Gap Junctions Induced Bistability Conductance in Cardiac Tissue

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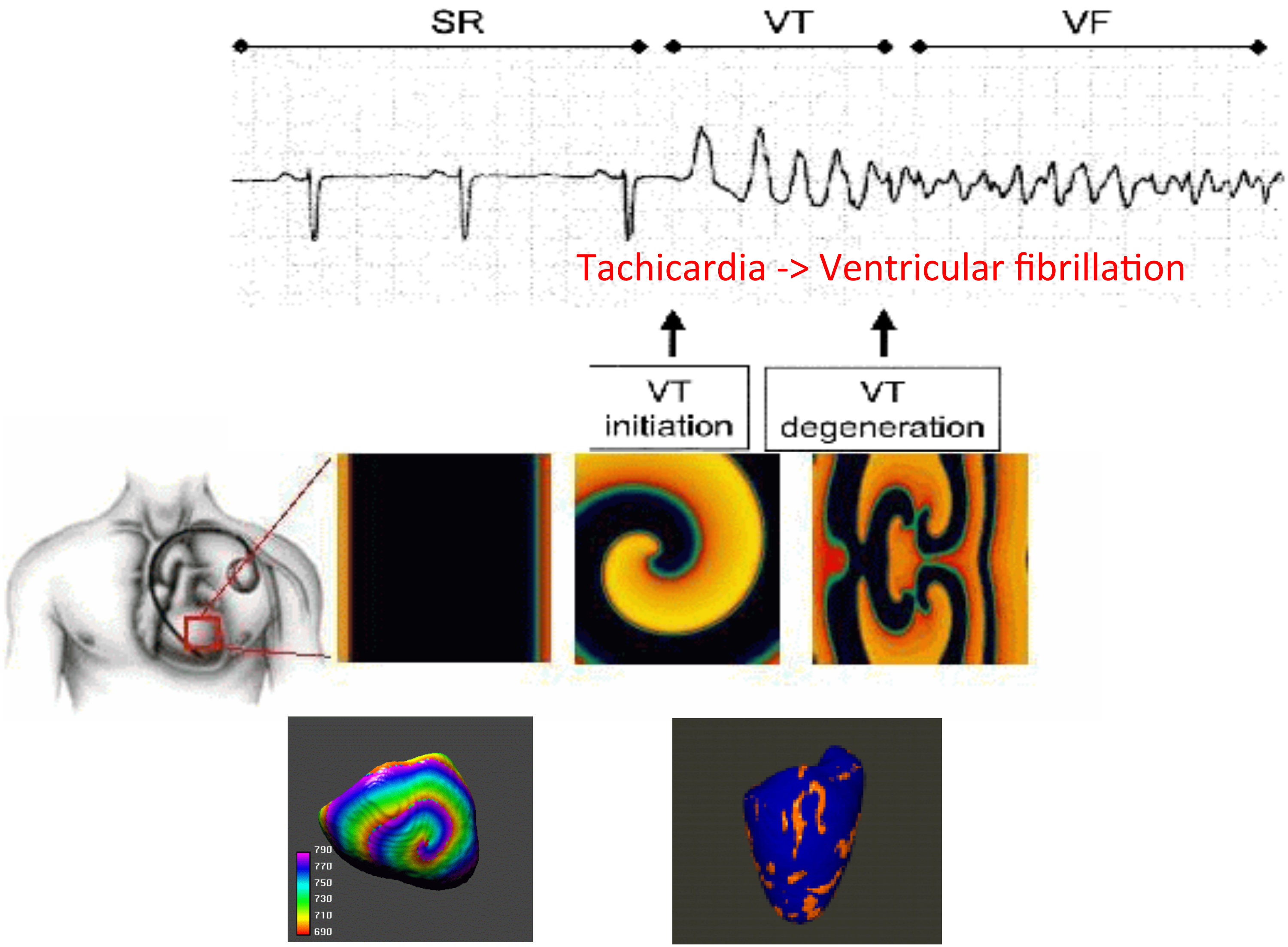
Why are we interested in studying cardiac dynamics ?

Rank[1]	Cause of death (based on ICD–10, 1992)		Number	Percent of total deaths	2005 crude death rate
...	All causes		2,448,017	100.0	825.9
1	Diseases of heart	(I00–I09,I11,I13,I20–I51)	652,091	26.6	220.0
2	Malignant neoplasms	(C00–C97)	559,312	22.8	188.7
3	Cerebrovascular diseases	(I60–I69)	143,579	5.9	48.4
4	Chronic lower respiratory diseases	(J40–J47)	130,933	5.3	44.2
5	Accidents (unintentional injuries)	(V01–X59, Y85–Y86)	117,809	4.8	39.7
6	Diabetes mellitus	(E10–E14)	75,119	3.1	25.3
7	Alzheimer's disease	(G30)	71,599	2.9	24.2
8	Influenza and pneumonia	(J10–J18)	63,001	2.6	21.3
9	Nephritis, nephrotic syndrome and nephrosis	(N00–N07,N17–N19,N25–N27)	43,901	1.8	14.8
10	Septicemia	(A40–A41)	34,136	1.4	11.5
11	Intentional self-harm (suicide)	(*U03, X60–X84, Y87.0)	32,637	1.3	11.0
12	Chronic liver disease and cirrhosis	(K70, K73–K74)	27,530	1.1	9.3
13	Essential (primary) hypertension and hypertensive renal disease	(I10,I12)	24,902	1.0	8.4
14	Parkinson's disease	(G20–G21)	19,544	0.8	6.6
15	Assault (homicide)	(*U01–*U02, X85–Y09, Y87.1)	18,124	0.7	6.1
...	All other causes (residual)		433,800	17.7	146.4

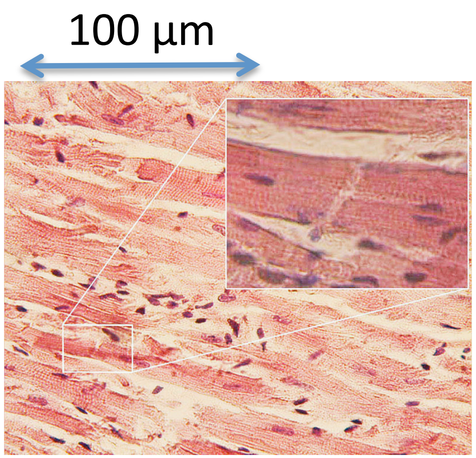
Cardiac diseases are among the leading causes of death and
we should understand better all the mechanisms associated with them.

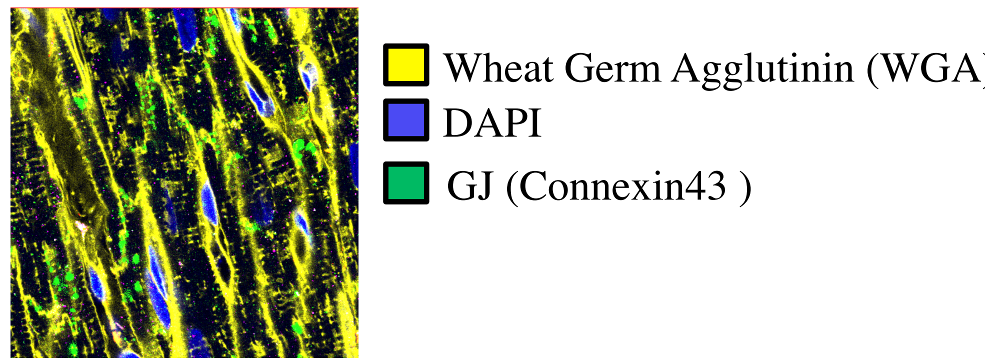
Normal electric activity may be disrupted by failures in the propagation of the action potentials



(Keener y Panfilov (1995))

The structure of the cardiac muscle is complex and influences its electrical behavior and dynamics

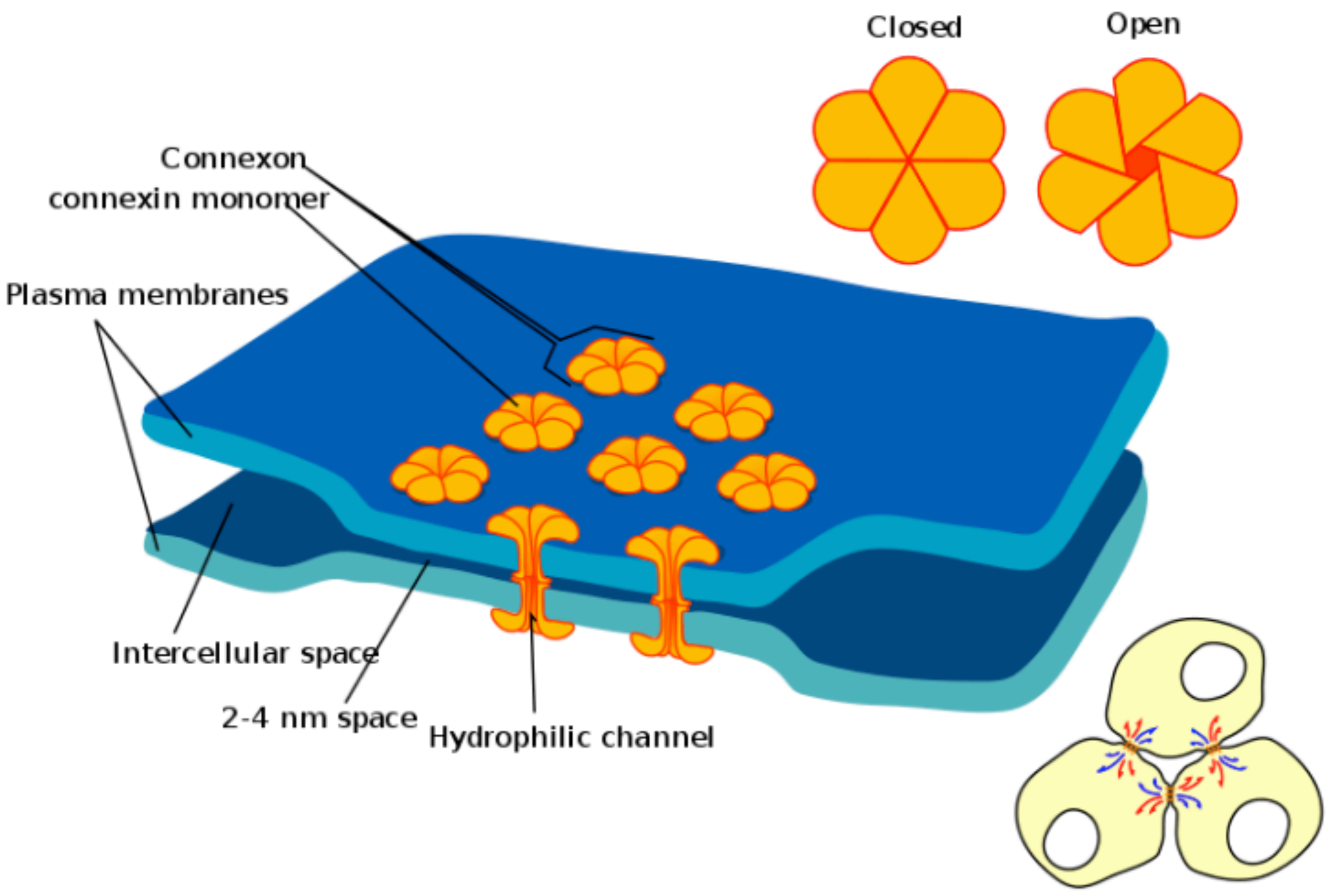




The cardiac muscle is formed with cardiomyocytes, gap junctions (GJ), collagen fibres, fibroblasts, blood vessels,…

Sources : Wikipedia; Sachse's lab.

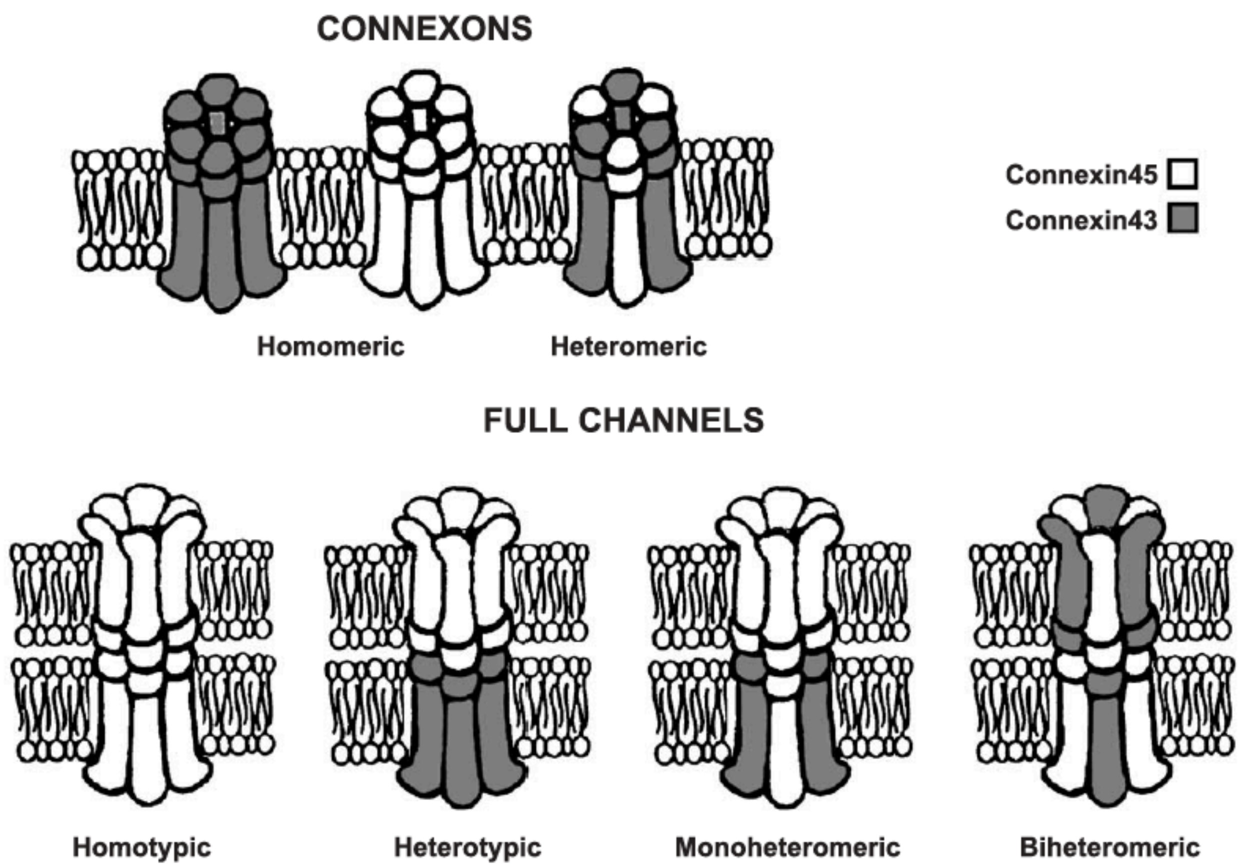
Gap junctions (GJ) are essential for the propagation of the electrical impulse AP from one myocyte to the next.



GJs form low resistance passages between cardiomyocytes.

Source : Wikipedia

Different types of gap junctions (GJ) have been identified in the cardiac muscle

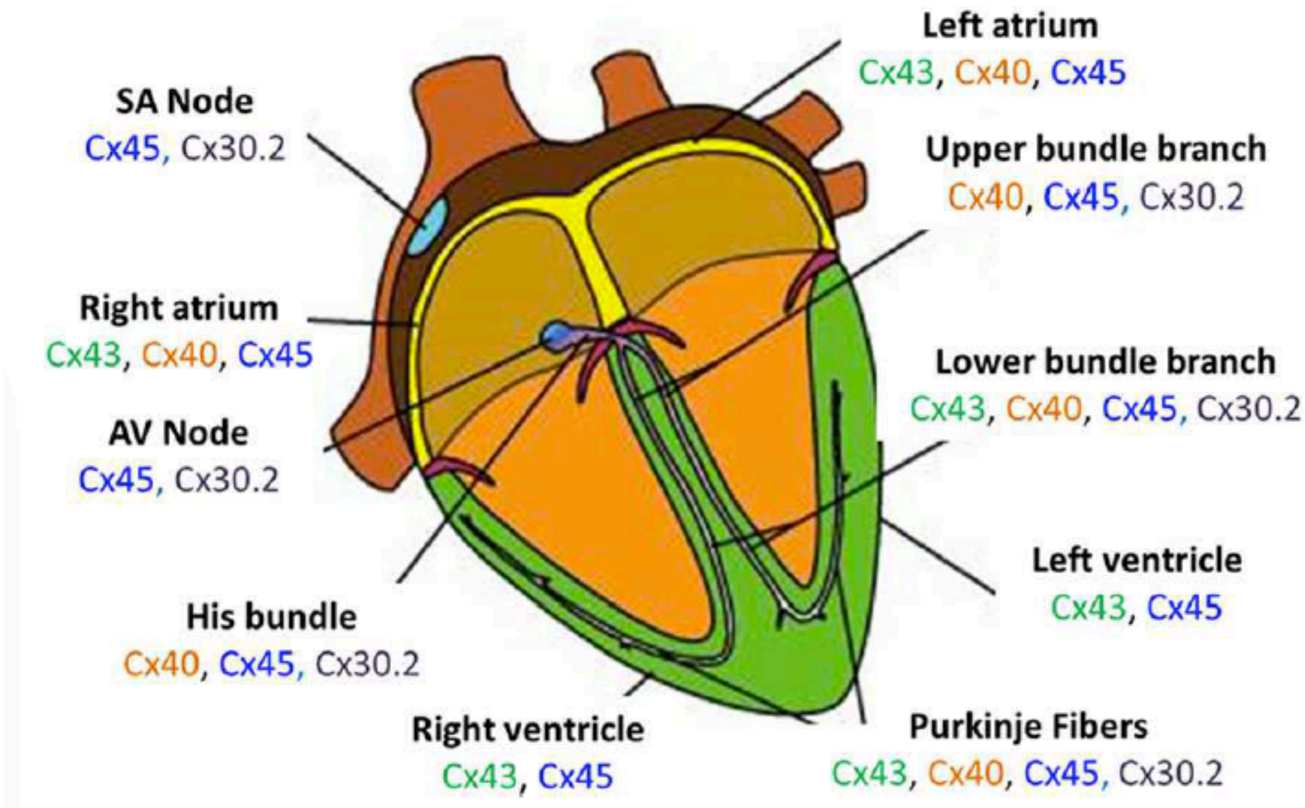


In cardiac tissue of mammalian, connexins type Cx40, Cx43 and Cx45 are the most common.

The permeability of the GJ depends on its structure.

Source : AP Moreno, Cardiovasc. Res. **62** , 2004

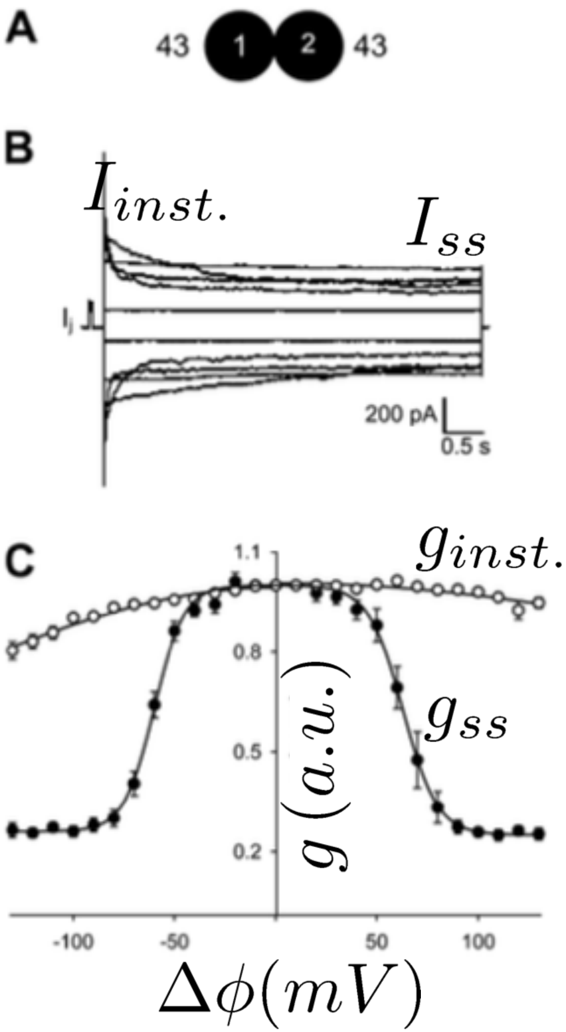
Different types of gap junctions (GJ) have been identified in the cardiac muscle (II)



The connexin's expression pattern varies in different location of the heart

Source : T. Desplantez et al., BMC Cell Biol. **18** , 2017

Dual voltage-clamp method and whole-cell recording allow to measure the electrical properties of the GJ



a) Fix the membrane potential of both cells

$$\Delta\phi = V_2 - V_1$$ transjunctional voltage

b) Measure the current between cells

$$I_{inst.} \qquad I_{ss}$$

c) Calculate the normalized conductances

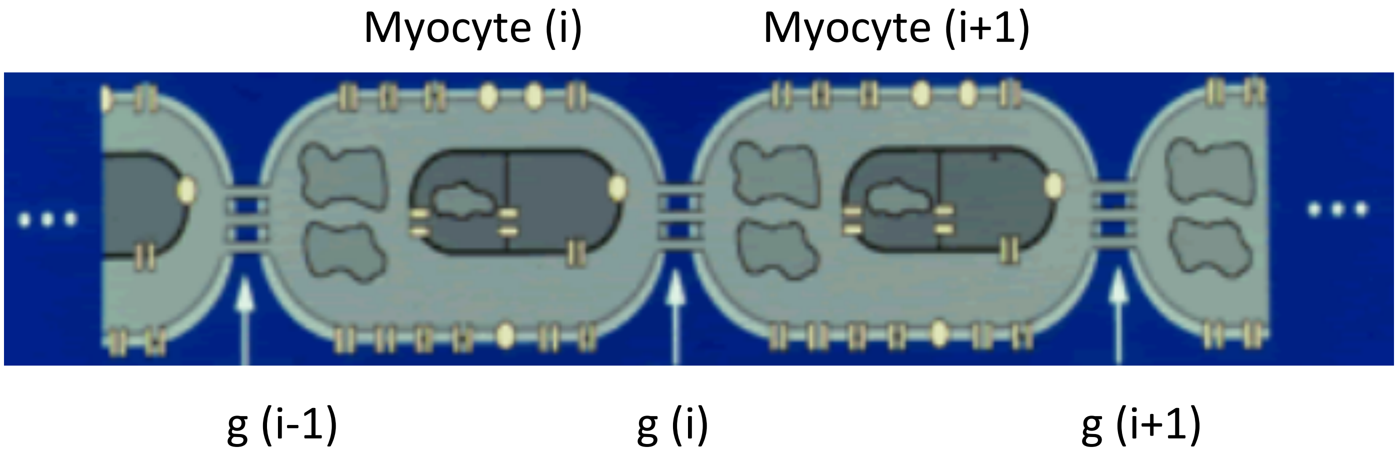
$$g_{inst.} = I_{inst.}/\Delta\phi \quad \sim 100\,pS$$

$$g_{ss} = I_{ss}/\Delta\phi$$

The conductance between the two cells is a dynamical variable

Source : T. Desplantez et al., Eur. J. Physiol. **448** , 2004

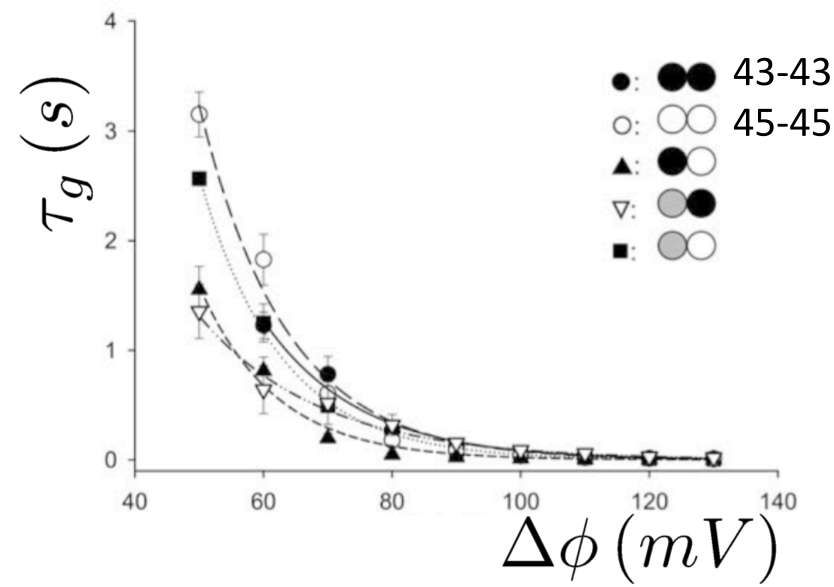
Mathematical model of a strand of cardiac tissue



1) Connexin's dynamics

$$\frac{dg_i}{dt} = \frac{g_{ss}(\Delta\phi_i) - g_i}{\tau_g(\Delta\phi_i)}$$

$$\Delta\phi_i = V_{i+1} - V_i$$

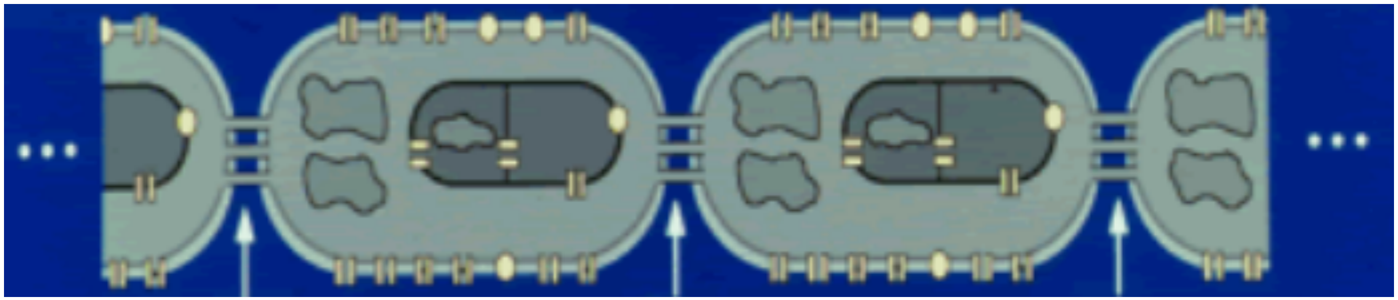


The time constant τ_g is highly dependent of the connexin's transjunctional voltage

Source : T. Desplantez et al., Eur. J. Physiol. **448** , 2004

Mathematical model of a strand of cardiac tissue (ii)

Myocyte (i) Myocyte (i+1)



g (i-1) g (i) g (i+1)

2) Myocyte's transmembrane dynamics

$$\frac{\partial V}{\partial t} + \frac{I_{myo} + I_{ext}}{\mathcal{C}} = \nabla \cdot (D \nabla V)$$

$$\frac{\partial \mathbf{s}}{\partial t} = f(V, \mathbf{s})$$

5 variables model (BCN)

Monodomain approximation

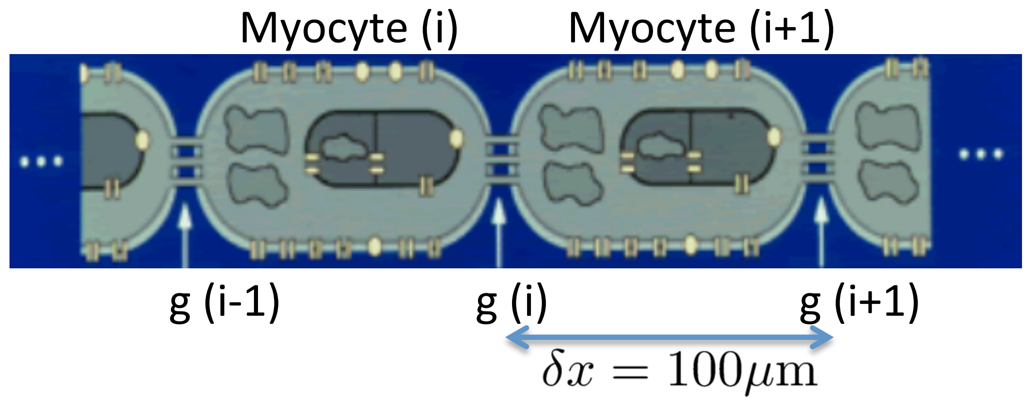
$$D(x,t) = \bar{D}\, g(x,t)$$

$$\bar{D} = 1.5\,\mathrm{cm}^2/\mathrm{s}$$

- The gap junctions are the primary sites of membrane potential changes
- The entire myocyte cytoplasm becomes effectively iso-potential.

Sources : Y. Rudy, Circ. Res. 1997; Cantalapiedra et al. PRE **82** 2010.

Numerical method



$$V_i^{(n+1)} = V_i^{(n)} + \bar{D}\frac{\delta t}{\delta x^2}\left\{g_i^{(n)}\left[V_{i+1}^{(n)} - V_i^{(n)}\right] - g_{i-1}^{(n)}\left[V_i^{(n)} - V_{i-1}^{(n)}\right]\right\} - \delta t\,\frac{I_{myo}^{(n)} + I_{ext}^{(n)}}{\mathcal{C}}$$

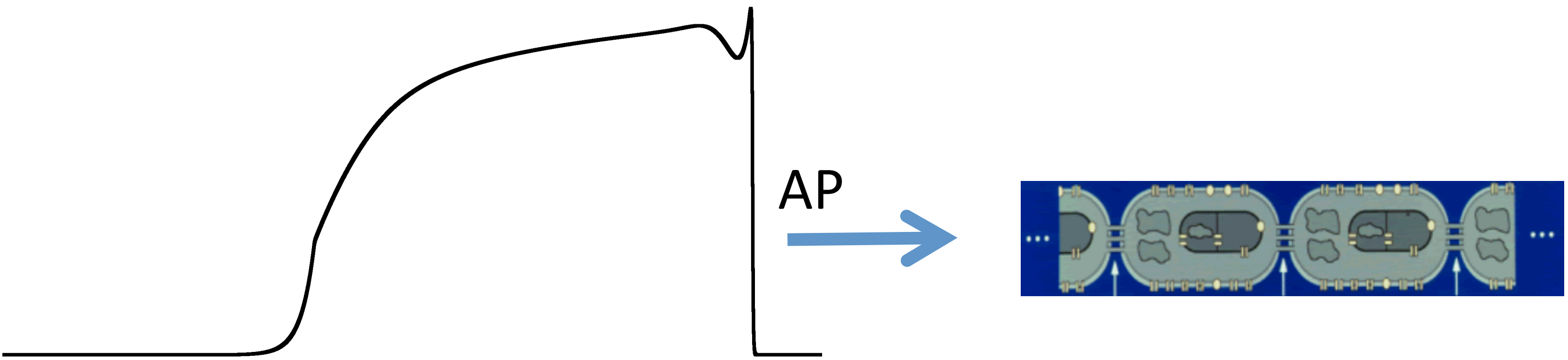
$\delta t = 10\mu\text{s}$ Integration time step

$$g_i^{(n+1)} = g_i^{(n)} + \delta t\,\frac{g_{ss}(\Delta\phi_i^{(n)}) - g_i^{(n)}}{\tau_g(\Delta\phi_i^{(n)})}$$

Super-index (n) refers to time step n. Subscript i refers to position i in the chain.

Source : Keener 1991

Stimulation protocol (L=400 cells)

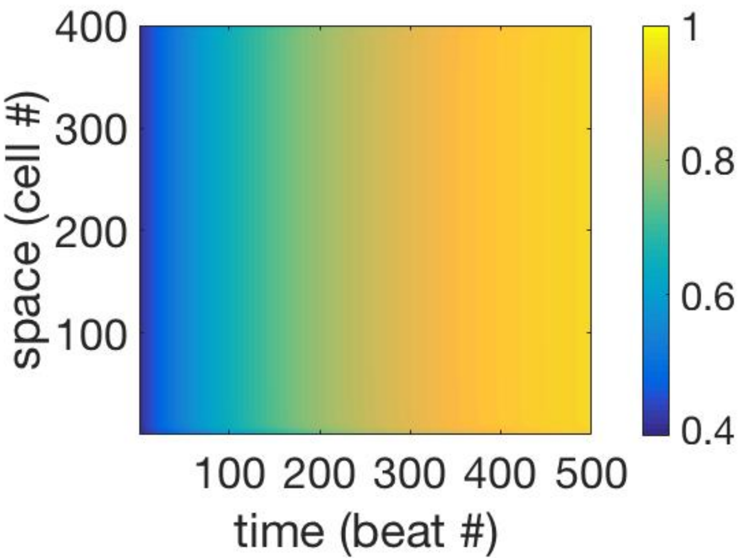


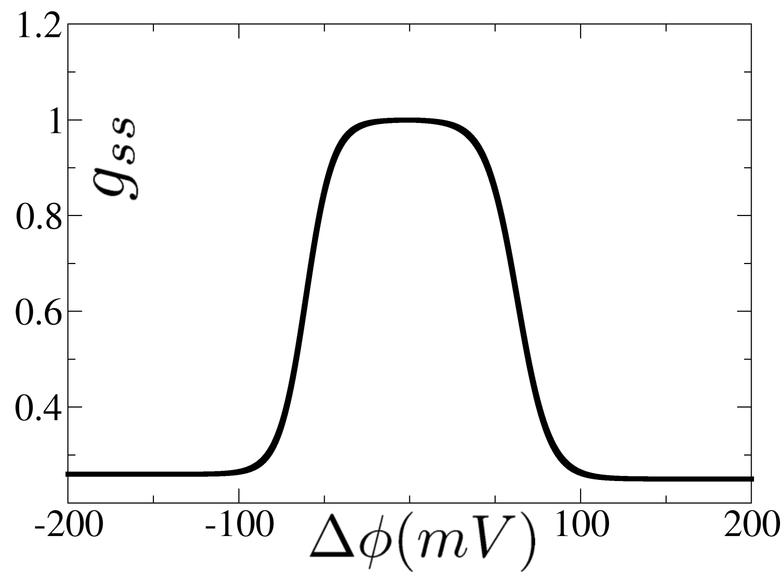
i = 1 … 400

1. Same initial values are set to all the GJ conductances ($g_i = g_{ini}$)
2. We excite the first 7 cells (i=1..7) to elicit an AP that propagates through the fiber
3. We repeat the stimulation with a period of T = 480 ms
4. We measure the time evolution of the GJ conductances after each stimulation

Source : Hawks et al. **IJBC** 2019

Results for the normal case (healthy)





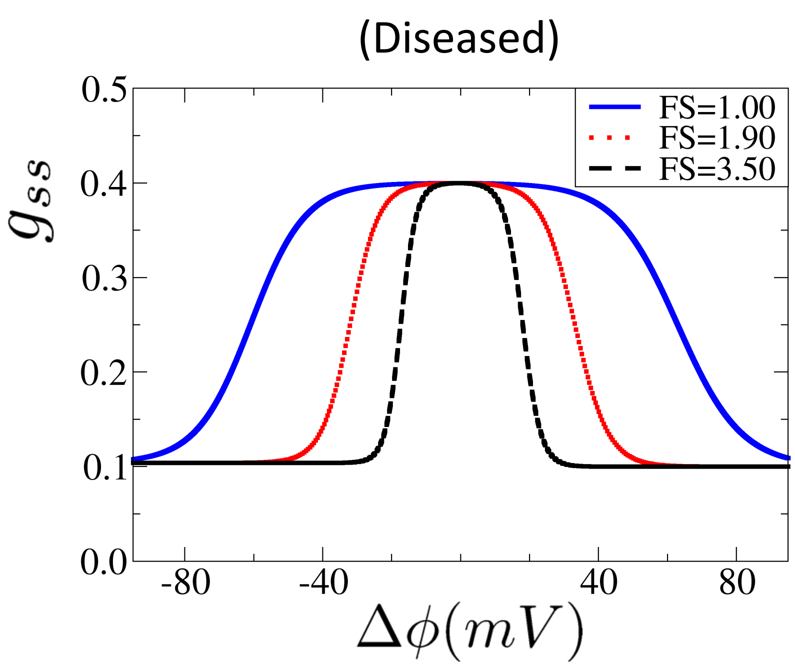
Here we set $g_{ini} = 0.4$

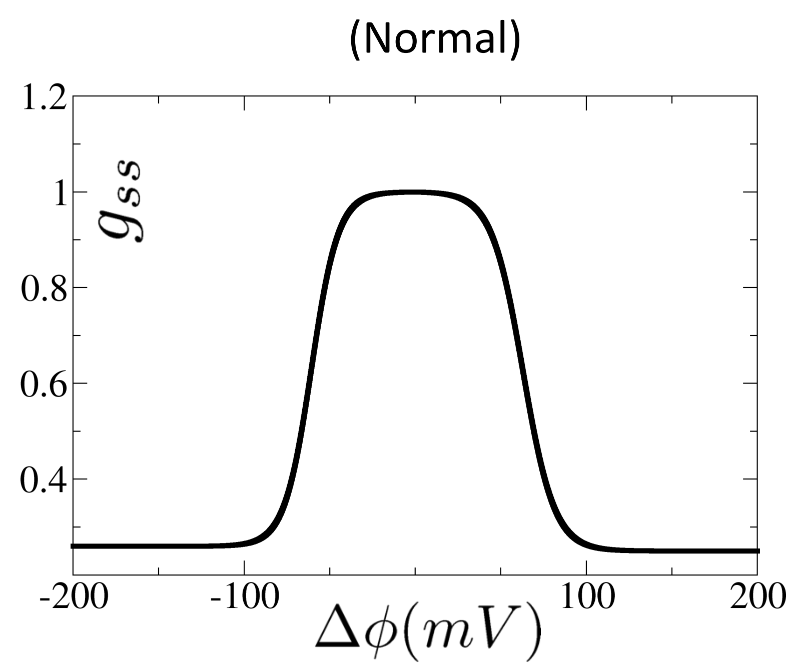
The conductances of all the GJ are returning to the max value $g \sim 1$

Nothing fancy happens !

Source : Hawks et al. **IJBC** 2019

Modification of the GJ dynamics (diseased case)





In order to model a diseased tissue we modify the characteristics of the GJ

- We reduce the overall conductance to 40% of the normal values (ischemia)
- We introduce the 'shrinking factor' FS that alters the width of the plateau

Source : Hawks et al. **IJBC** 2019

Results of the GJ bistability induced by varying FS

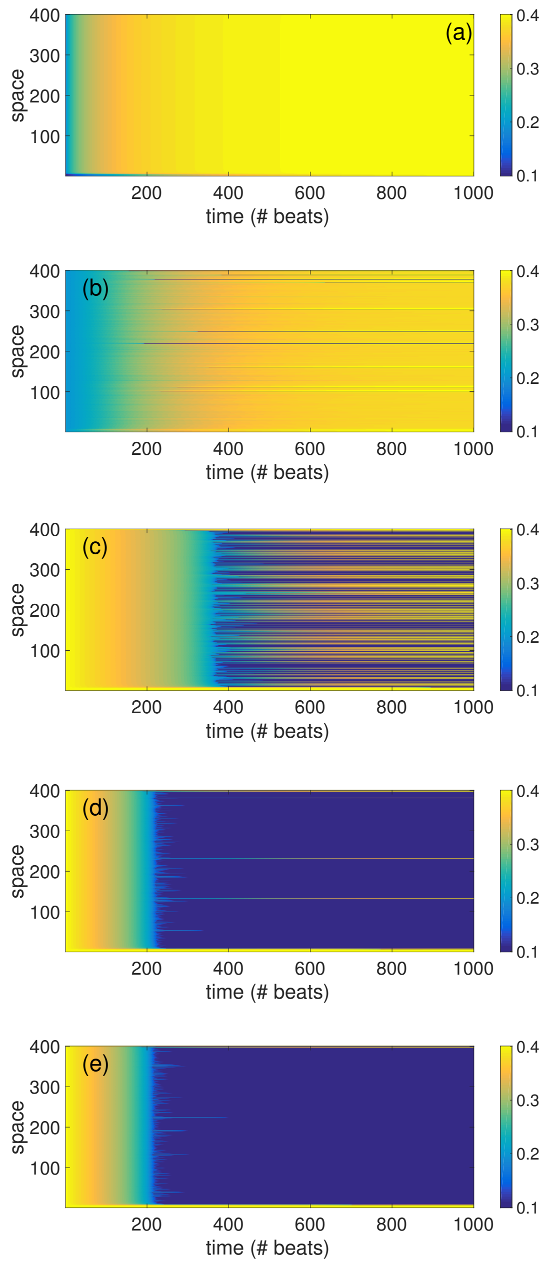
FS=1

FS=1.44

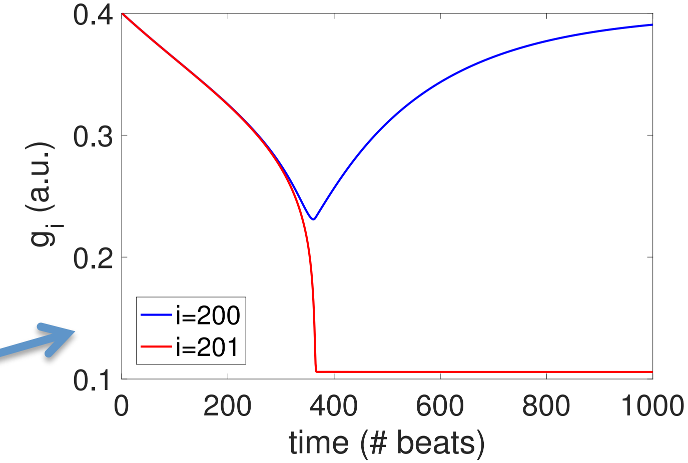
FS=1.9

FS=3.5

FS=20



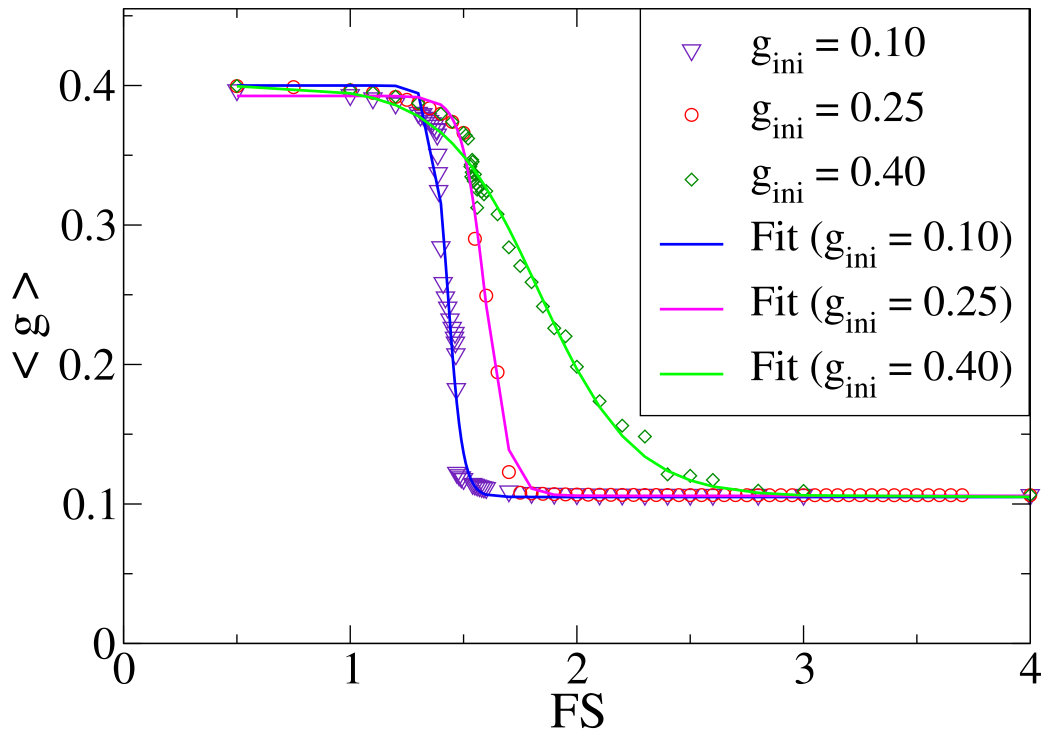
FS=1.9



We observe a transition by increasing FS from GJ conductance close to 0.4 (upper state) to GJ conductance close to 0.1 (lower state). For intermediate values of FS, we observe a spatially mixed state.

Source : Hawks et al. **IJBC** 2019

Study of the transition from UP to LOW GJ conductances



We have studied the influence of both FS and g_{ini}

for characterizing the transition between upper and lower states of conductance

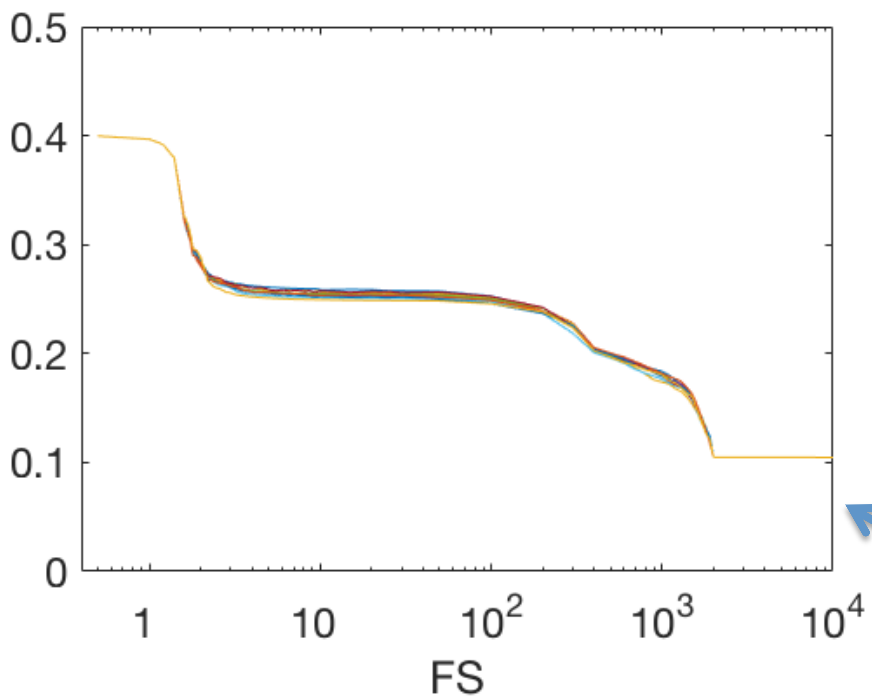
The spatial average of the conductance $< g >$

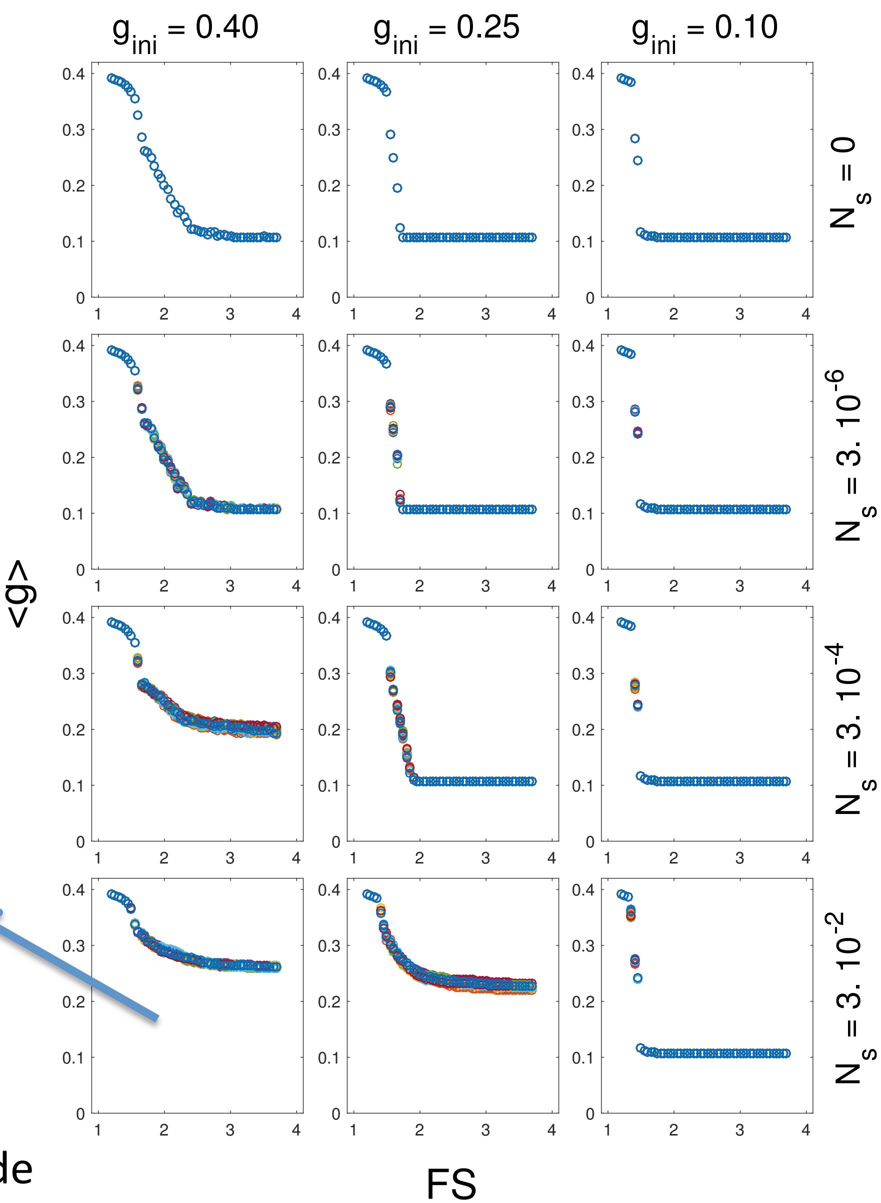
is used as an order parameter to characterize this transition

Hysteresis is observed when varying the initial values of the conductance

Influence of g_{ini} and added noise on the transition

We have studied the influence of an initial added noise $g_i^{(0)} = g_{ini} + N_s\,\sigma_u$ to the transition.





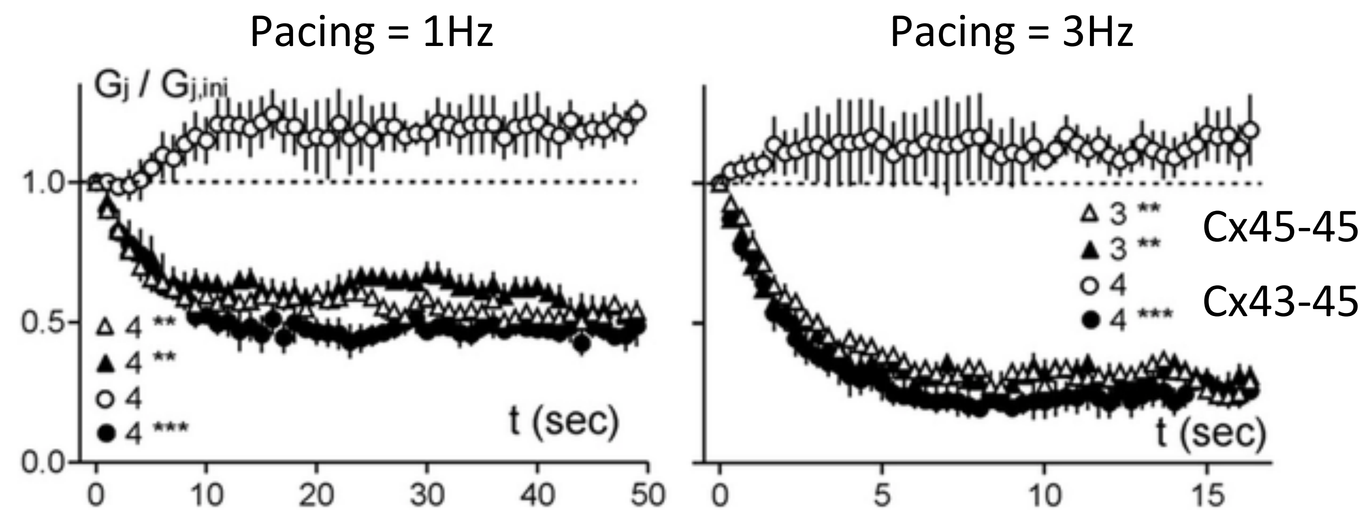
Persistent mixed state over 3 orders of magnitude

Related experimental study showing bistability for GJ

Junctional delay, frequency, and direction-dependent uncoupling of human heterotypic Cx45/Cx43 gap junction channels

Willy G. Ye [a,1], Benny Yue [a,1], Hiroshi Aoyama [b], Nicholas K. Kim [a], John A. Cameron [a], Honghong Chen [a], Donglin Bai [a,*]

$\Delta t = 10\text{ms}$



By varying the junctional delay Δt and the pacing frequency, they observe a different dynamics for the GJ conductances.

It also highly depends on the GJ composition

Source : W.G. Ye et al., JMCC. **111** , 2017

Conclusions

- We have studied the conductance dynamics of the GJ in a 1D model
- In some simulated diseased situations we observe bistability in the values of the GJ conductances.
- The high to low level of conductance is mediated by parameter FS
- In the intermediate mixed state we observe a highly alternating spatial distribution of the GJ conductances
- Future Plan: Connect our findings to electrophysiology experiments

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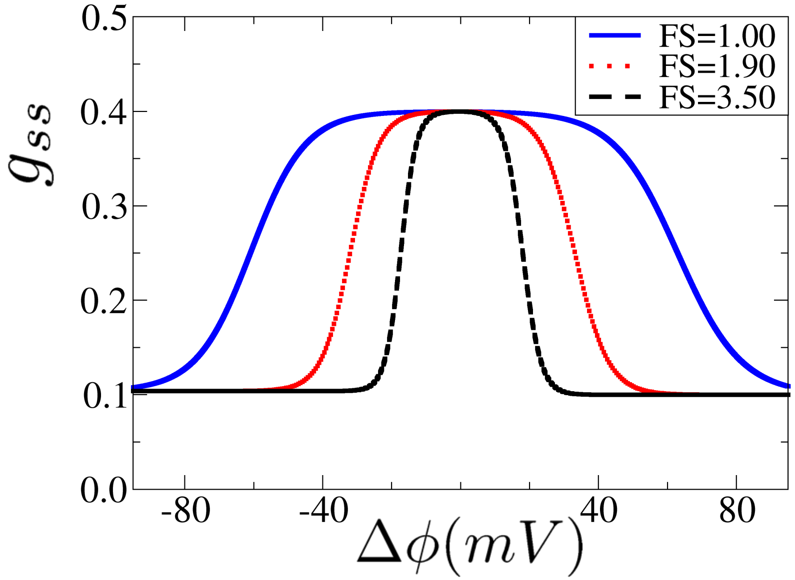
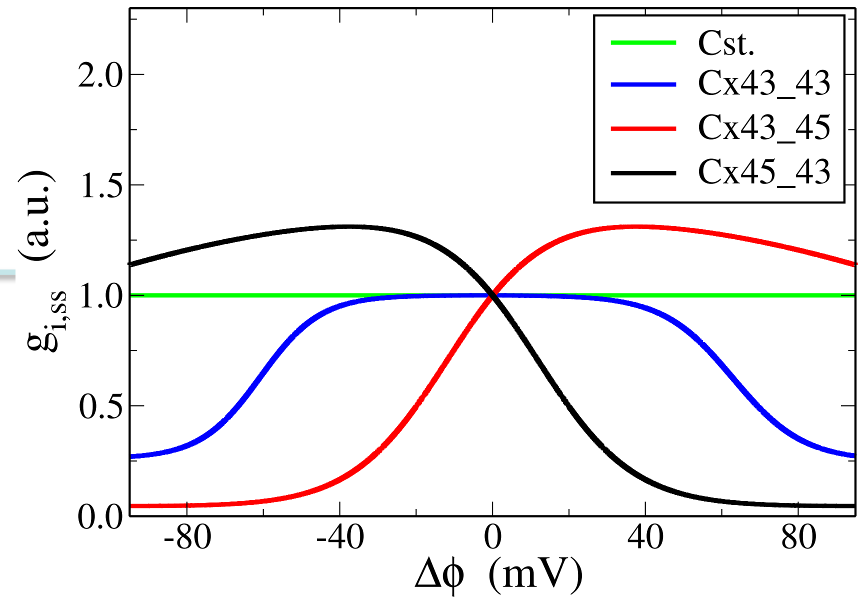
Thank you !

Justification of the FS factor

(Diseased)



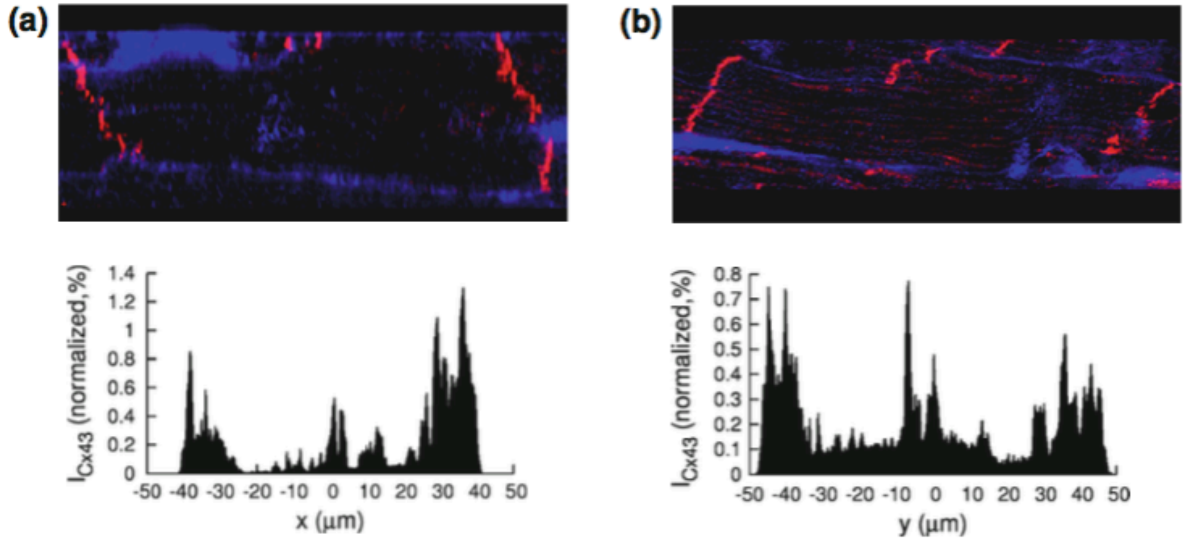


Heterotypic GJs have asymmetrical g_{ss} functions.

A blend of several type of GJ types may justify the FS parameter

Source : Hawks et al. **IJBC** 2019

Justification of the introduction of noise (Ns)



Spatial heterogeneities and different geometric orientation

lead to variability in the GJ conductance

This may justify the noise factor

Source : DP Lackey et al. **Ann. BE** 2011