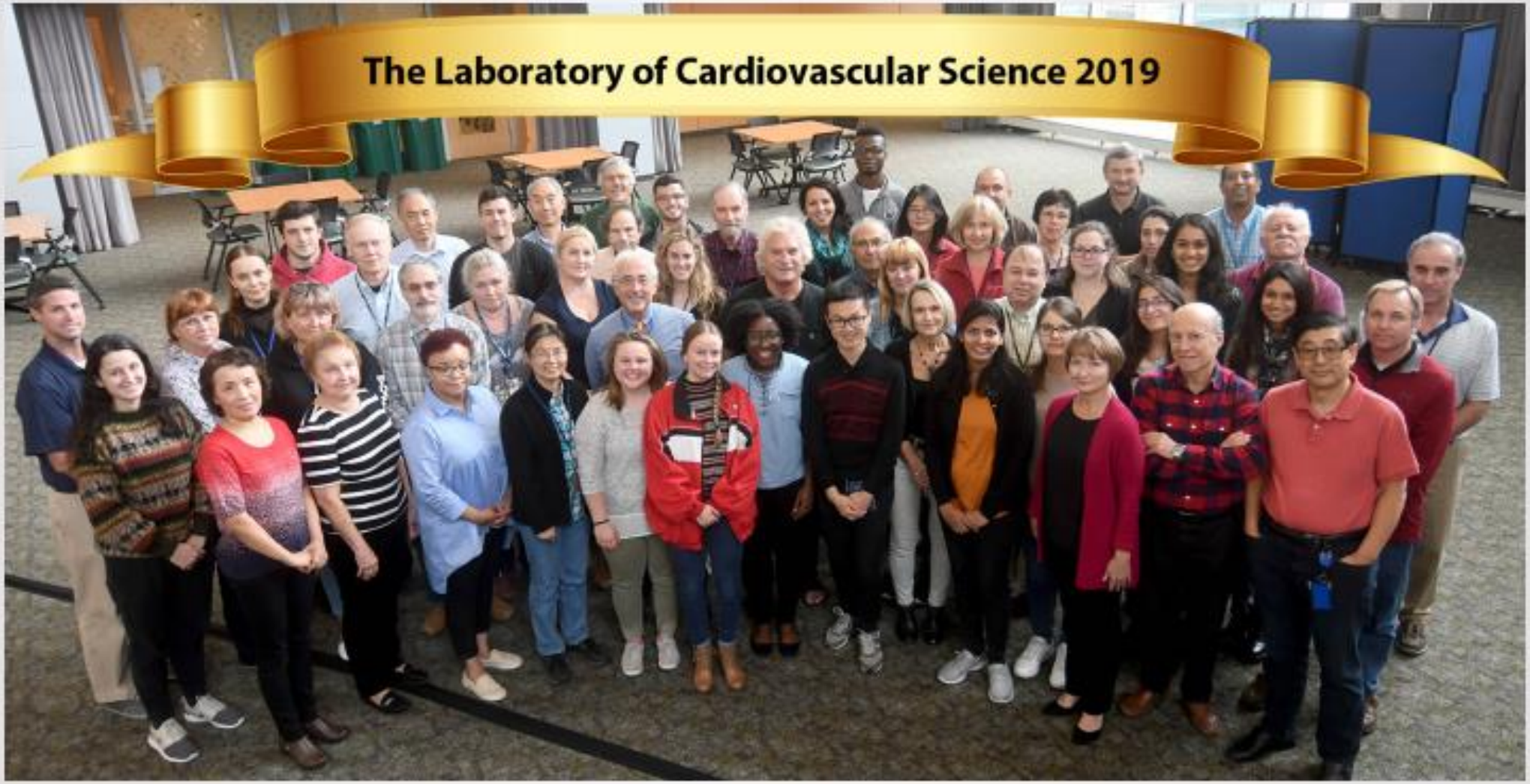

The Laboratory of Cardiovascular Science 2019

"The Heart Sings Off-Key in Advanced Age"

A Laboratory of Cardiovascular Science Noble Presentation

Made in Castalia

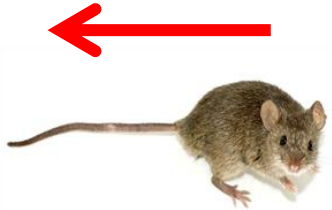
"The Heart Sings Off-Key in Advanced Age"

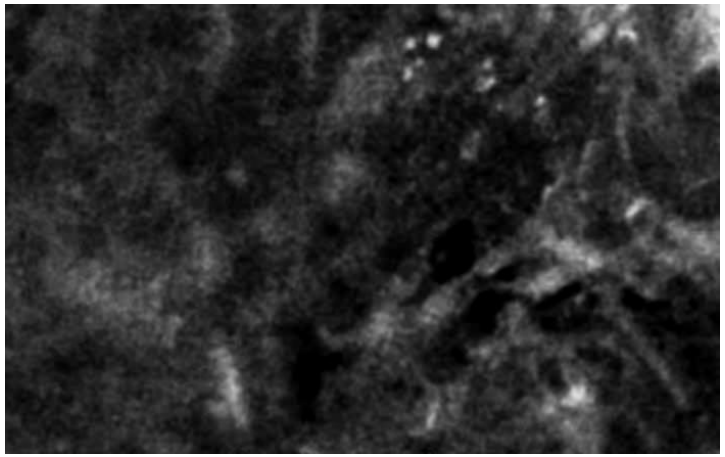
short

A Laboratory of Cardiovascular Science ~~Noble~~ Presentation

Made in Castalia

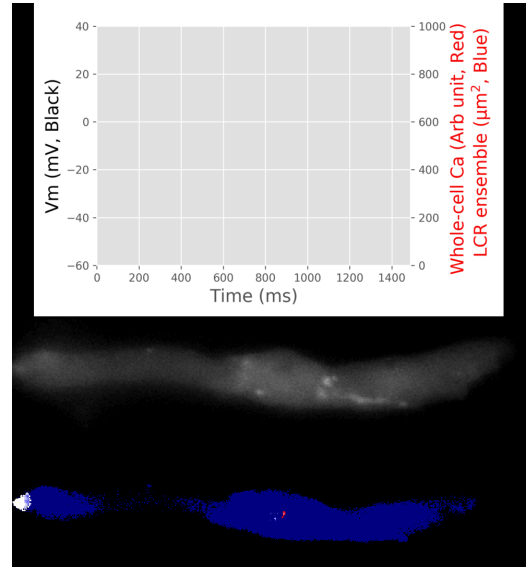
The heartbeat results from multi-scale synchronization processes that self-organize at each scale

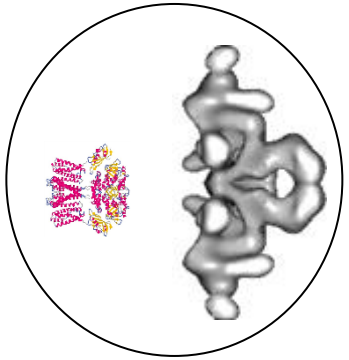




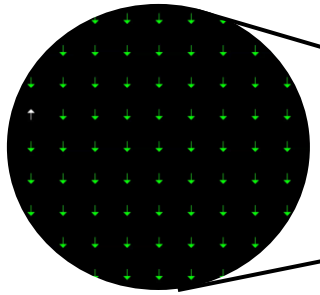
Network of pacemaker cells in the SA node

Single cardiac Pacemaker Cell

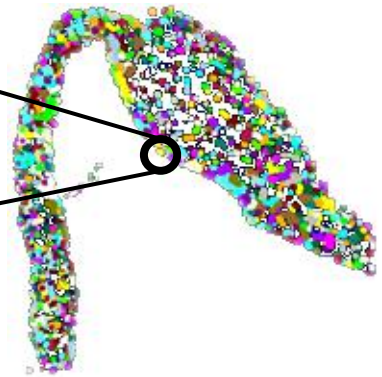




Ion Channels



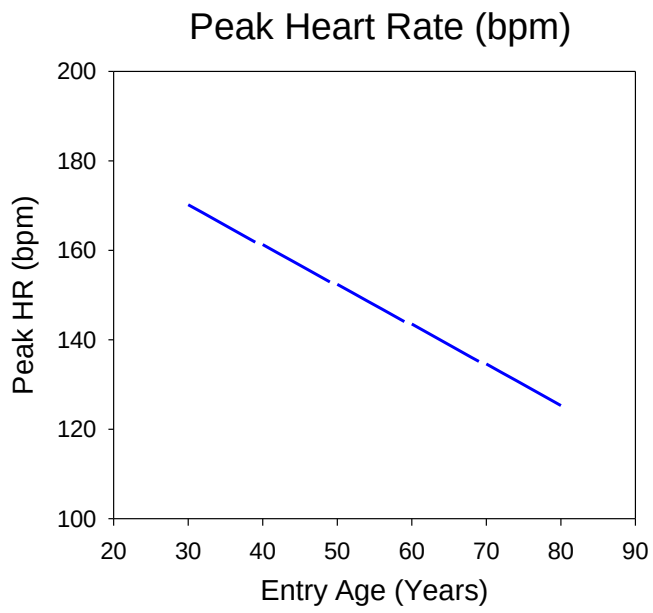
Ion channel clusters

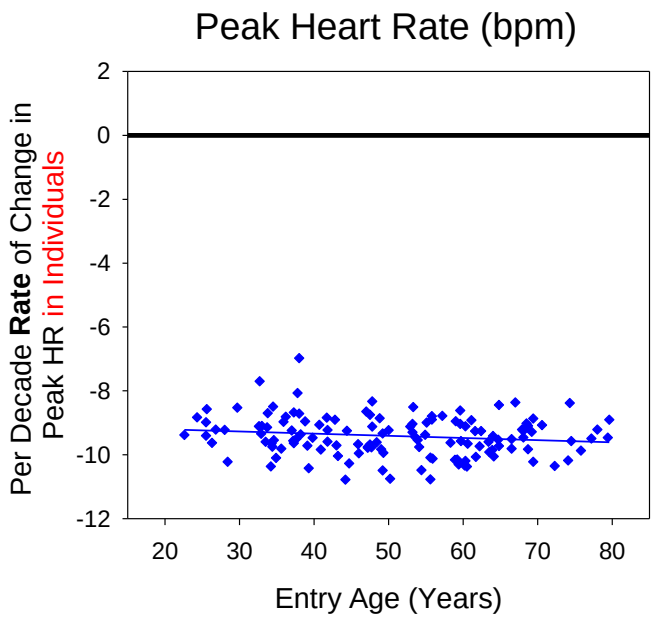


Clusters of ion channel clusters

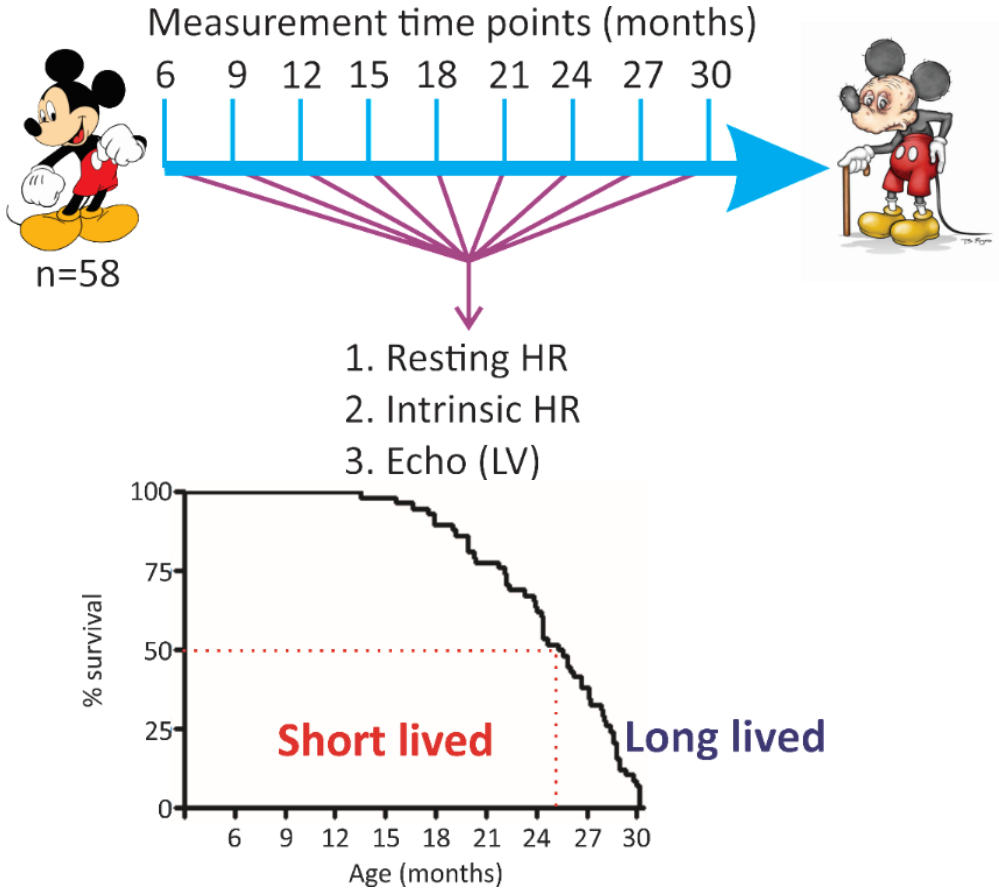
Natural History of Age-Associated Deterioration of Heart Rate Reserve and its Determinants in Apparent Health:

A 30-Year Longitudinal Perspective from the Baltimore Longitudinal Study on Aging.





The BLSA in mice



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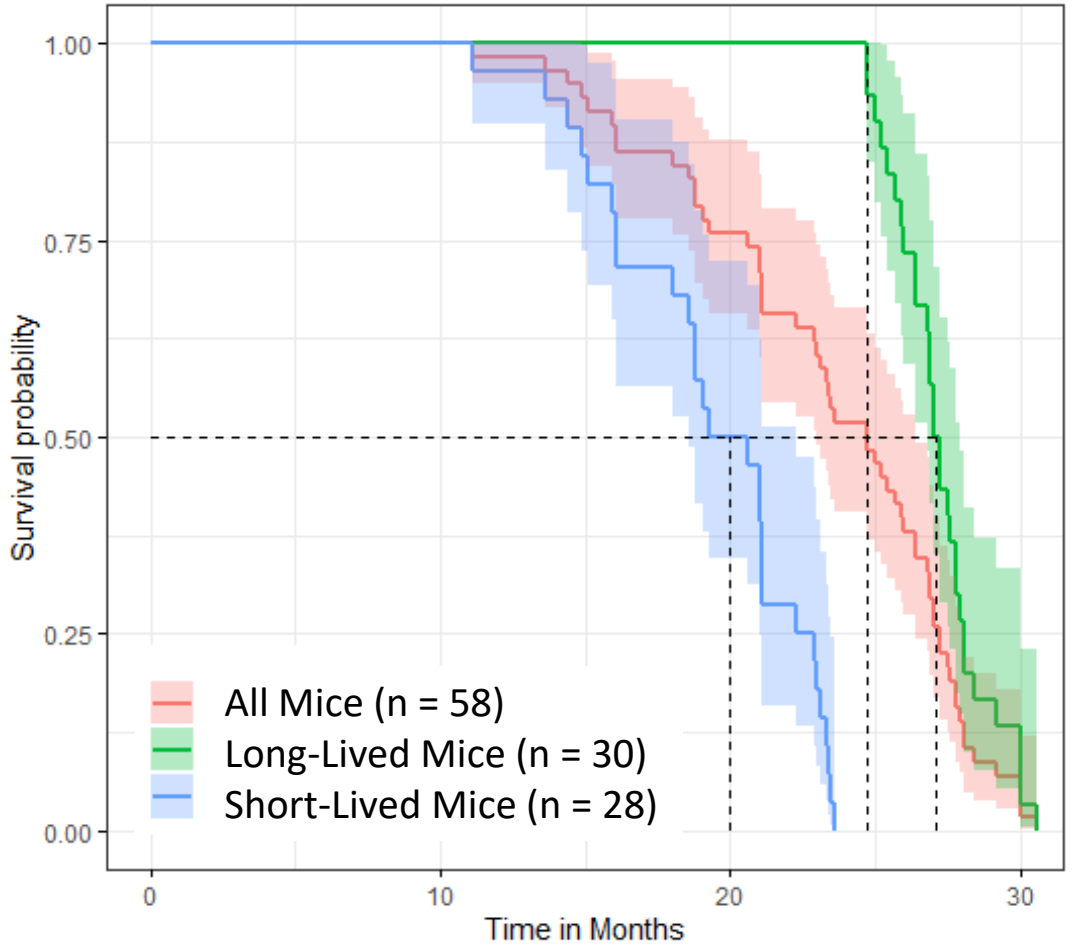
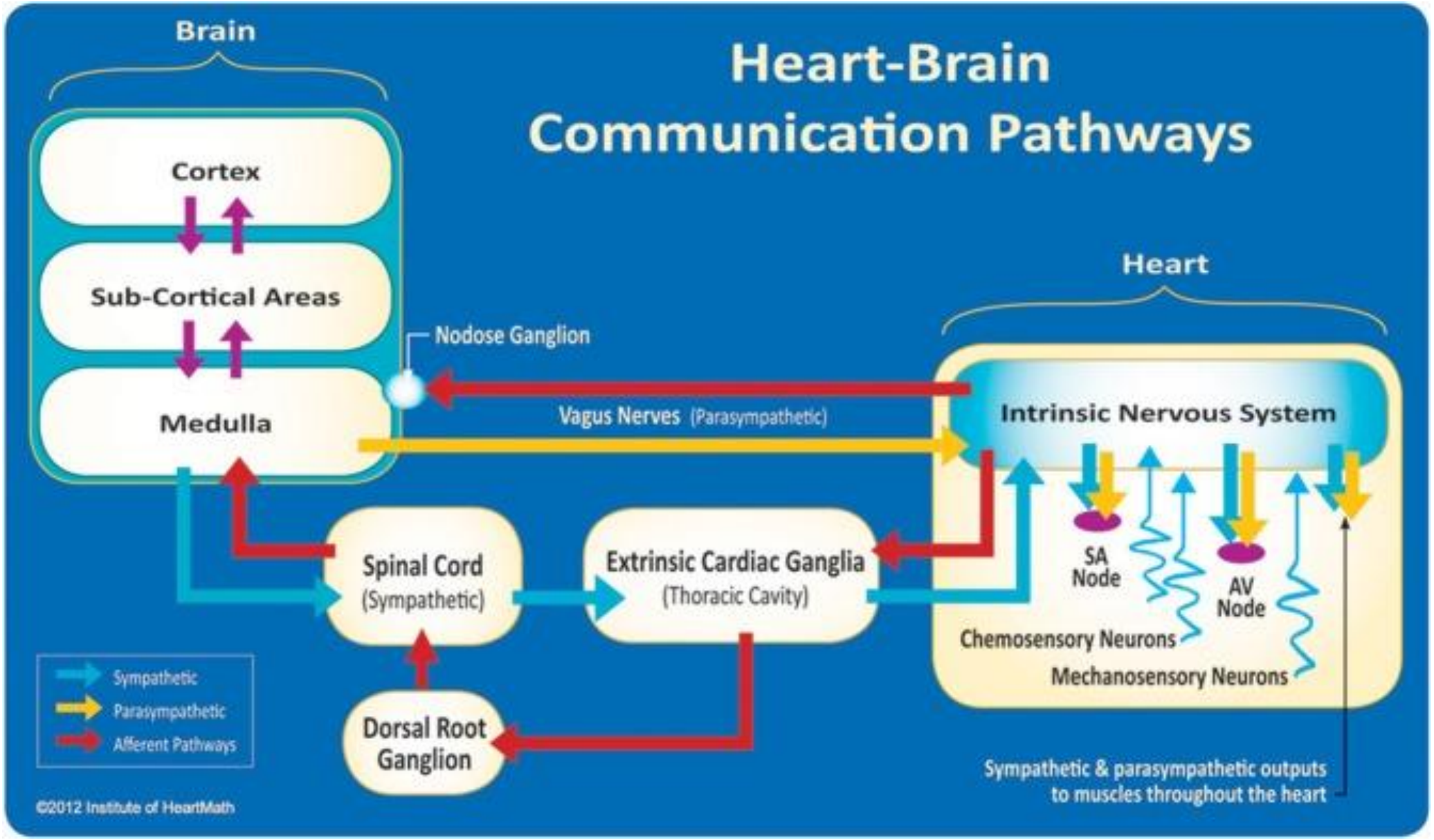
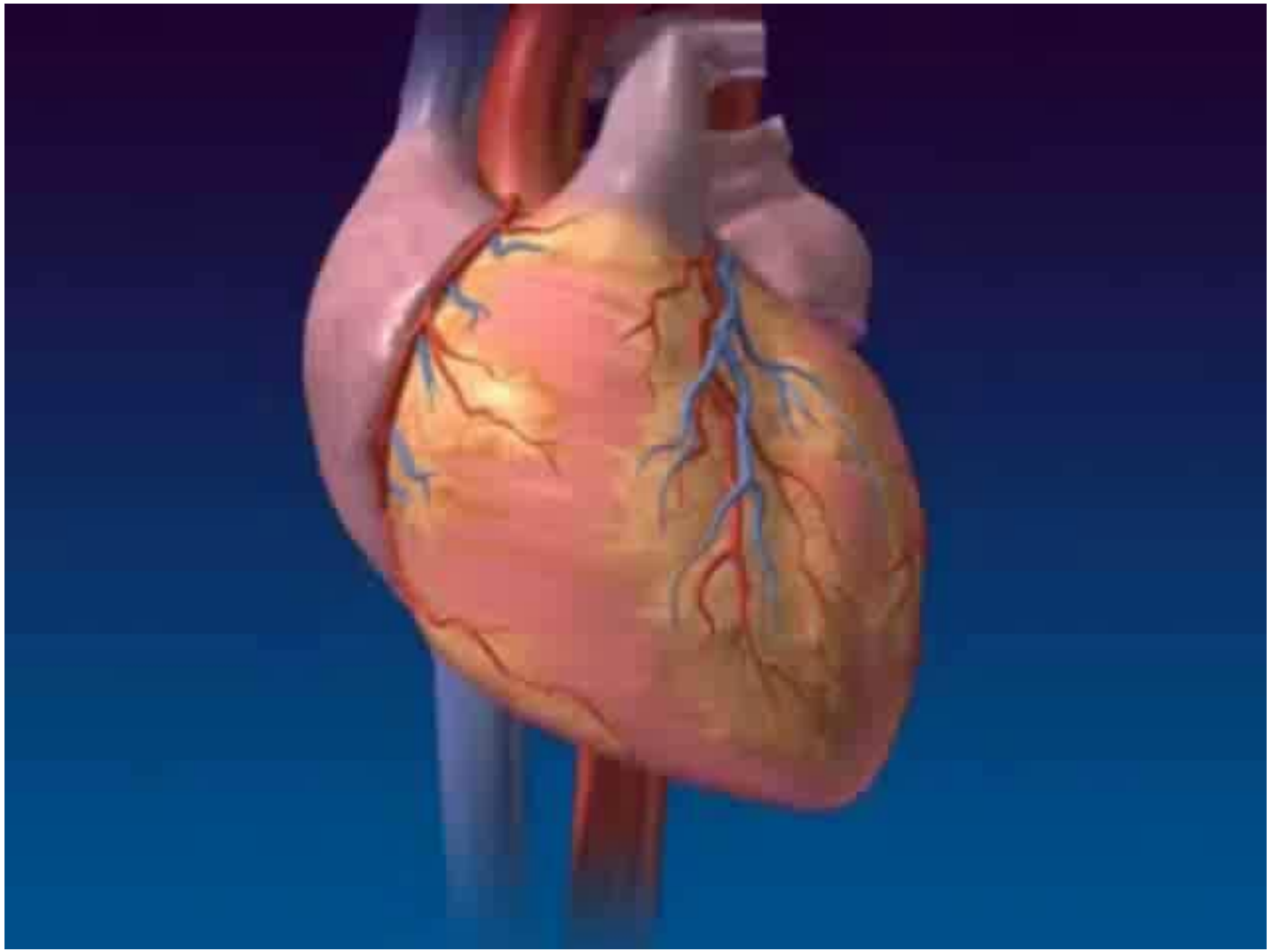


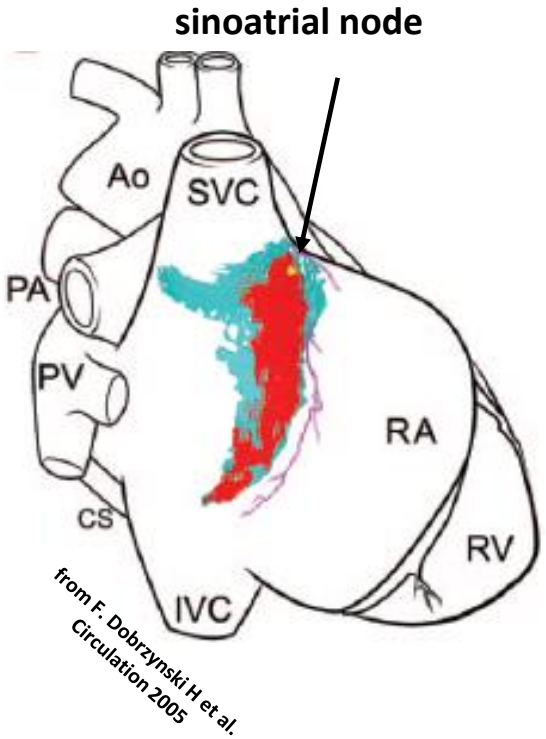


Front Psychol. 2014; 5: 1040

Why can the heart beat outside of the body?

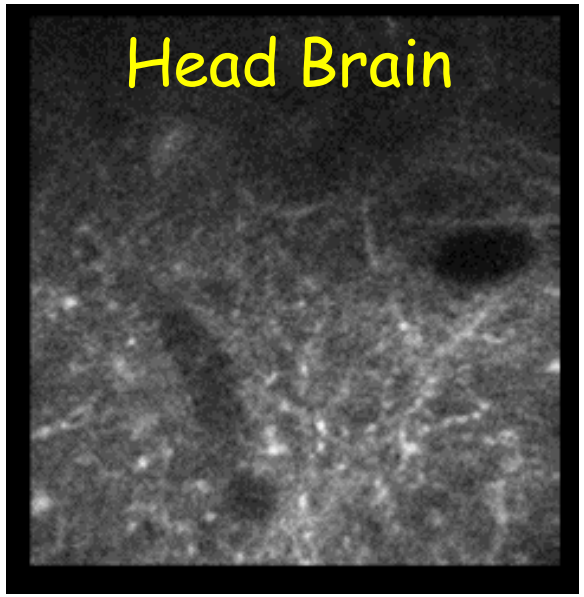


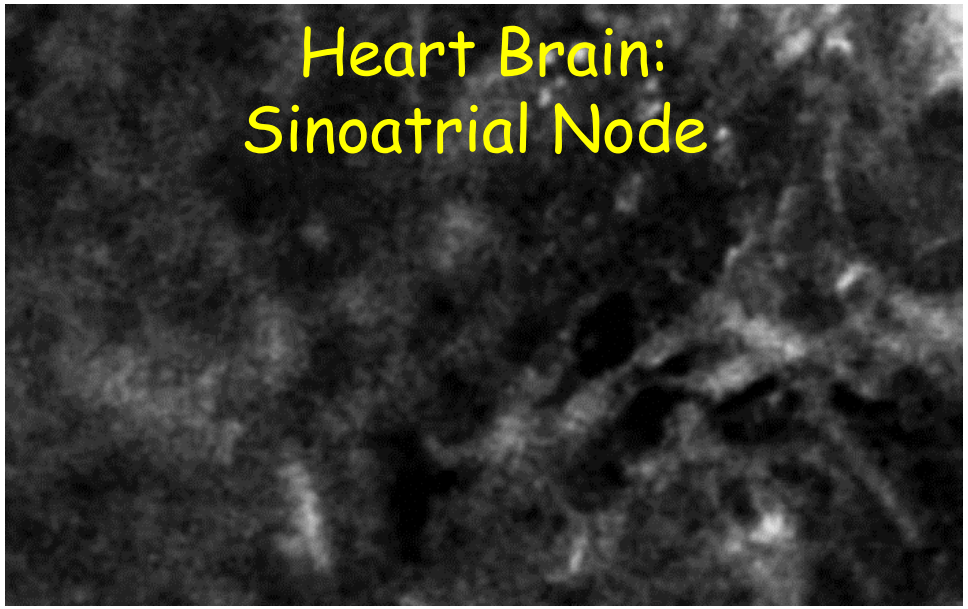
Because it has its own brain in the sinoatrial node

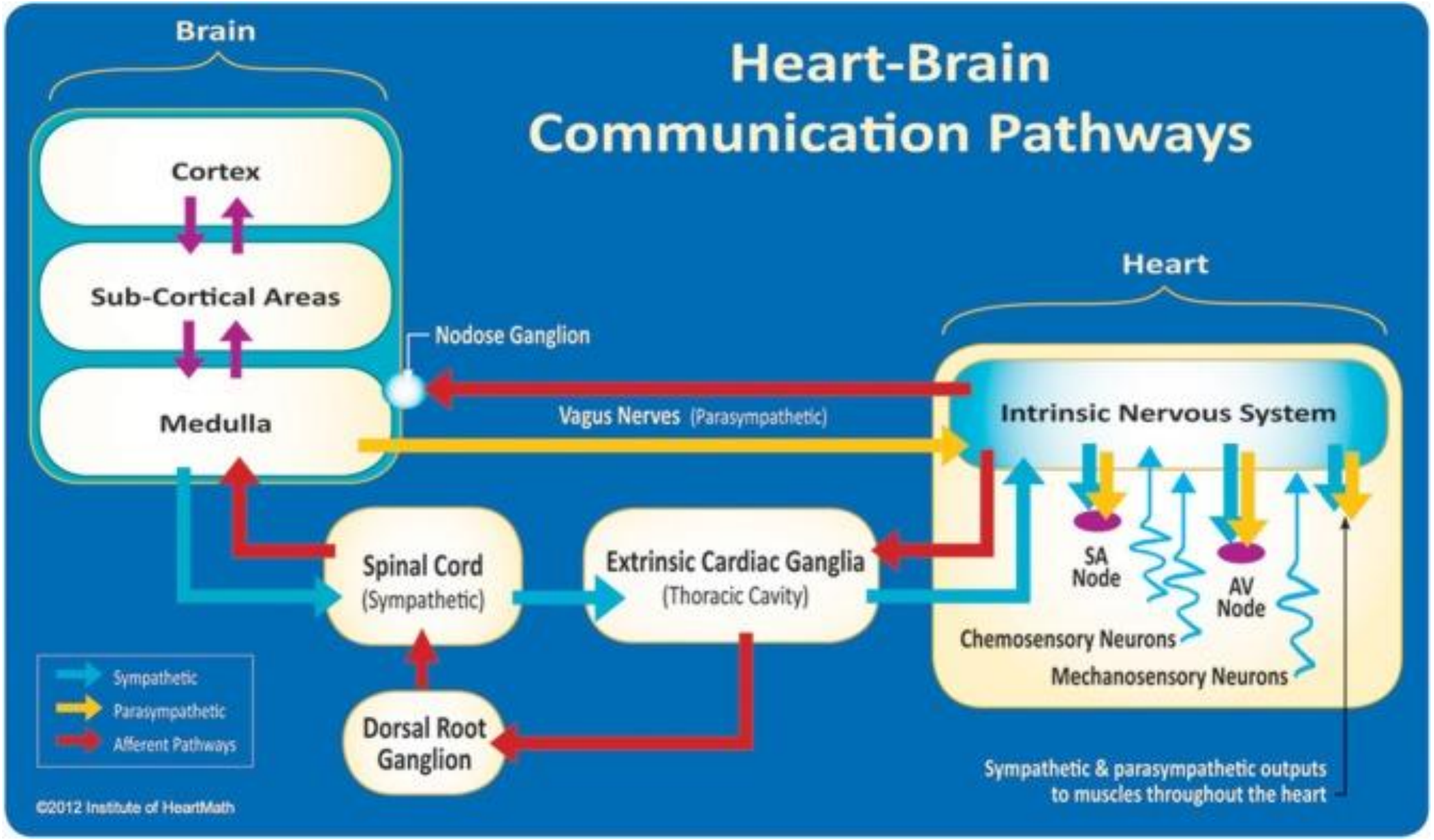


from F. Dobrzynski H et al. Circulation 2005

WHICH IS THE MOUSE HEAD BRAIN AND WHICH IS THE HEART BRAIN?







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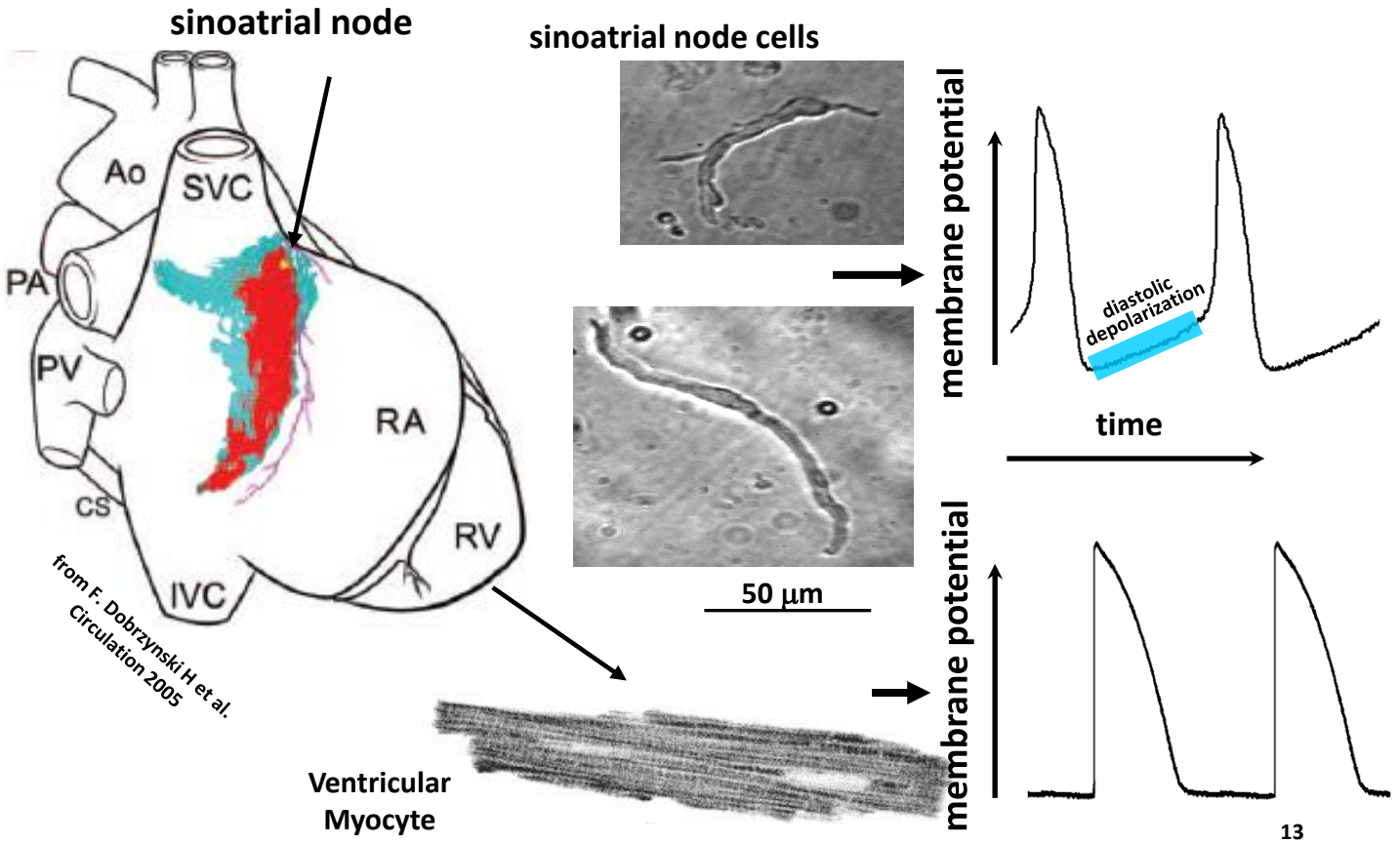
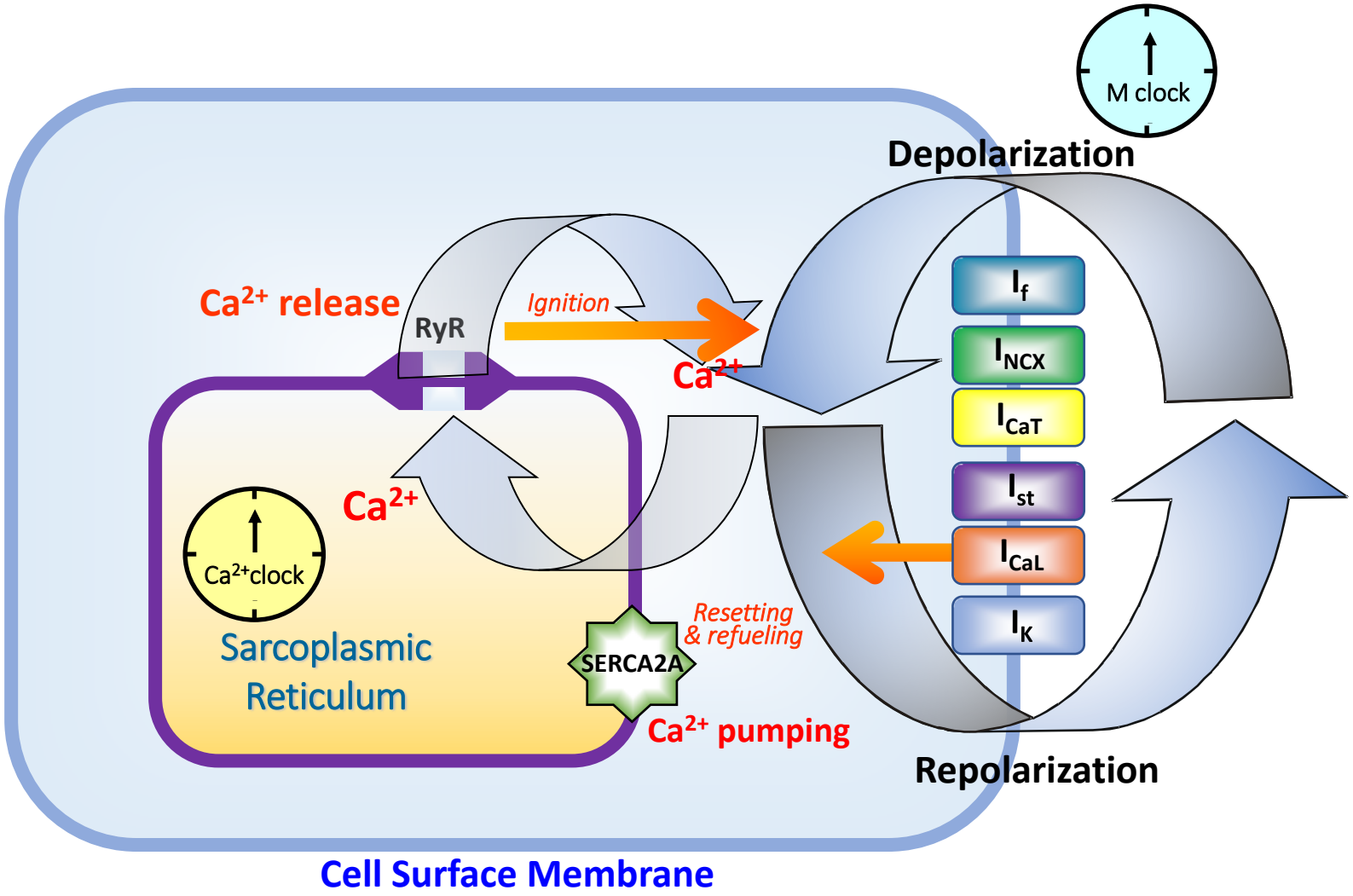
Cells that Control the Rate and Strength of the Heart Beat



A Coupled-System of Chemical and Current Oscillators



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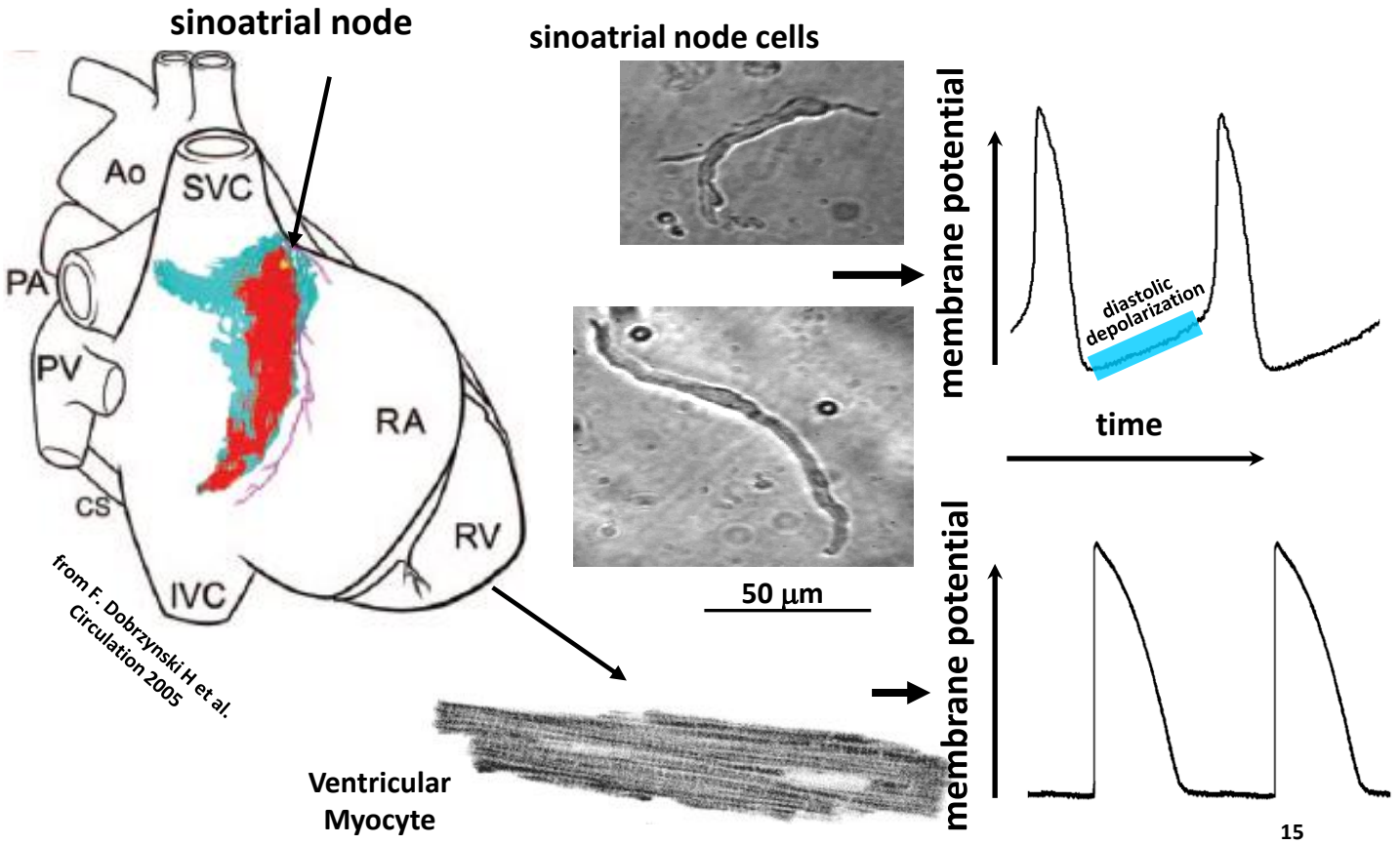
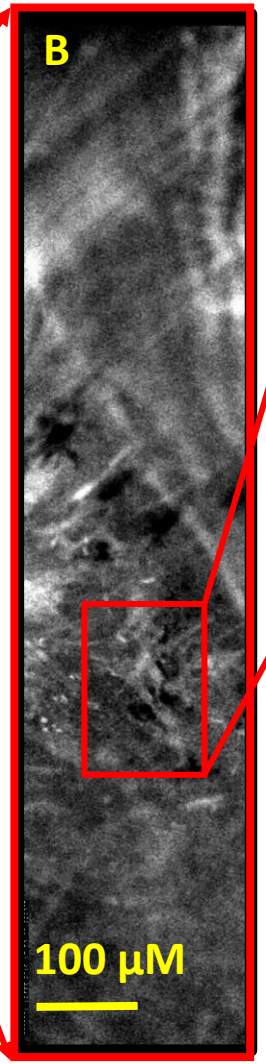
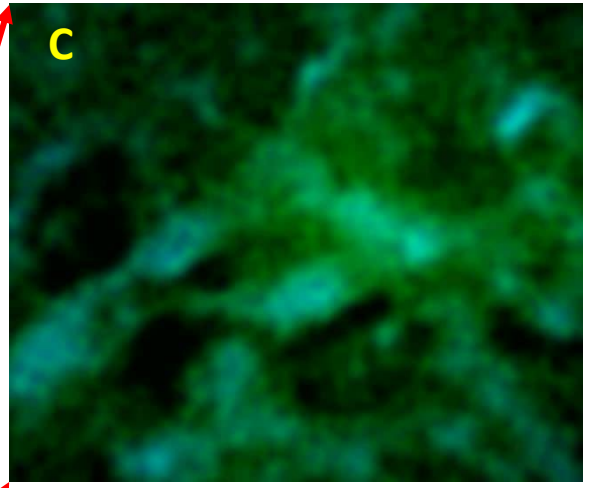
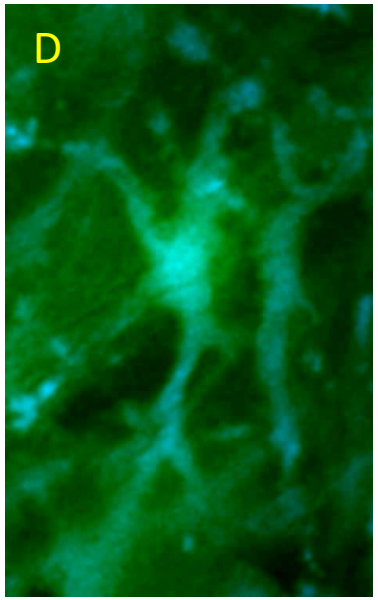


New method of microscpic optical mapping opens unknown frontiers in SAN research

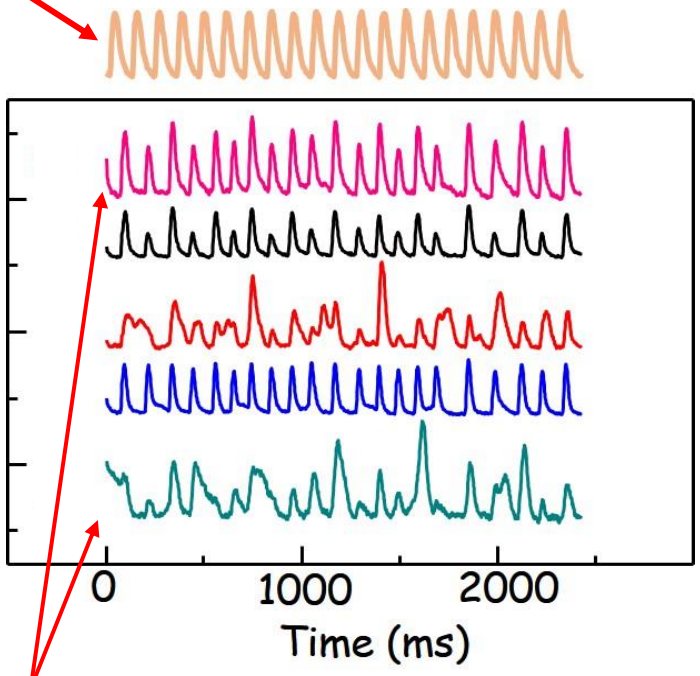






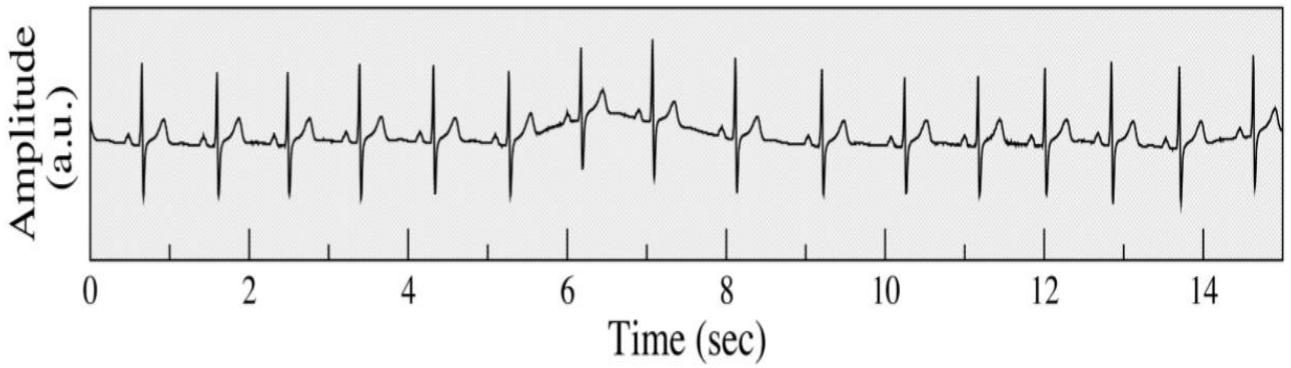
E How do heterogeneous calcium signals within and among cells self organize into rhythmic Aps ?

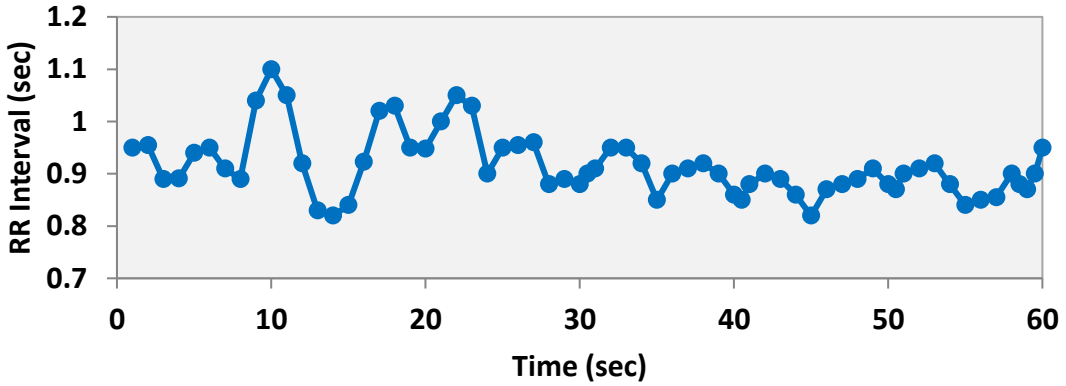
Rhythmic APs emanating from the SA node



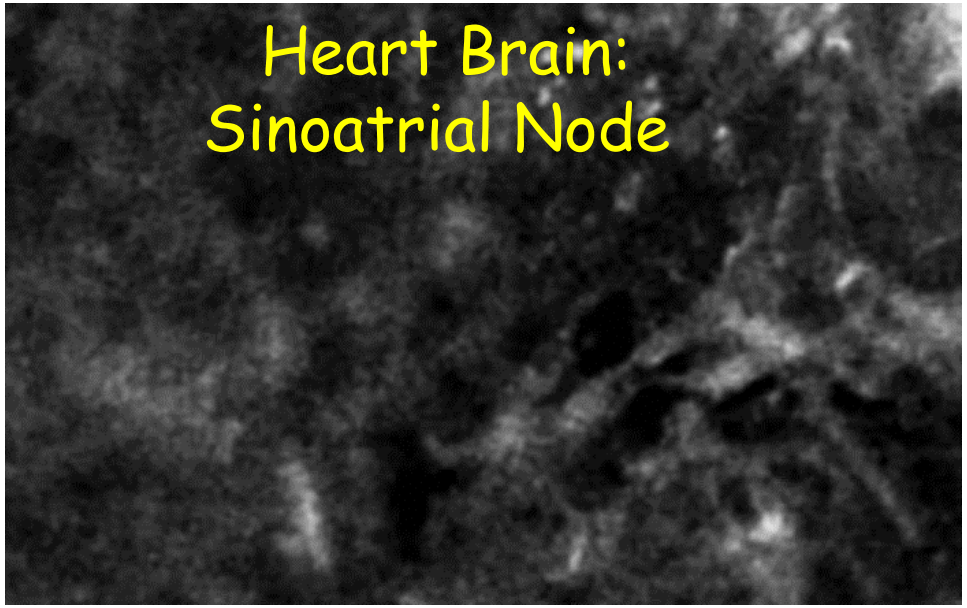
Heterogeneous calcium signals within and among SAN cells

The heart is not a metronome:
Its rhythm is never in a true steady state!

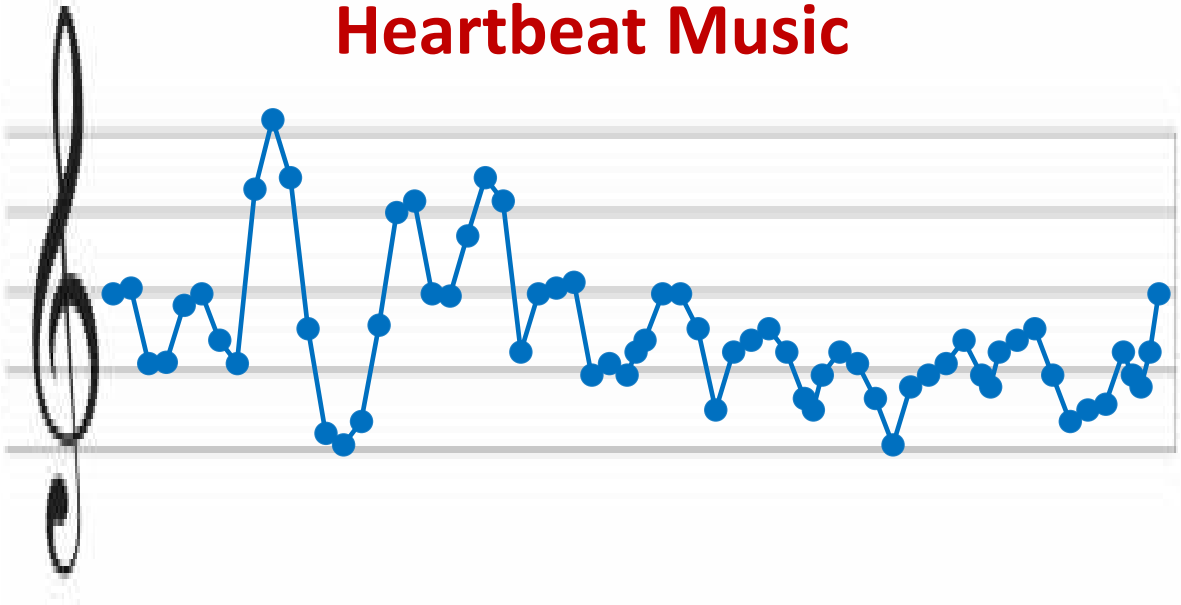




Costa M, Davis R, Goldberger E, Frontiers in Physiology (2017)



Heartbeat Music



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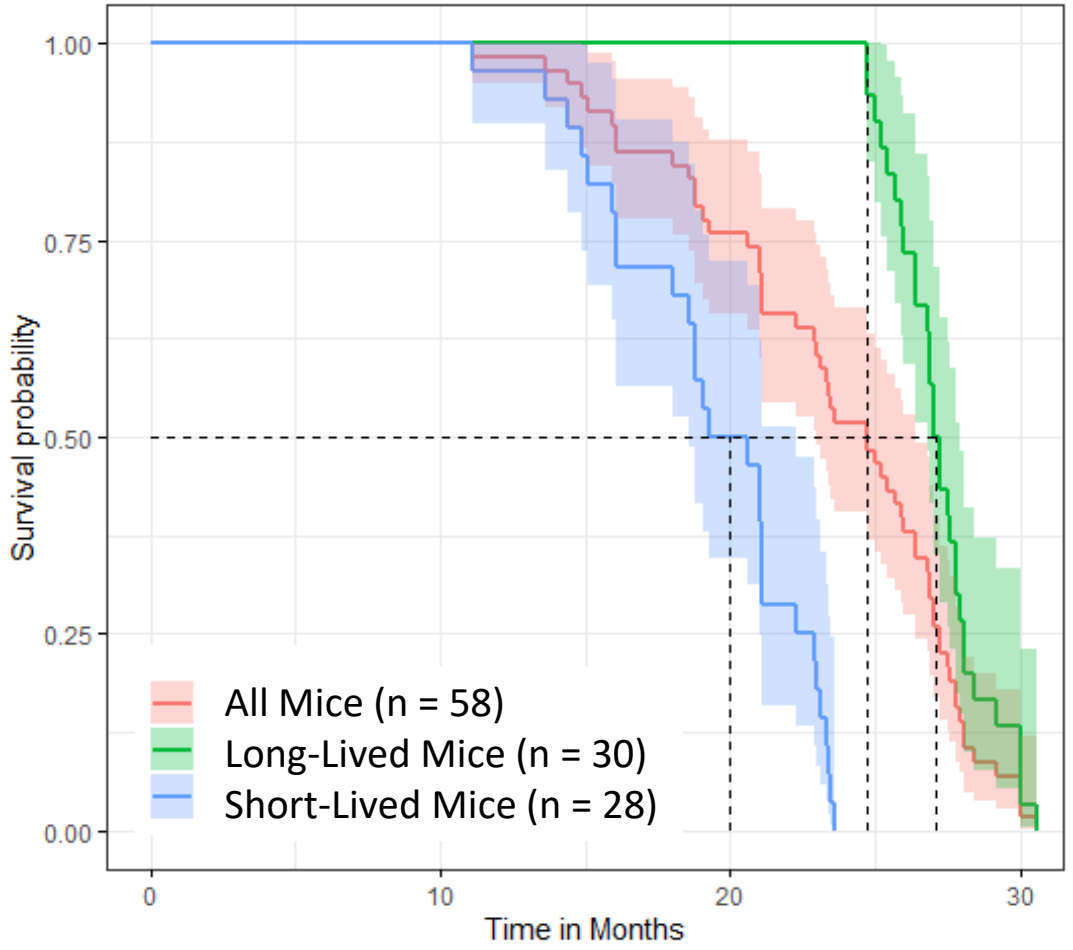
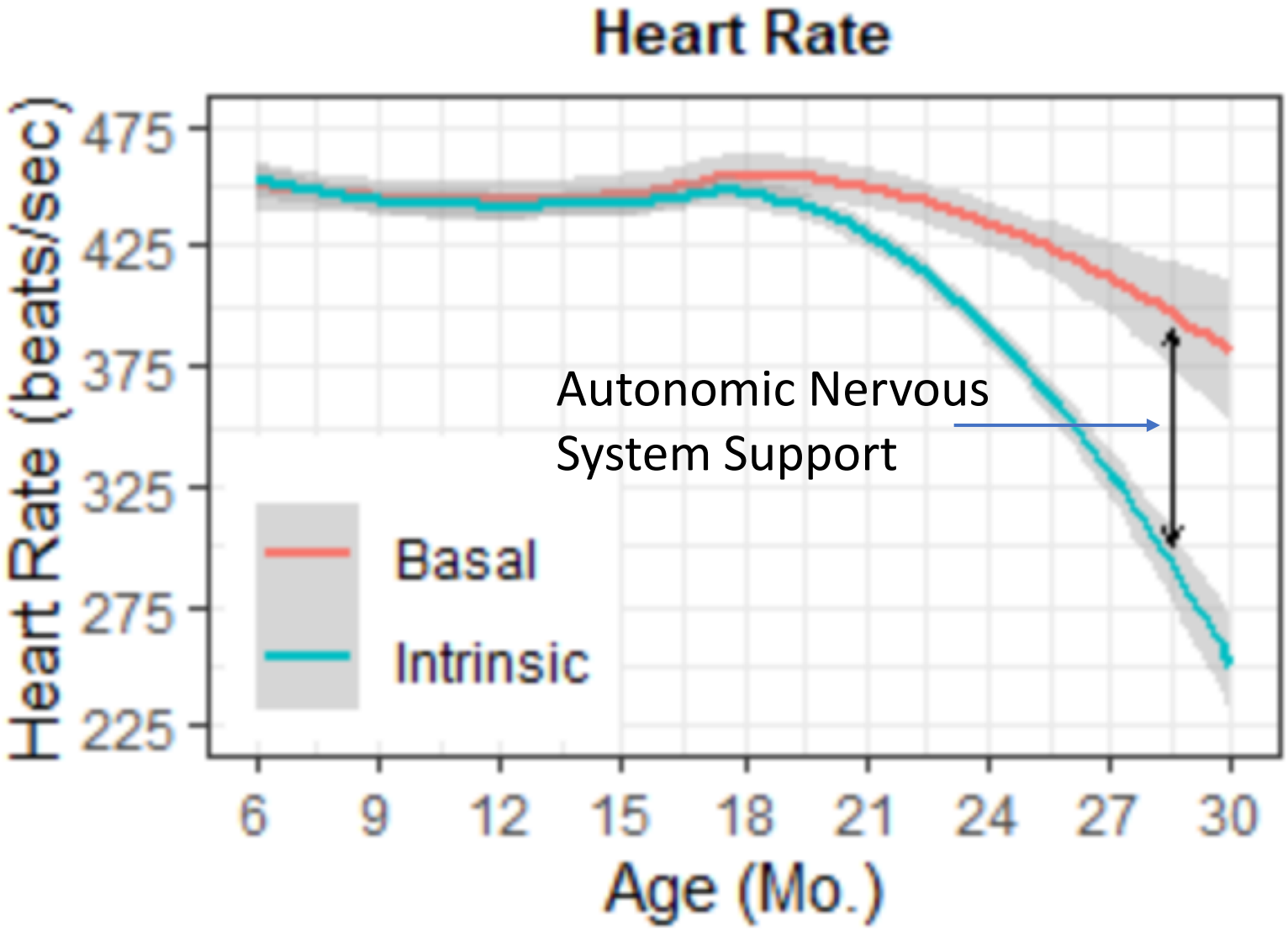
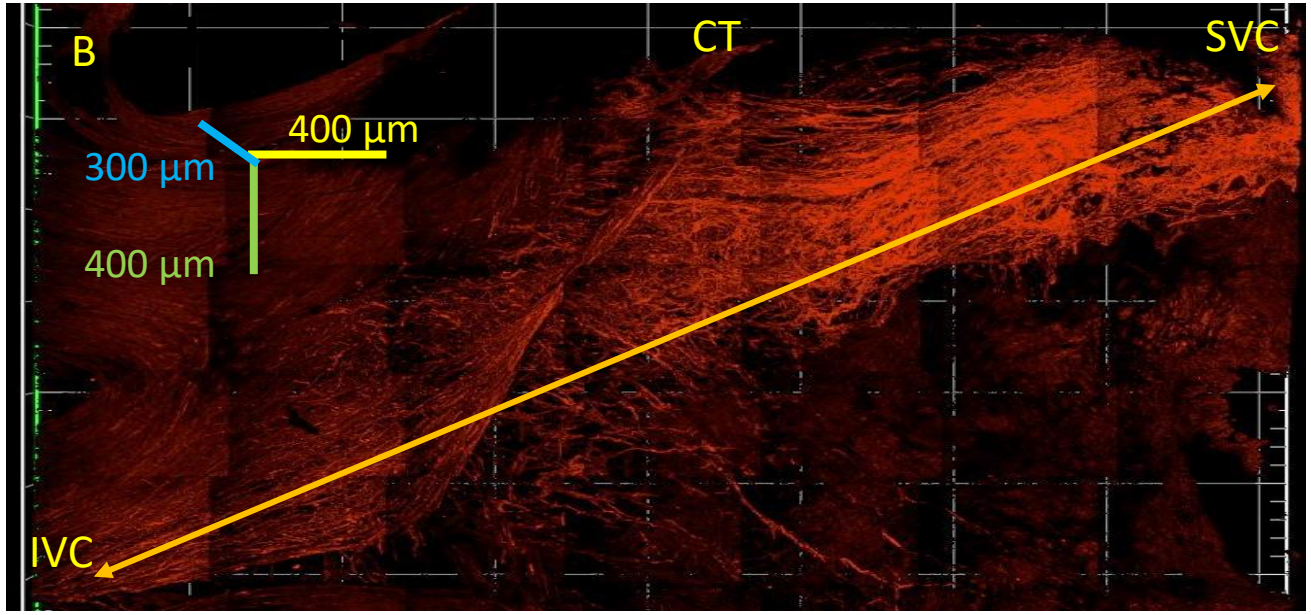
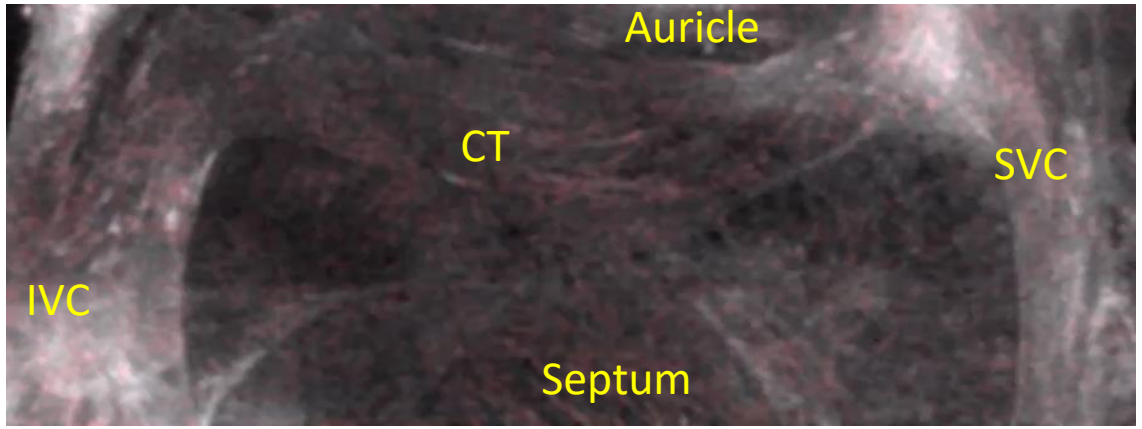



Heart Rate
Heart Rate (beats/sec)
475
425
375
325
275
225
6
9
12
15
18
21
24
27
30
Age (Mo.)
Basal
Intrinsic
Autonomic Nervous
System Support

4 month old mouse heart's brain

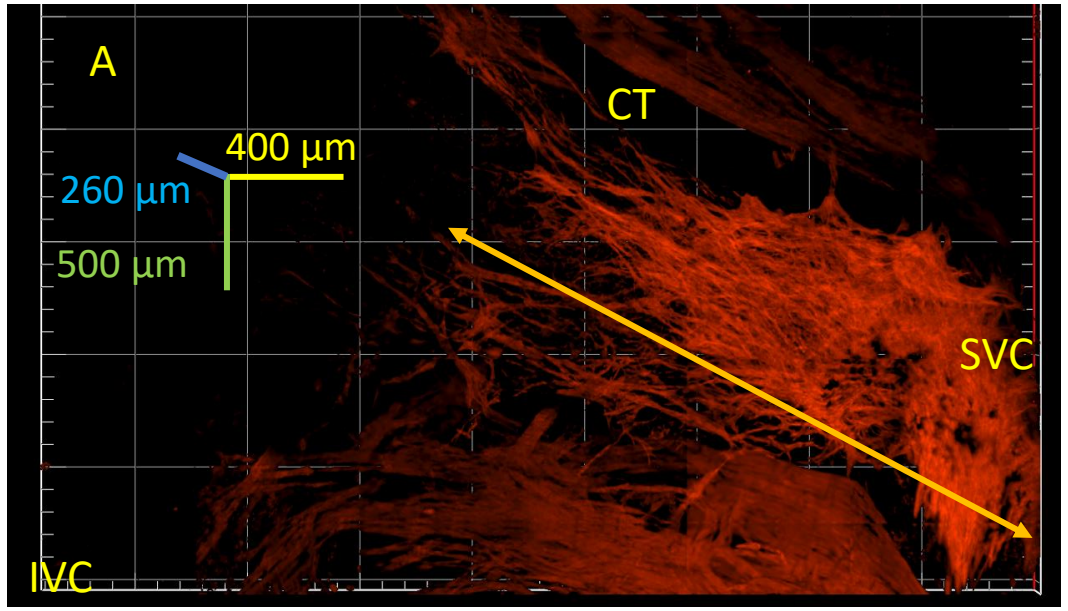


Immunostaining HCN4



Ca signals

29 month old mouse heart's brain



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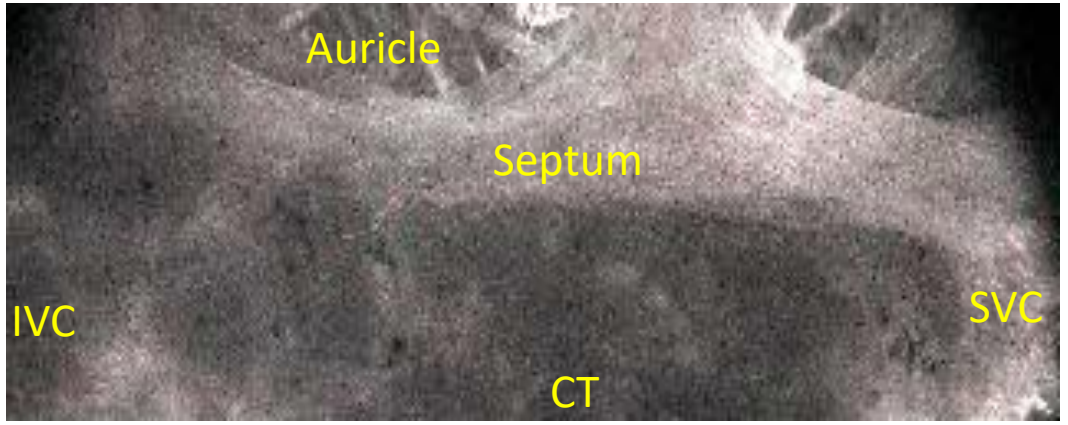

Ca signals

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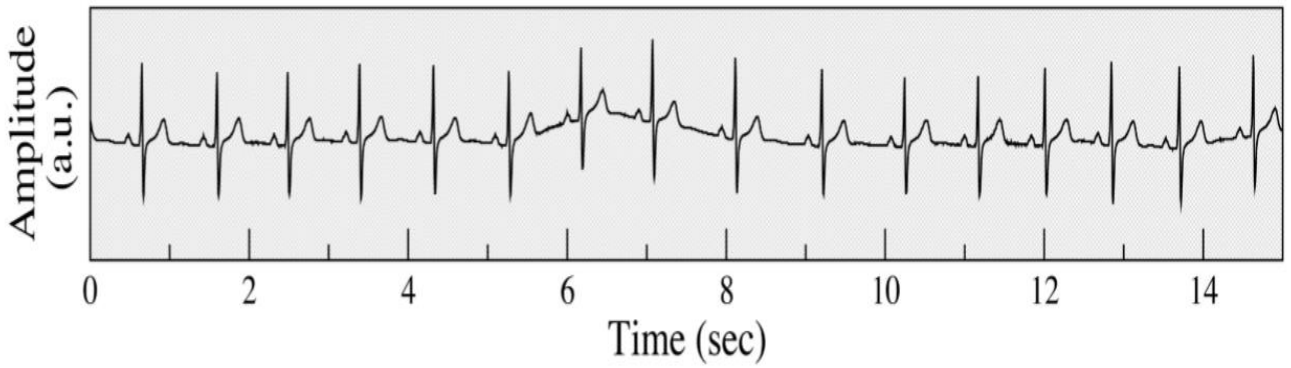

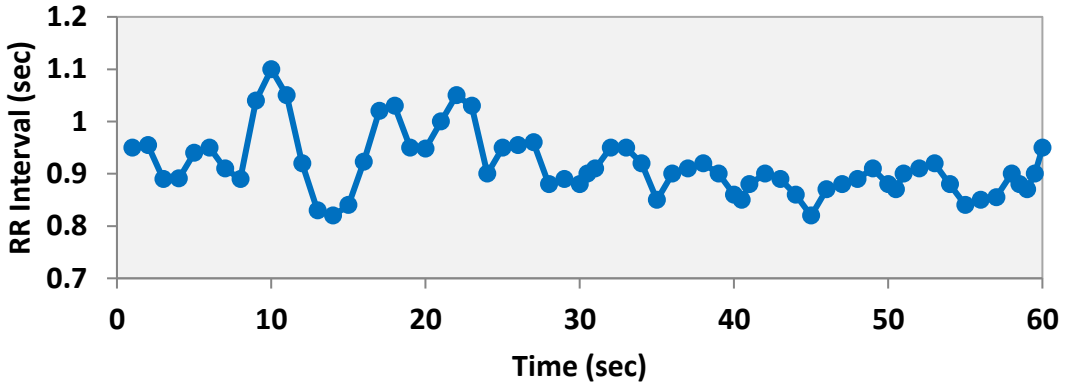

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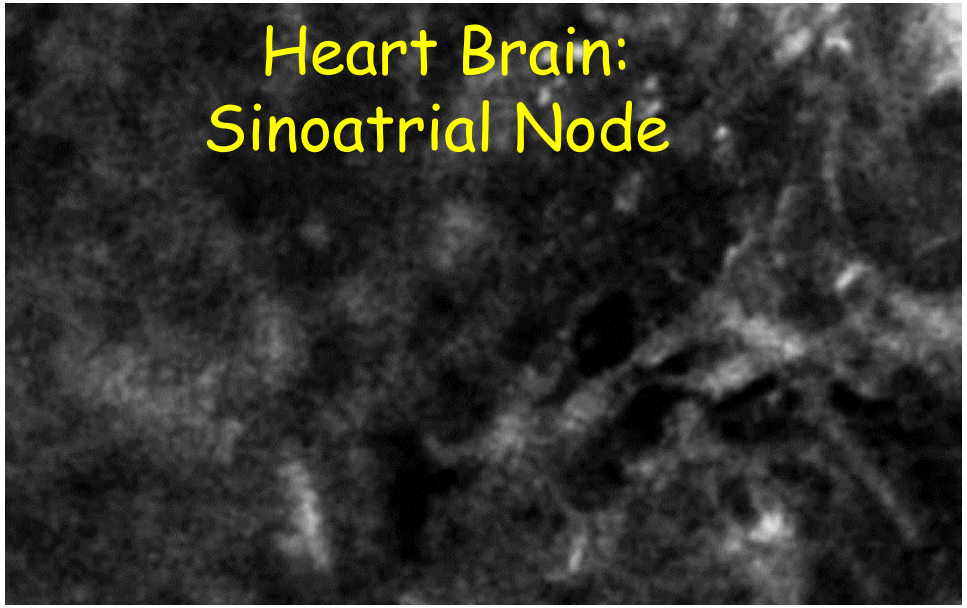
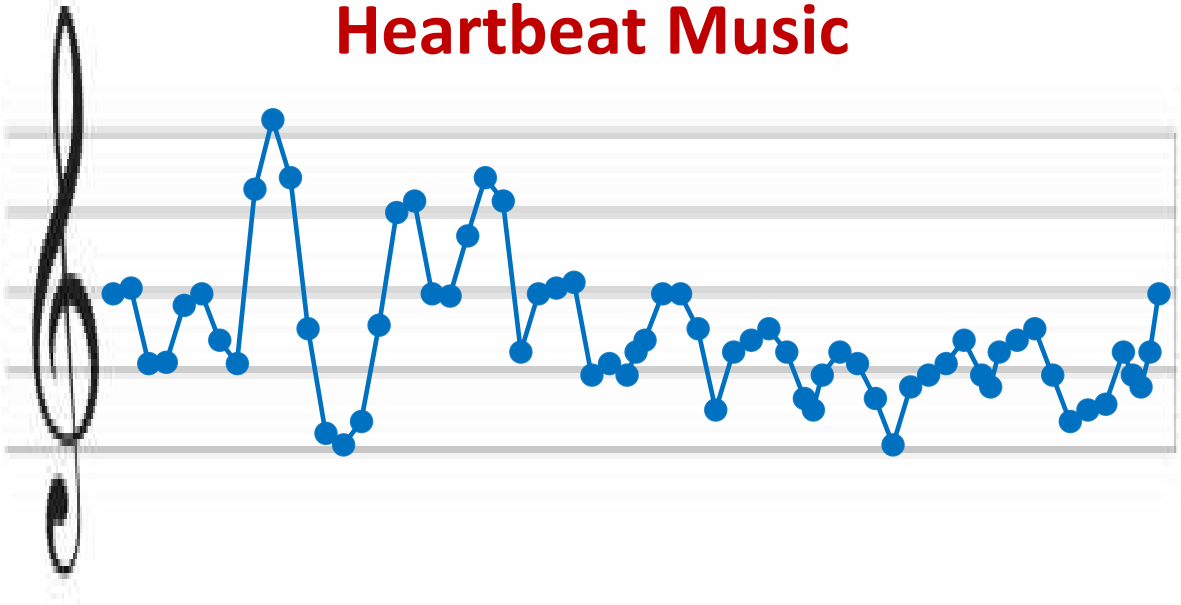
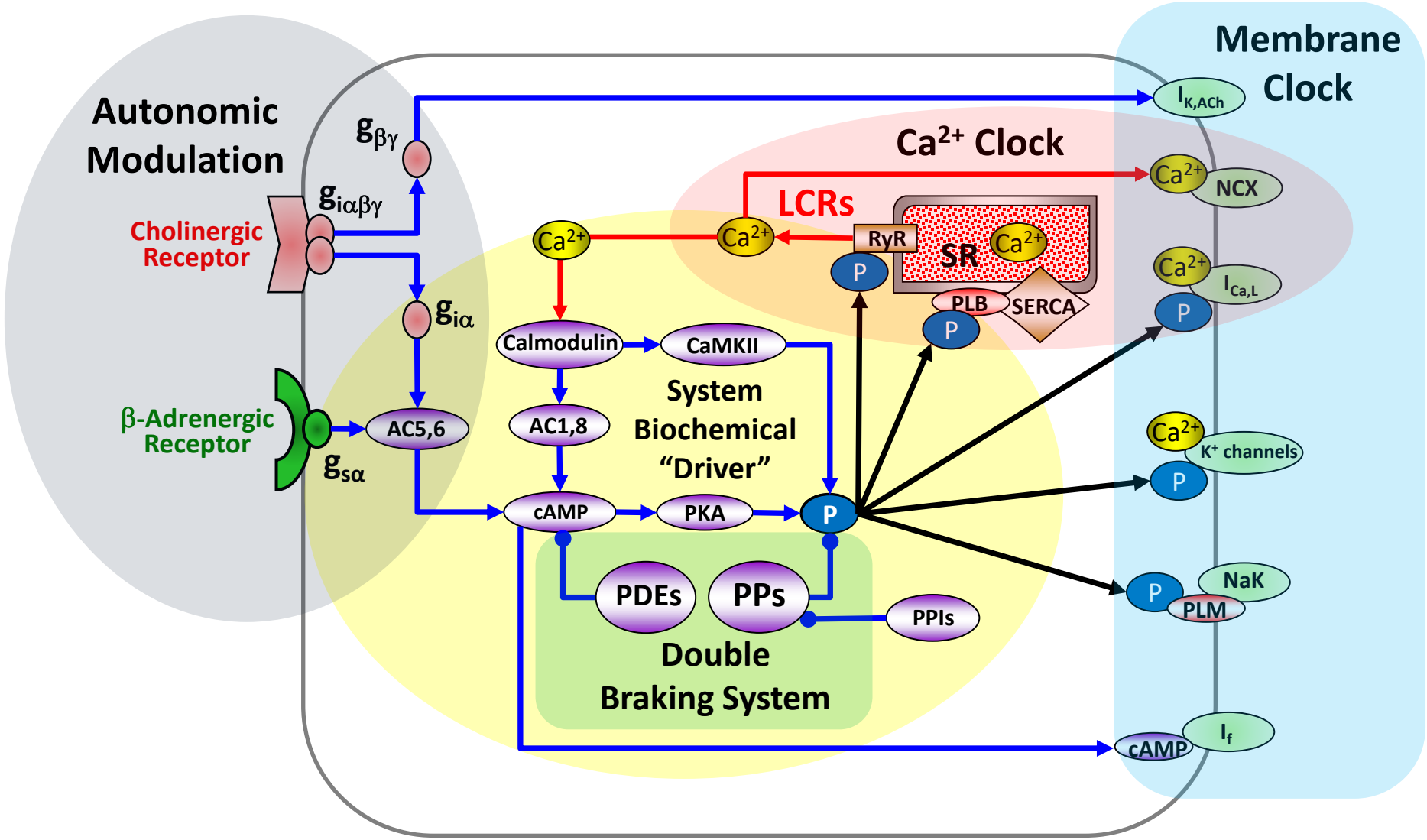


Heartbeat Music



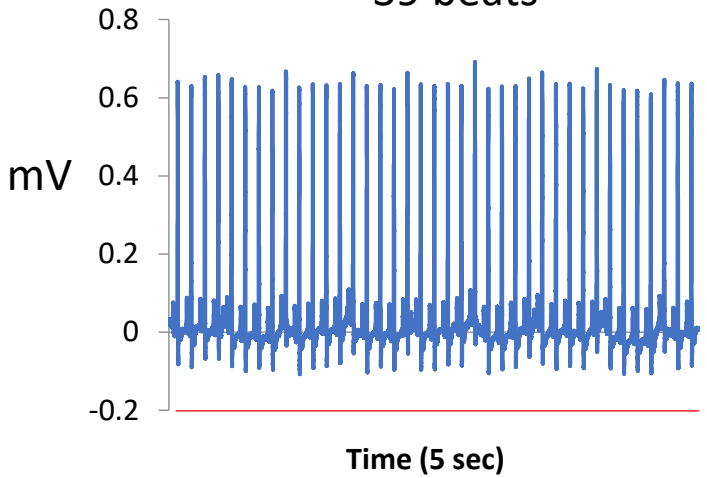
The Coupled-Clock System within Sinoatrial node cells



Heartbeat Interval "Music" in the **Time Domain**

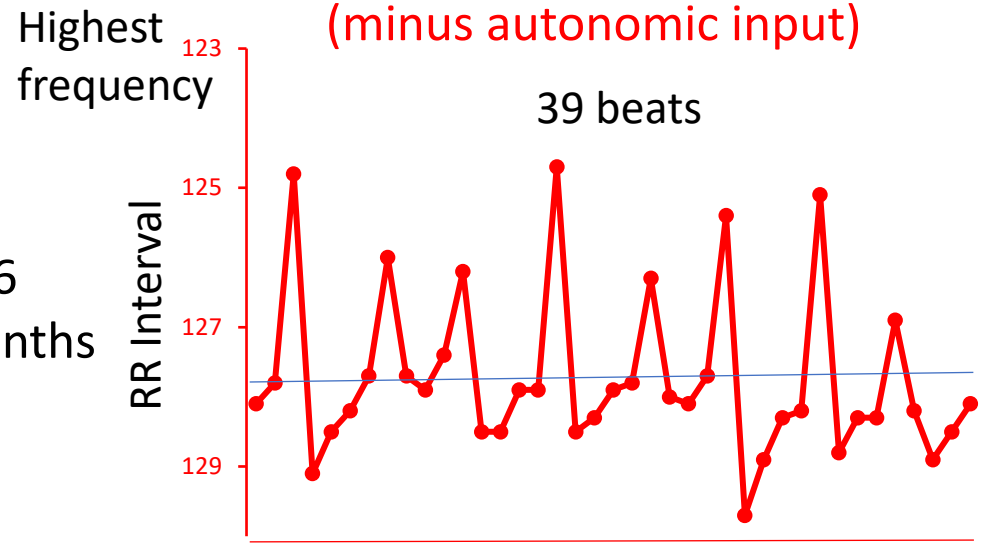
EKG RR intervals
(minus autonomic input)

39 beats

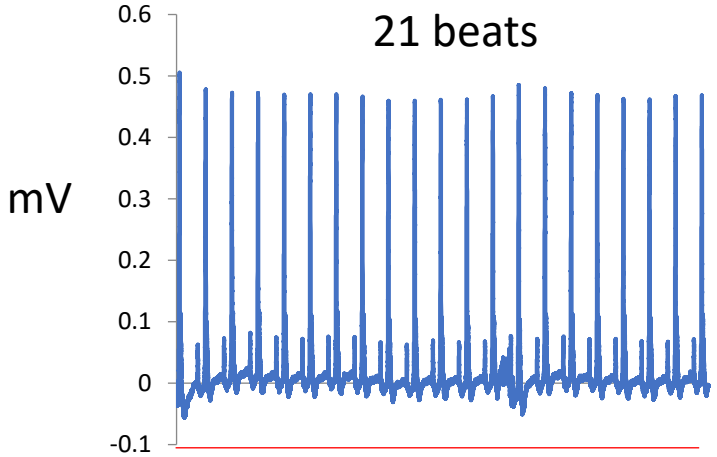


At 6 months

RR Interval Variability
(minus autonomic input)



Same mouse at 30 Months



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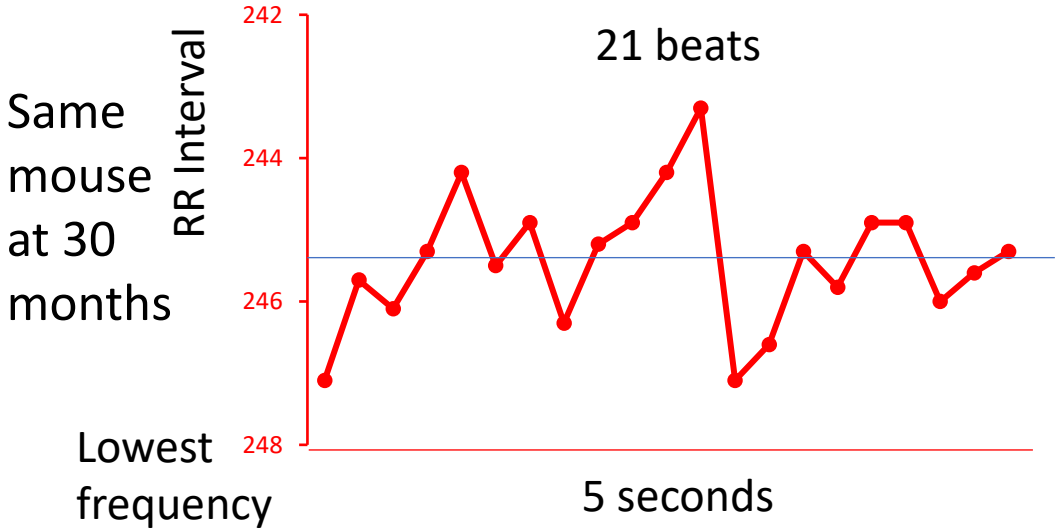
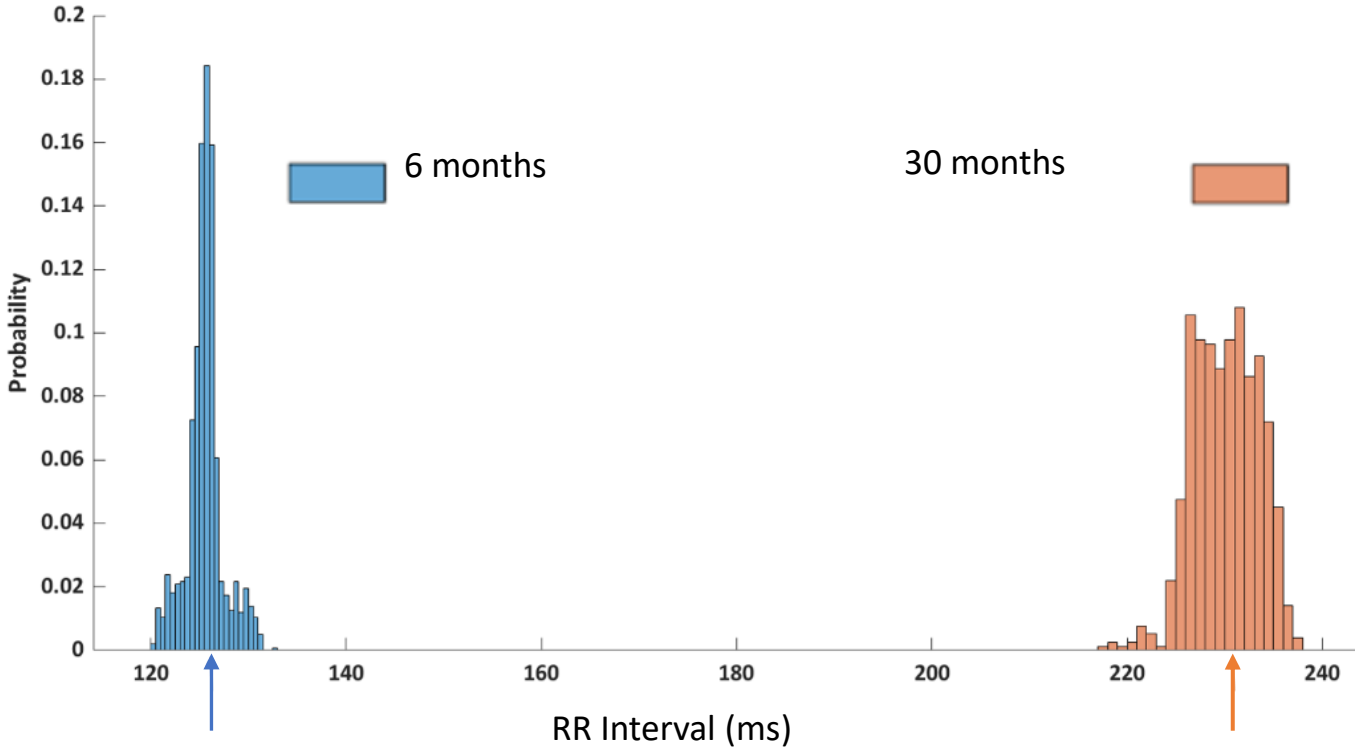
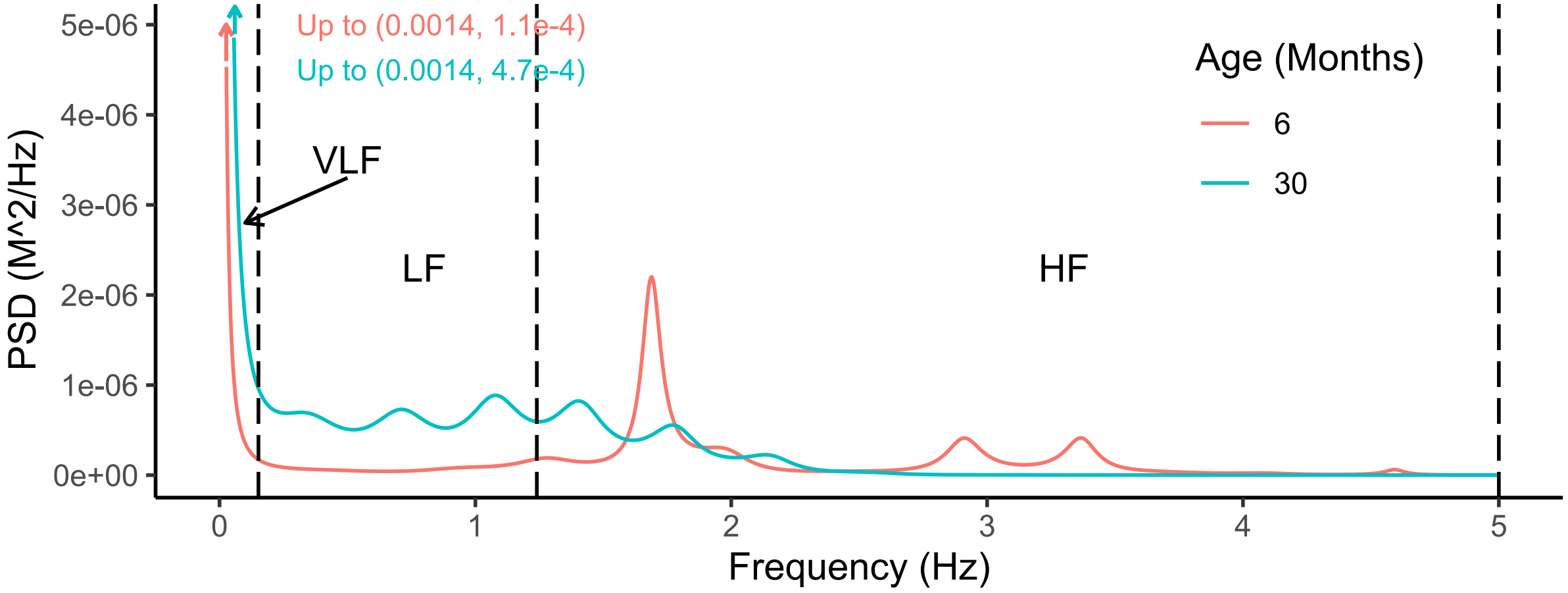


Same mouse at 30 months

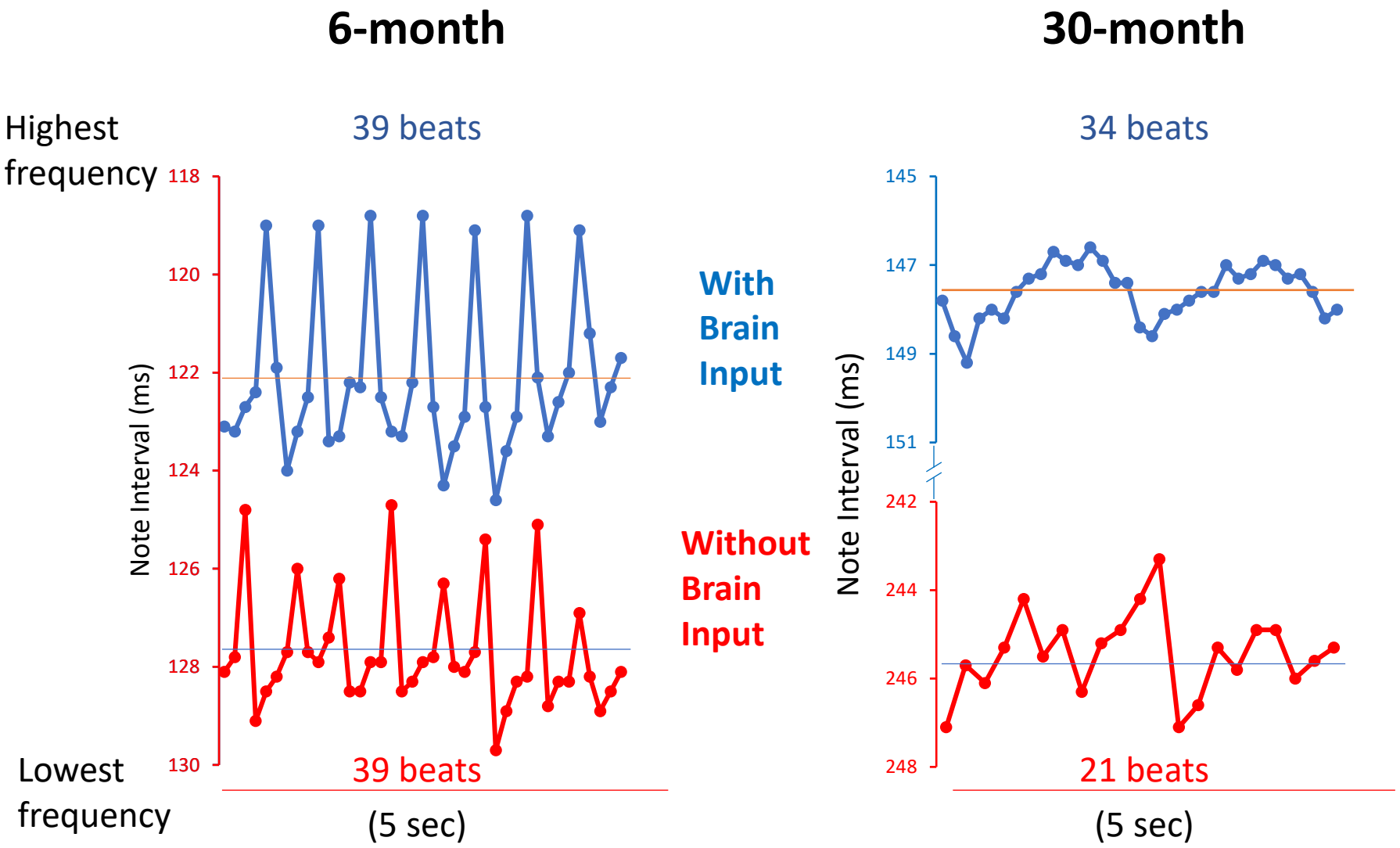
Synchronization within distributions of EKG RR Intervals in the absence of autonomic input in the same mouse at 6 and 30 months



EKG intervals in the Intrinsic state in the frequency domain at 6 and 30 months for the same mouse.

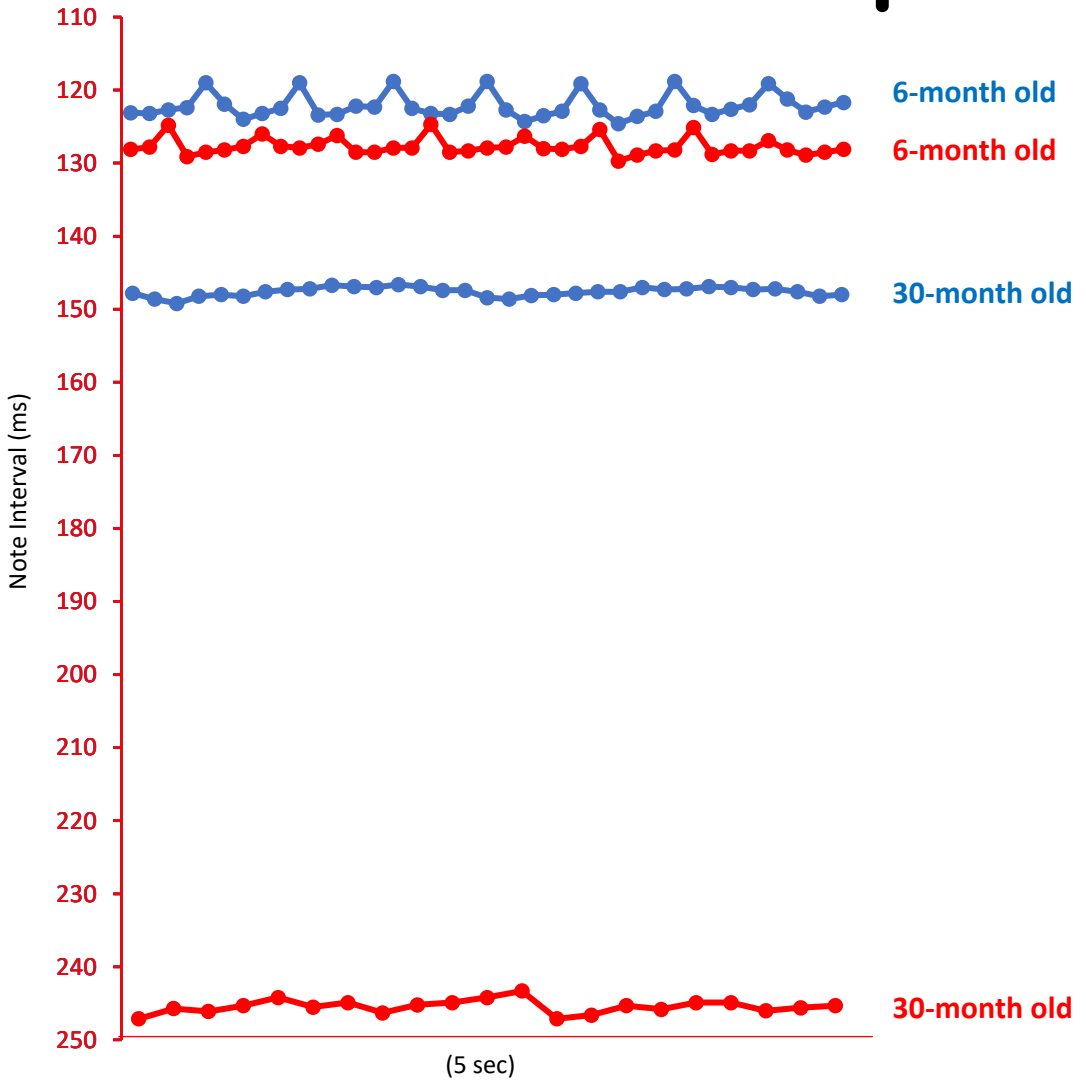


EKG RR Intervals in the same mouse at 6 & 30-months of age with & without autonomic nerve input signals



Heartbeat note pitch with & without autonomic neural input

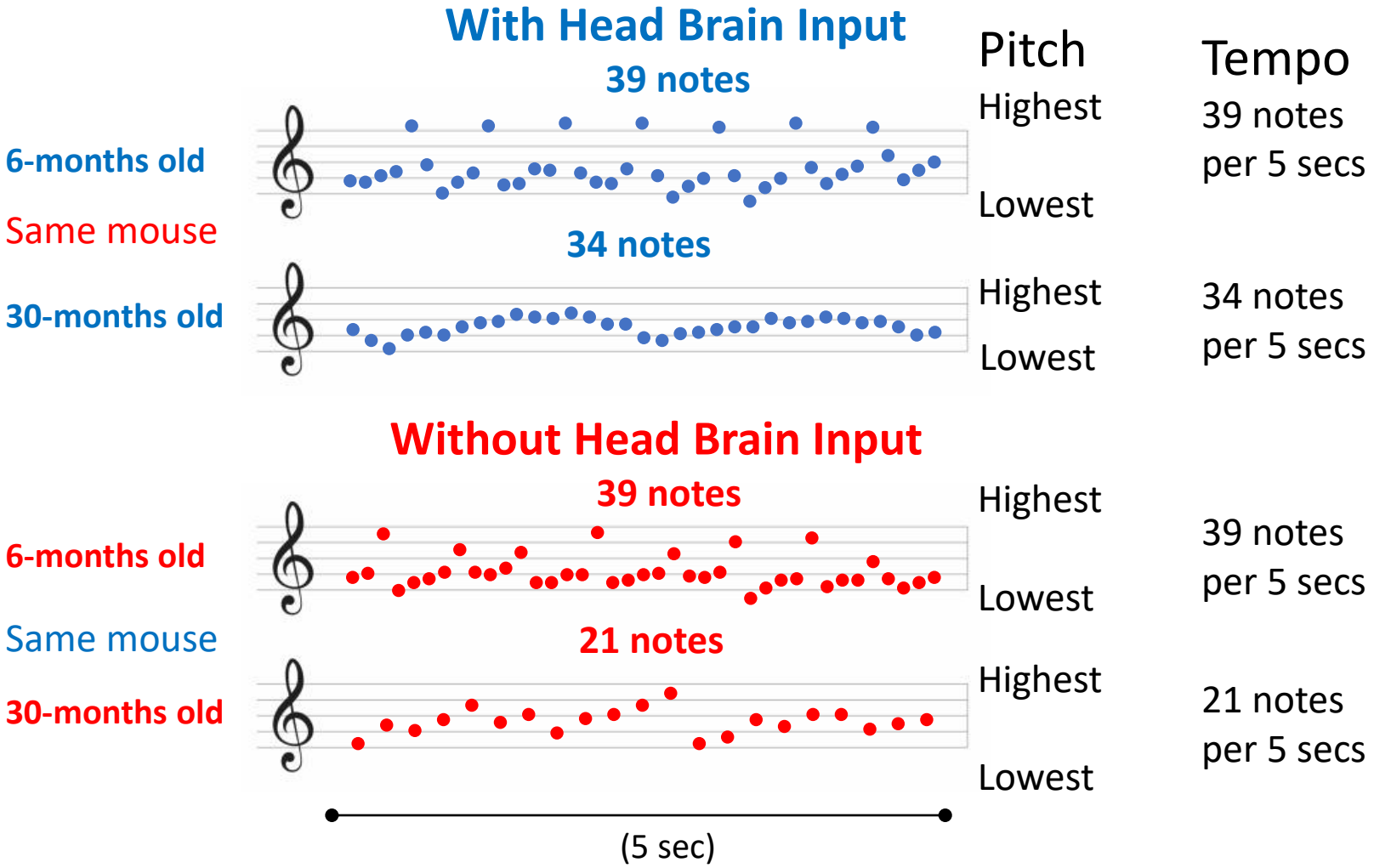
Note: The human ear cannot hear this music generated by the mouse heart between 4 and 8 Hz because frequency of noise audible to the human ear is in the kHz range.



With Autonomic Neural Input

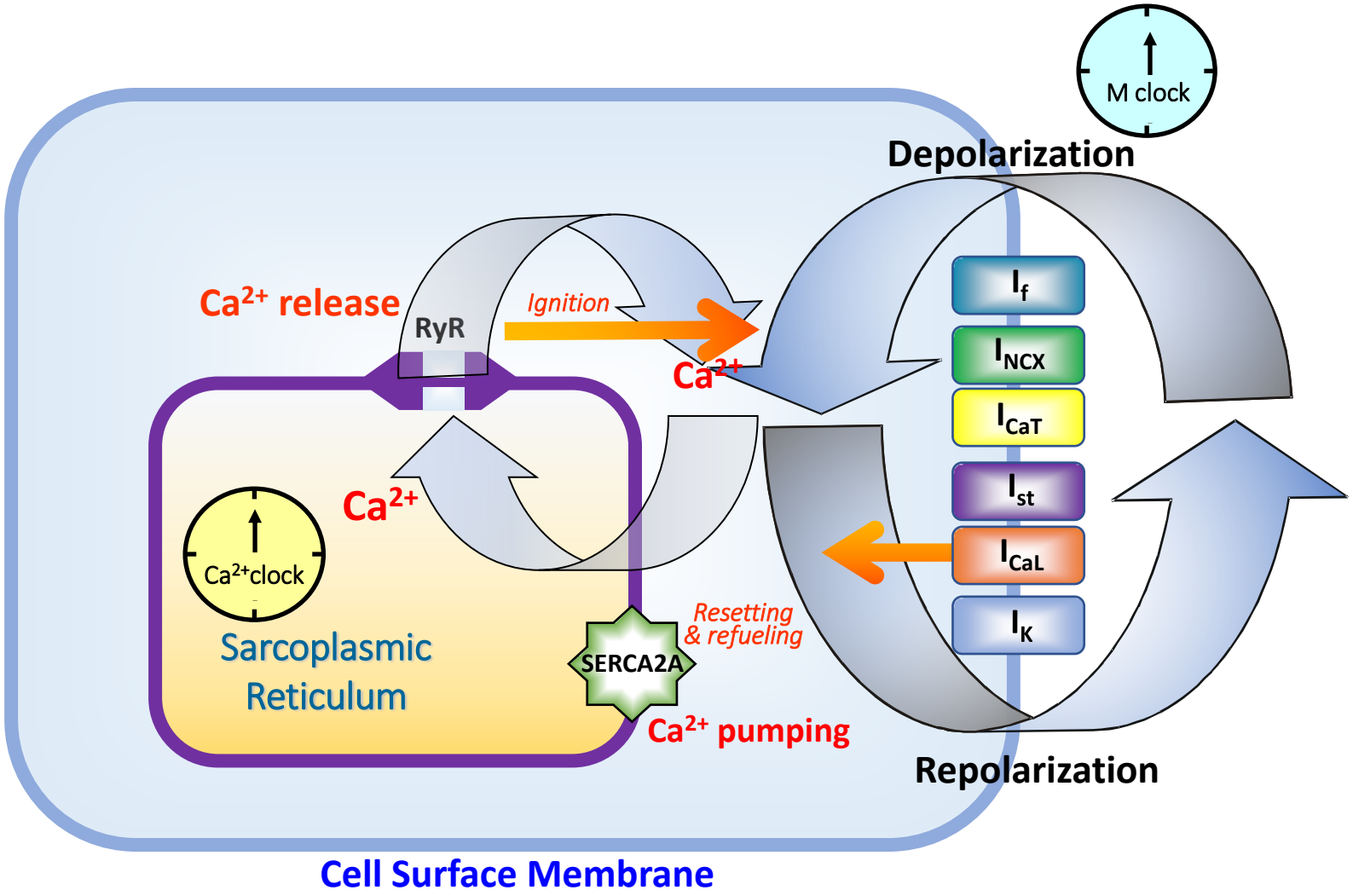
Without Autonomic Neural Input

Heart brain musical notes at 6 and 30 months of age with and without head brain input



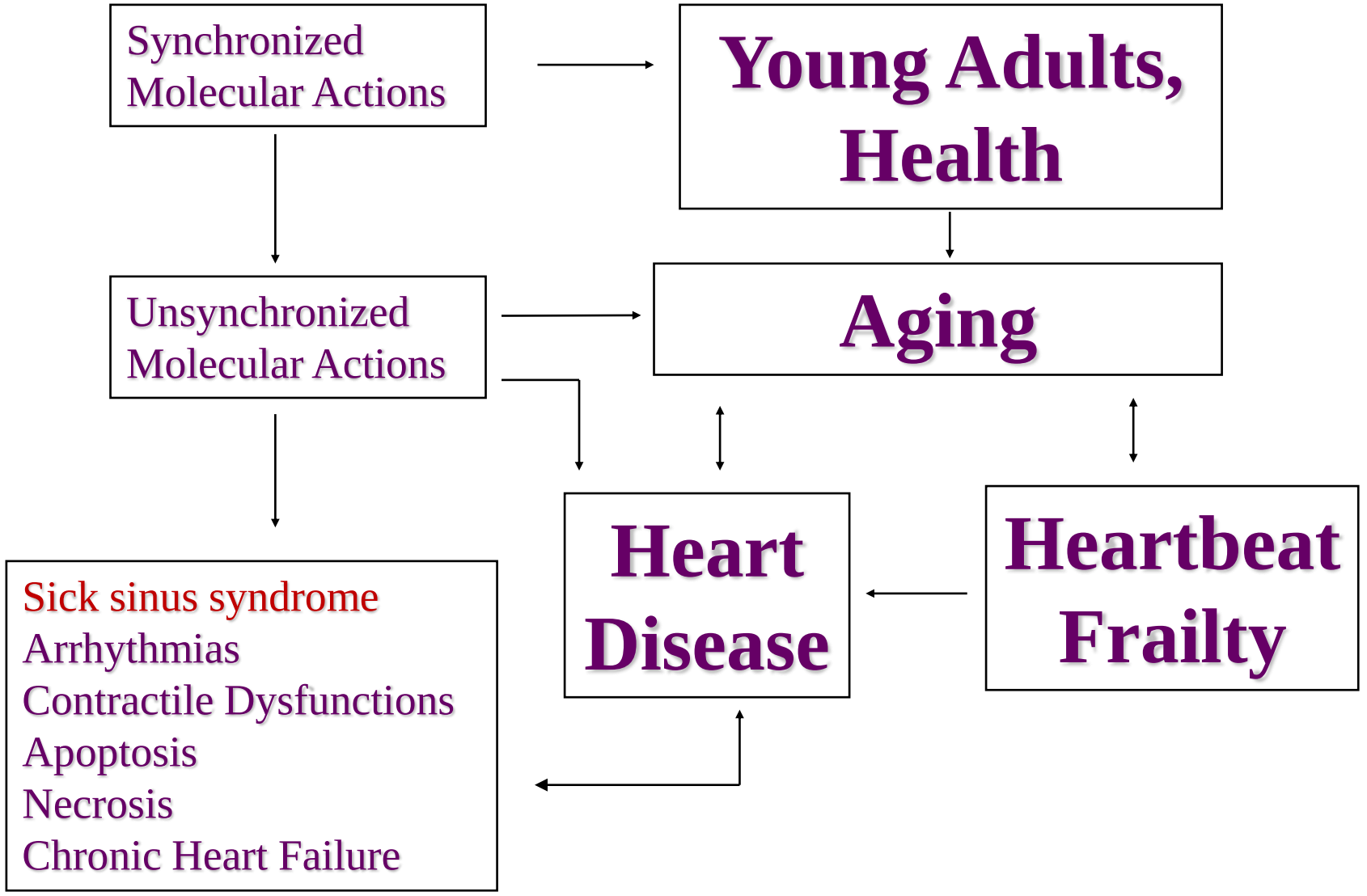
Scale axis (time between notes) is in same for all four scales.

A Coupled-System of Chemical and Current Oscillators



Molecular De-synchronization of Aging

The Aged Frail Heart's Pacemaker Brain Operates at the Edge of Disease



E.G. Lakatta / Cell Calcium 35 (2004) 629–642

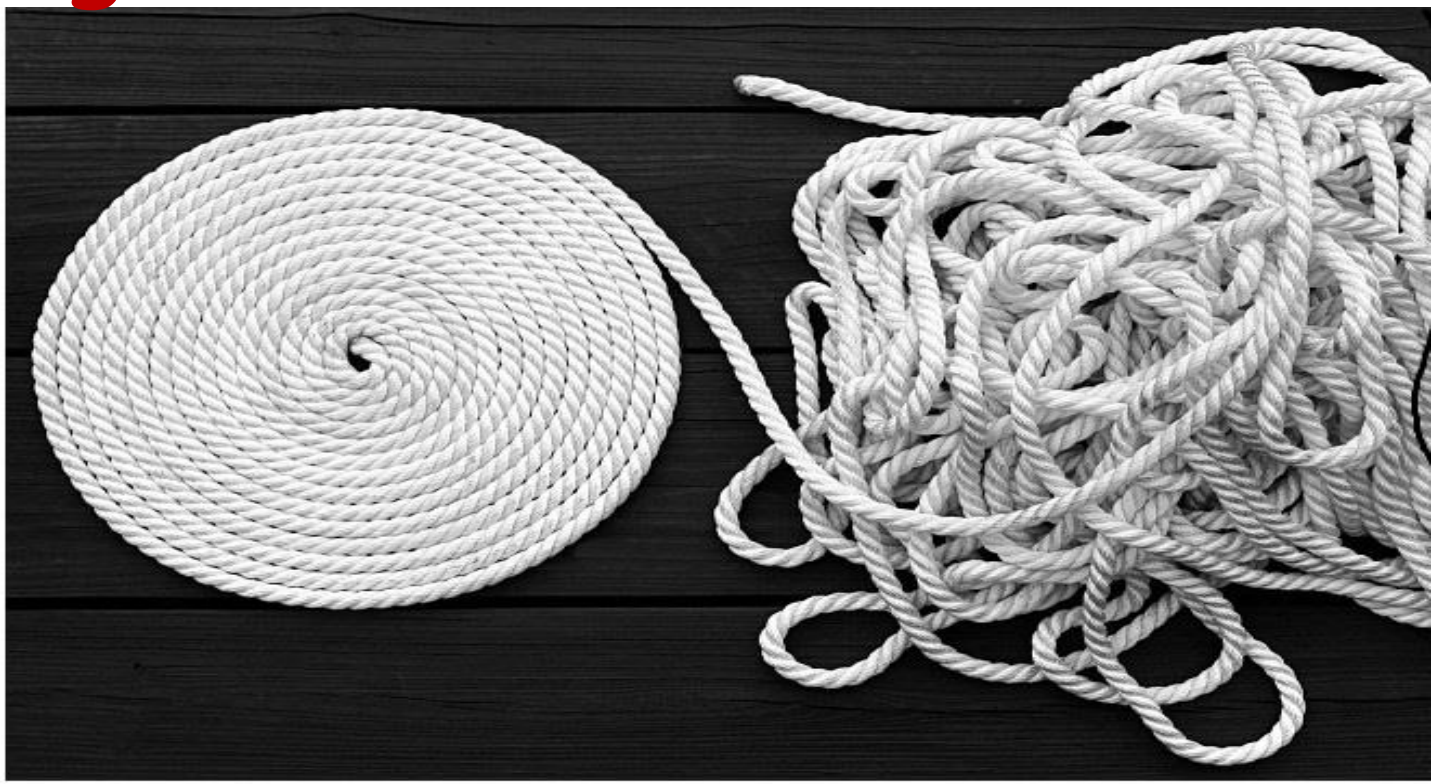
Summary

- The best aging biomarker – maximum heart rate: Both the decline and rate of decline with increasing age are inevitable and cannot be slowed by any know intervention.
    - Why does heart rate decline?
- Because of deterioration of the kinetics of oscillator functions within and among cells within the sinoatrial node, the heart's pacemaker, leading to desynchronization within and among functions, both within and among cells, and to reduced autonomic neural modulation of these functions.
    - So what?
- This desynchronization causes prolonged inter-heartbeat intervals and increased variability of heartbeat intervals (heartbeat musical notes) in the absence of autonomic input and failure of autonomic input to fully tune this music.
    - Why?

Summary-2

- Because precisely synchronized kinetics of functional transitions within pacemaker cells are required to generate short inter-heartbeat intervals, i.e. to "hit the high notes".
    - Why?
- Because the ability to hit high notes requires a precise **memory** of the pitch of immediately preceding notes.
    - Thus!
- "Flat heartbeat music" is the essence of the heart rate reduction with advancing age, the most genuine biomarker of aging.
    - And guess what?
- This "memory failure" to desynchronized molecular kinetic transitions within and among cells is NOT just an issue with the heart's pacemaker, but may be an essential feature of aging of all cells within all body organs, as exemplified by brain dementia in advanced age.

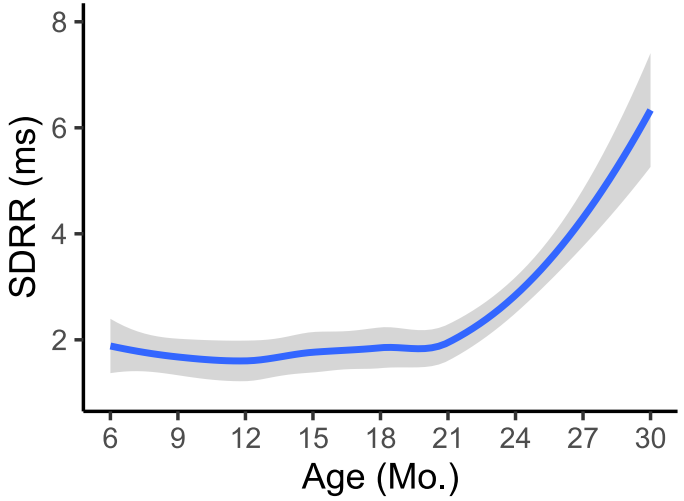
Aging Extracts Chaos from Order

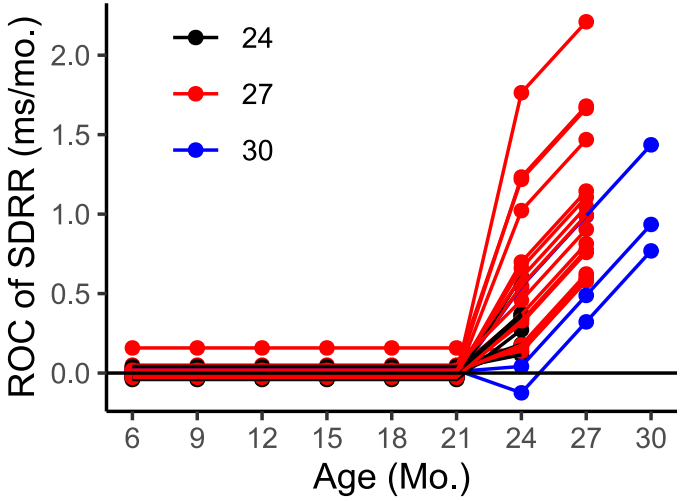


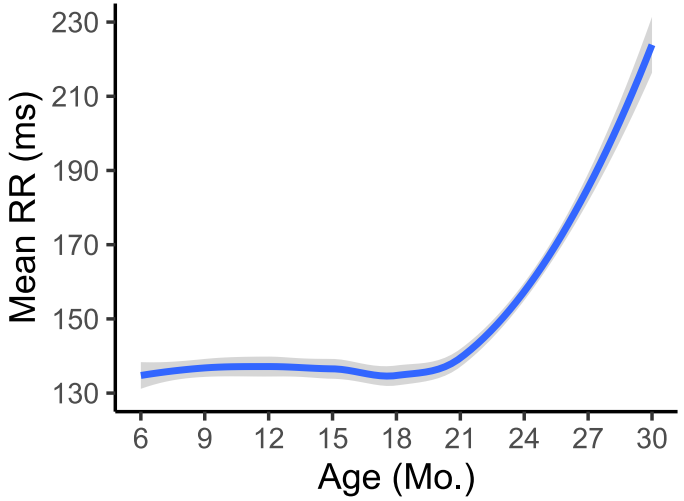
Ed Lakatta, 2016

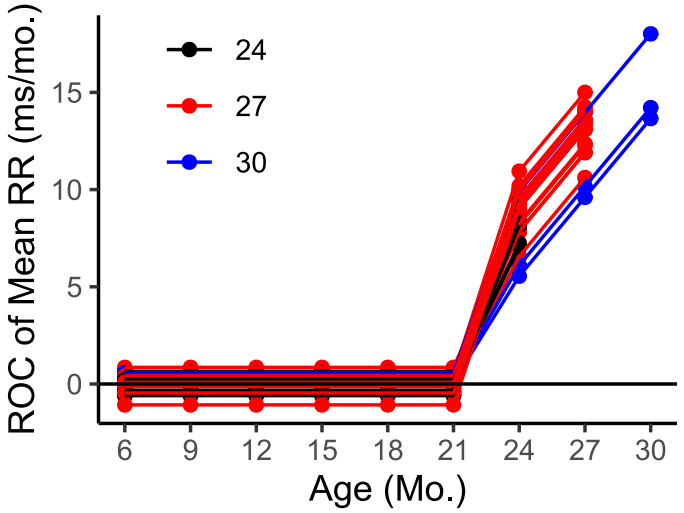

Thanks for your attention!
BALTIMORE
The Greatest City in America

Average loess smooth curves for Mean Intrinsic EKG RR interval and RR interval variability; and Mouse-specific rates of change of the intrinsic mean RR and RR interval variability in long-lived mice.

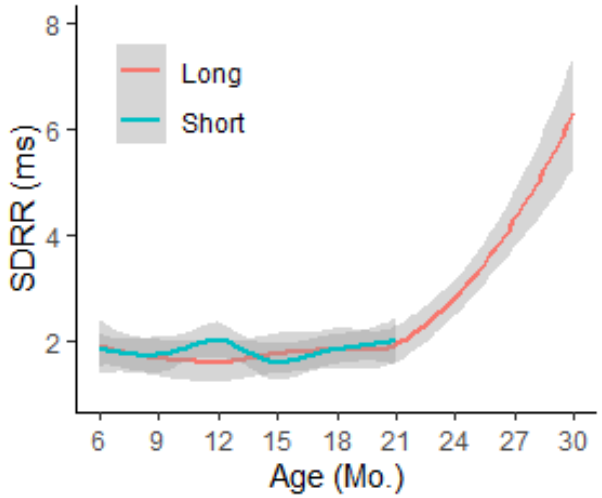


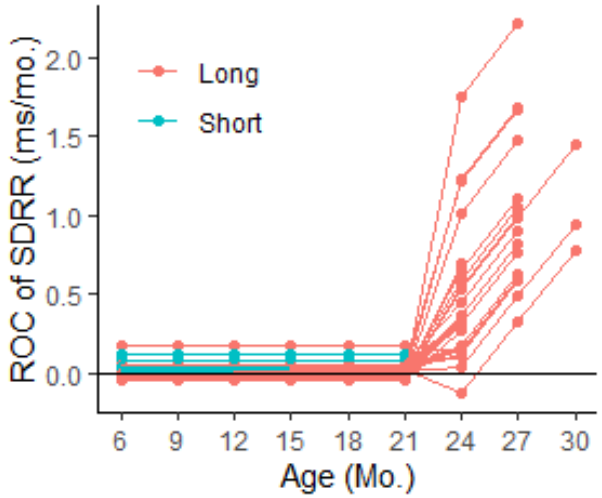


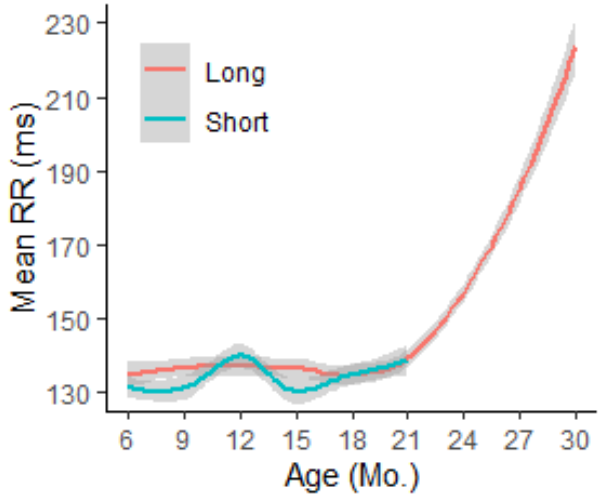


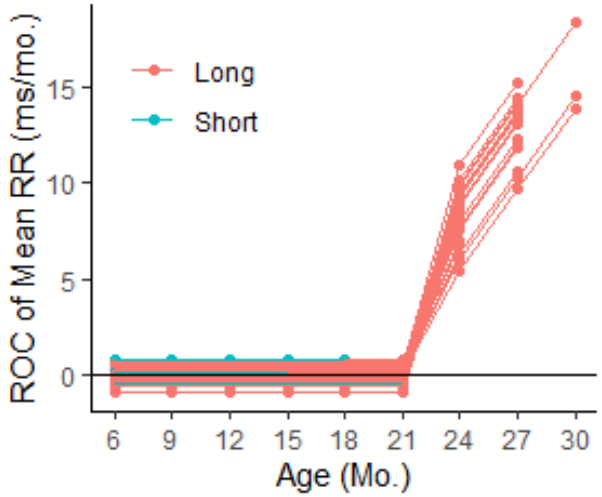


Average loess smooth curves for Mean Intrinsic EKG RR interval and RR interval variability; and Mouse-specific rates of change of the intrinsic mean RR and RR interval variability in short- and long-lived mice.

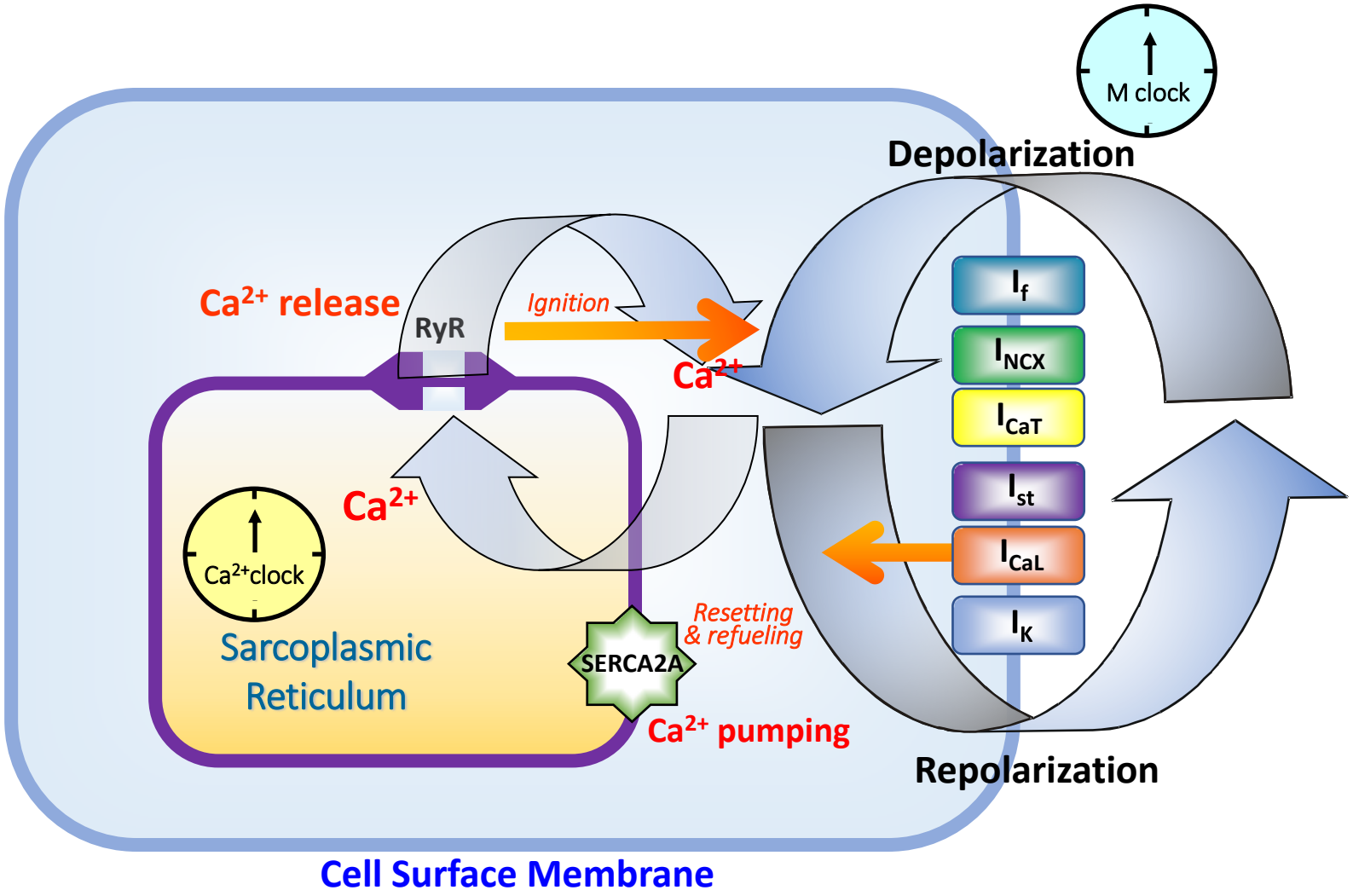




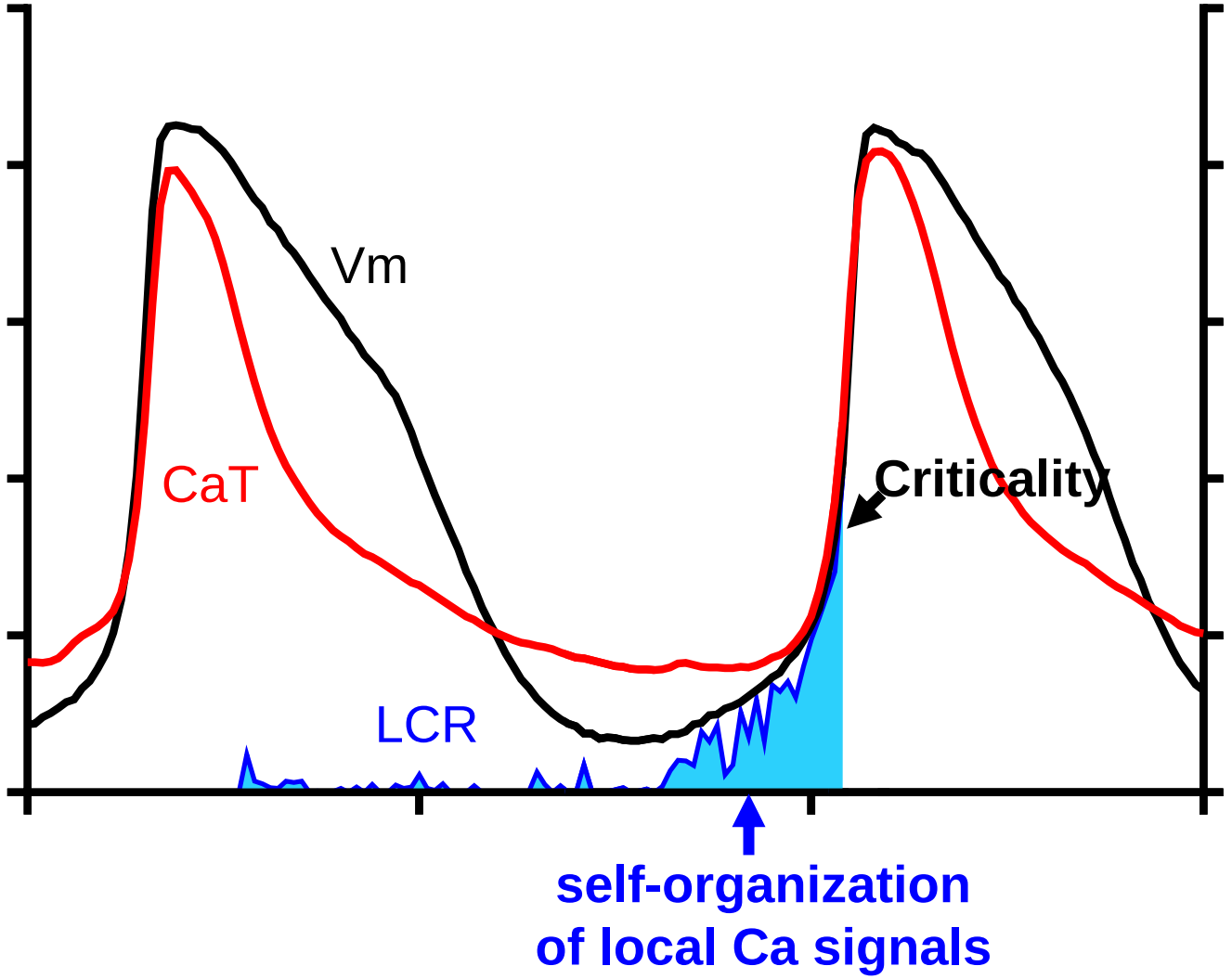




A Coupled-System of Chemical and Current Oscillators

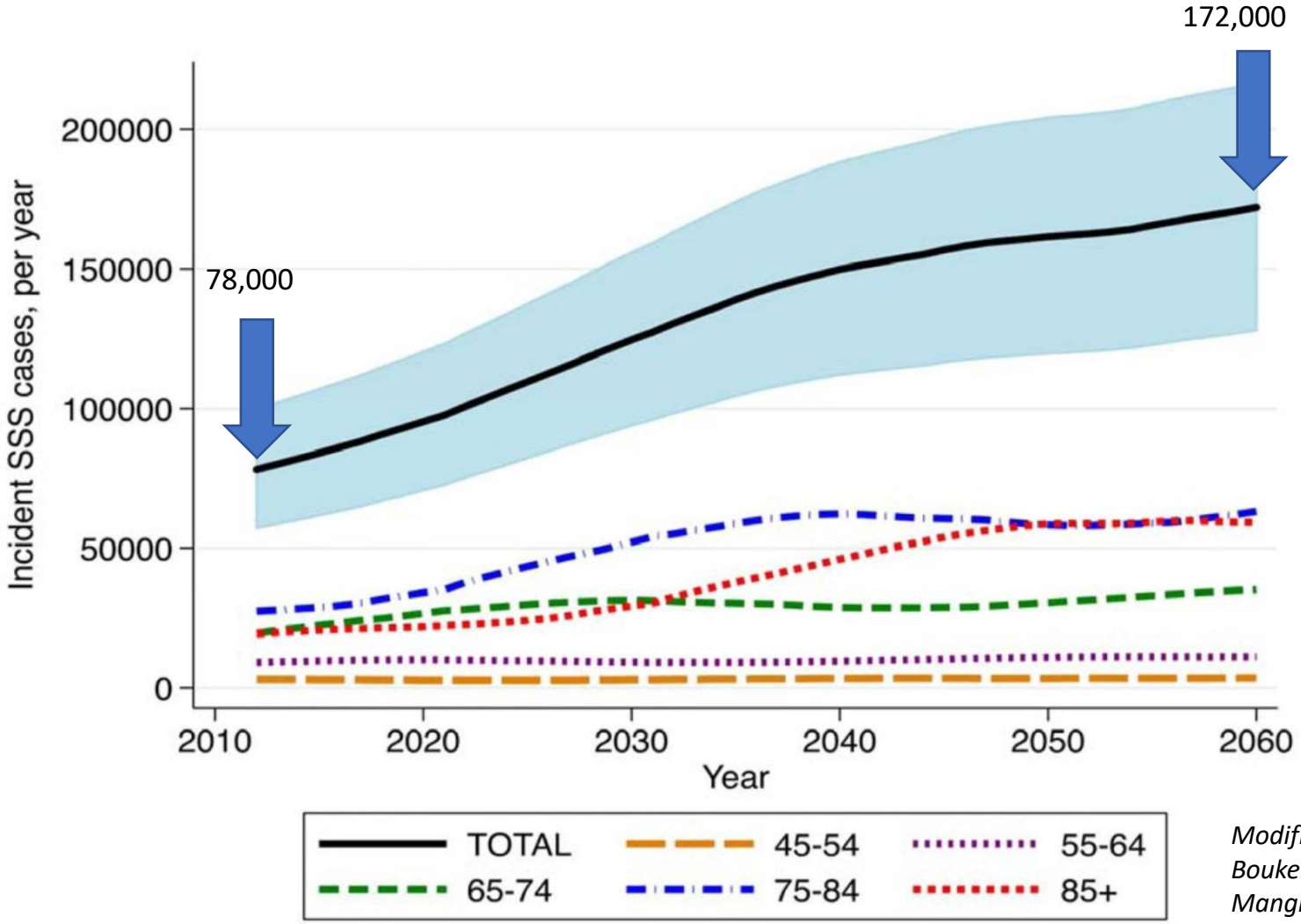


Self-organized criticality



The Aging Heart's Brain Operates at the Edge of Disease

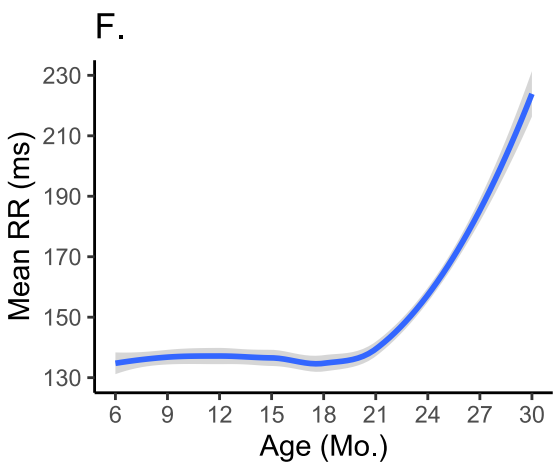
There is no greater risk factor for arrhythmia than aging
Sick Sinus Syndrome

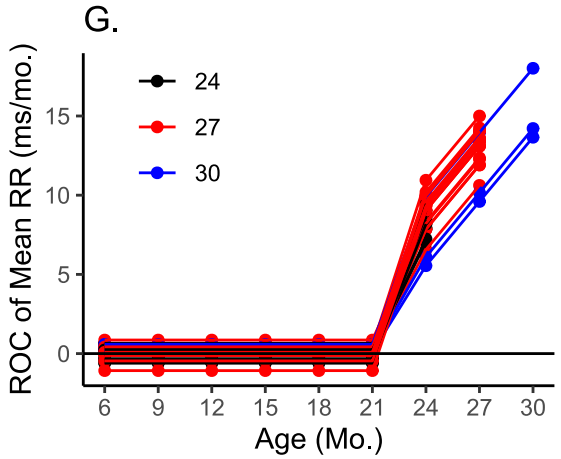


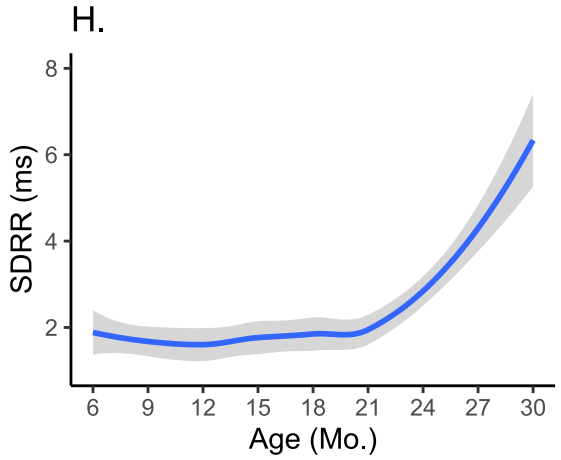
Modified from:
Boukens et al. J Clin Invest (2012) ***122****:810-3*
Mangrum et al. NEJM (2000) ***342****:703-9*

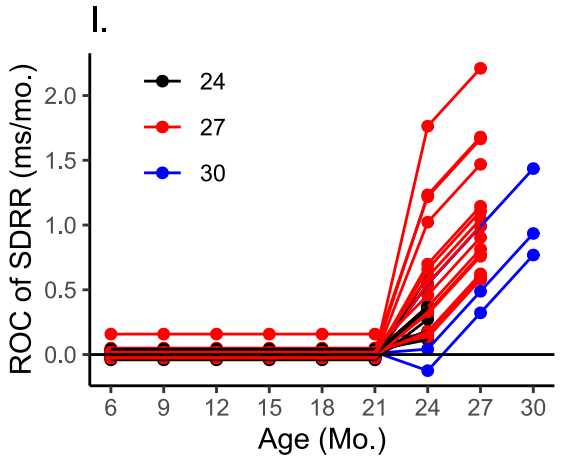
Jensen et al. (2014) J Am Coll Cardiol ***64****:531-8*

Average loess smooth curve for Intrinsic Mean RR. G. Average loess smooth curve of intrinsic SDRR. H. Mouse-specific rates of change of SDRR in long-lived mice.

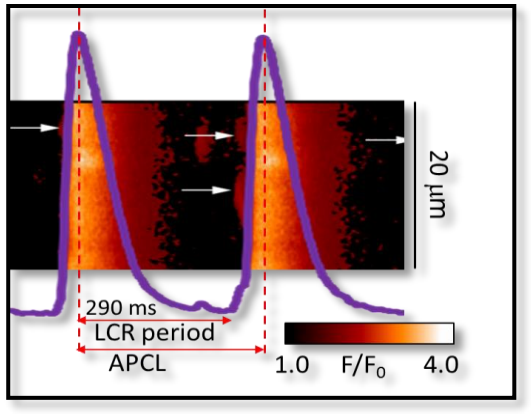


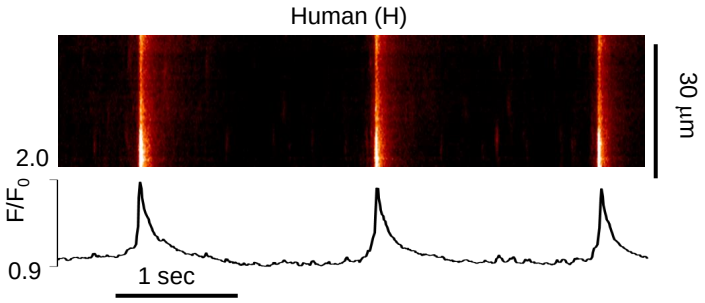


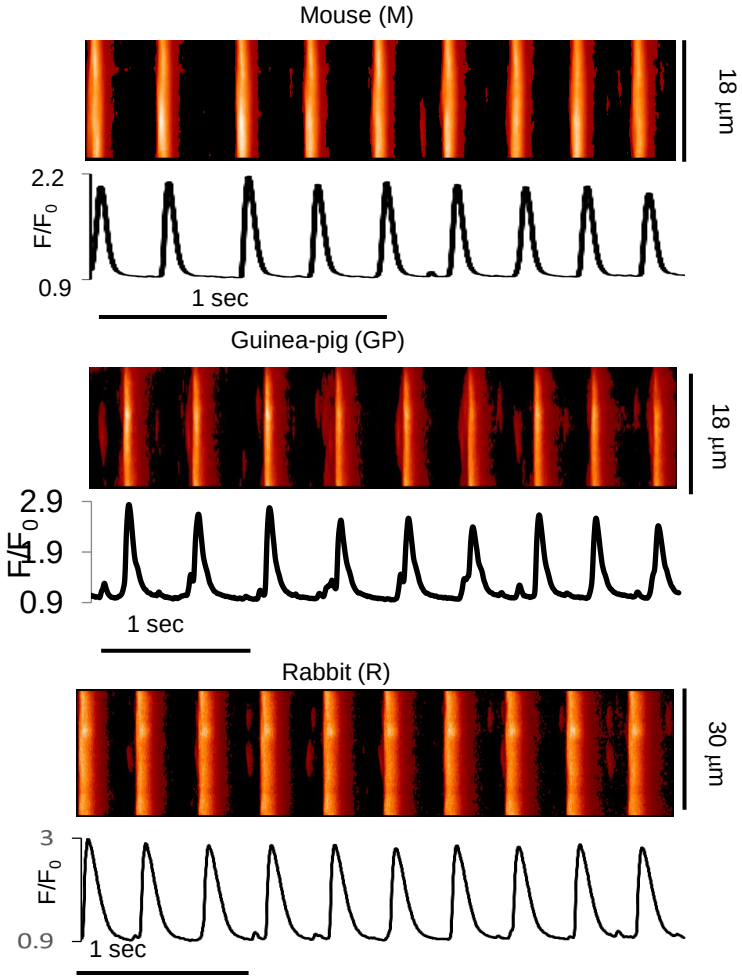




SAN cells of mouse (M), (B) guinea-pig (GP), rabbit (R) and human (H), all generate spontaneous diastolic local Ca^{2+} releases (LCRs)

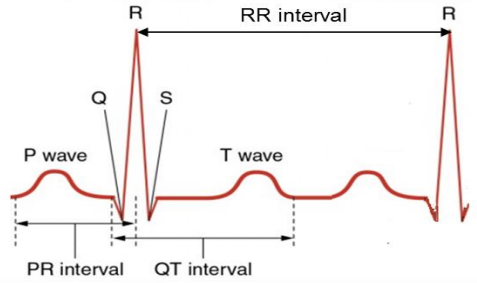




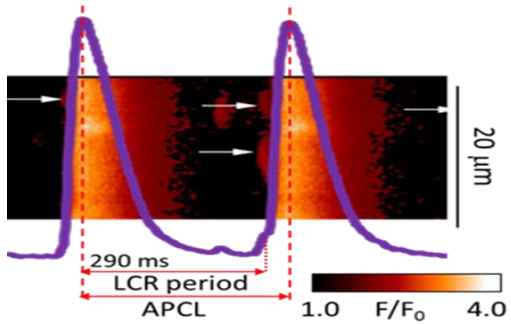


Variations in the coupled-clock LCR period predict variations in the EKG parameters in vivo

in vivo EKG parameters

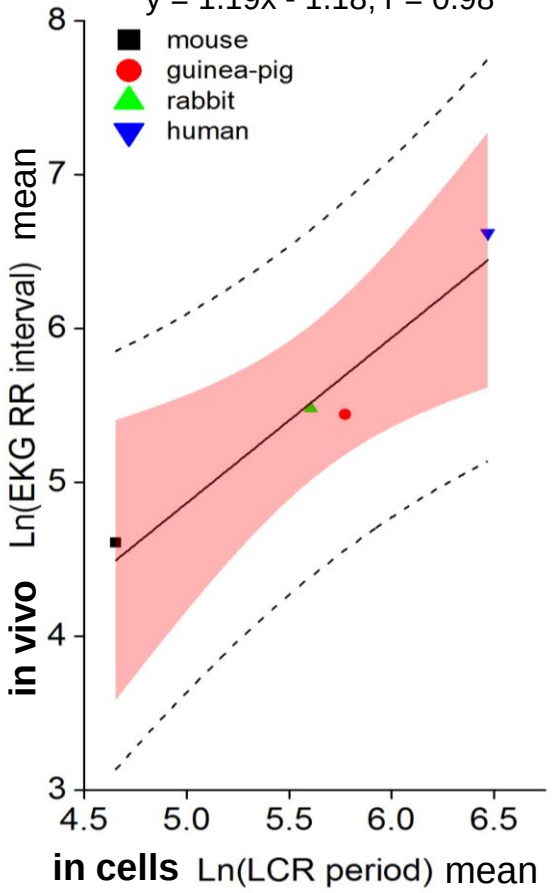


LCR period in pacemaker cells



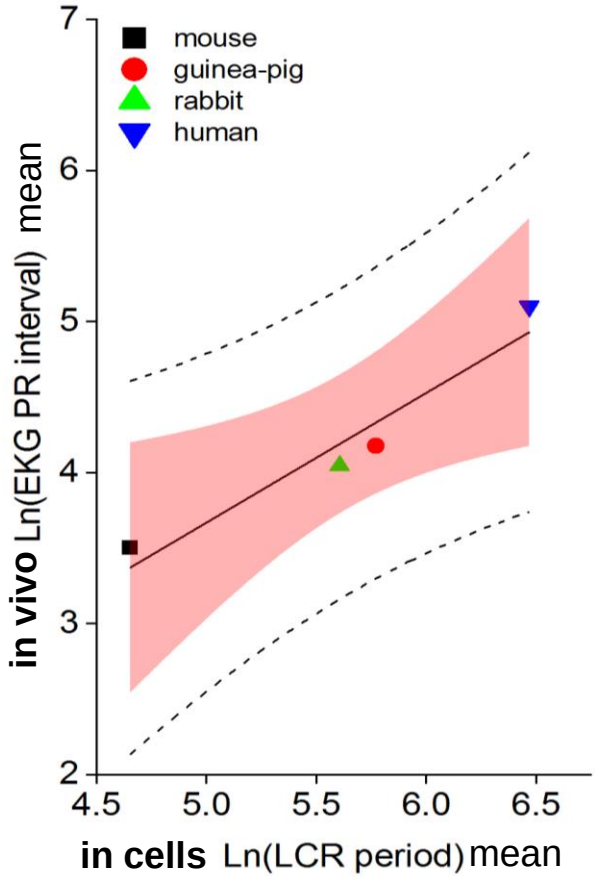
RR interval

y = 1.19x - 1.18; r = 0.98



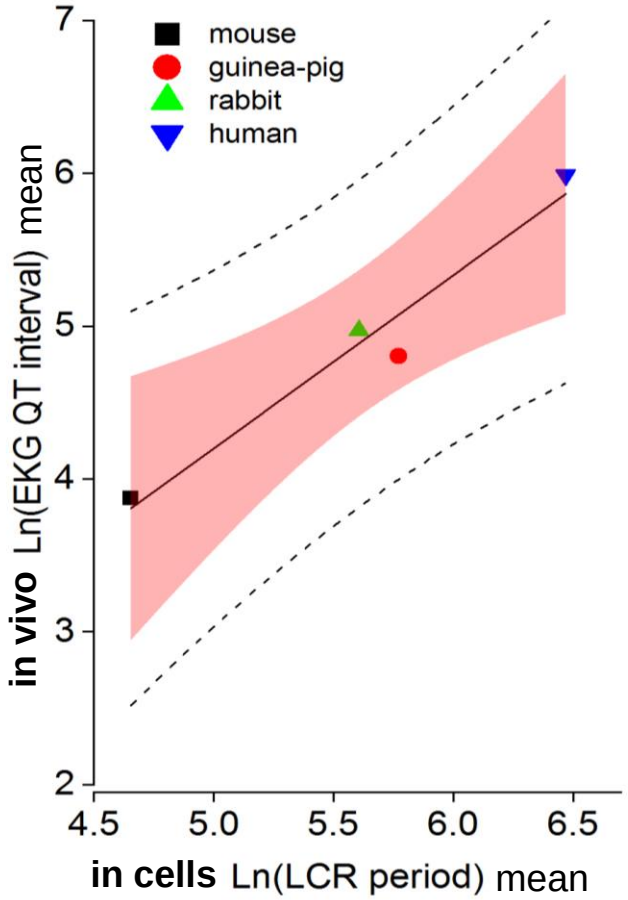
PR interval

y = 0.86x - 0.62; r = 0.97

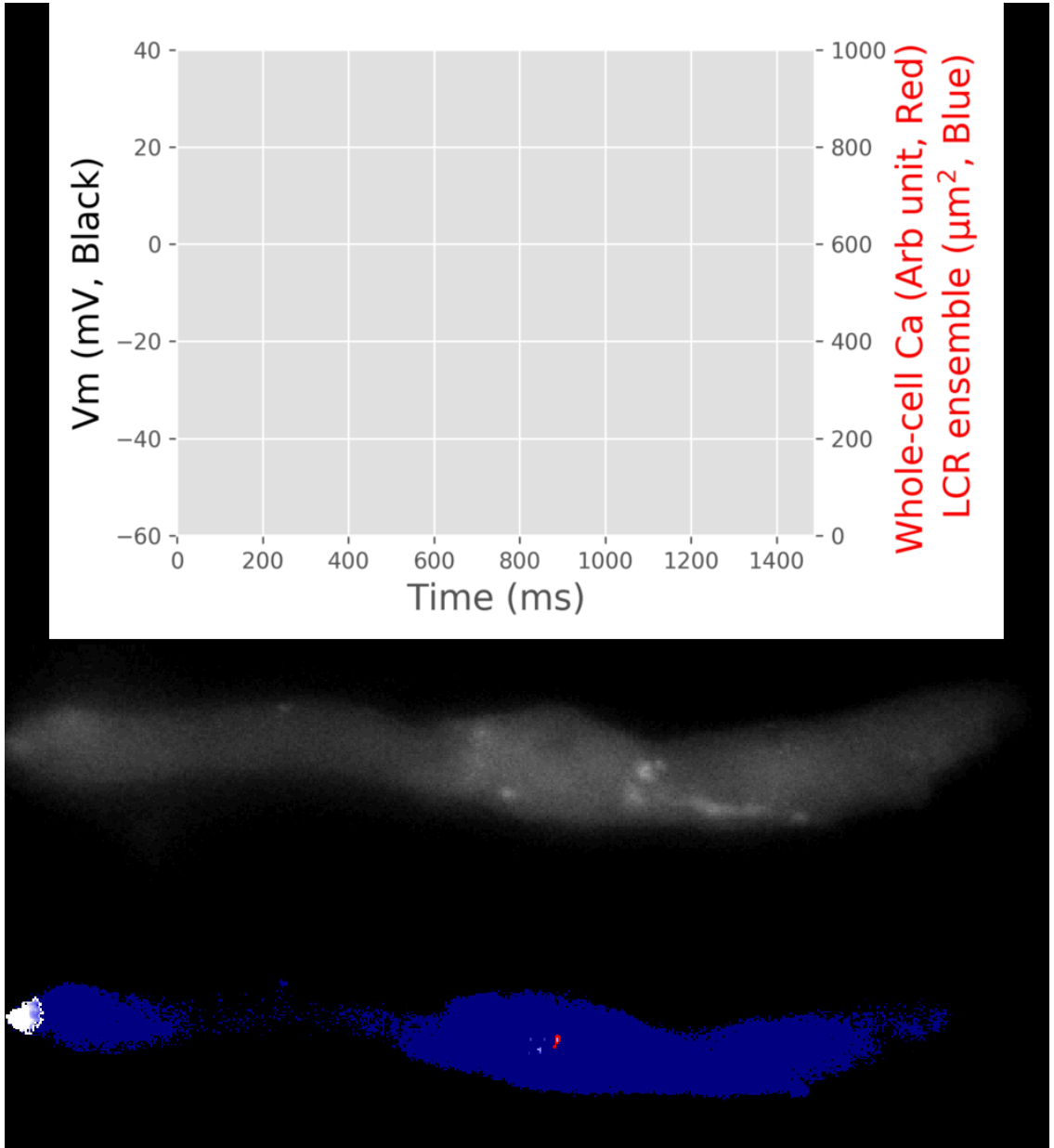


QT interval

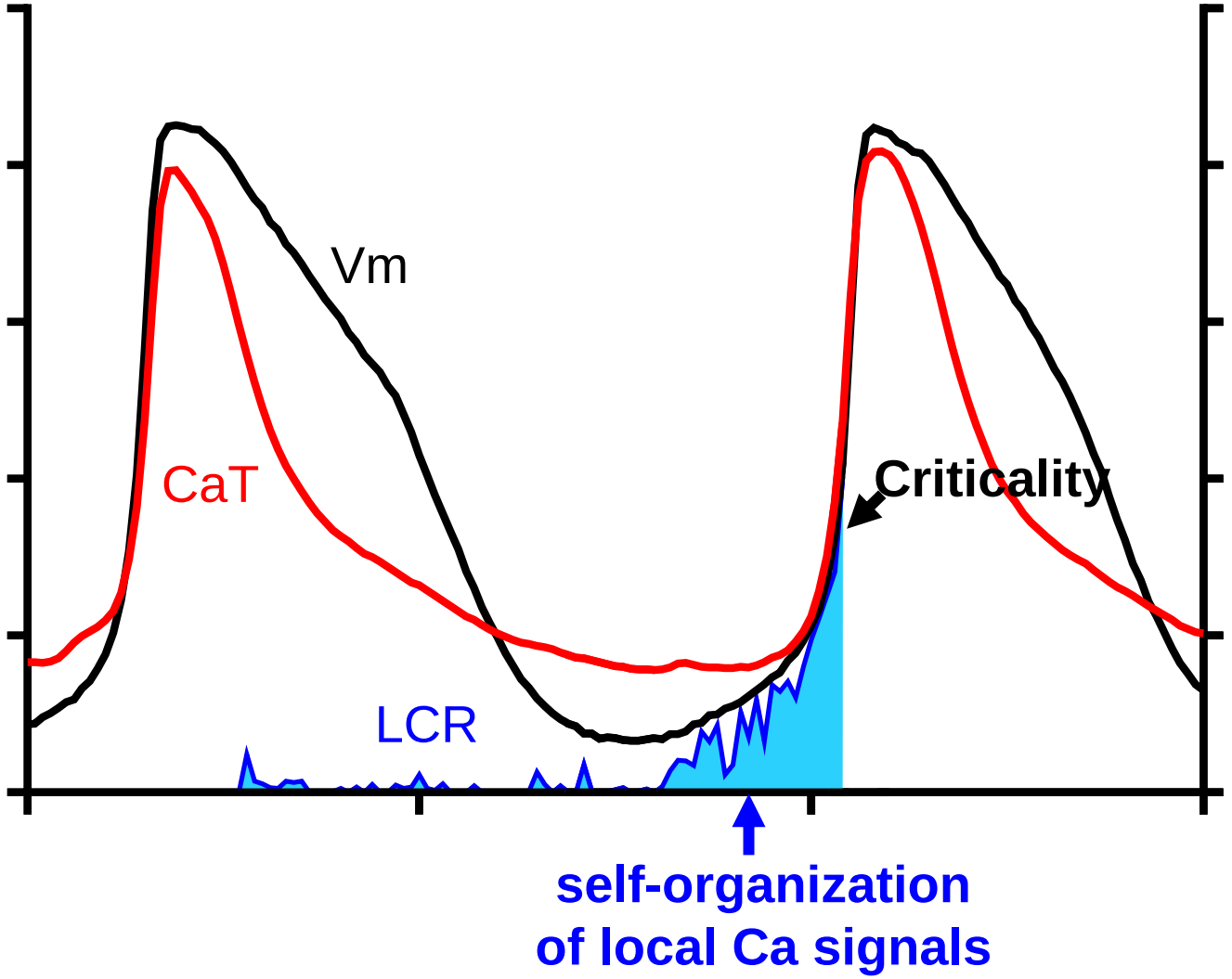
y = 1.13x - 1.47; r = 0.98



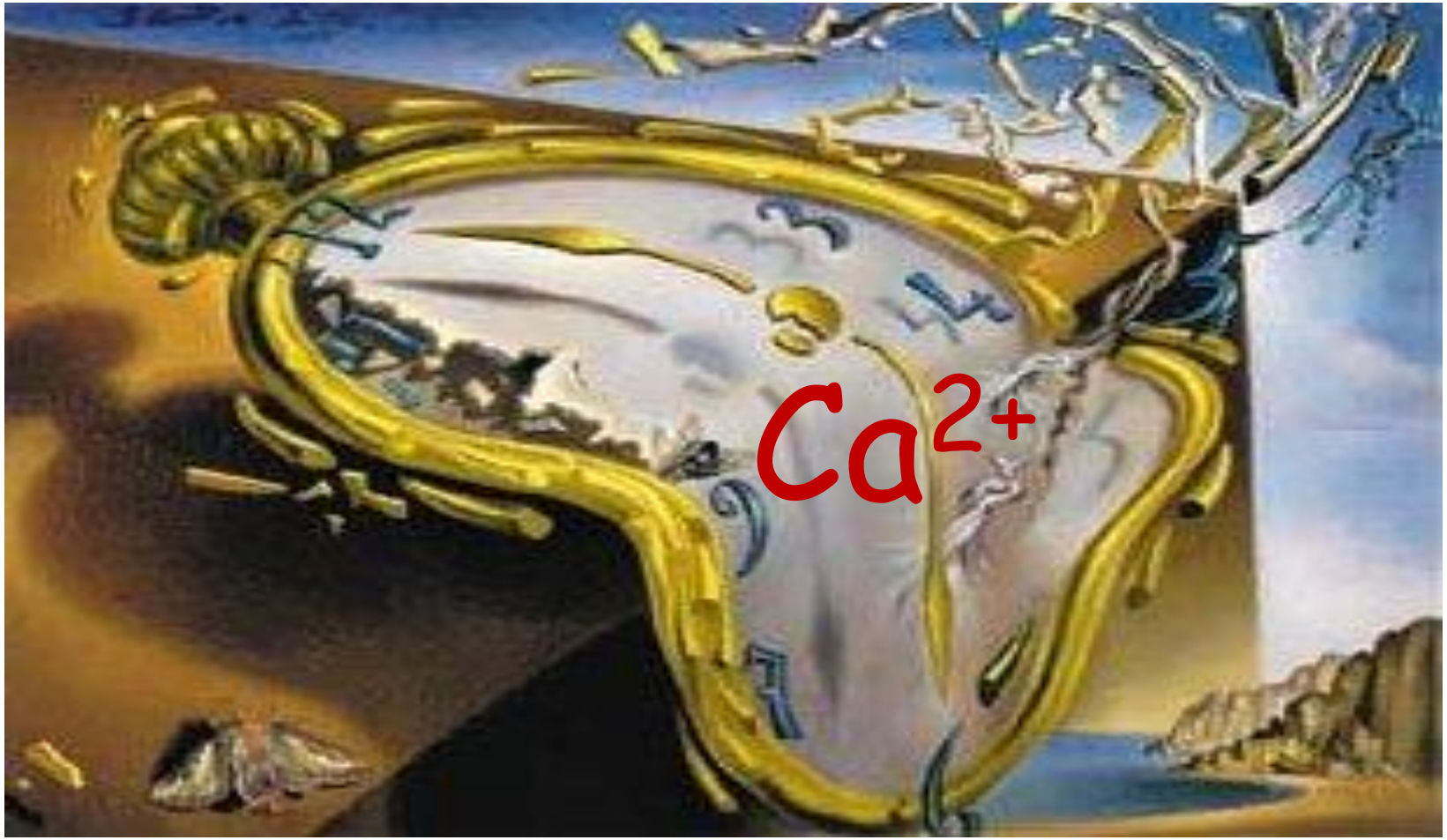
A coupled-oscillator system drives human pacemaker cell automaticity



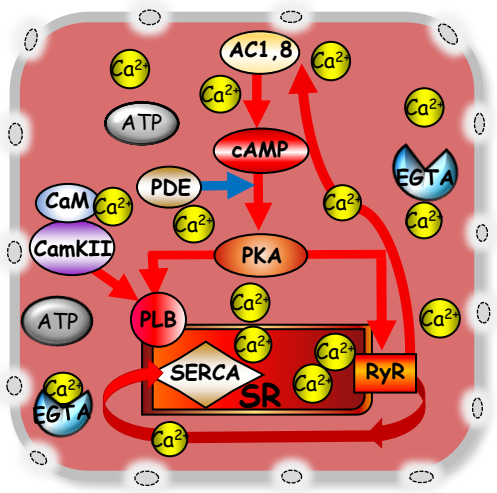
Self-organized criticality

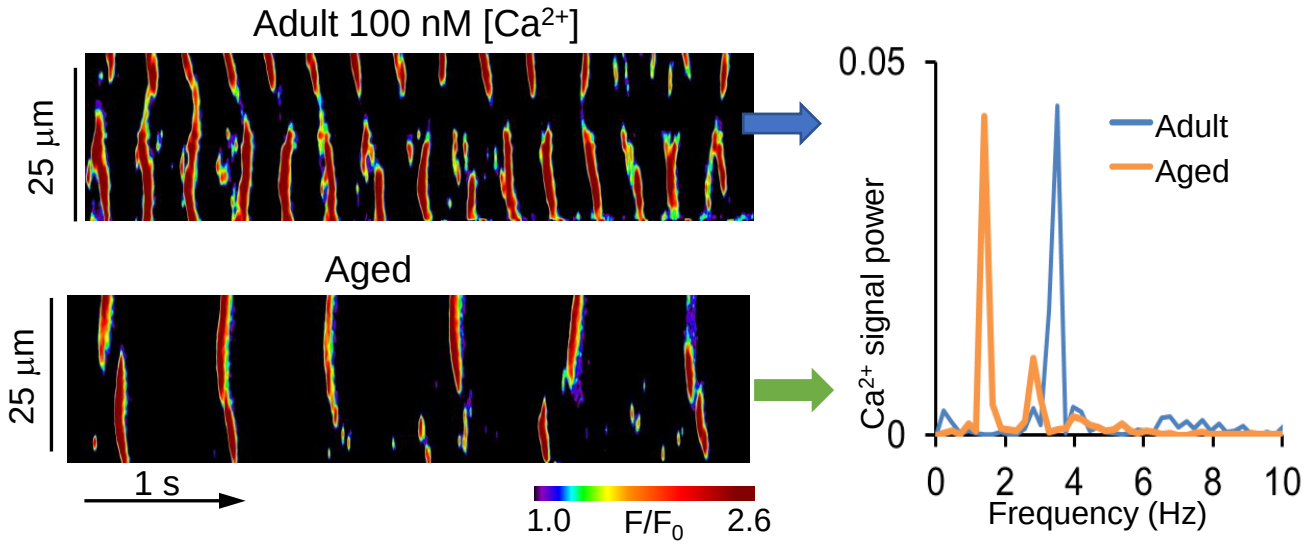


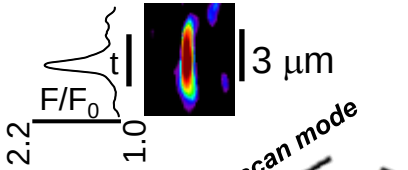
This is what happened

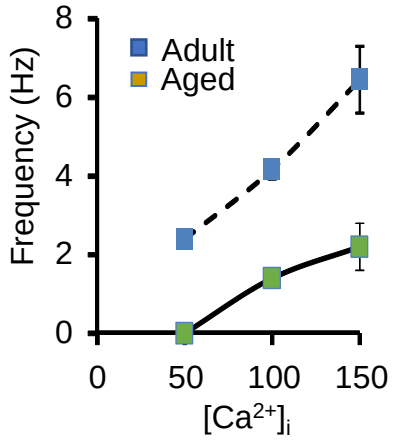


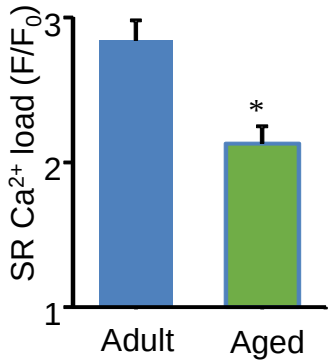
Pacemaker Cell Ca^{2+} Clock Rhythmicity and SR Ca^{2+} load Declines with Aging



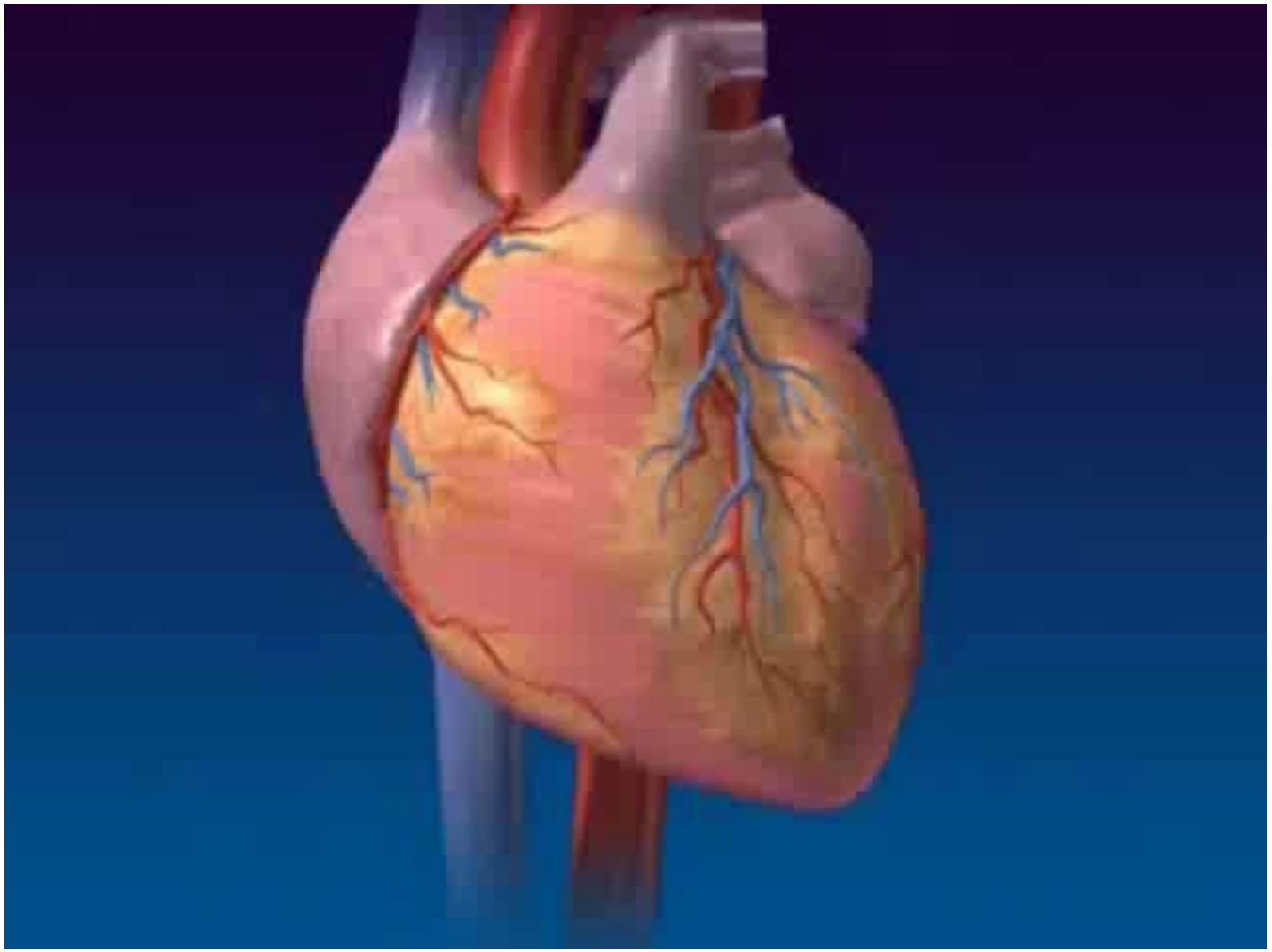




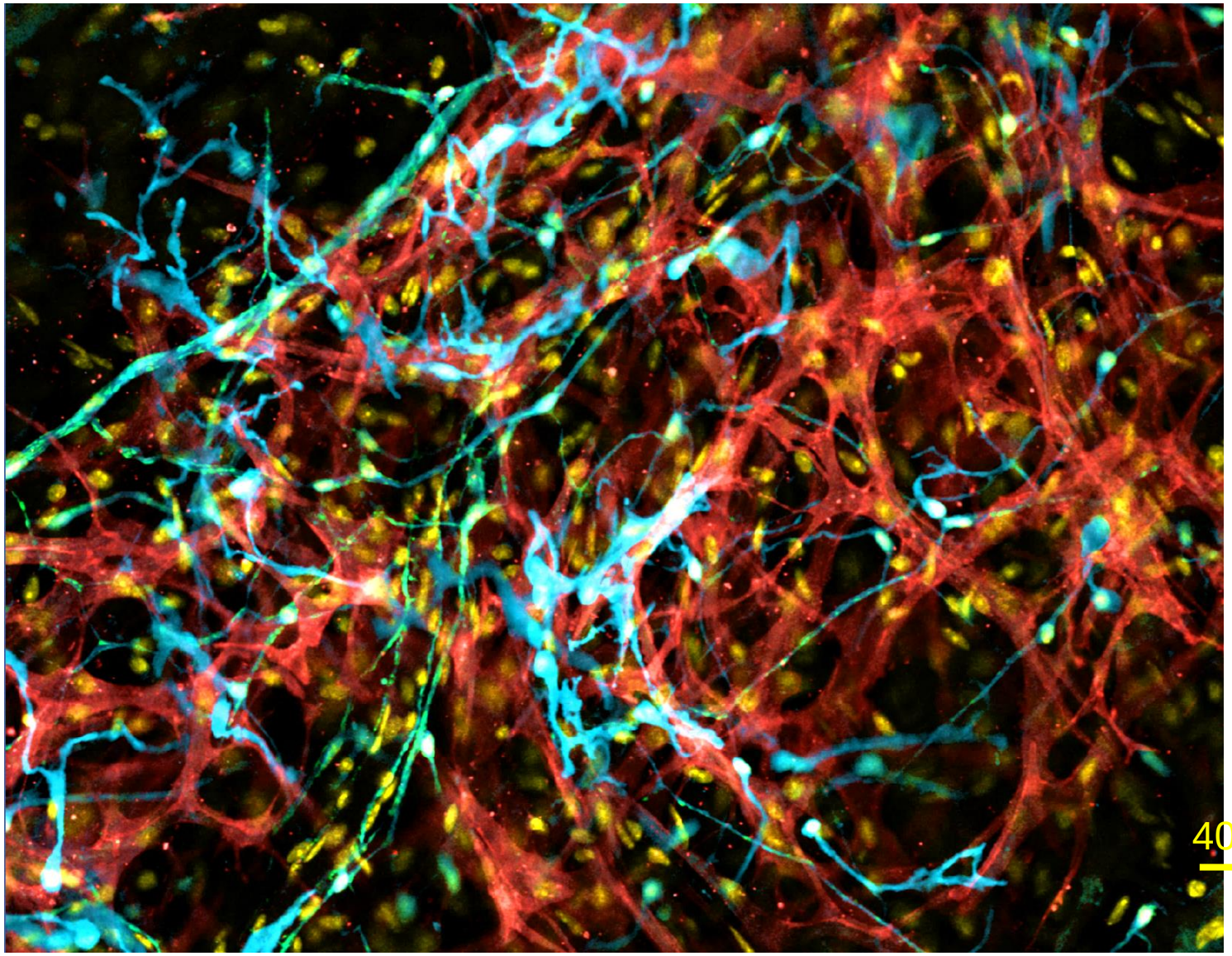




The heartbeat operates in a critical state, i.e. it undergoes continuous phase transitions

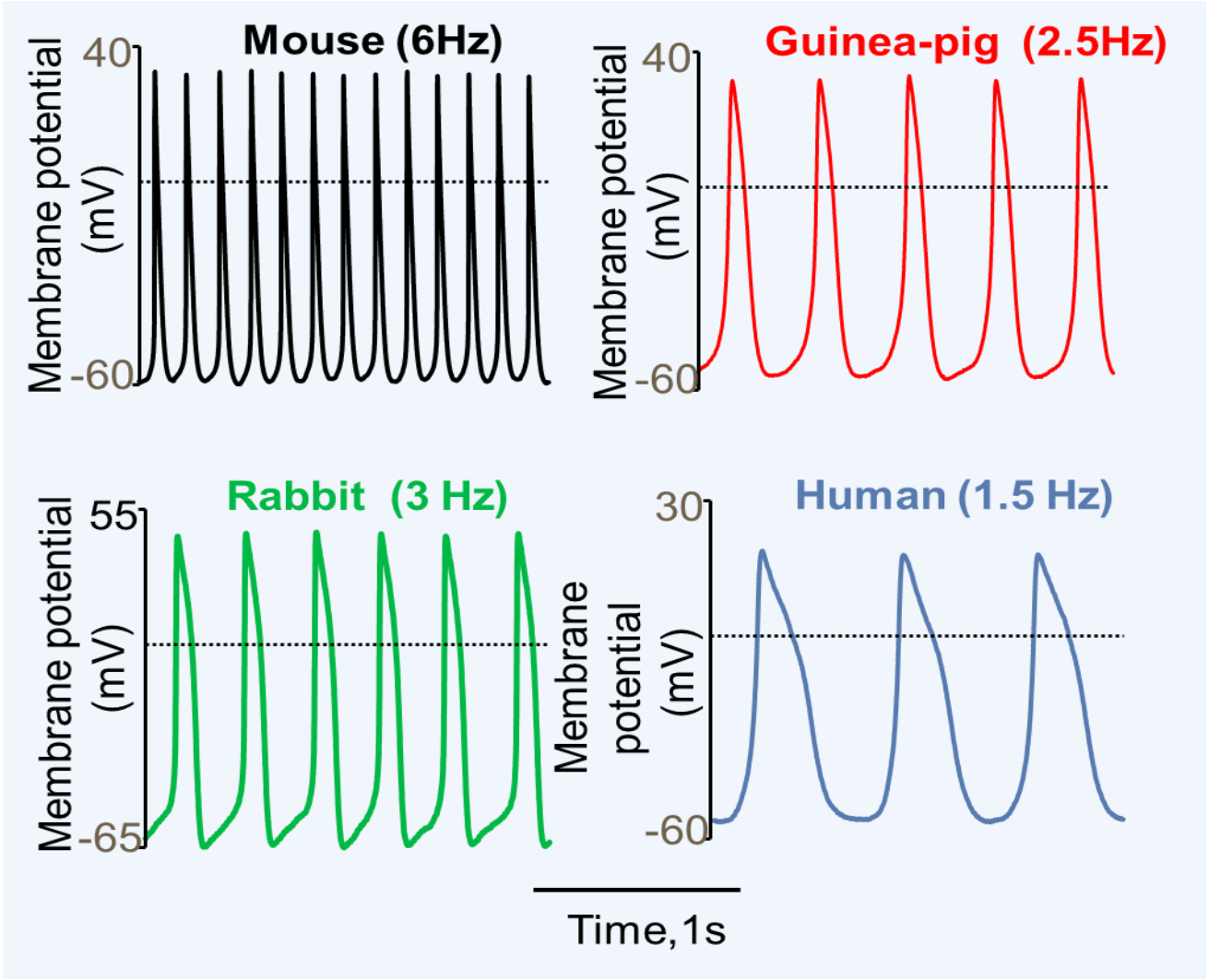


A glial cell network, nerves, and pacemaker cells work together in the heart's brain

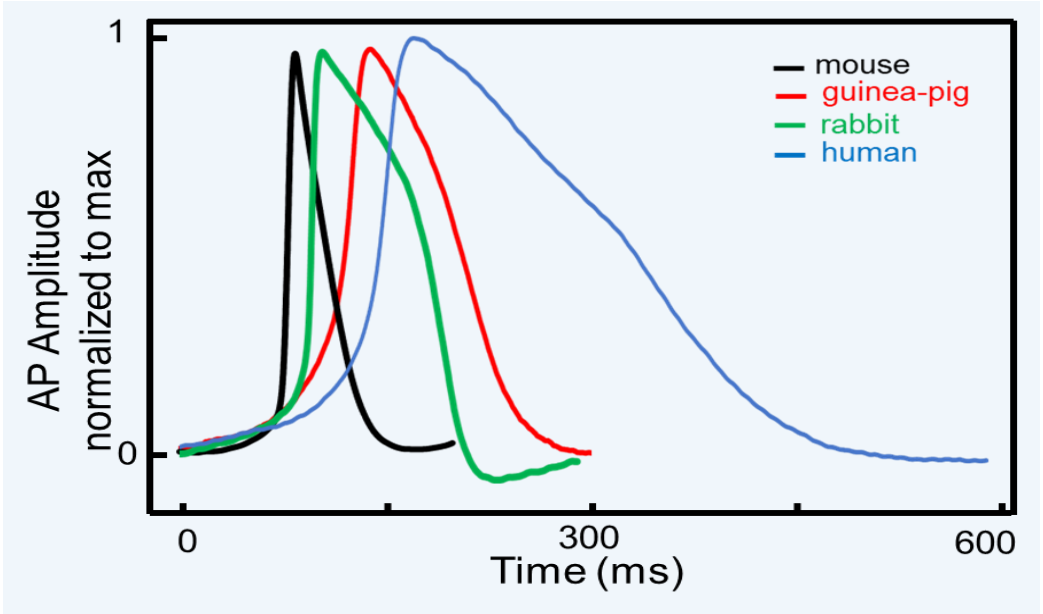


HCN4 (red) S100B (cyan) vCHAT (green) nuclei (yellow)

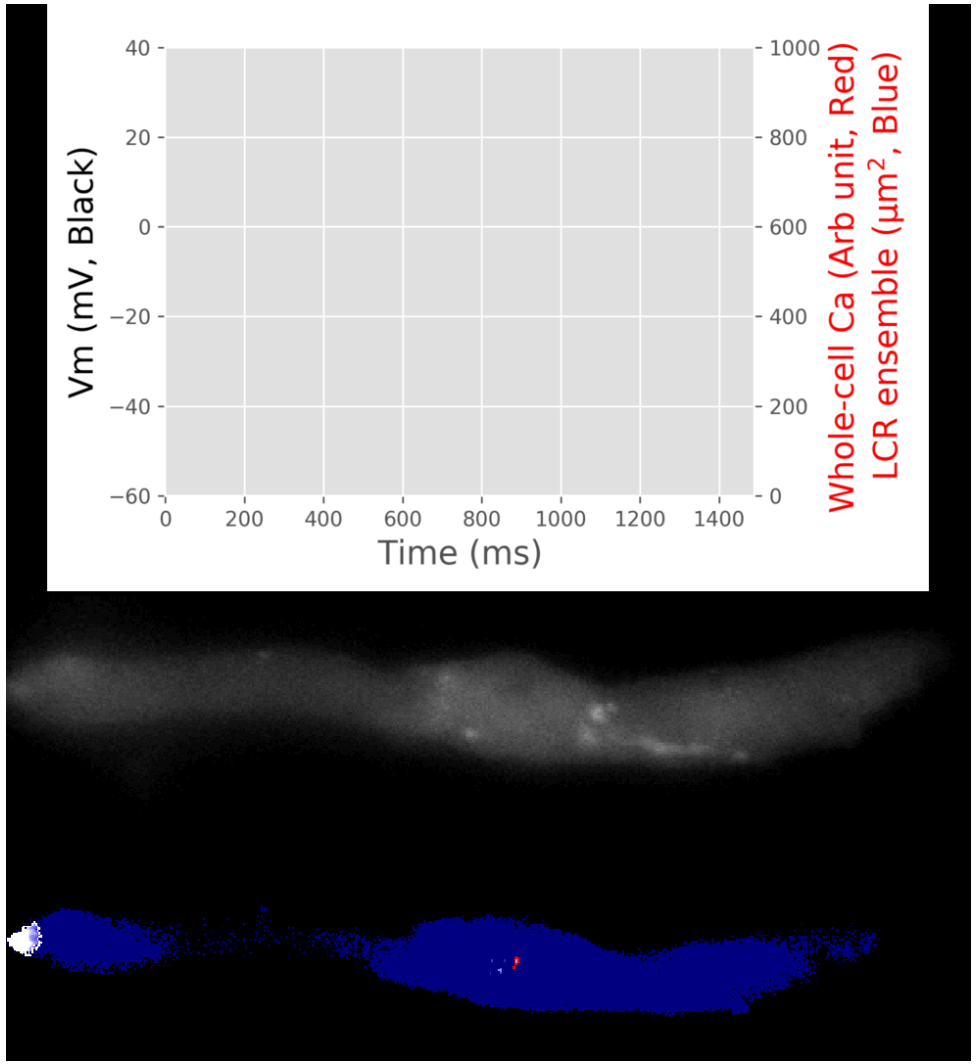
The Absolute AP Cycle Lengths, Shapes and Durations Differ Markedly From Mouse to Humans in Single Pacemaker Cells in Vitro



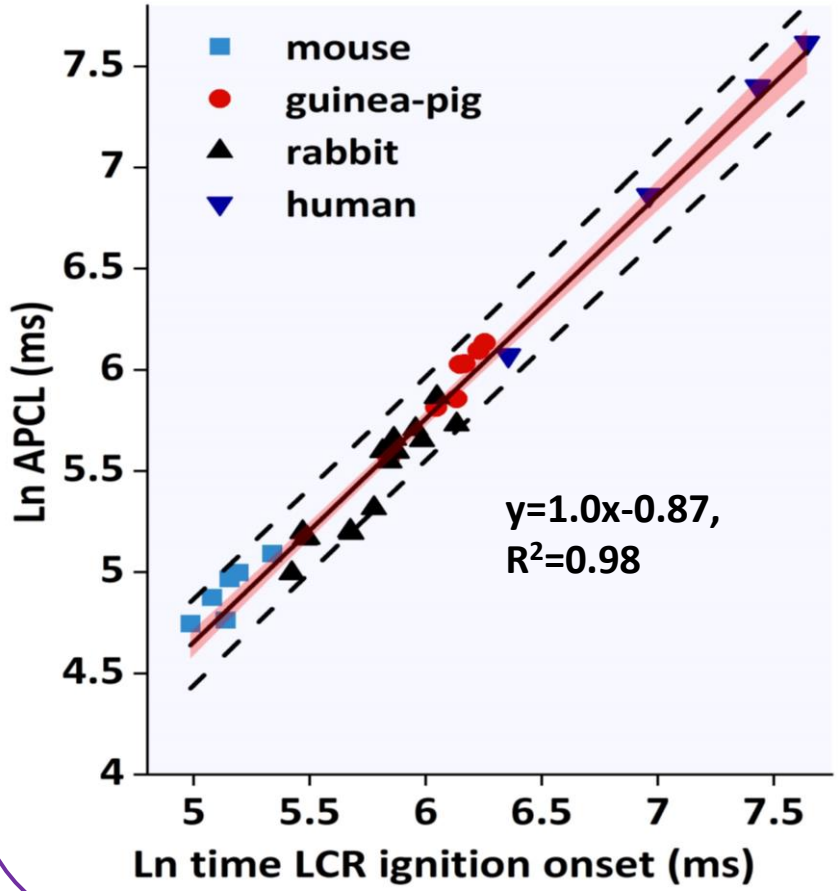
Superimposed AP traces

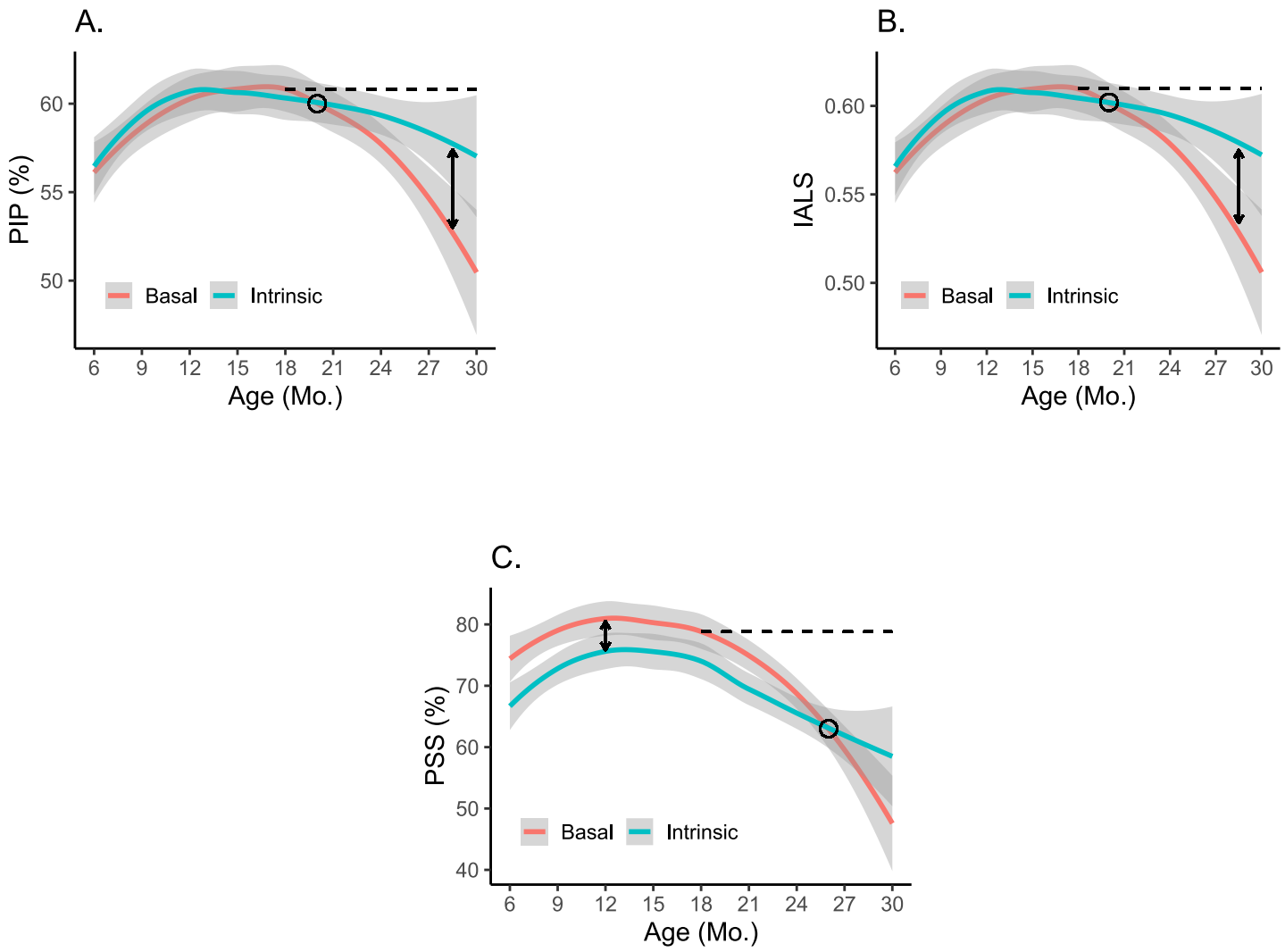


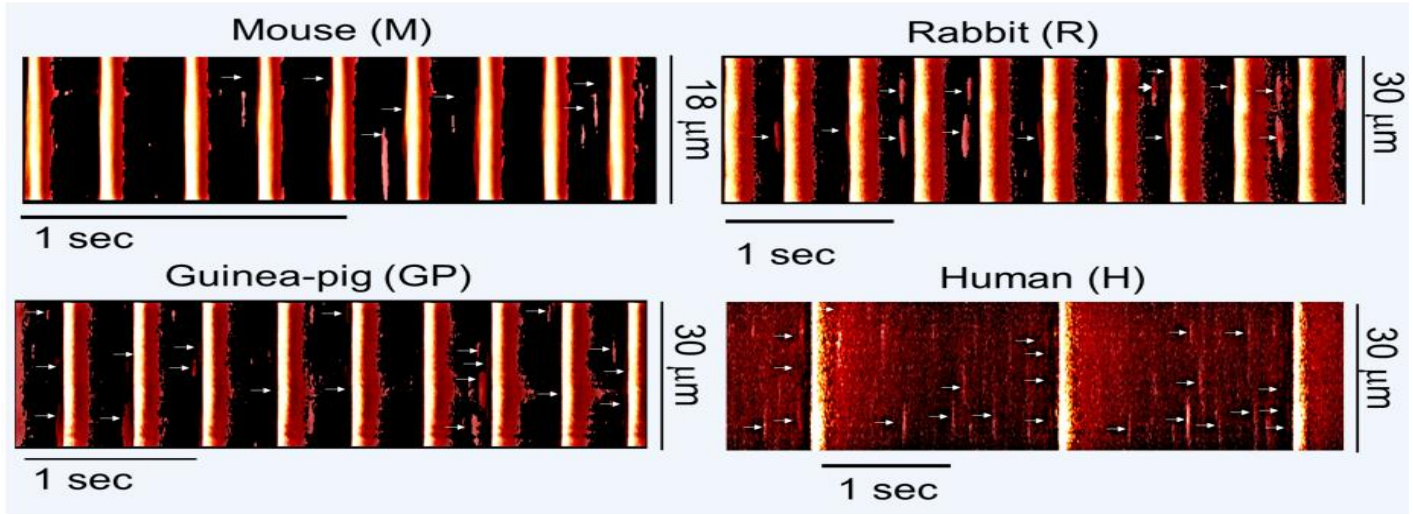
The initiation of the cell beat is driven by local calcium releases (LCR)

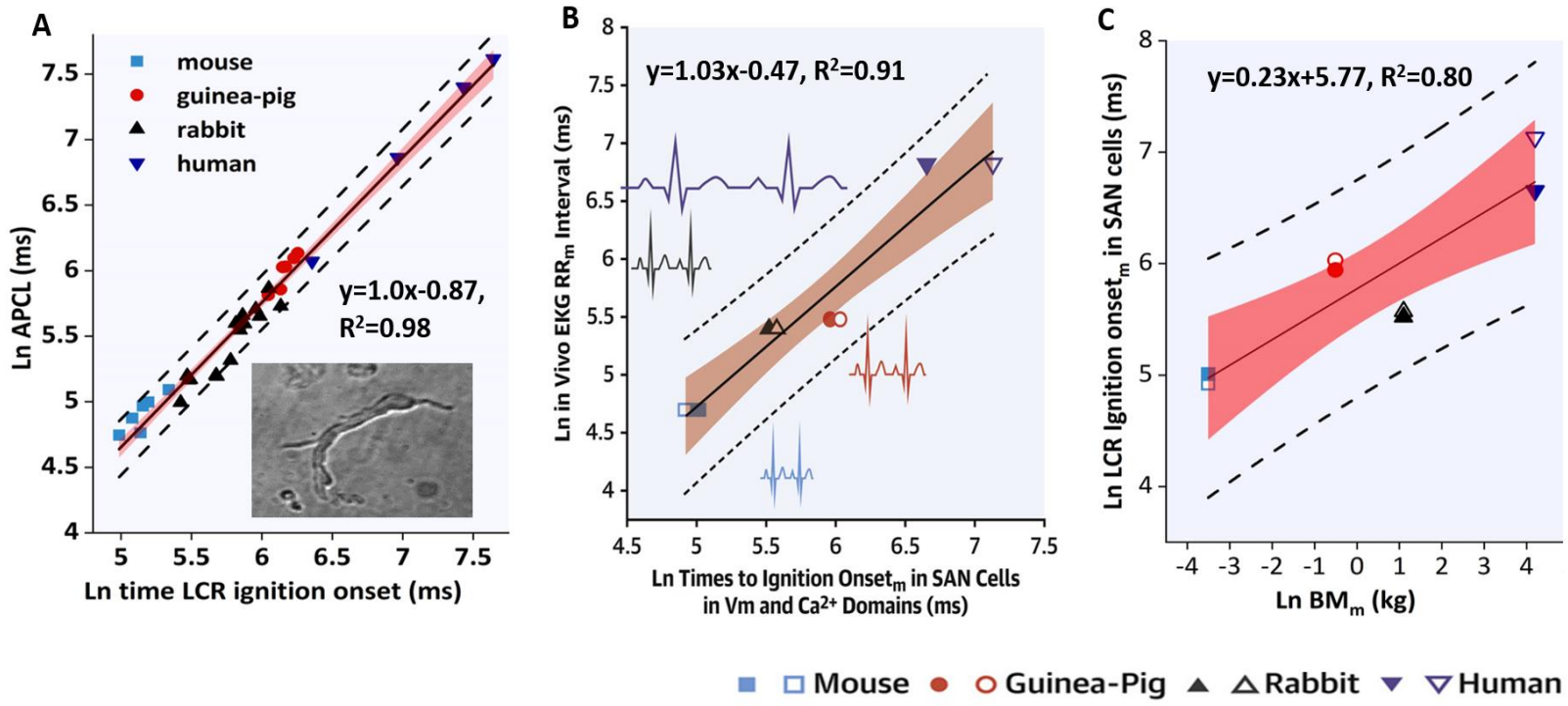


Self-similarity of ignition to action potential firing of isolated pacemaker cells across species.

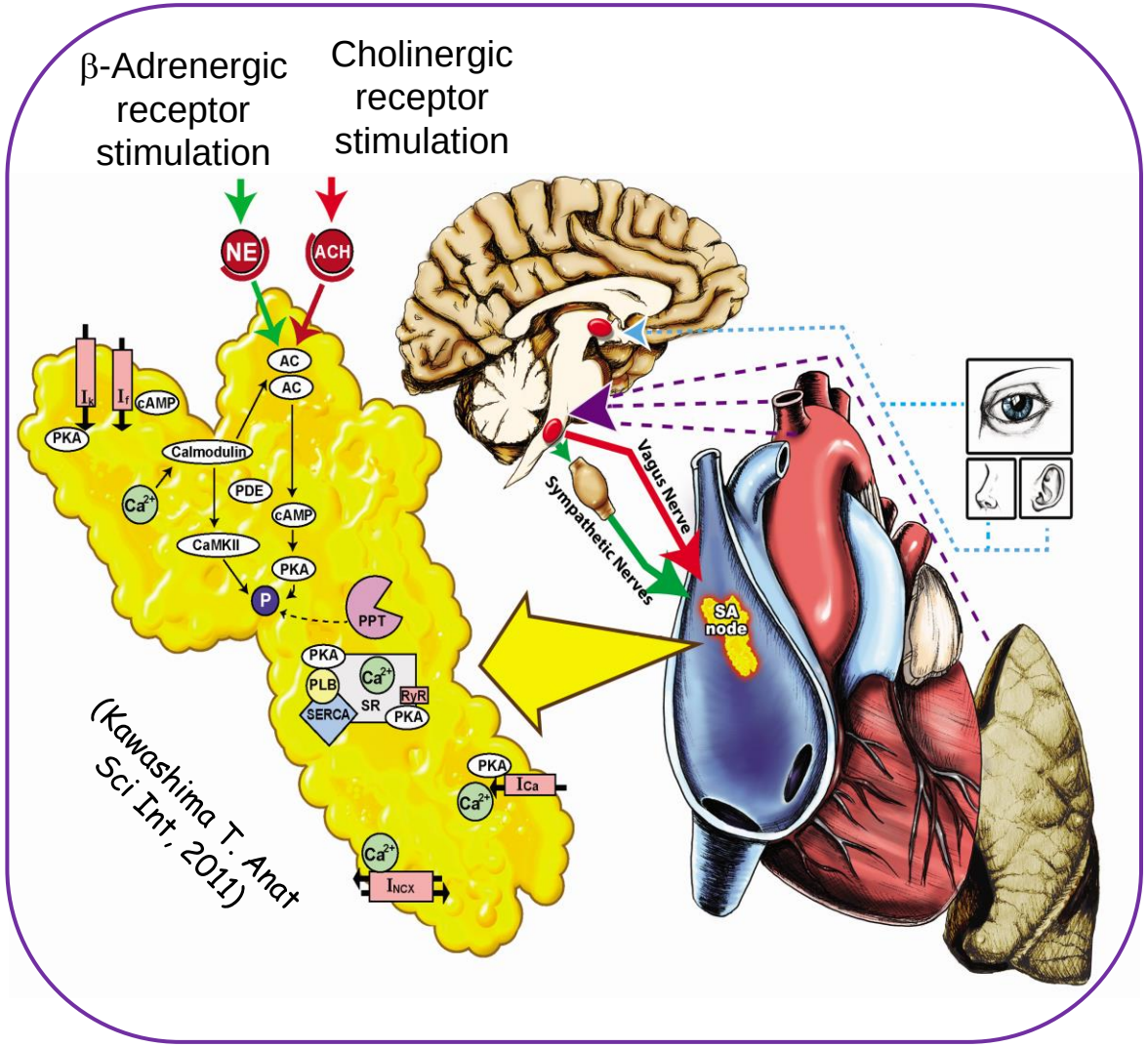


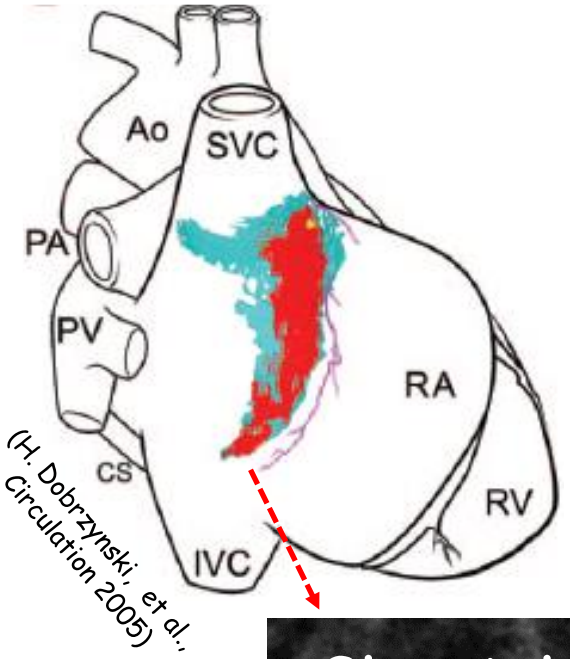

A.
PIP (%)
60
55
50
Basal
Intrinsic
6
9
12
15
18
21
24
27
30
Age (Mo.)
B.
IALS
0.60
0.55
0.50
Basal
Intrinsic
6
9
12
15
18
21
24
27
30
Age (Mo.)
C.
PSS (%)
80
70
60
50
40
Basal
Intrinsic
6
9
12
15
18
21
24
27
30
Age (Mo.)


Mouse (M)
18 μm
1 sec
Rabbit (R)
30 μm
1 sec
Guinea-pig (GP)
30 μm
1 sec
Human (H)
30 μm
1 sec

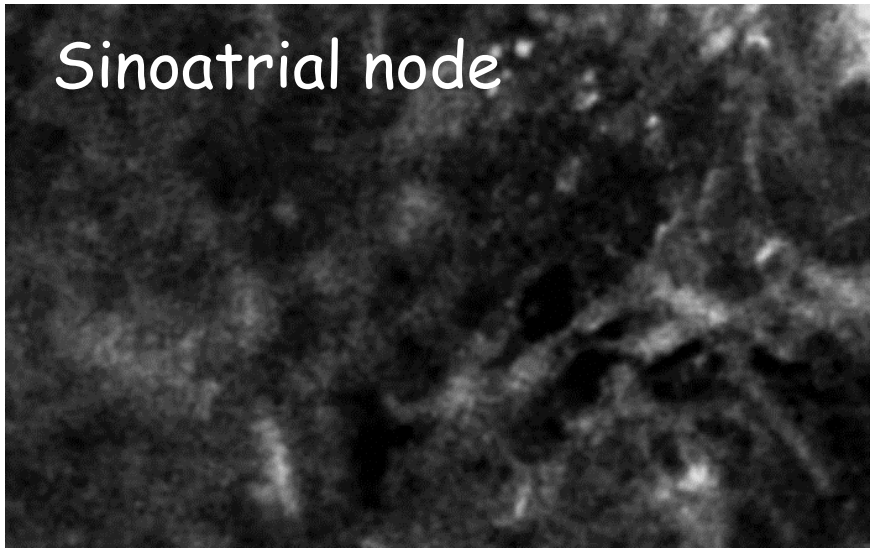

A
mouse
guinea-pig
rabbit
human
y=1.0x-0.87,
R²=0.98
Ln APCL (ms)
Ln time LCR ignition onset (ms)
B
y=1.03x-0.47, R²=0.91
Ln in Vivo EKG RRm Interval (ms)
Ln Times to Ignition Onsetm in SAN Cells in Vm and Ca2+ Domains (ms)
C
y=0.23x+5.77, R²=0.80
Ln LCR Ignition onsetm in SAN cells (ms)
Ln BMm (kg)
Mouse
Guinea-Pig
Rabbit
Human

Sinoatrial node is the heart's brain





Sinoatrial node cell
(cardiac pacemaker cell)



So, what's aging?
Desynchronization

- Desynchronization of activation states among molecules
- Desynchronization of molecular signaling pathway activation
- Desynchronization of organelle functions within cells
- Desynchronization of cell functions within tissues
- Desynchronization of organ functions within organisms

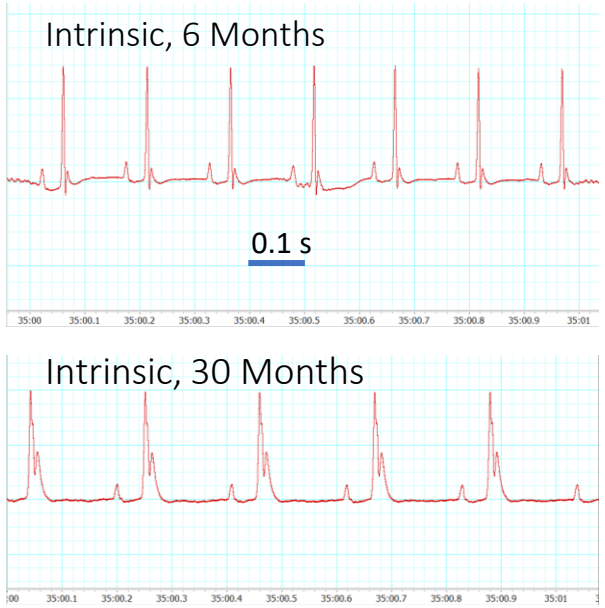
Conclusions:

- **We can conclude that we discovered a brain-like cytoarchitecture of the SAN comprised of $HCN4^{+}$ meshwork and its intertwining $S100B^{+}$ glial-like interstitial network.**

- **We may even envision the sinoatrial node as a rudimentary brain, creating, and coordinating signals within and among SAN pacemaker cells.**

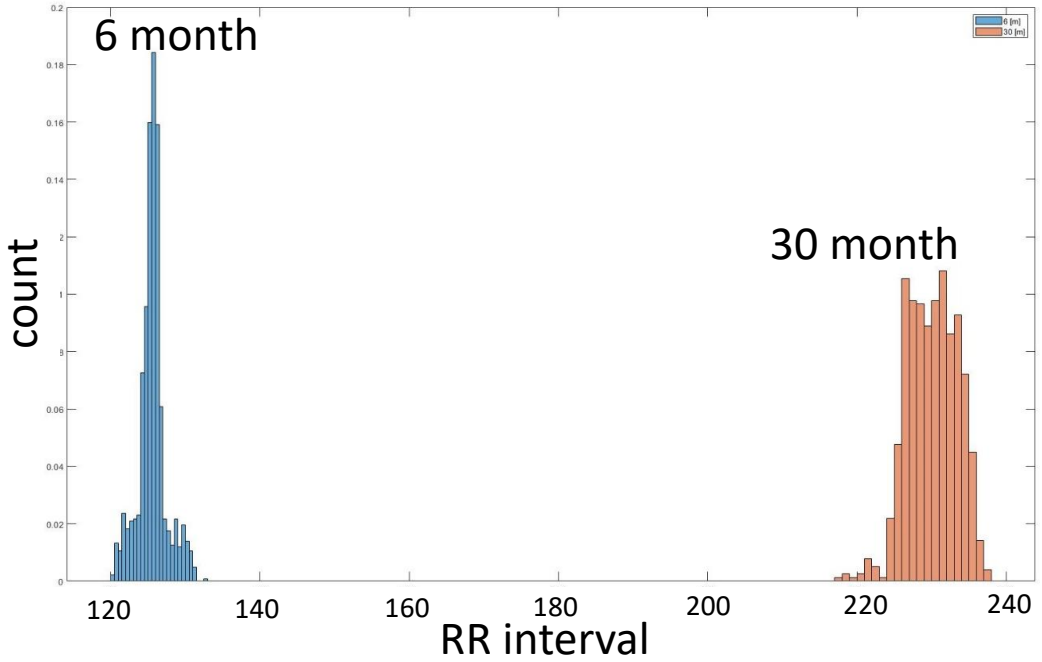
A

B

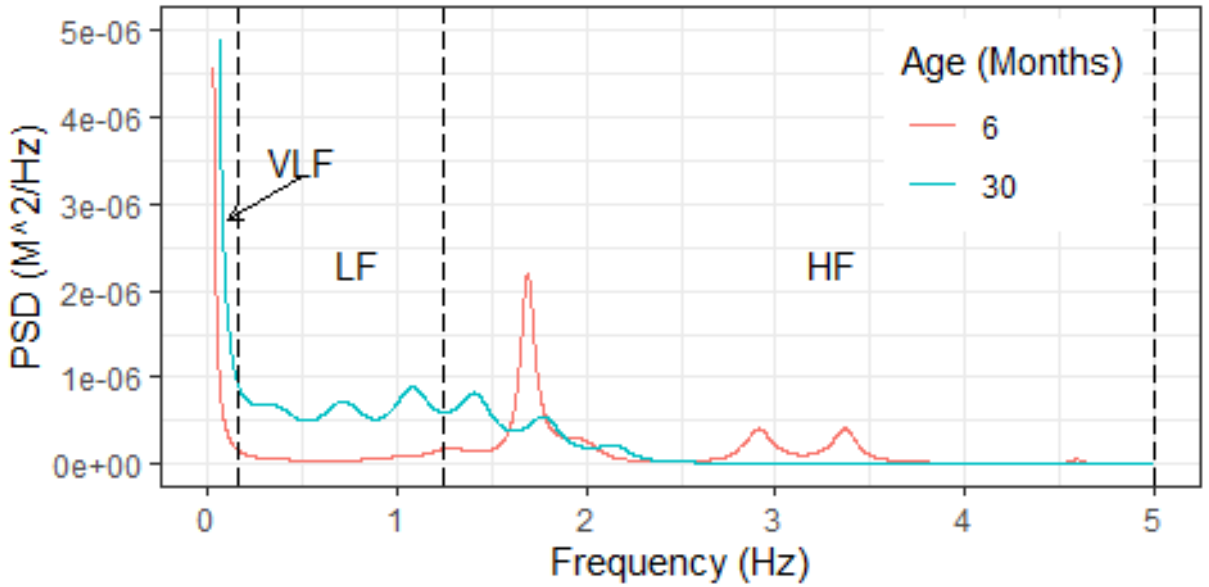


C

Distributions of EKG RR intervals for mouse 1730.



Heartbeat music in the frequency domain for mouse 1730.



EKG heartbeat interval music channels

- Variable Heartbeat intervals can be appreciated as musical notes, each having a pitch and tempo.
- Heartbeat interval musical notes are broadcast to the body surface on different EKG channels.
  - Time domain “channel”
  - Frequency domain “channel”
  - Nonlinear domain channel “channel”
  - Fragmentation domain “channel”
  - Circadian “channel”
- Note bene: the mean RR interval is a post-hoc calculation by an external observer: counting the number of notes (RR intervals) over a fixed time period and dividing by the time period.
- The mean RR interval does not capture the notes of the heartbeat interval music.

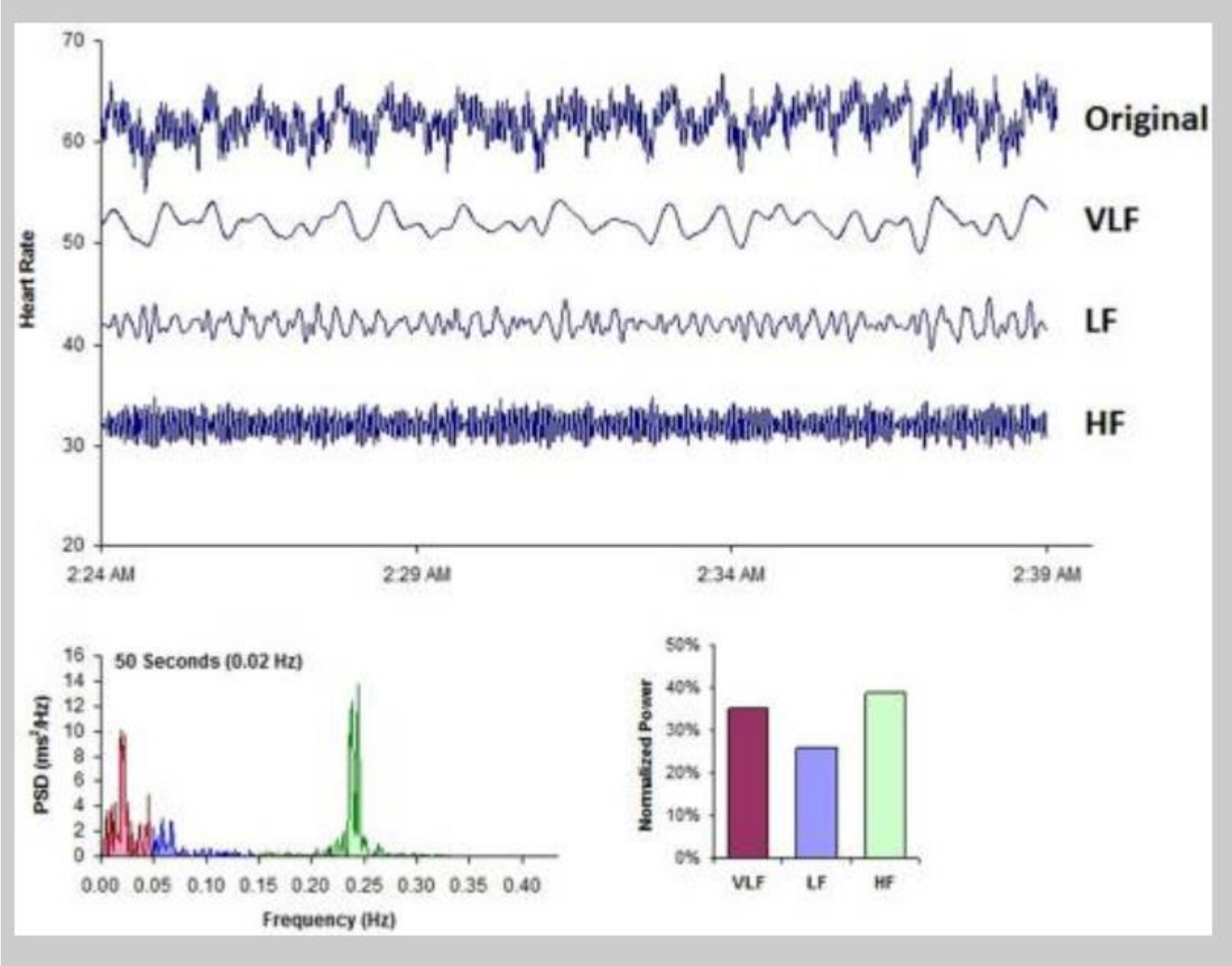
Synchronization

- A consilience of activation states among molecules
- Consilient molecular signaling pathway activation
- Consilient organelle functions within cells
- Consilient cell functions within tissues
- Consilient functions of organs within organisms

EKG heartbeat interval music channels

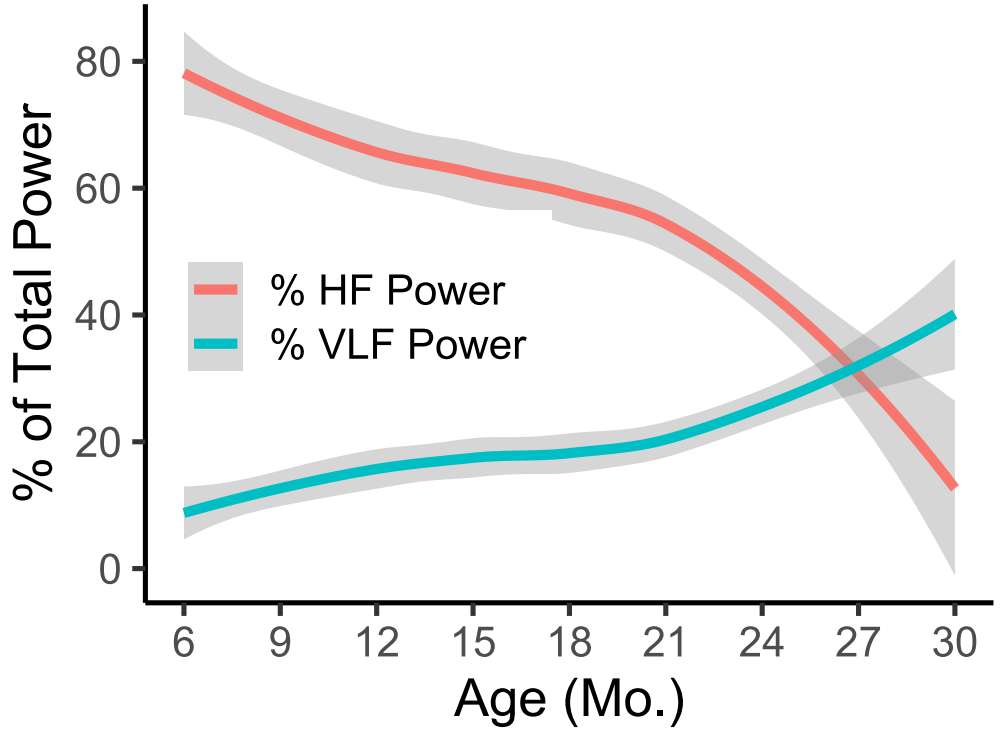
- Heartbeat interval music is broadcast to the body surface on different EKG channels.
  - Time domain "channel"
  - Frequency domain "channel"
  - Nonlinear domain channel "channel"
  - Fragmentation domain "channel"
  - Circadian "channel"

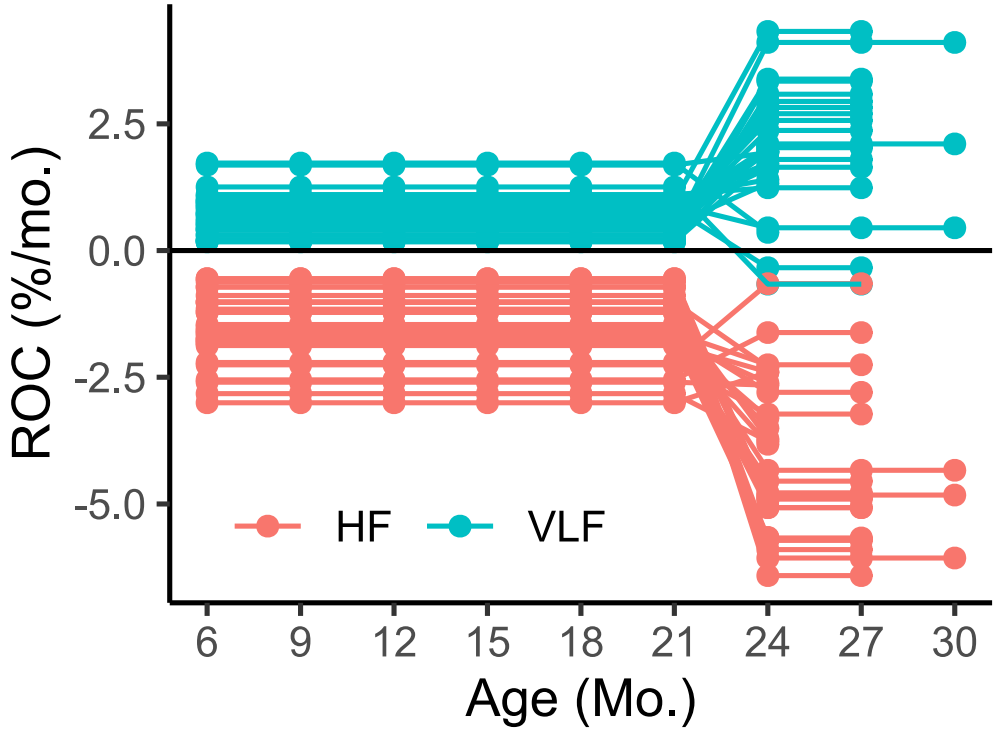
“Heartbeat music” in the frequency domain



Front Psychol. 2014; 5: 1040

Average loess smooth curves of % intrinsic VLF and HF and Mouse-specific rates of change of % intrinsic VLF and HF in long-lived mice.

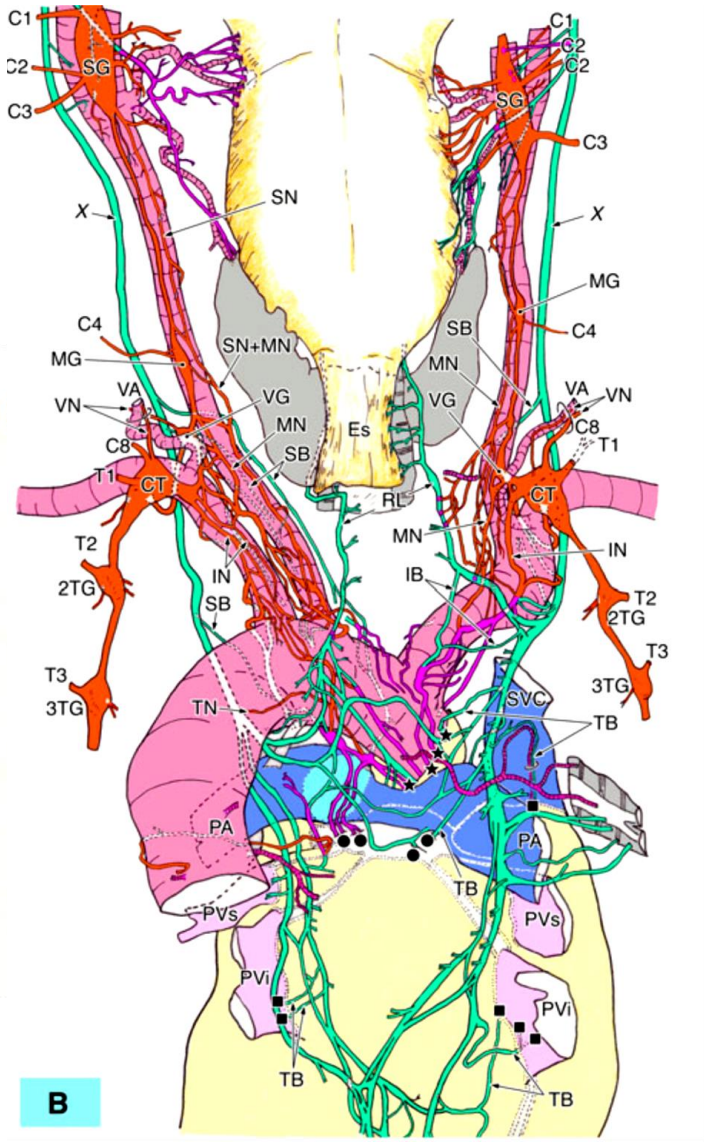




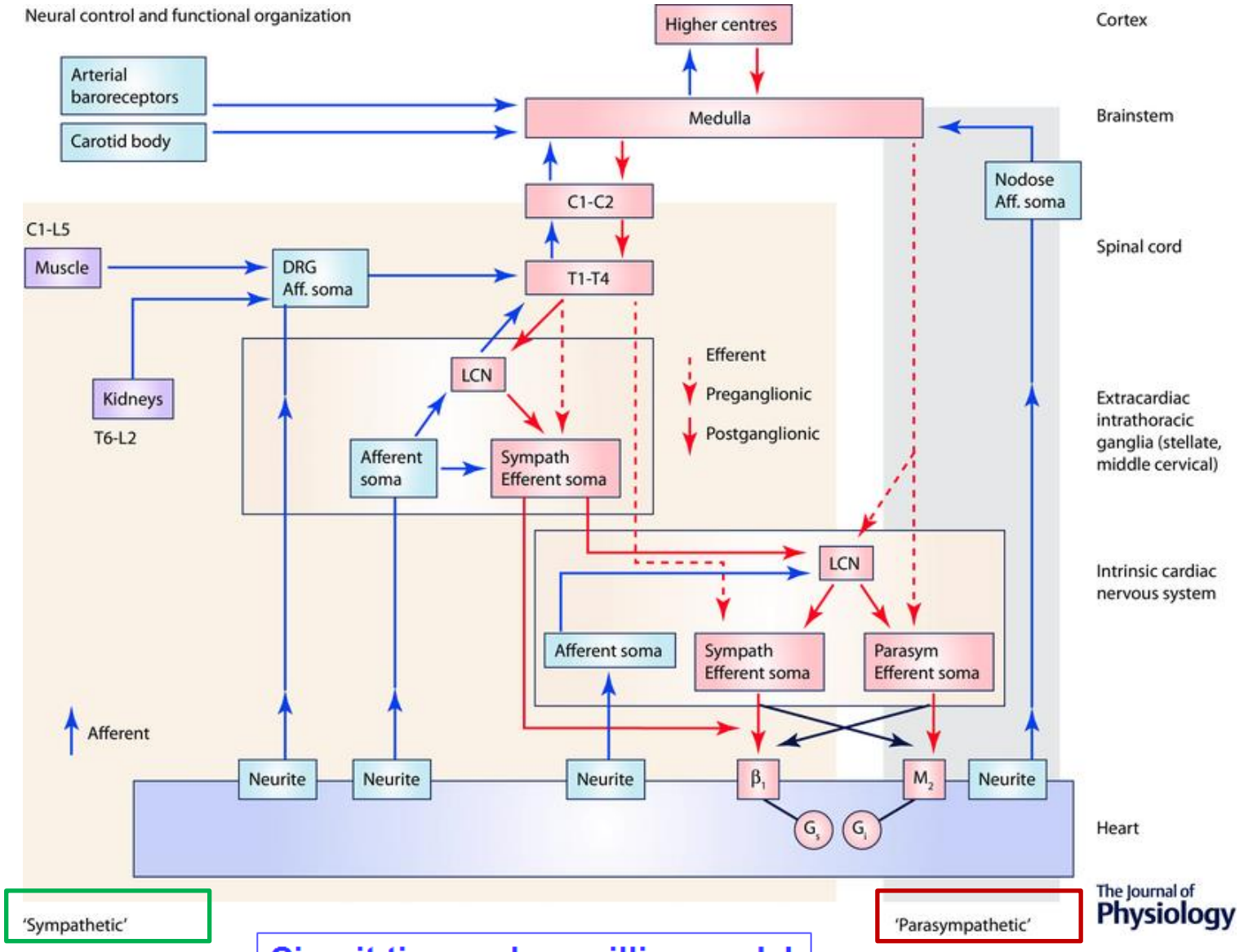
Autonomic input to the heart fine-tunes "heartbeat musical notes" more effectively in younger than in older hearts.

- Heartbeat intervals can be appreciated as musical notes.
- Variable heartbeat intervals can be appreciated as musical notes having a different pitch (in kHz) depending on the duration of the interval.
- Autonomic input tunes the pitch of heartbeat interval notes in younger hearts to a greater extent than in older ones.

CARDIAC NEURAL CONTROL CIRCUITRY- TERMINOLOGY AND SCHEMATICS



Kawashima T. Anat Sci Int (2011) 86:30–49



Circuit timescales- milliseconds!

Shivkumar K, Ajijola OA, Anand I, Armour JA, Chen PS, Esler M, De Ferrari GM, Fishbein MC, Goldberger JJ, Harper RM, Joyner MJ, Khalsa SS, Kumar R, Lane R, Mahajan A, Po S, Schwartz PJ, Somers VK, Valderrabano M, Vaseghi M, Zipes DP. Clinical neurocardiology defining the value of neuroscience-based cardiovascular therapeutics. The Journal of Physiology. 2016;594(14):3911-54.