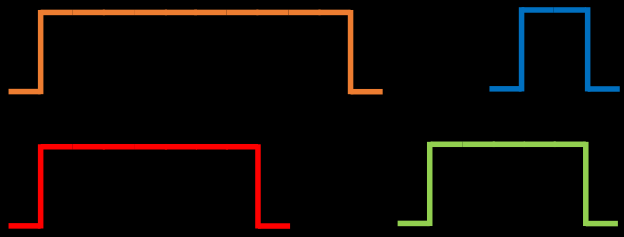
- Inversely proportional to nerve excitability
- Due to passive property of the node (capacity)
- Increased when there is damage in the myelin sheet
- Depends also of extraneural parameters



1. Strentgh-duration curves

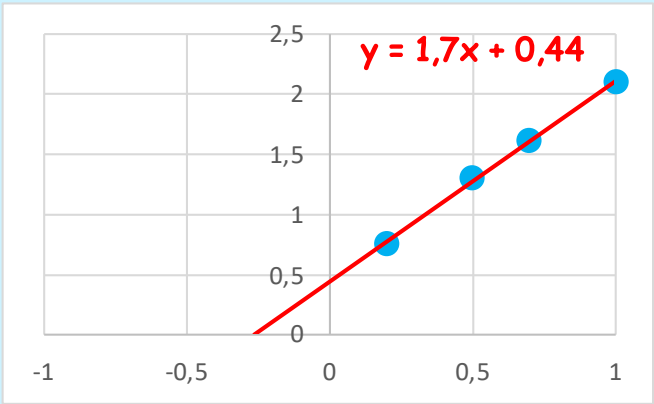


Weiss Law : $Q = R(t + \tau)$



- Define a threshold (ex. **2 mV**)
- What's the intensity needed to reach the threshold with 4 different stimulus durations?
- Excel

1	0,7	0,5	-0,265	0,2	Q 1,0	Q 0,7	Q 0,5	Q 0,2	
2,1	2,3	2,6		3,8	2,1	1,61	1,3	0,76	0



1. Strentgh-duration curves

In peripheral neuropathies

- **Demyelinating neuropathies (CMT1A, CIDP, GBS), the rheobase is increased due to passive membrane property. (Kiernan *et al.*, 2019)**

- **There is a relationship between survival and chronaxie in ALS. (Kanai *et al*, 2012)**

- **CIDP, one of direct action mechanism of intravenous immunoglobulin could depend of Nap Channel. (Boërio *et al.*, 2010)**

	Chronaxia	Rheobase
ALS	increased	normal
CMT1a	normal	increased
GBS	normal	increased
CIDP	decreased	increased

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2. Axonal excitability recovery cycle

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=> Node excitability

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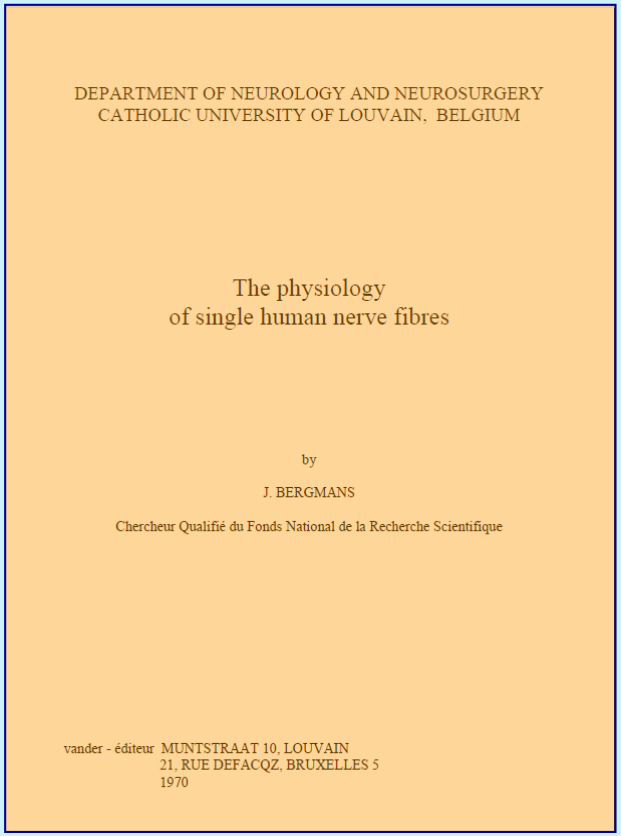
2. Axonal excitability recovery cycle

1952 Hodgkin & Huxley -> ionic channels

Joseph Bergmans (ca. 1970)



DEPARTMENT OF NEUROLOGY AND NEUROSURGERY
CATHOLIC UNIVERSITY OF LOUVAIN, BELGIUM

The physiology
of single human nerve fibres

by

J. BERGMANS

Chercheur Qualifié du Fonds National de la Recherche Scientifique

vander - éditeur MUNTSTRAAT 10, LOUVAIN
21, RUE DEFACQZ, BRUXELLES 5
1970

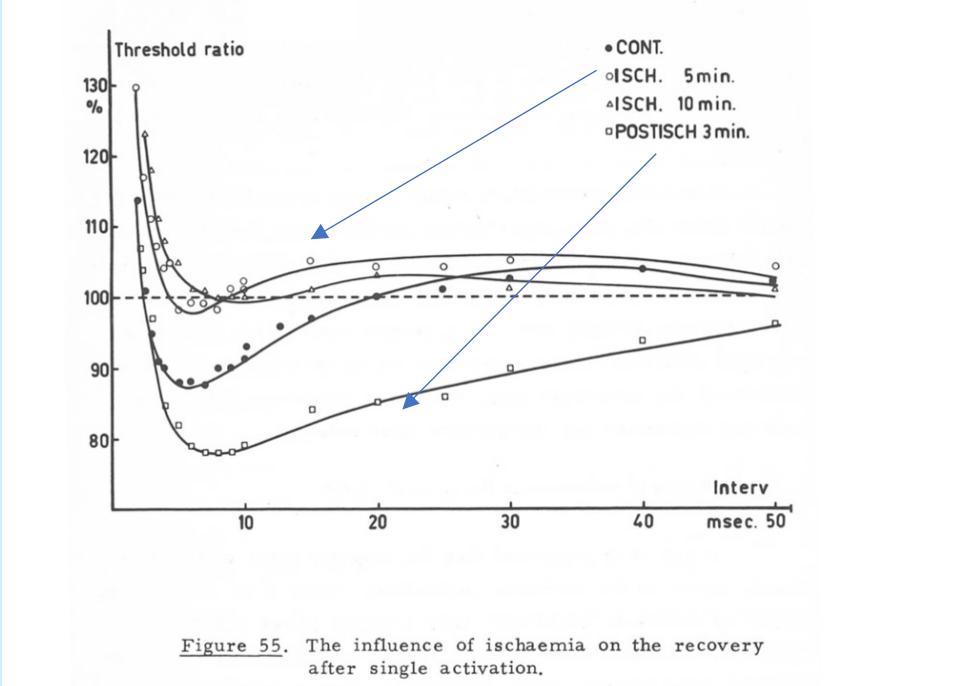
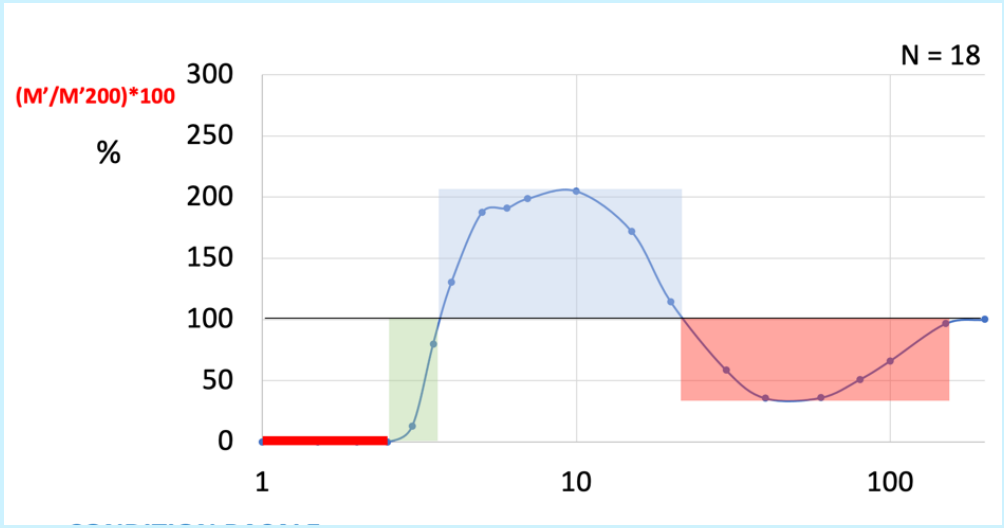


Figure 55. The influence of ischaemia on the recovery after single activation.

2. Axonal excitability recovery cycle

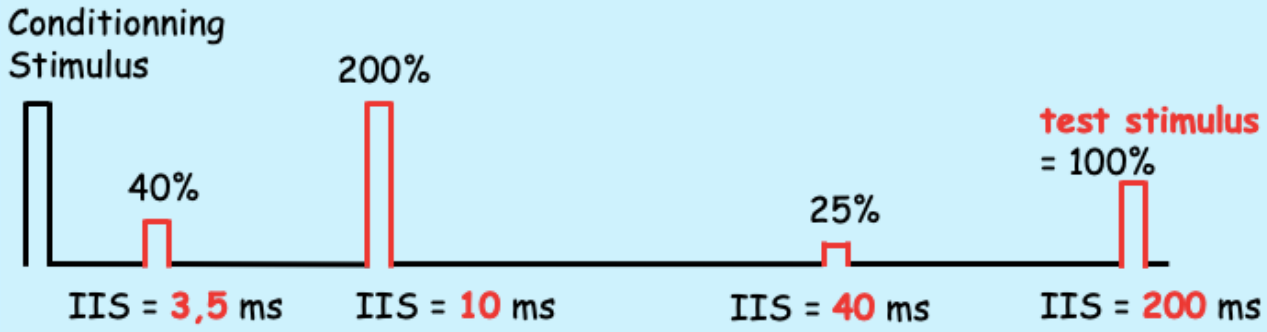


Absolute refractory period

Relative refractory period

Superexcitable period

Late subexcitable period



Double shock

2 successive stimuli with 2 different intensities

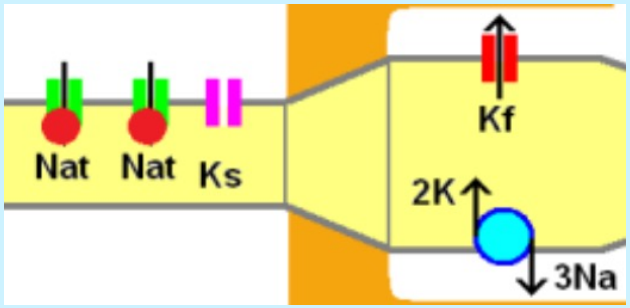
- Conditioning stimulus (supramaximal)

- Test stimulus (i40)

Variation of the interstimulus interval between 1-200 ms

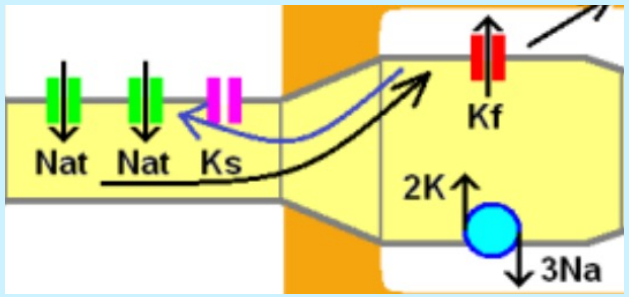
2. Axonal excitability recovery cycle

Absolute refractory period :
Nodal Na_t inactivation
Relative refractory period:
Nodal Na_t gradual reactivation



Superexcitable period:

During the action potential, there is a large influx of Na ions at the node which spread over nodal and internodal axolemma. After the action potential, there is a reflow of current coming from the large capacitance of the internode which depolarized the node.



Late subexcitable period :

Slow openning of nodal **Ks** => post potentiel hyperpolarization

2. Axonal excitability recovery cycle

In peripheral neuropathies

- **CMT1a and CIDP, refractory period and superexcitable period reduction is due to passive membrane property. (Kiernan *et al.*, 2019)**

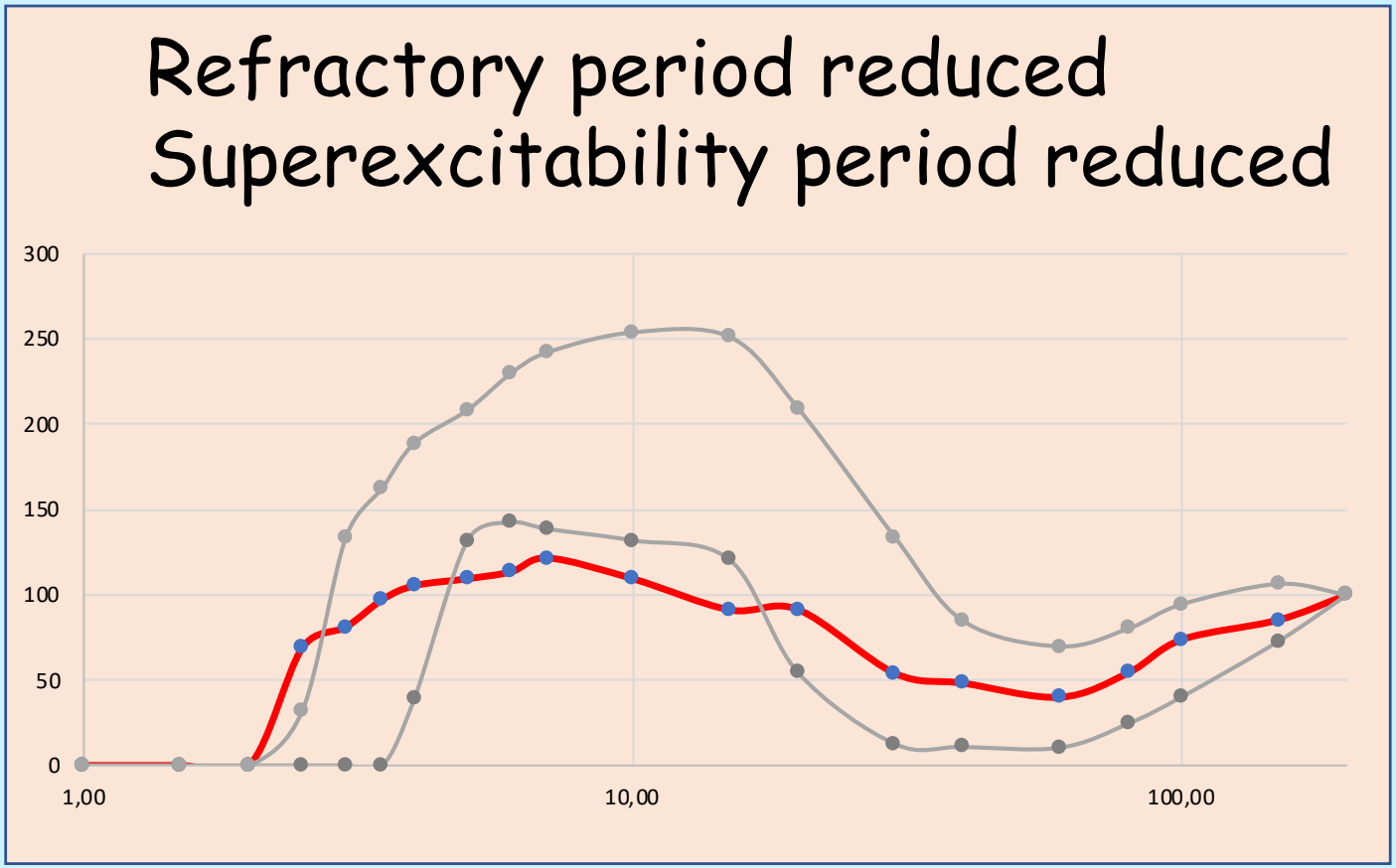
- **AMAN, the refractory period is increased** suggesting that nodal sodium channels are impaired by anti-ganglioside antibodies. ***(Pyun et al., 2017)***

- **MMN, the supernormal period is increased below the conduction bloc reflecting membrane hyperpolarization (overacivation of NaKATPase pumps ?). (Kiernan *et al*, 2002)**

	Refractory period	Superexcitable period
ALS	reduce	increase
CMT1a	**reduce**	**reduce**
AMAN	increase	reduce
CIDP	**reduce**	**reduce**

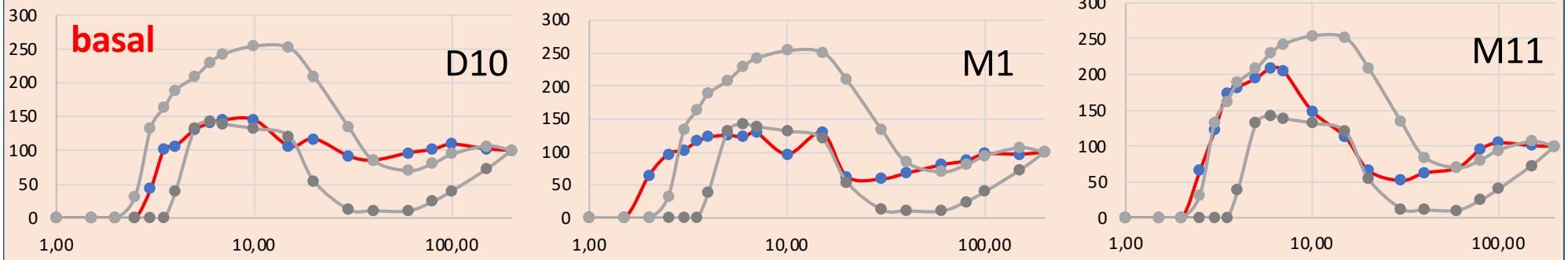
2. Axonal excitability recovery cycle

CMT1a



2. Axonal excitability recovery cycle

GBS

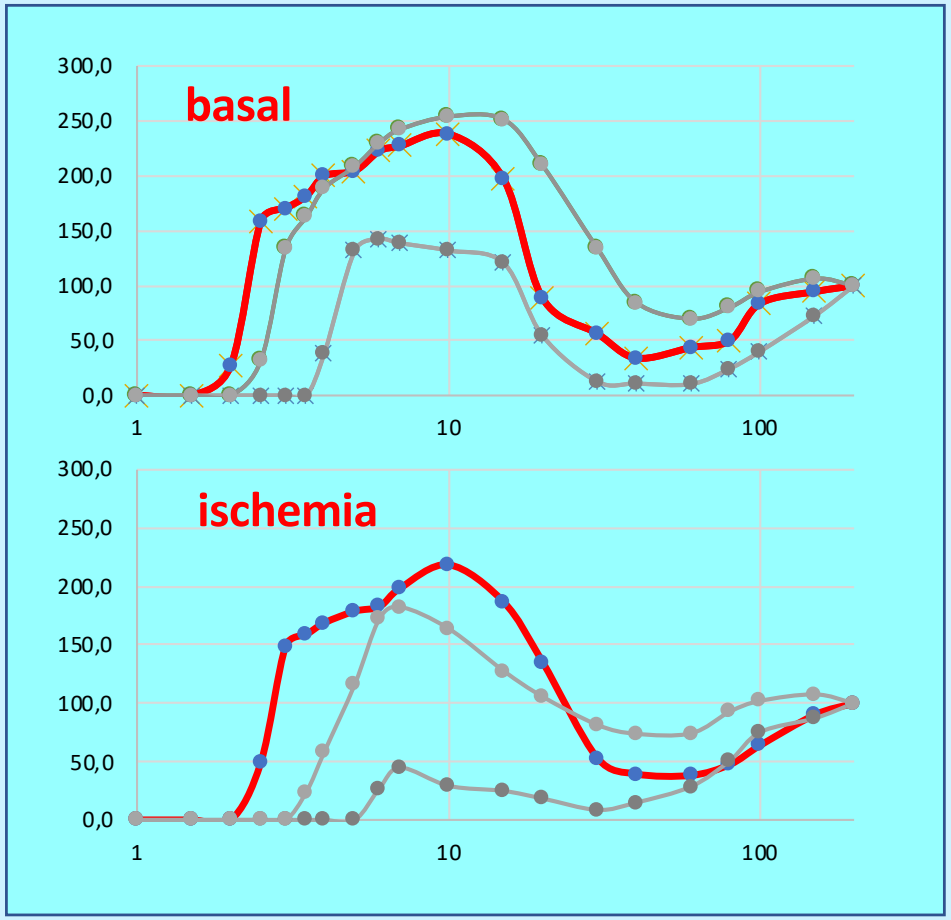


Refractory period reduced
Superexcitabiity reduced
Improvement with time

2. Axonal excitability recovery cycle

Lewis & Sumner

Membrane hyperpolarization
- Refractory period reduced
- Superexcitability increased
  (especially in ischemia)



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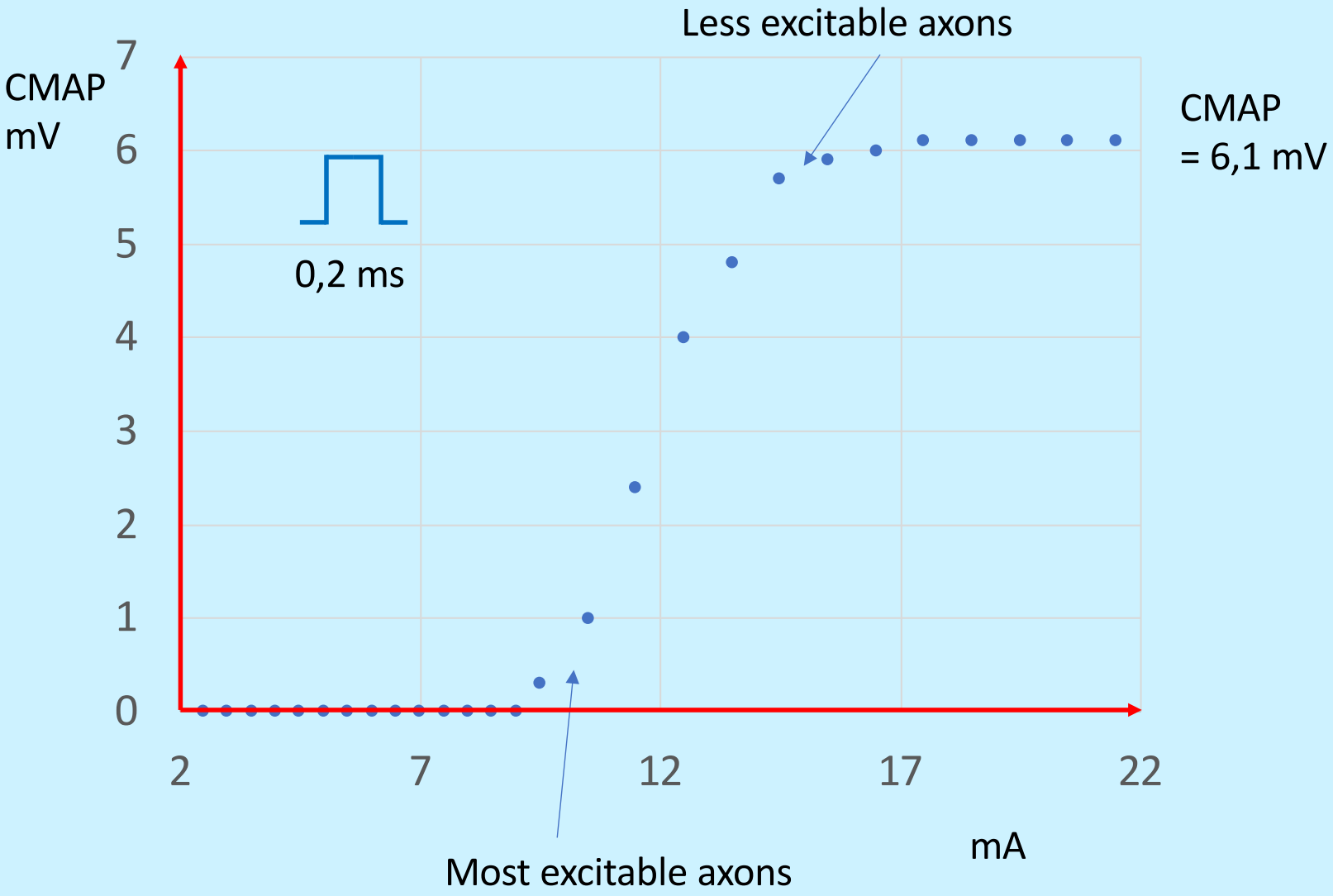
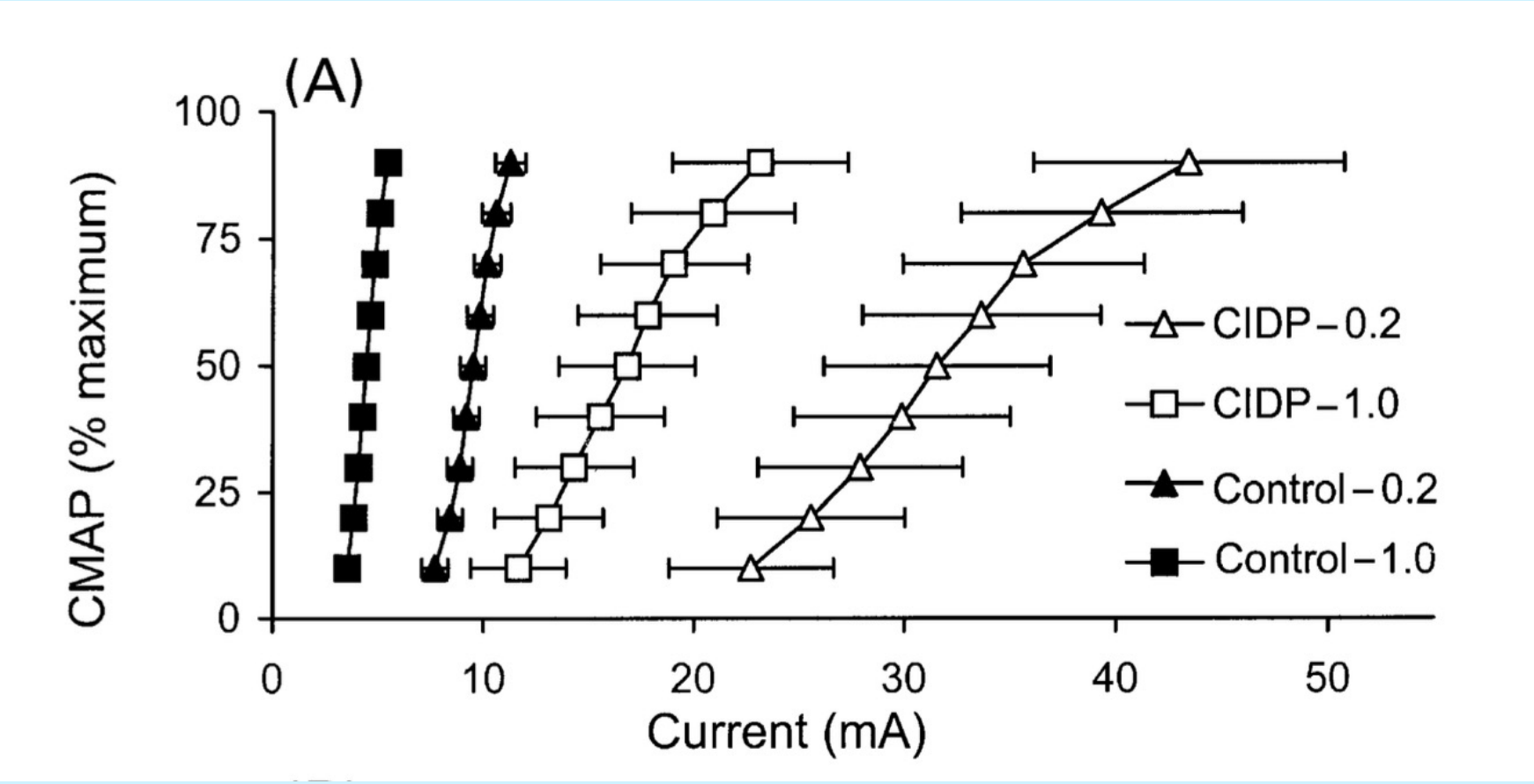
4. Threshold tracking

=> Internodal accomodation

3. Stimulus response curve



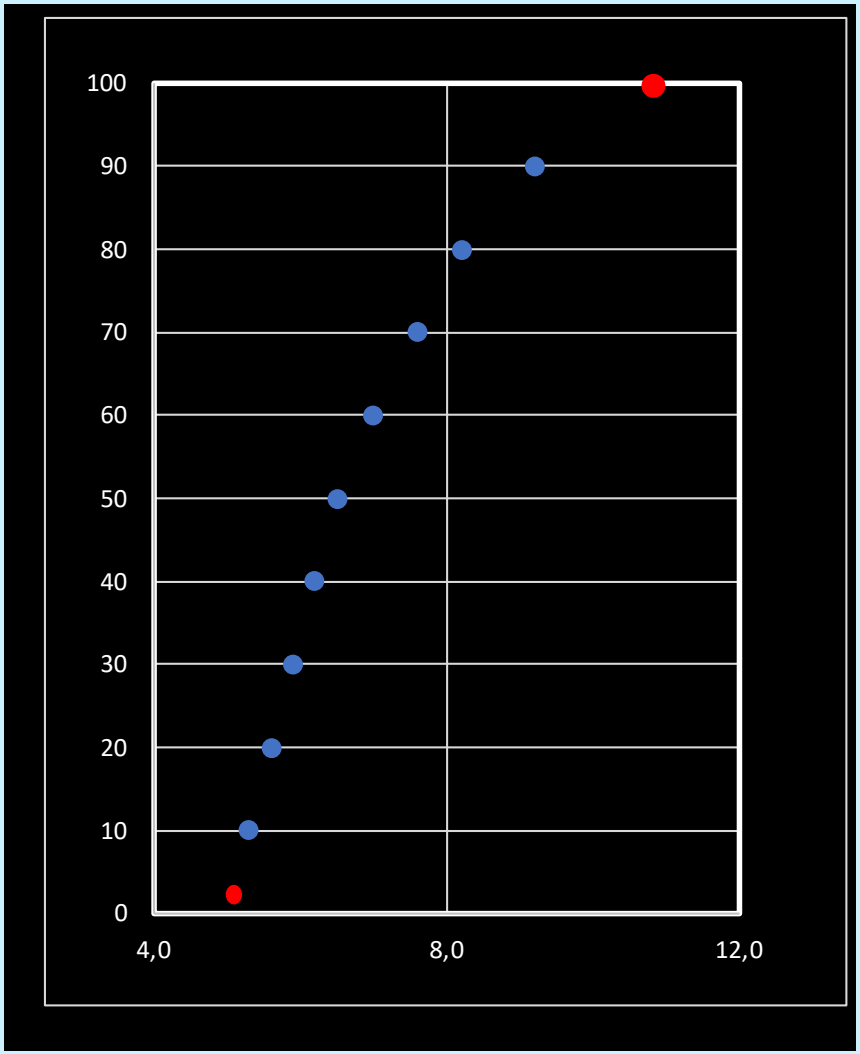
3. Stimulus response curve



(Cappelen-Smith *et al*, 2001)

3. Stimulus response curve

iMAX the minimal intensity needed to evoke a maximal response



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journal homepage: www.elsevier.com/locate/clinph

iMAX: A new tool for assessment of motor axon excitability. A multicenter prospective study

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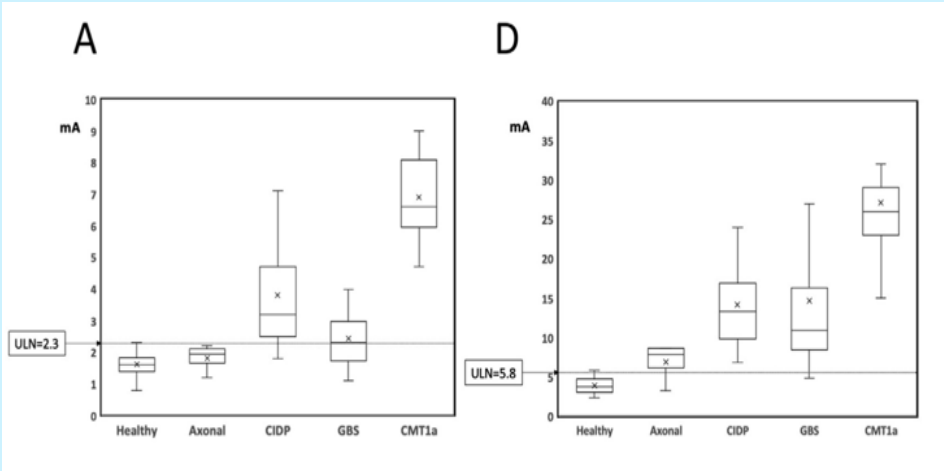
[d] Université Côte d'Azur, Peripheral Nervous System & Muscle Department, Pasteur 2 Hospital, Centre Hospitalier Universitaire de Nice, Nice, France

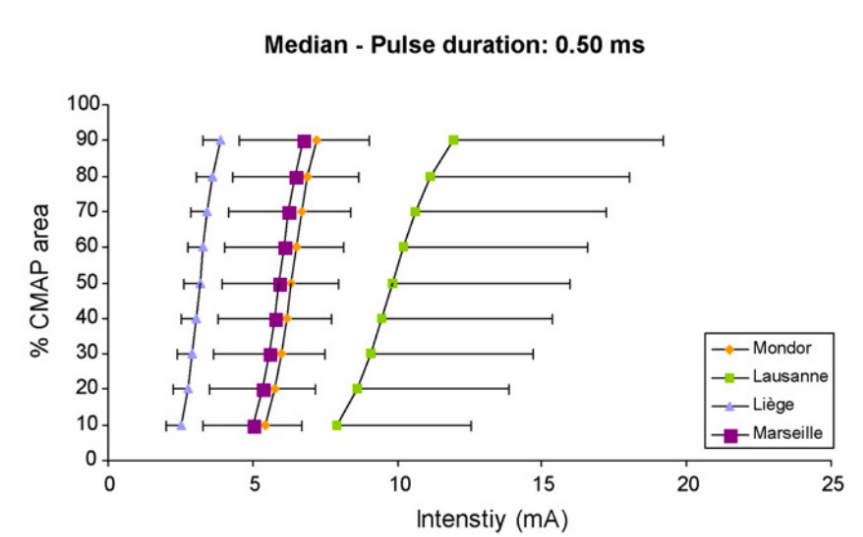


3. Stimulus response curve

	Shift of the curve	Slope
CMT1a	Right +++	---
GBS	Right +	-
CIDP	Right ++	--

Like the rheobase, the stimulus response curve depends on passive property of the membrane
+ impedance of electrodes
+ resistance of the extraneural tissue

Great variability of results (Boërio *et al*, 2008)
We need to control the impedance



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4. Threshold Tracking (1990- 2010)

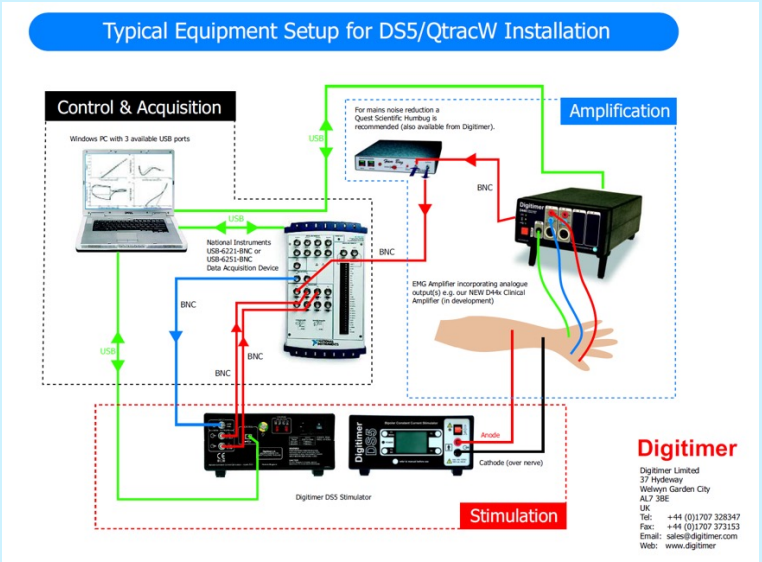
First row from left: Inger Rudvin, Neshat Golparian, Kjeld Andersen, Hugh Bostock, David Burke
Second row: Sture Hansson, John Smale Lundemo, Per Martin Roos, Christer Swerup, John Wilson, Anita Herigstad, Matthew Kiernan, Kari Todnem, Martin Ballegaard, Esa Kaupplia,John-Anker Zwart. Other participants: Trond Sand, Ole Støren.

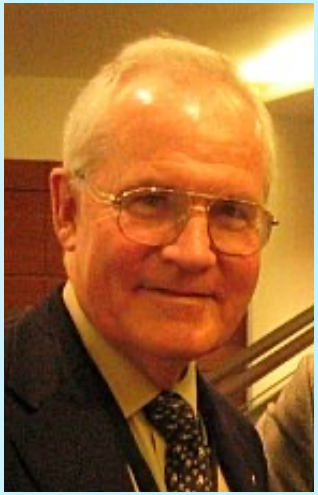
INVITED REVIEW *Muscle Nerve* **21:** 137–158, 1998

THRESHOLD TRACKING TECHNIQUES IN THE STUDY OF HUMAN PERIPHERAL NERVE

HUGH BOSTOCK, PhD,[1*] KATIA CIKUREL, BSc, MRCP,[2] and DAVID BURKE, MD, DSc[3]

Study of the internode

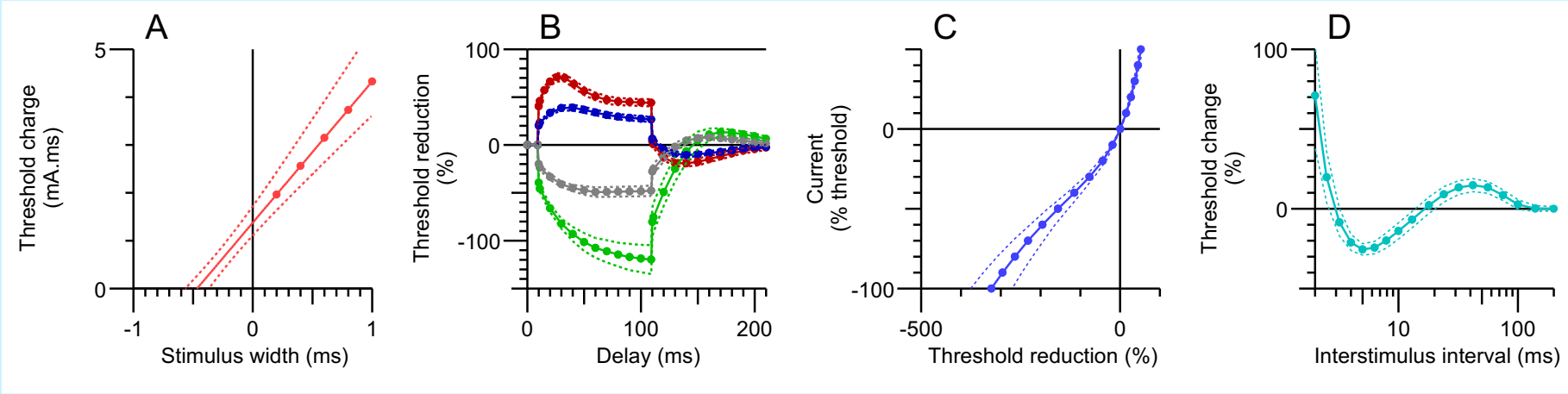


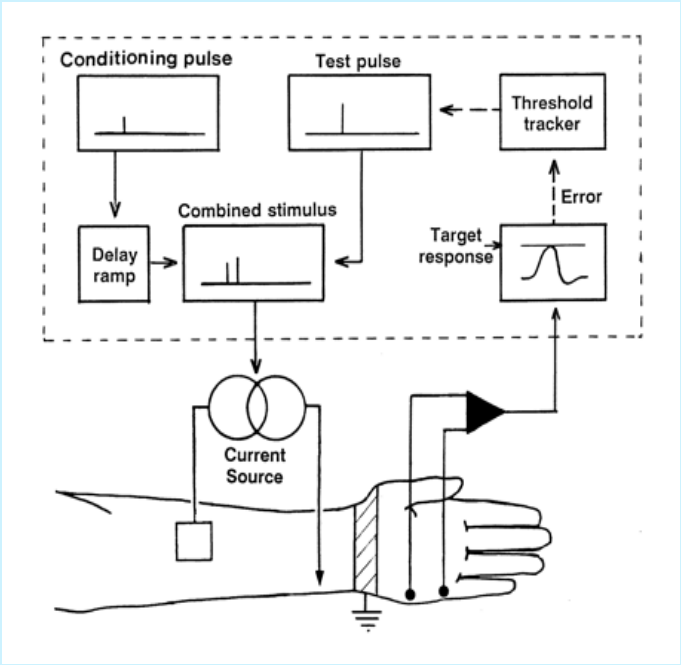


David Burke

Matthew Kiernan

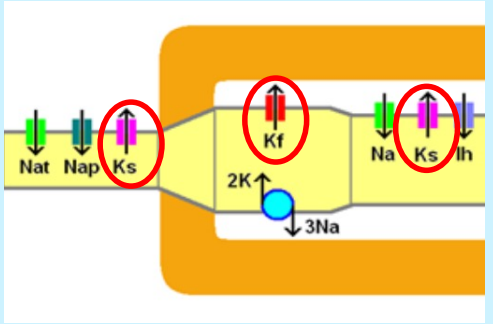
4. Threshold tracking

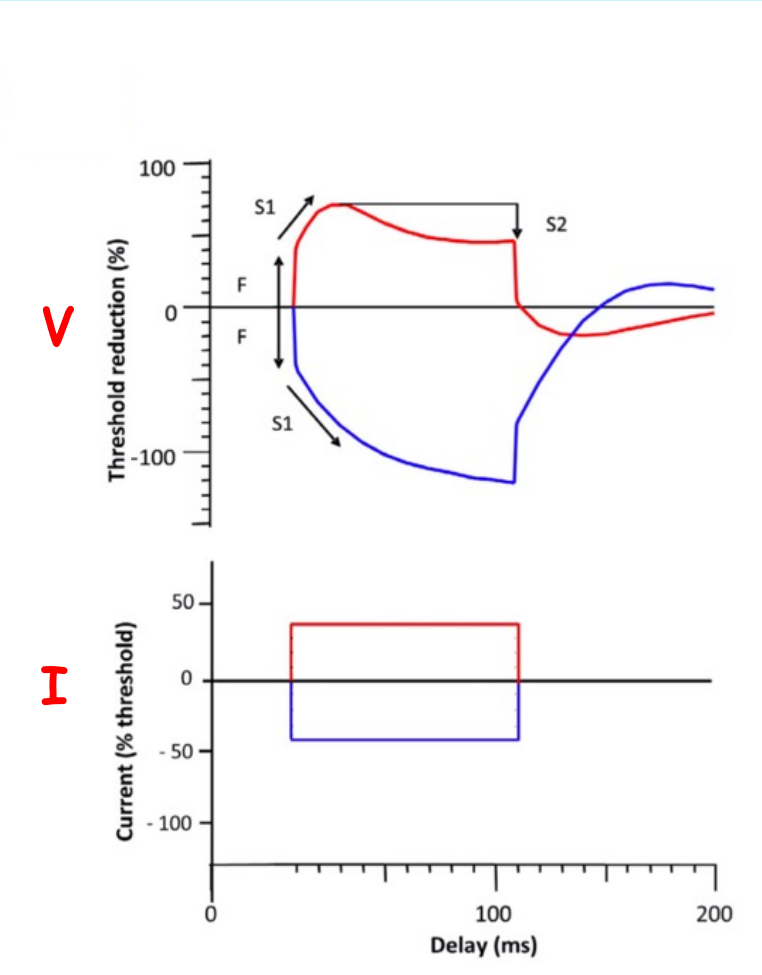


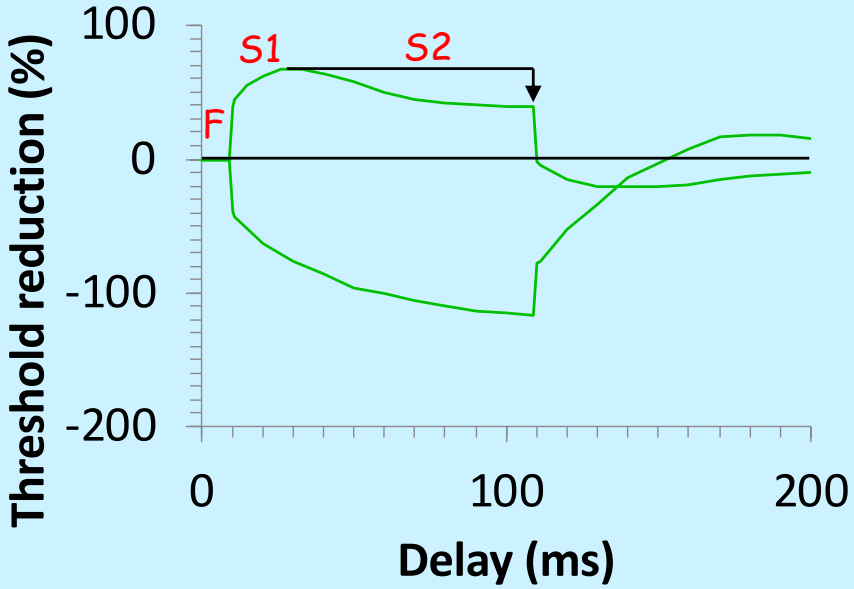


- Target : CMAP = 40-50% maximale CMAP
- Threshold : stimulation intensity needed to reach the target => depends on membrane potential
- Conditionning stimuli of long duration
  - depolarising de 100-200 ms
  - hyperpolarising de 100-200 ms
  - intensity: 20% et 40% of the threshold
- **Threshold variations = membrane potential variation**

4. Threshold tracking

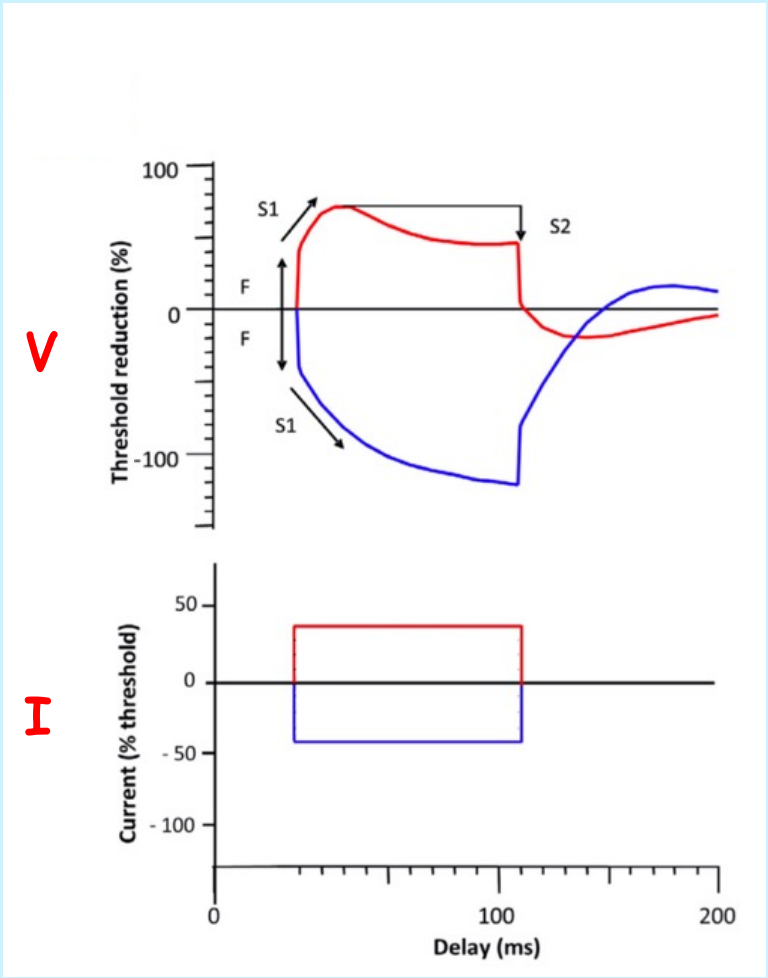


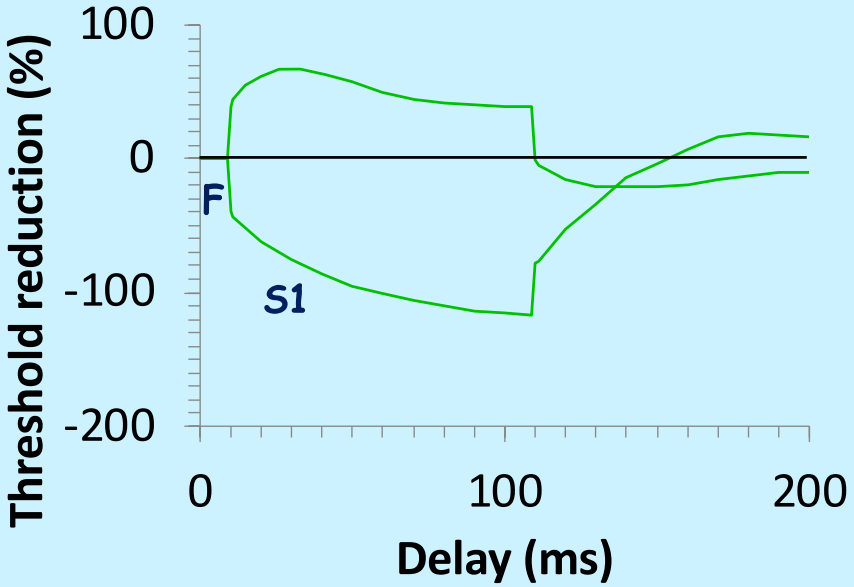




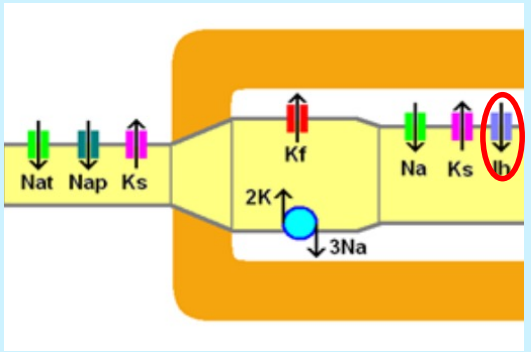
I depolarising (40% of the threshold)
- **F** : fast threshold reduction (nodal depolarisation)
- **S1** : threshold reduce more slowly (depolarisation in the internode, limited by K_f)
- **S2** : threshold increase (K_s nodal and internodal)

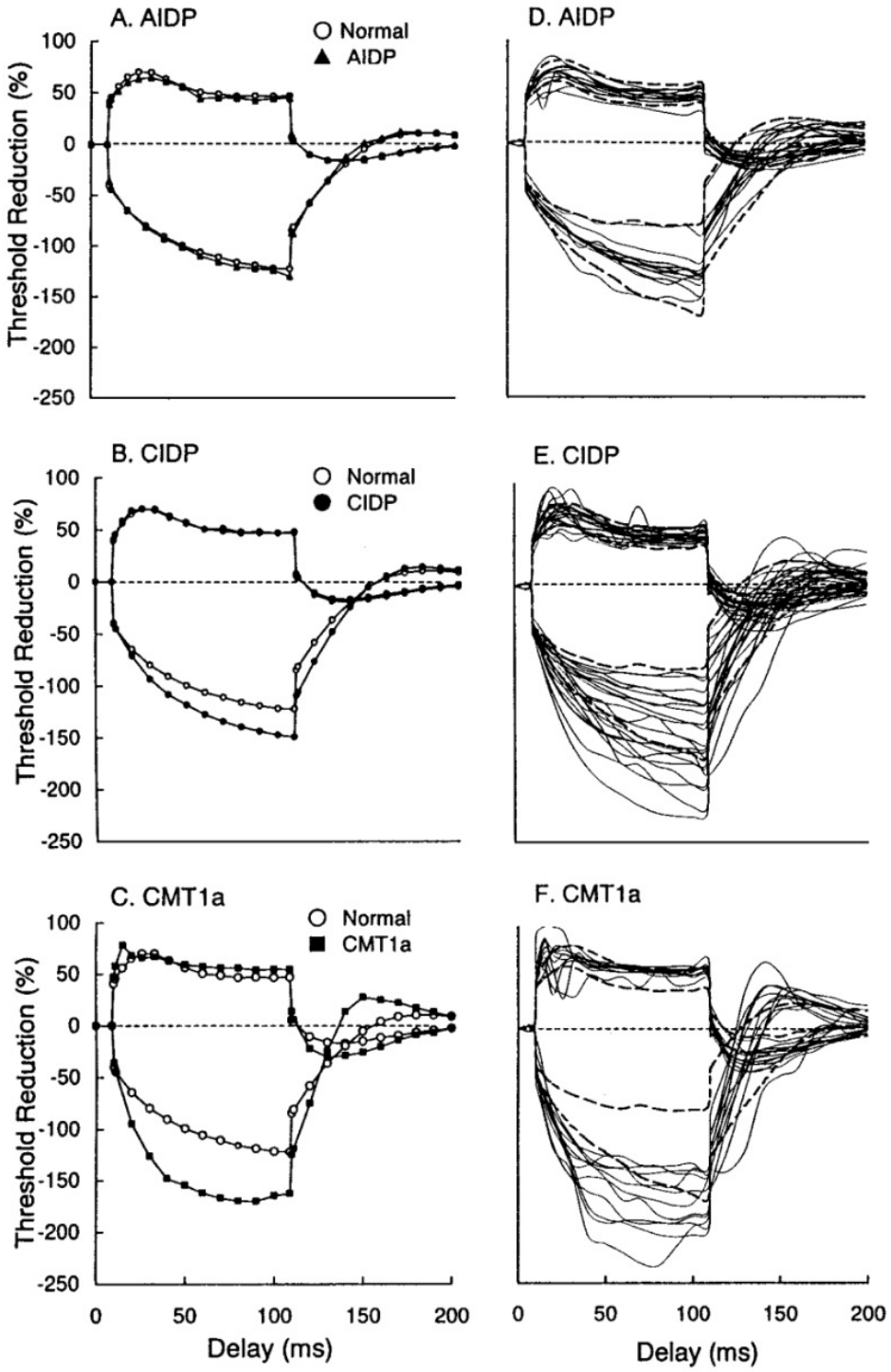
4. Threshold tracking



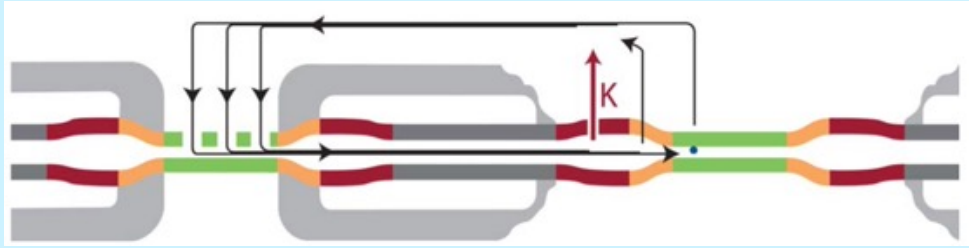


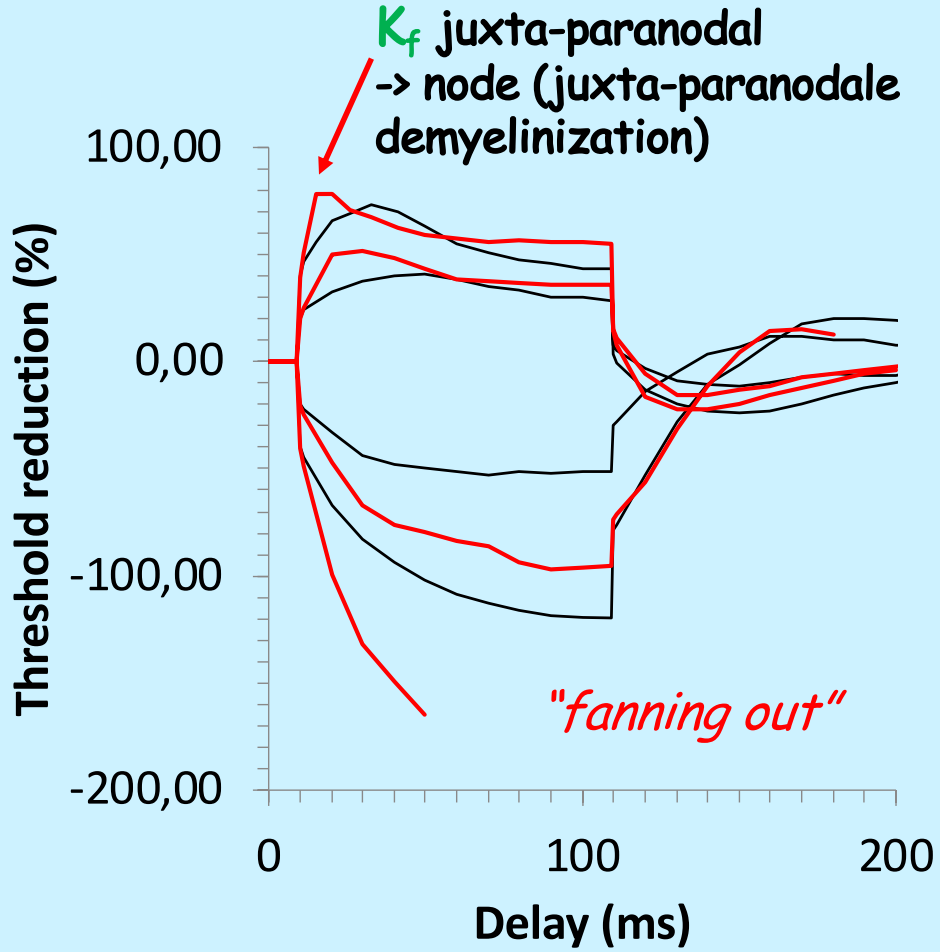
I hyperpolarising (40% of the threshold)
- **F** : fast increase of the threshold (nodal hyperpolarisation)
- **S1** : threshold increase more slowly (hyperpolarisation diffusion in the internode, limited by **Ih current**)




A. AIDP
Normal
AIDP
D. AIDP
B. CIDP
Normal
CIDP
E. CIDP
C. CMT1a
Normal
CMT1a
F. CMT1a
Threshold Reduction (%)
100
50
0
-50
-100
-150
-200
-250
0
50
100
150
200
Delay (ms)

CMT1a

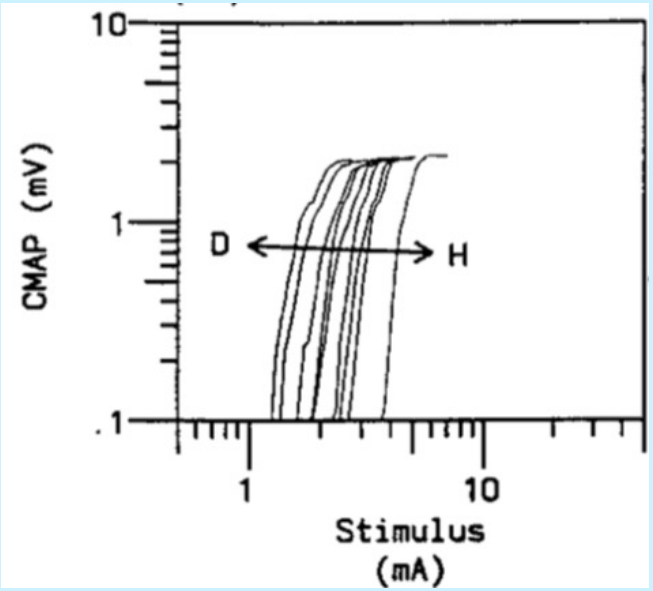

K

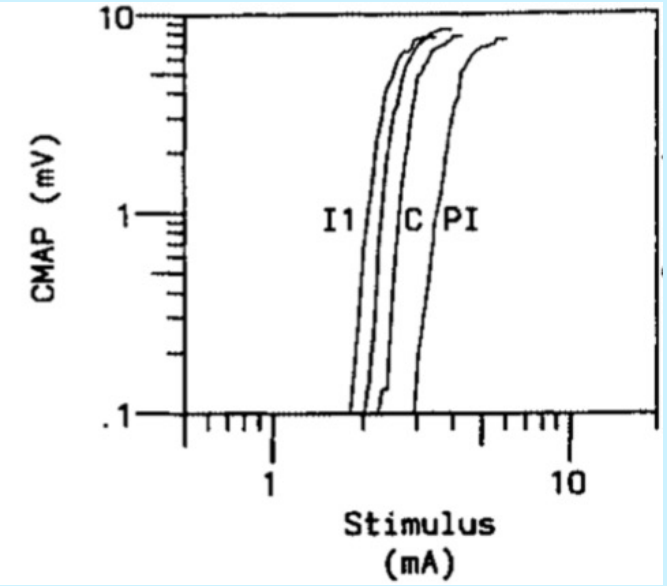

Kf juxta-paranodal
-> node (juxta-paranodale demyelinization)
100,00
0,00
-100,00
-200,00
Threshold reduction (%)
"fanning out"
0
100
200
Delay (ms)

Study of membrane polarity
Depolarization/hyperpolarization

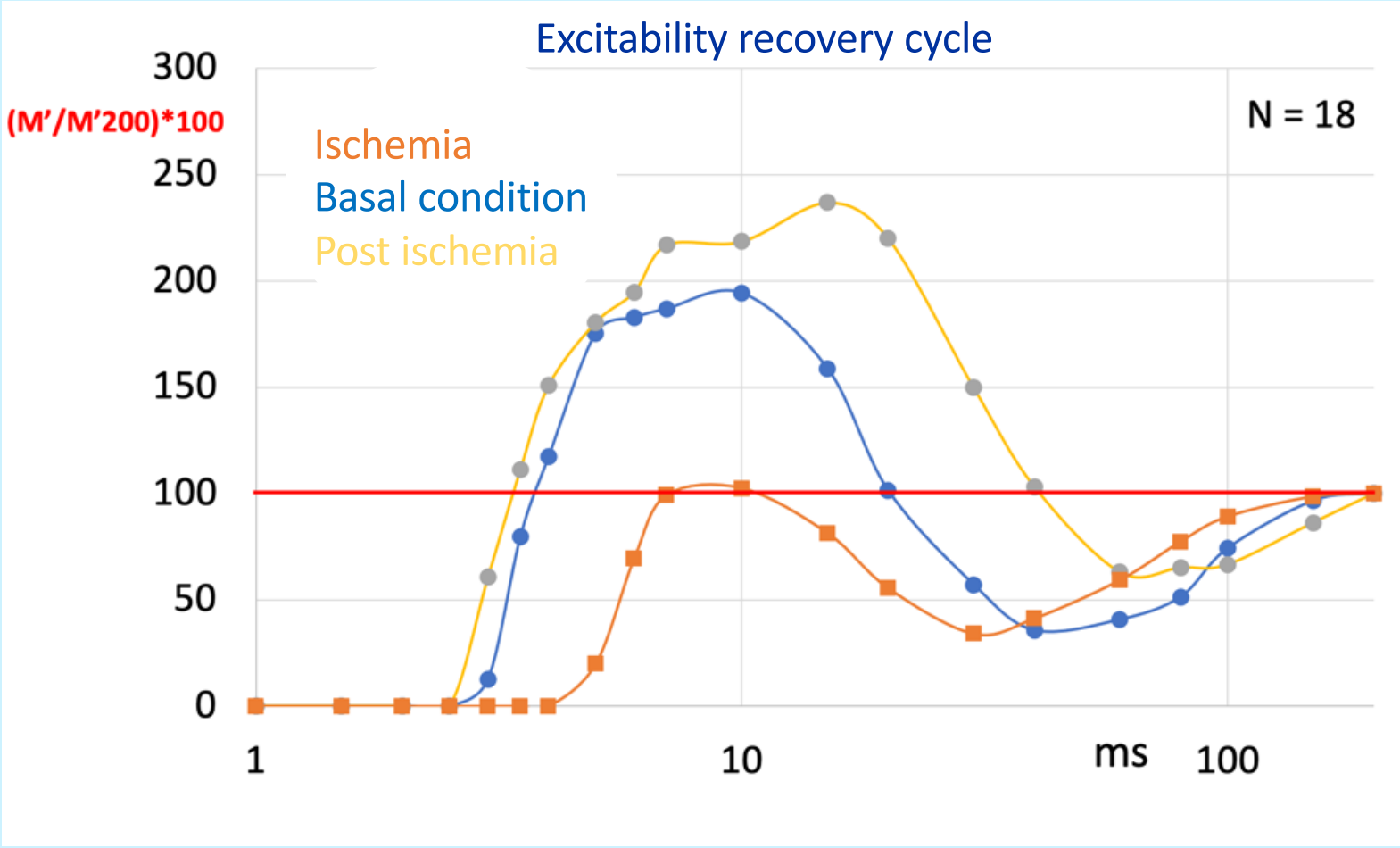
Ischemia = NaKATPase inactivation
=> depolarisation
Post-ischémia = NaKATPase overactivation
=> hyperpolarisation

Stimulus – Response curves

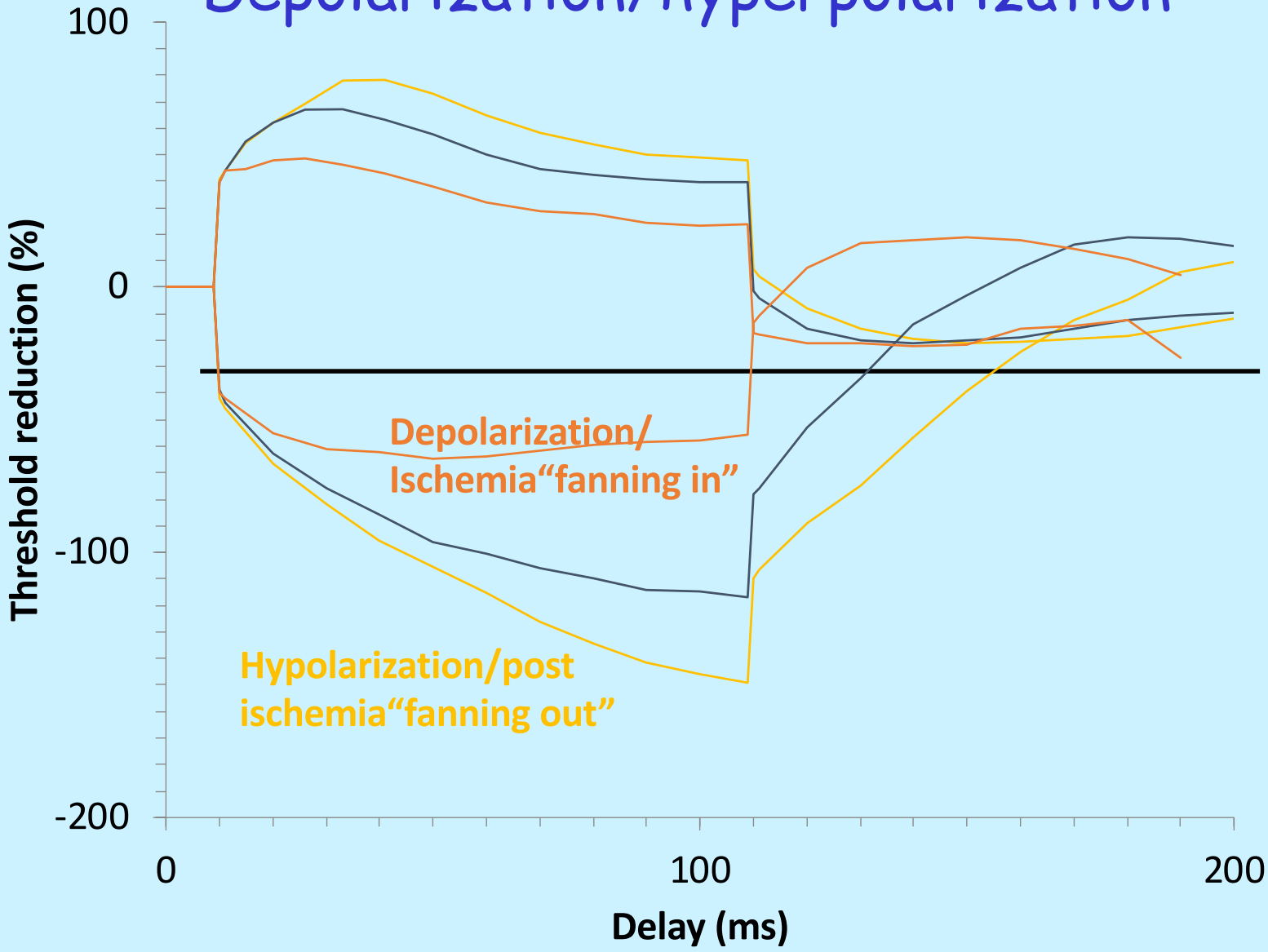




Study of membrane polarity
Depolarization/hyperpolarization



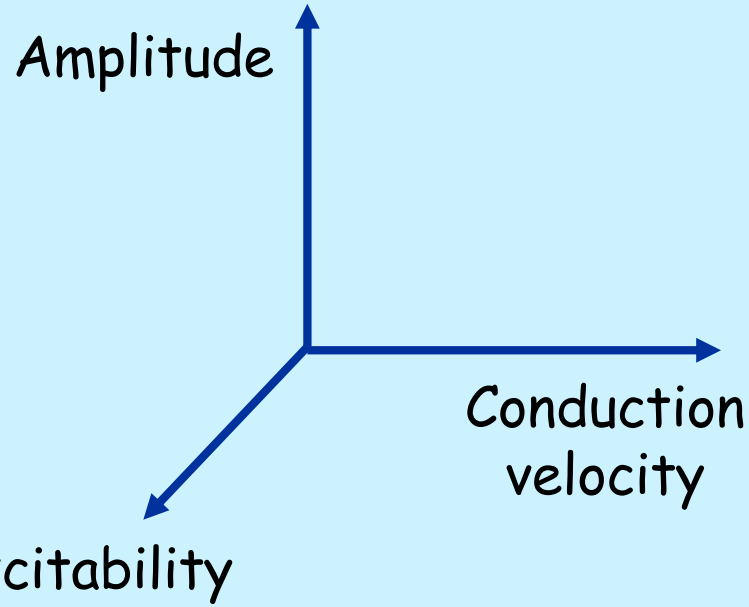
Study of membrane polarity
Depolarization/hyperpolarization



Conclusion

Why study axonal excitability?

- Membrane polarity
- Ion channels
- Passive membrane properties



How can we study excitability?