“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”

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Noble

Presentation

short

Made in Castalia
The heartbeat results from multi-scale synchronization processes that self-organize at each scale.
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

Measurement time points (months)

6  9  12  15  18  21  24  27  30

n=58

1. Resting HR
2. Intrinsic HR
3. Echo (LV)

% survival

0  25  50  75  100

Age (months)

6  9  12  15  18  21  24  27  30

Short lived  Long lived
LCS Approach to Studying Aging

Long-lived mice lived achieved the median lifespan of the entire cohort (24.7 months).
Why can the heart beat outside of the body?
Because it has its own brain in the sinoatrial node
WHICH IS THE MOUSE HEAD BRAIN AND WHICH IS THE HEART BRAIN?

Head Brain

Heart Brain: Sinoatrial Node
Cells that Control the Rate and Strength of the Heart Beat

Sinoatrial node cells are responsible for controlling the rate and strength of the heart beat.
**A Coupled-System of Chemical and Current Oscillators**

- **Ca**$^{2+}$ release
- **Ca**$^{2+}$ clock
- **Sarcoplasmic Reticulum**
- **SERCA2A**
- **Ca**$^{2+}$ pumping
- **Cell Surface Membrane**

**Processes:**
- **Depolarization**
- **Repolarization**

**Components:**
- **RyR**
- **Ca**$^{2+}$ release
- **Ca**$^{2+}$ clock
- **SERCA2A**
- **Ca**$^{2+}$ pumping

**Currents:**
- $I_f$
- $I_{NCX}$
- $I_{CaT}$
- $I_{CaL}$
- $I_k$

**M clock**

**Resetting & refueling**
Cells that Control the Rate and Strength of the Heart Beat

- **sinoatrial node**
- **sinoatrial node cells**
- **Ventricular Myocyte**

Diagram showing the sinoatrial node and sinoatrial node cells with corresponding membrane potential over time.
New method of microscopic optical mapping opens unknown frontiers in SAN research

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!

LCS Approach to Studying Aging

Long-lived mice lived achieved the median lifespan of the entire cohort (24.7 months).
Autonomic Nervous System Support
4 month old mouse heart’s brain

29 month old mouse heart’s brain

Immunostaining HCN4

Ca signals
The heart is not a metronome: Its rhythm is never in a true steady state!
The Coupled-Clock System within Sinoatrial node cells

Autonomic Modulation

Cholinergic Receptor

\( g_{\beta\gamma} \)

\( g_{\alpha\beta\gamma} \)

\( g_{\alpha\delta} \)

\( g_{\delta\alpha} \)

\( \alpha \)

\( \beta \)

\( \gamma \)

\( \delta \)

\( \alpha\beta\gamma \)

\( \alpha\gamma \)

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\( \delta\alpha \)

\( \beta\gamma \)
Heartbeat Interval “Music” in the Time Domain

EKG RR intervals
(minus autonomic input)

39 beats

RR Interval Variability
(minus autonomic input)

39 beats

At 6 months

Same mouse at 30 Months

21 beats

Same mouse at 30 months

21 beats

39 beats
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

6-month

Highest frequency

With Brain Input

39 beats

Note Interval (ms)

118

120

122

124

126

128

39 beats

(5 sec)

Lowest frequency

Without Brain Input

39 beats

30-month

With Brain Input

34 beats

Note Interval (ms)

145

147

149

151

153

155

157

242

244

246

248

21 beats

(5 sec)
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.
Heart brain musical notes at 6 and 30 months of age with and without head brain input

**With Head Brain Input**
- 6-months old
  - Same mouse: 34 notes
  - 30-months old: 39 notes

**Without Head Brain Input**
- 6-months old
  - Same mouse: 21 notes
  - 30-months old: 21 notes

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

- **Pitch**
  - Highest: 39 notes
  - Lowest: 39 notes

- **Tempo**
  - Highest: 34 notes per 5 secs
  - Lowest: 21 notes per 5 secs

**Note:**
- Heart brain musical notes with and without head brain input at 6 and 30 months of age.
A Coupled-System of Chemical and Current Oscillators

Depolarization

Resetting & refueling

Cell Surface Membrane

SERCA2A

Ca^{2+} pumping

I_{CaL}

I_{CaT}

I_{NCX}

I_{f}

I_{st}

Ca^{2+} clock

Sarcoplasmic Reticulum

Ca^{2+} release

Ignition

M clock

Ca^{2+}
Molecular De-synchronization of Aging

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

Synchronized Molecular Actions → Young Adults, Health

Unsynchronized Molecular Actions

Heart Disease

Heartbeat Frailty

Sick sinus syndrome
Arrhythmias
Contractile Dysfunctions
Apoptosis
Necrosis
Chronic Heart Failure

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 known 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!
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

- **Sarcoplasmic Reticulum**
  - Ca$^{2+}$ release
  - Ca$^{2+}$ clock

- **Cell Surface Membrane**
  - RyR
  - SERCA2A
  - Ca$^{2+}$ pumping
  - I$_f$
  - I$_{CaT}$
  - I$_{Ncx}$
  - I$_{st}$
  - I$_{CaL}$
  - I$_{K}$

- **Giants Cycle**
  - Ignition
  - Resetting & refueling

- **M clock**
  - Depolarization
  - Repolarization
Self-organized criticality

Criticality

self-organization of local Ca signals
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:
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

**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

self-organization of local Ca signals
This is what happened

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

![Diagram of Pacemaker Cell Ca$^{2+}$ Clock Rhythmicity and SR Ca$^{2+}$ load Declines with Aging](image)

- **Adult**: 100 nM [Ca$^{2+}$]
  - Frequency (Hz)
  - [Ca$^{2+}$]$_i$
  - F/F$_0$
  - 25 μm
  - 1 s
  - 0.05
  - [Ca$^{2+}$] signal power
  - 0
  - 2.6

- **Aged**: F/F$_0$
  - 1.0
  - 3 μm
  - 1.0
  - 2.2

- **Coronal line scan mode**

- **Graphs**:
  - Frequency (Hz)
  - [Ca$^{2+}$]$_i$
  - SR Ca$^{2+}$ load (F/F$_0$)
  - Adult
  - Aged

- **Symbols**:
  - Adult
  - Aged
  - *
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.
The Absolute AP Cycle Lengths, Shapes and Durations Differ Markedly From Mouse to Humans in Single Pacemaker Cells in Vitro

- **Mouse (6Hz)**
- **Guinea-pig (2.5Hz)**
- **Rabbit (3 Hz)**
- **Human (1.5 Hz)**

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.
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.
Intrinsic, 6 Months

Heartbeat music in the frequency domain for mouse 1730.

Distributions of EKG RR intervals 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


Neural control and functional organization

Higher centres
Medulla
C1-C2
T1-T4
DRG
Aff.soma
LCN
Sympath
efferent
efferent soma
Afferent soma
Preganglionic
Postganglionic
Kidneys
T6-L2

Circuit timescales- milliseconds!

"Sympathetic"

"Parasympathetic"

Heart
Neurite
Neurite
Neurite

Cortex
Brainstem
Spinal cord
Extracardiac intrathoracic ganglia (stellate, middle cervical)
Intrinsic cardiac nervous system