Network Physiology in **adults** and infants

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Early detection of subacute potentially catastrophic illnesses

Ivanov definition (2012)

- Linkage between organ systems was quantified by stable time delays between triggers and responses, as judged by the lag when cross-correlation was highest.
- Statistical significance was determined in an elegant way using interesting surrogate data.
- Identification of linkages ***does not*** require identification of the trigger and response events.
- It ***does*** require fidelity of the system.
- Not a stringent requirement.
- Usually.

Another view of Network Physiology

- The study of simultaneous physiological signals representing dynamically adaptive regulation of organ systems that work best in concert.
- “In concert” means that the activity of one organ informs the activity of another.
- “Informs” means that a signal is sent, received and acted upon. The time-varying nature of the system is reflected in the activity of both the transmitter and receiver, and can be quantified using signal processing techniques in the time-, frequency-, phase-, non-linear dynamical and other domains.
- These couplings, which themselves vary in time, reflect the closeness of the coupling of dynamic regulation of systems and can give insight into health and illness.
- A hallmark is ***entrainment***.

Towards mechanisms

- Understanding the mechanisms that result in changing levels of organ interaction that comprise Network Physiology is important for the interpretation and application of findings in the field.
- New kinds of mechanisms are ***not, in my view,*** immediately required to begin this understanding.
- Physiology has evolved towards reductionism, from measuring behavior of whole organs like heart, lung, brain and muscle towards that of excitable membranes and the molecules that allow the movement of charged ions resulting in the cellular functions that lead to heartbeats and breaths, thoughts and actions.

Outline

- **Network Physiology in adults**
- An example of entrainment of heart and lungs, extremely reduced
- A counter-example
- Questions for the field

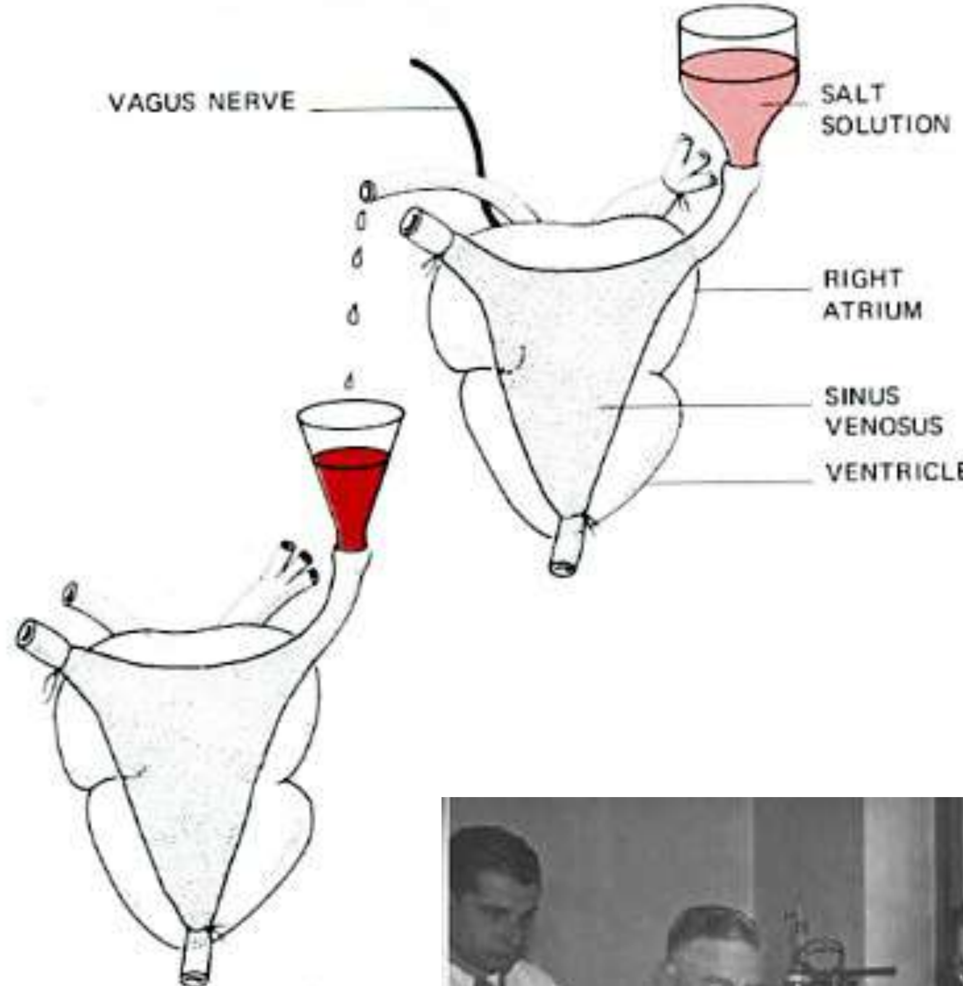
- Story line: entrainment of the heart by the lungs, basic mechanisms, & then triggers and responses that make sense and those that do not

- Take a deep breath…

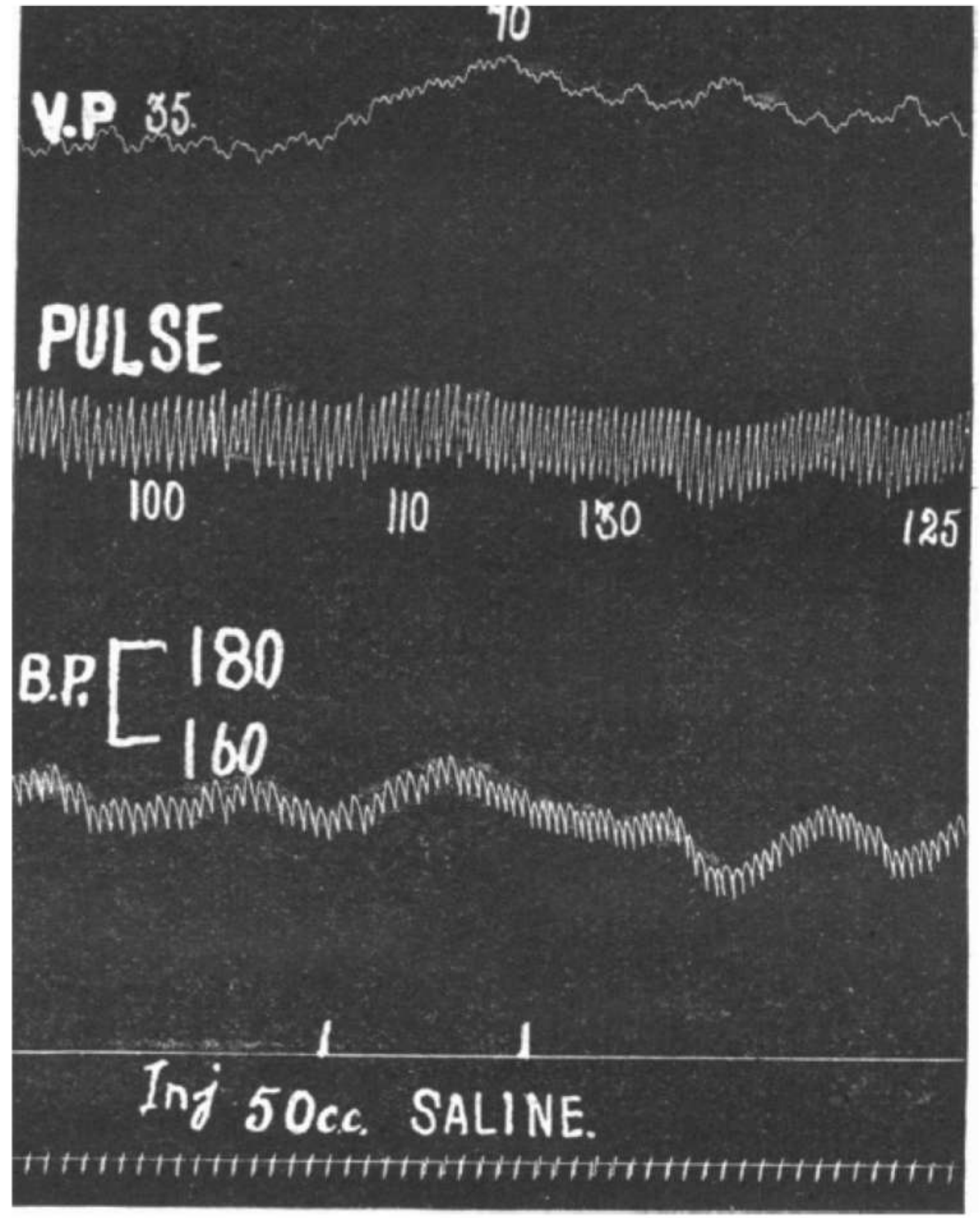
In 1920, following a dream on Easter Sunday, future Nobel laureate Otto Loewi isolated the hearts of two frogs. Into the cavity of one heart he put a salt solution - and stimulated the vagus. The expected immediate slowing of the heart rate occurred.

He transferred some of the salt solution to the second heart, and its beat was immediately slowed.

Later, he showed that this "Vagusstoff" was ACh.



THE INFLUENCE OF VENOUS FILLING UPON THE RATE OF THE HEART. BY F. A. BAINBRIDGE.



Bainbridge 1915

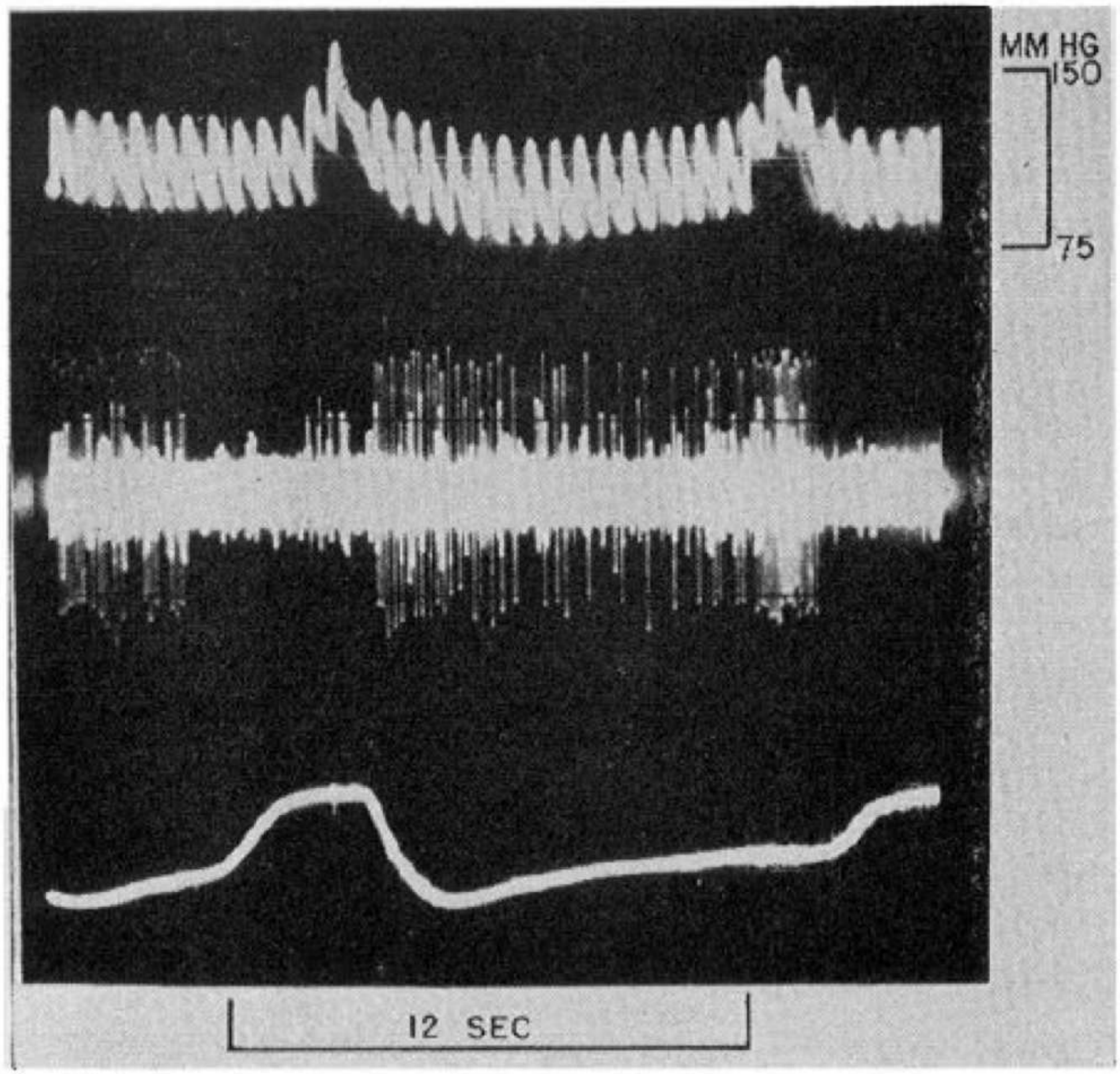
A vagal reflex between lungs and heart

Blood pressure

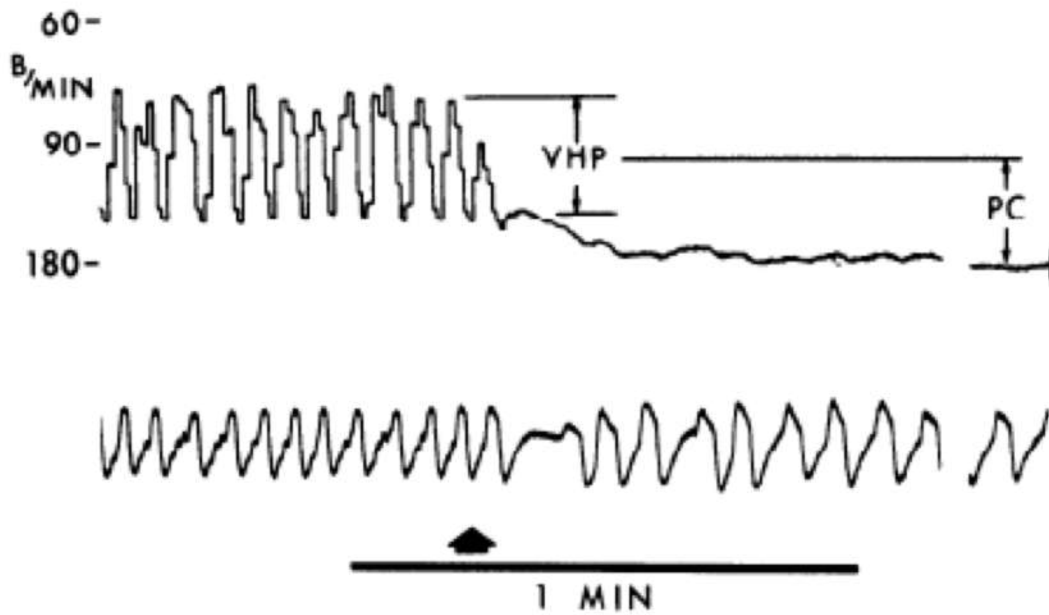
Vagus nerve

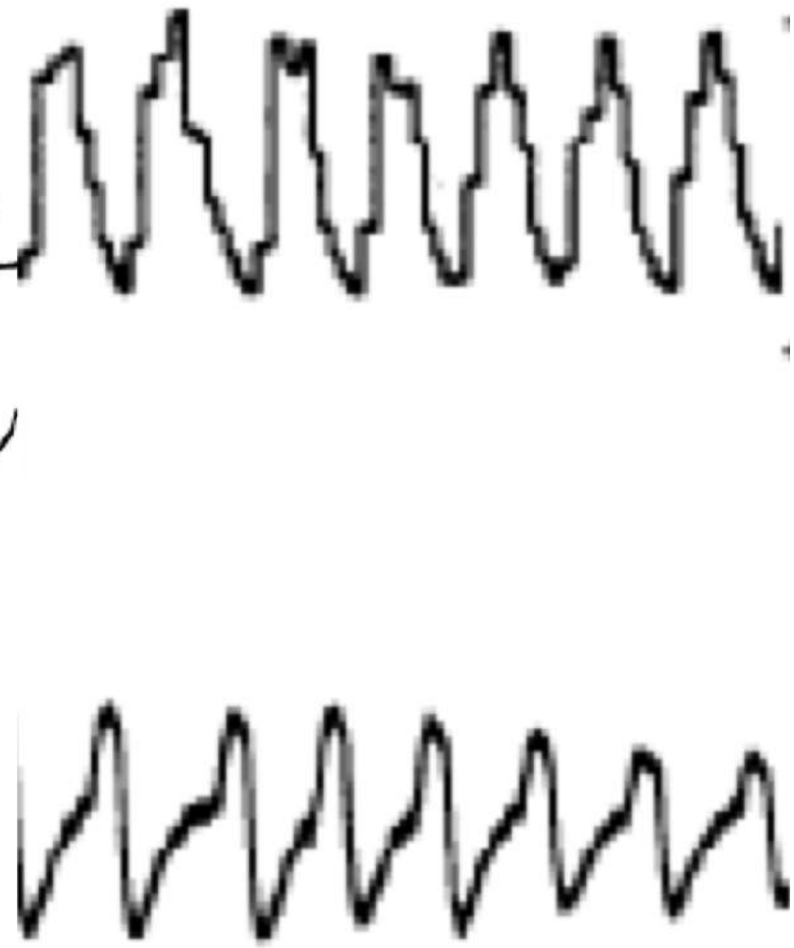
Inspiration ↑

Katona 1970

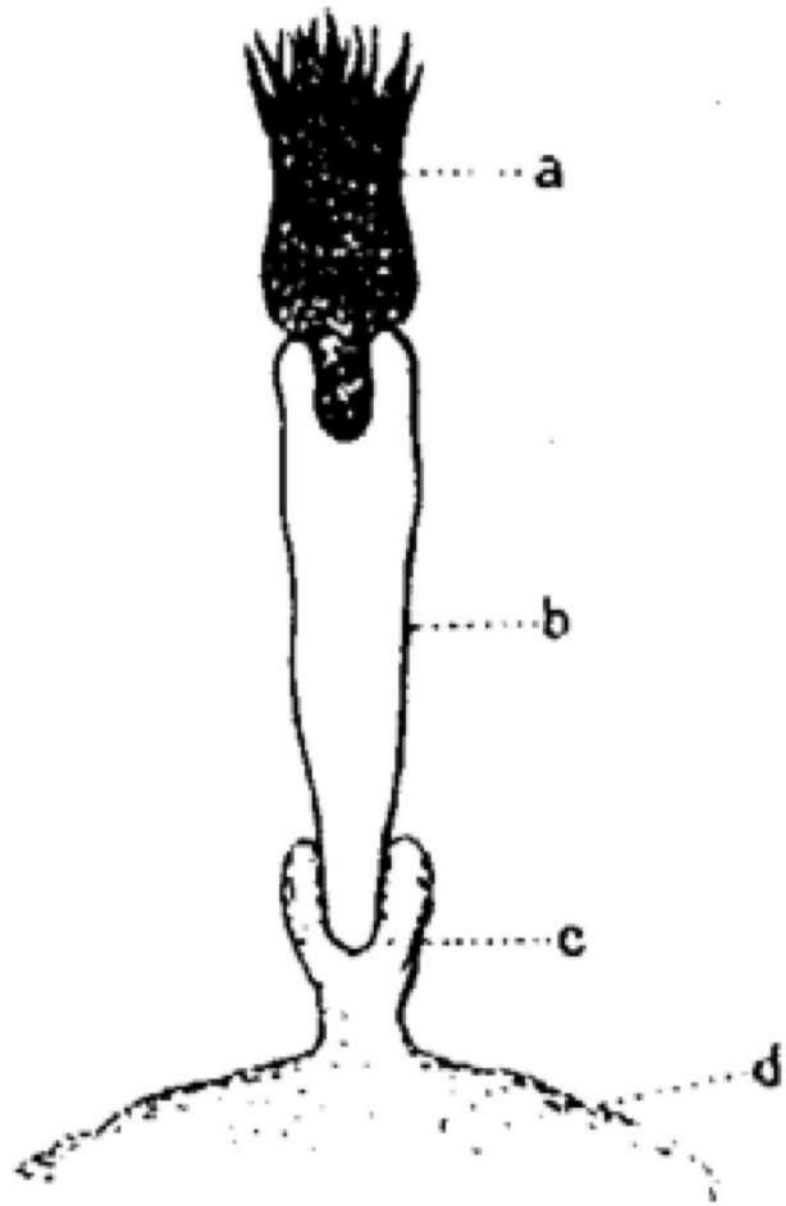


This explains respiratory sinus arrhythmia

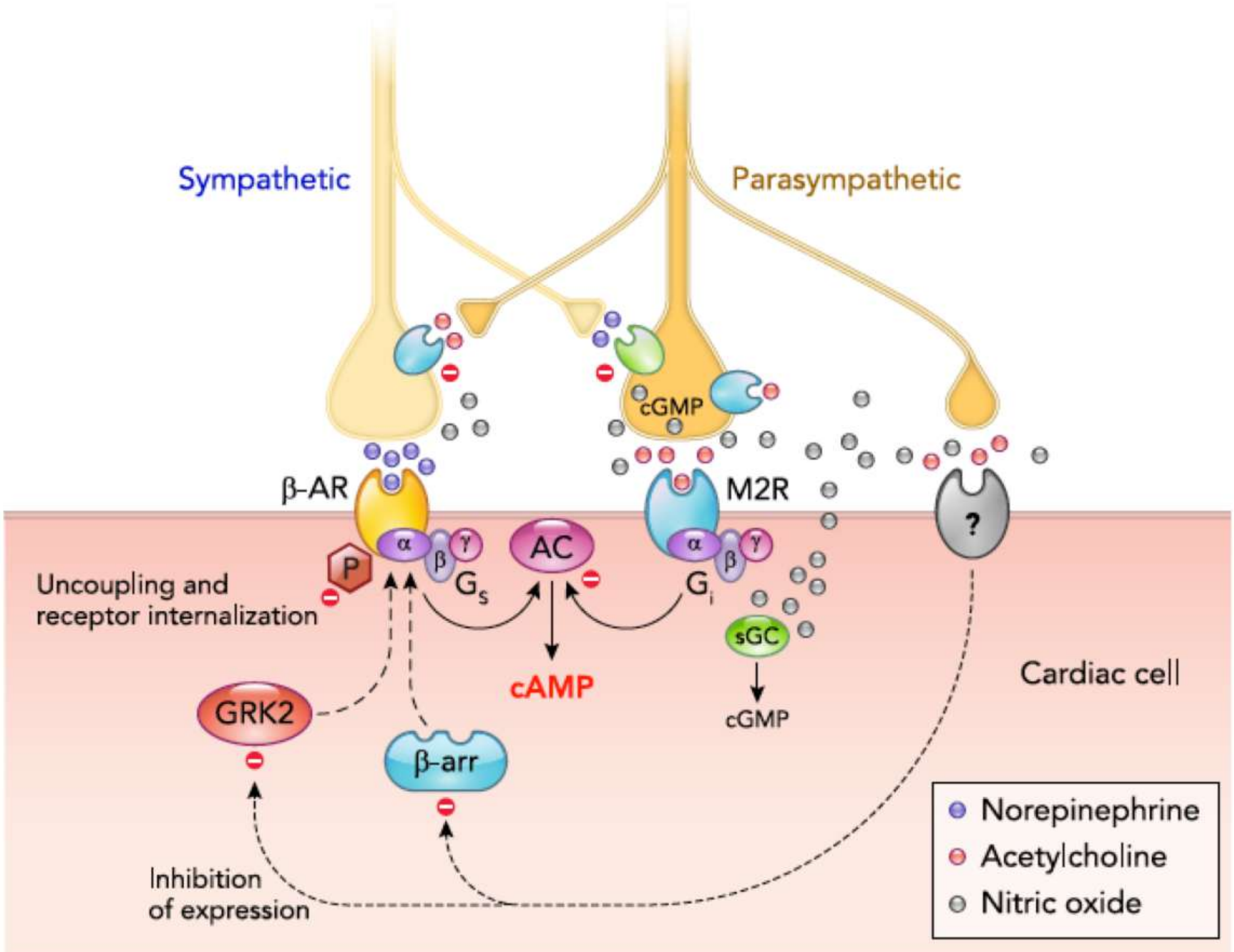




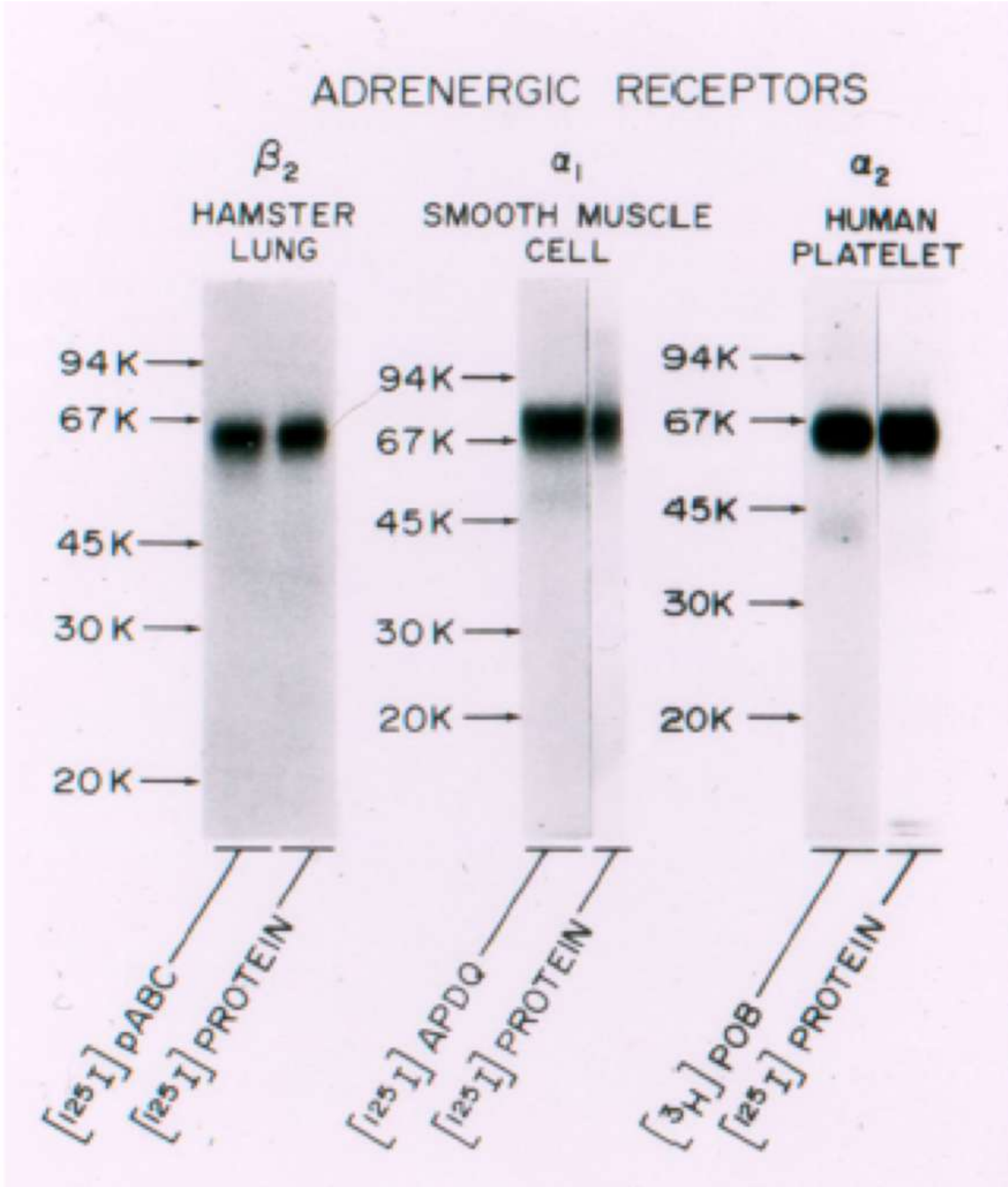
Katona 1970, 1975



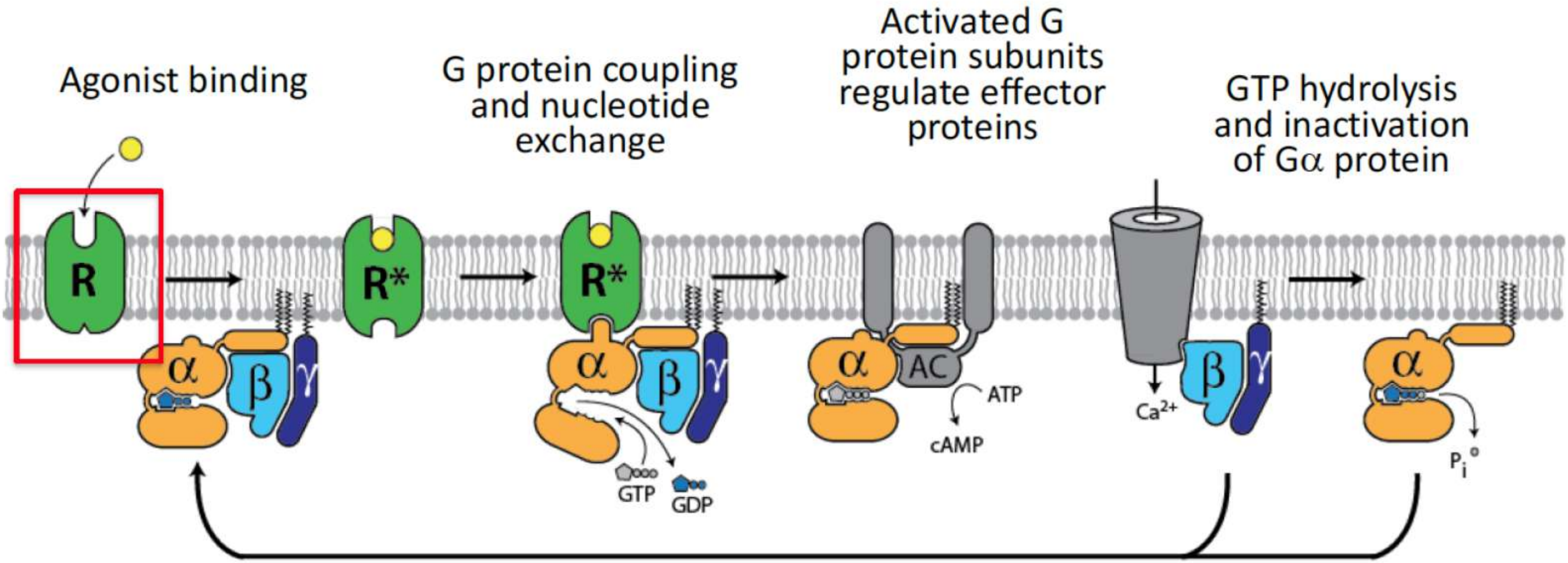
Ehrlich 1900



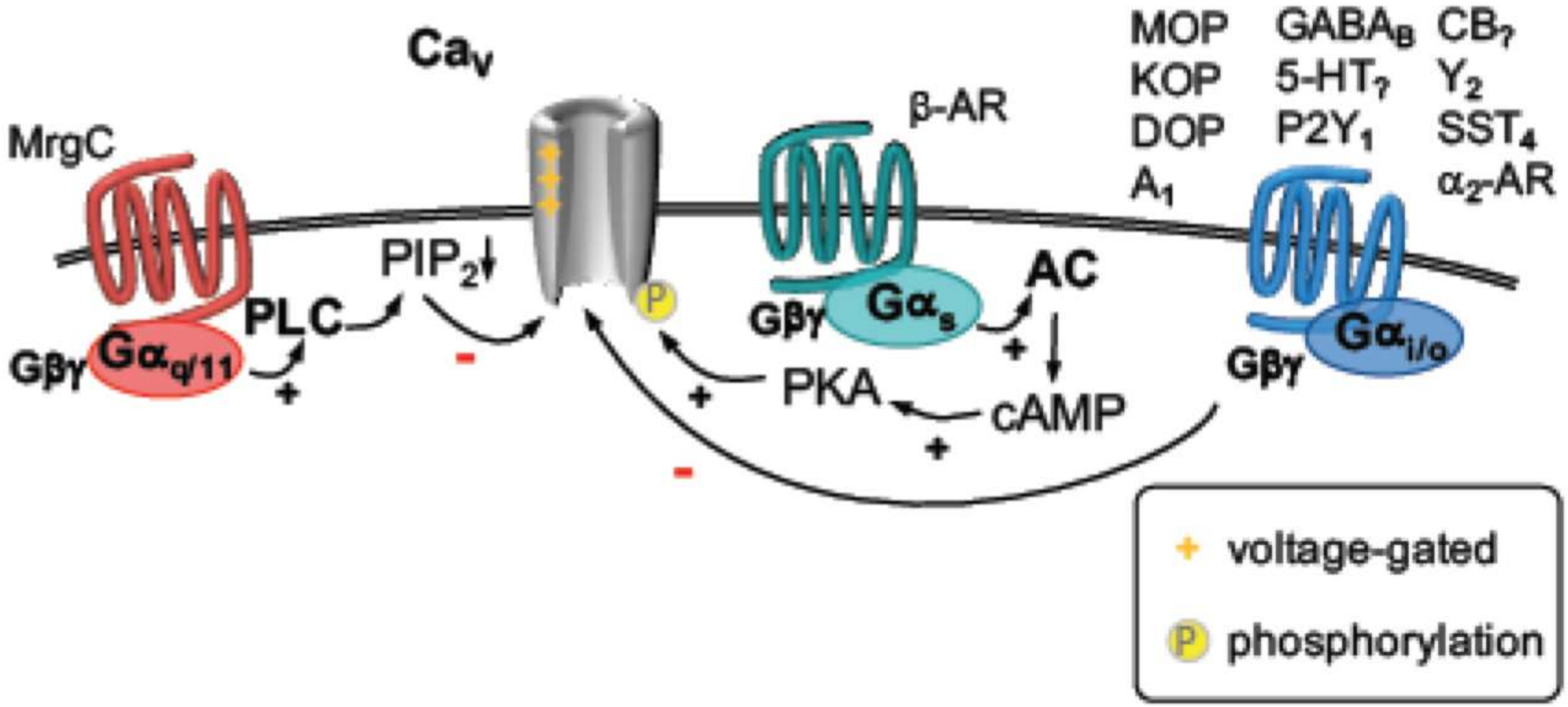
Sympathetic
Parasympathetic
cGMP
β-AR
M2R
?
P
α
β
γ
G_s
AC
G_i
Uncoupling and
receptor internalization
sGC
cGMP
cAMP
Cardiac cell
GRK2
β-arr
Inhibition
of expression
Norepinephrine
Acetylcholine
Nitric oxide



Lefkowitz 1980

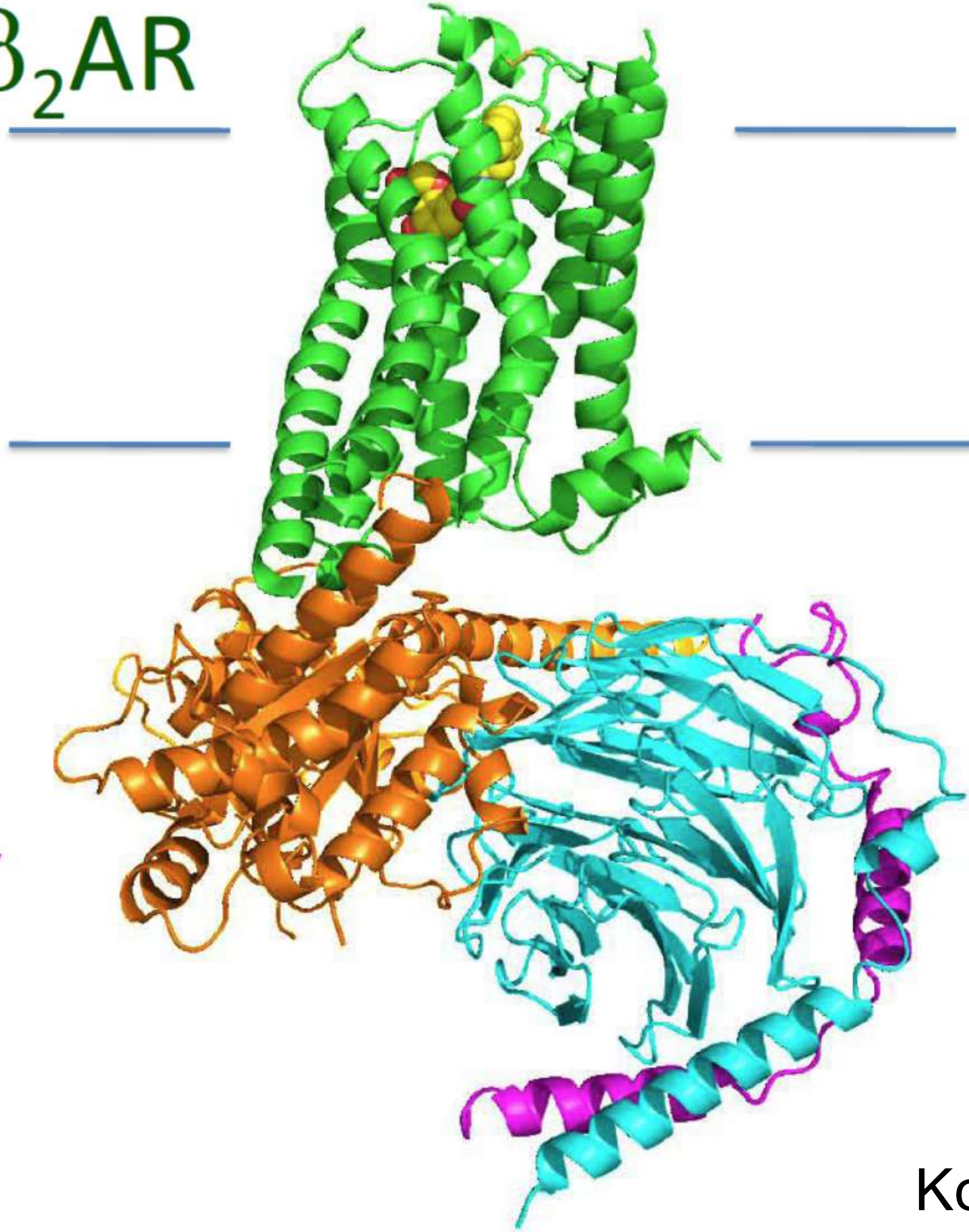


GPCR-G Protein Cycle

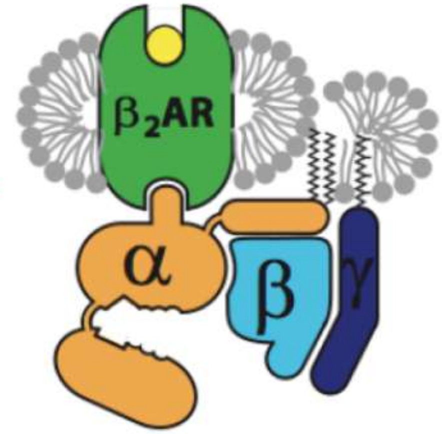


MrgC
Cav
β-AR
MOP
KOP
DOP
A1
GABAB
5-HT7
P2Y1
CB7
Y2
SST4
α2-AR
PIP2
PLC
Gβγ
Gαq/11
Gαs
AC
Gαi/o
PKA
cAMP
voltage-gated
phosphorylation

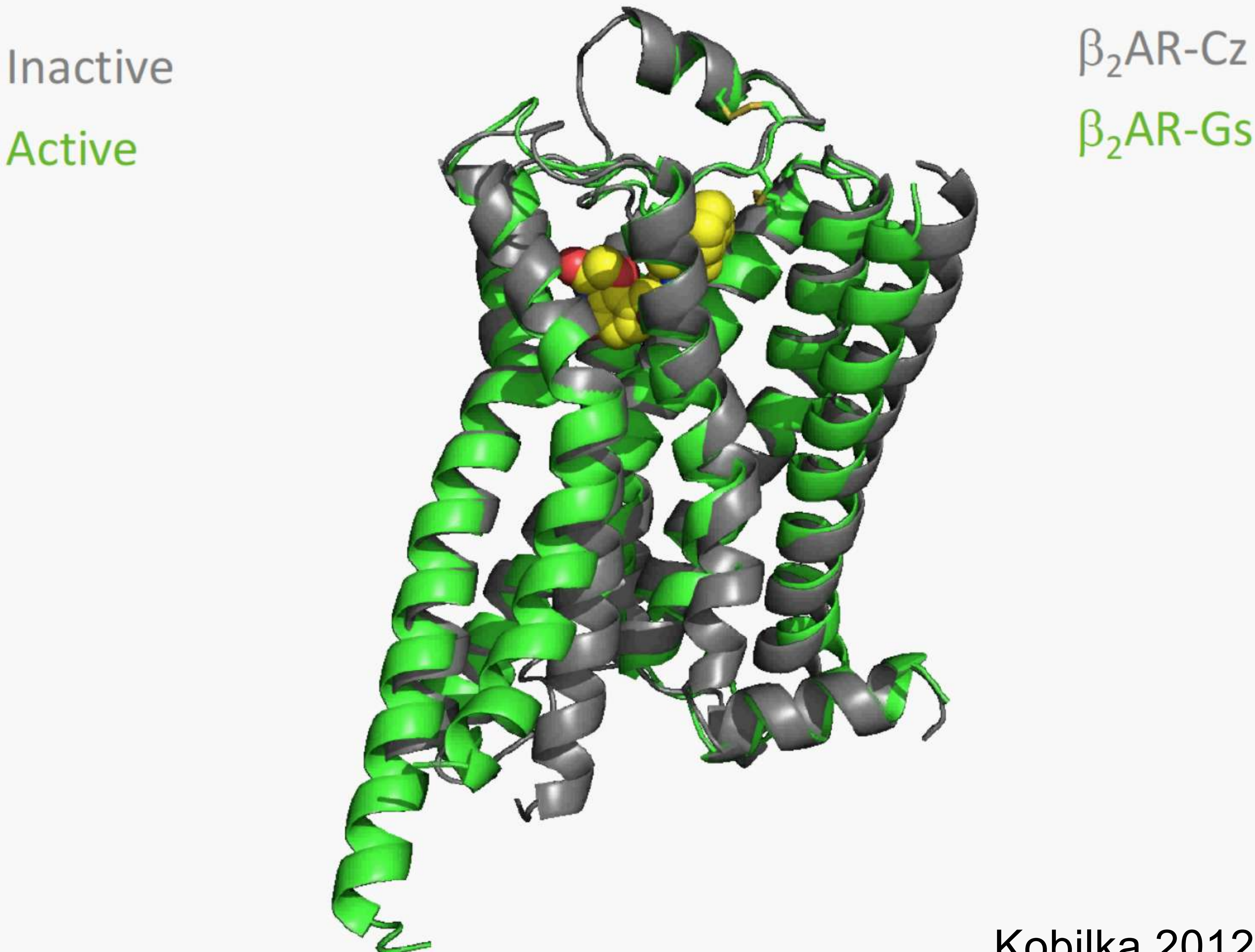
β_2AR



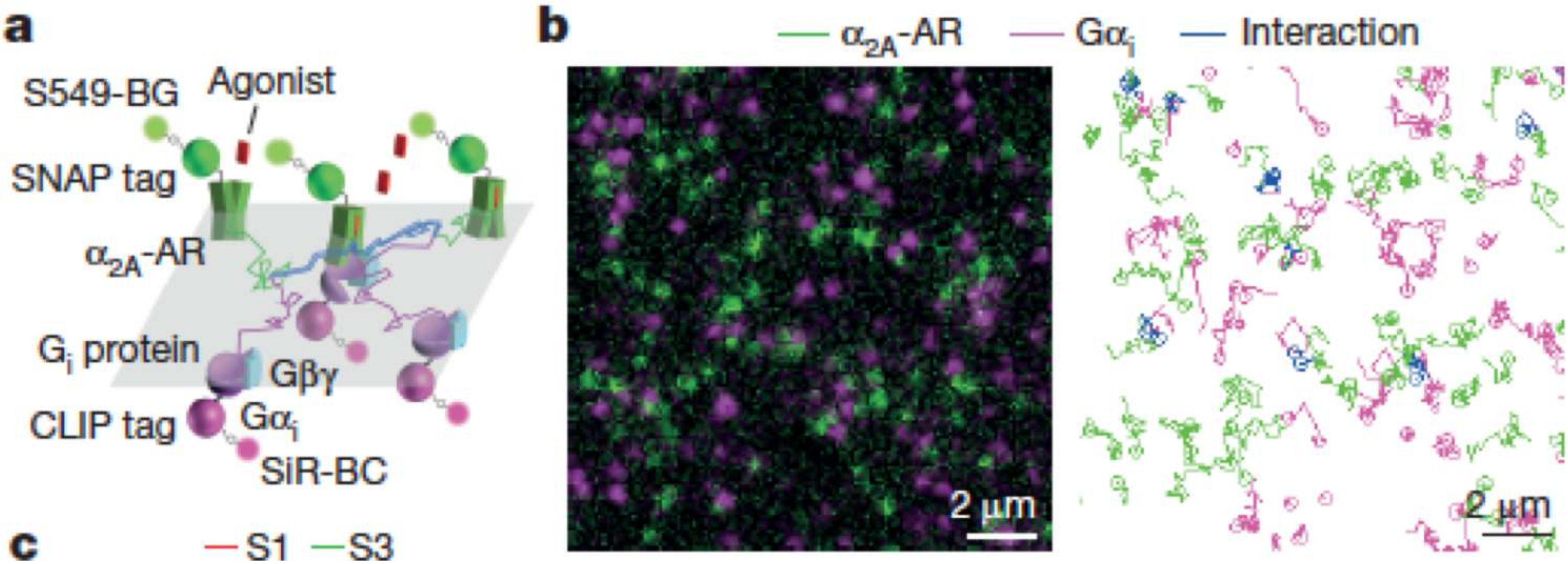
Gs$\alpha\beta\gamma$



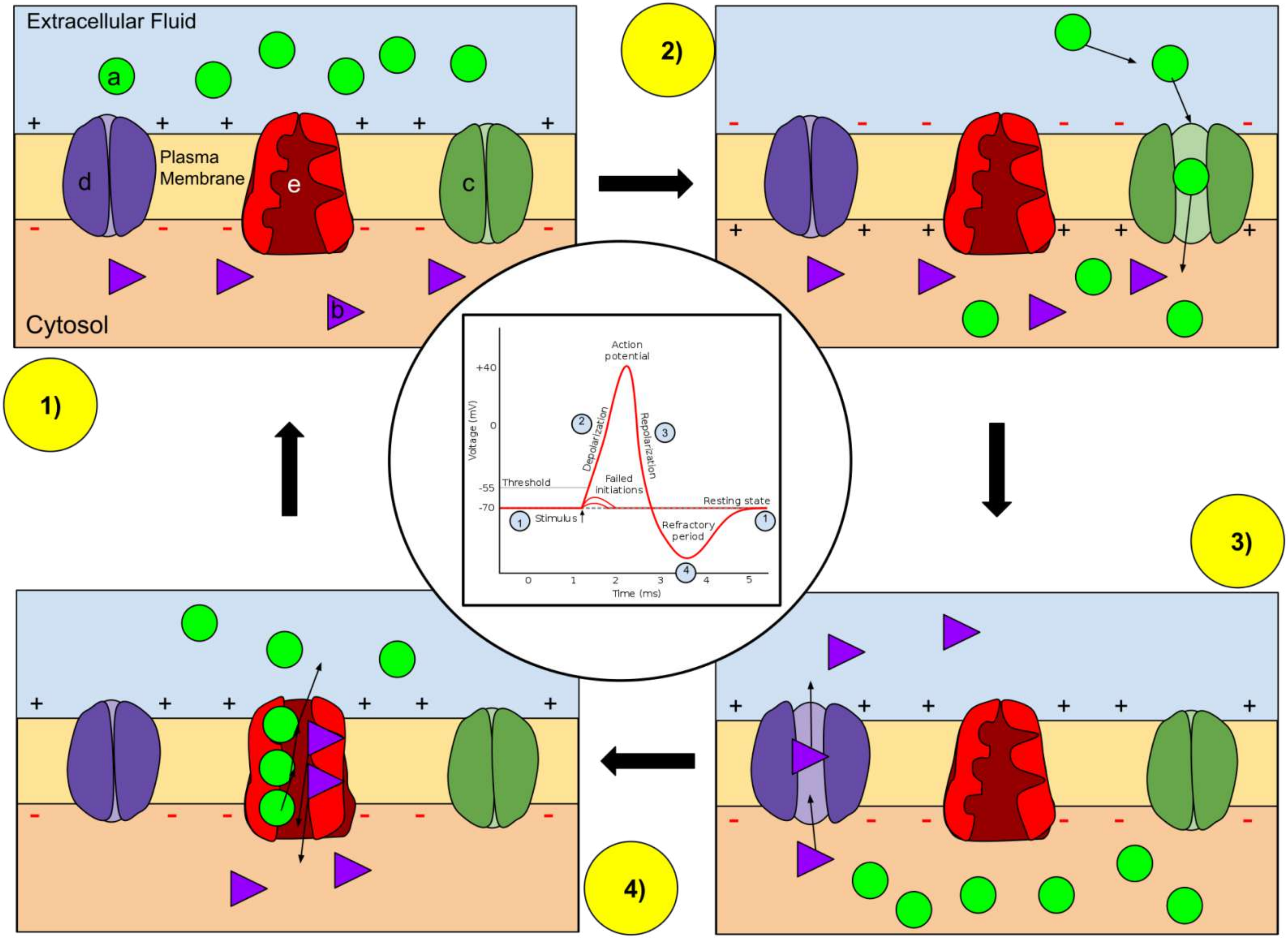
Kobilka 2012

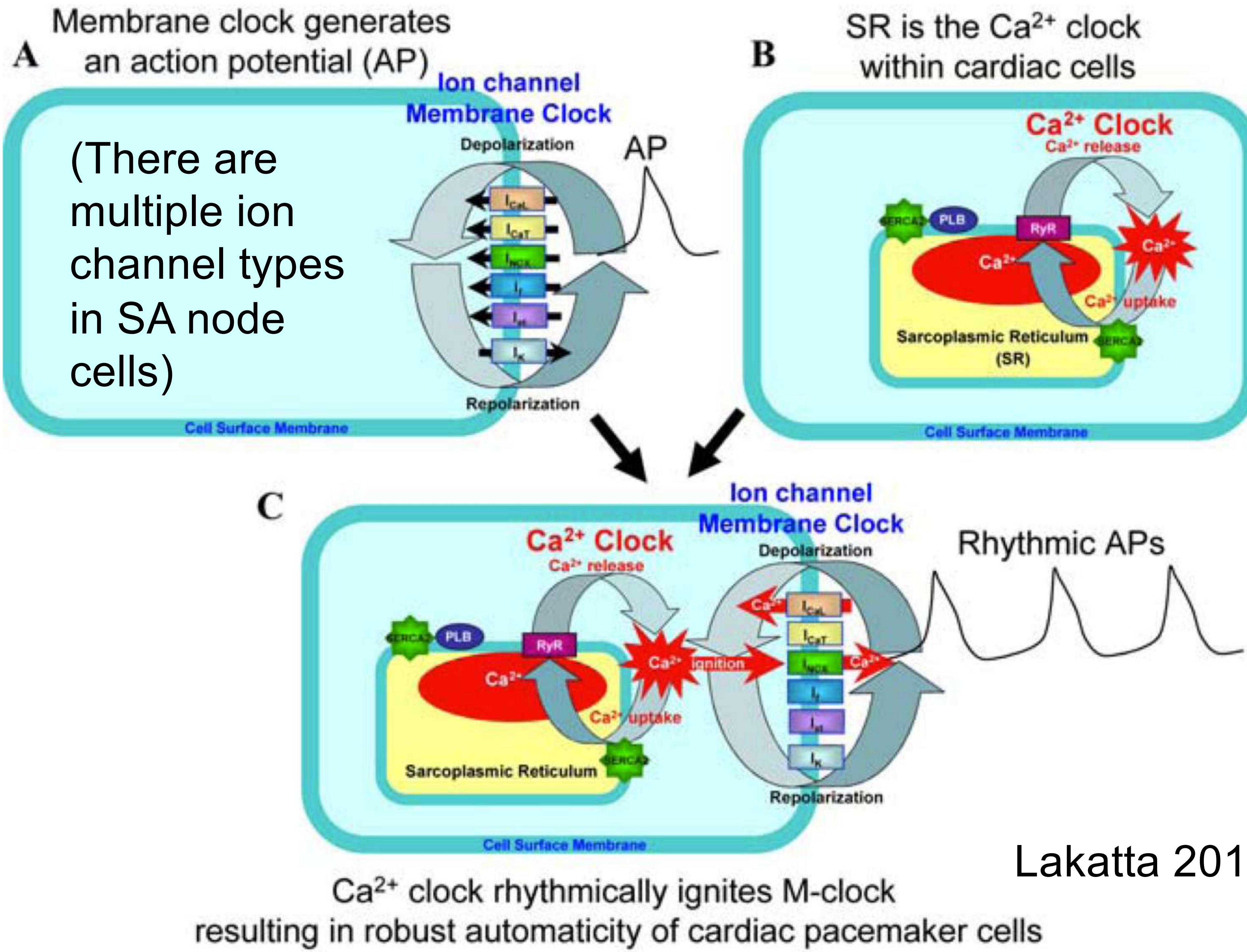


Kobilka 2012


a
b
S549-BG
Agonist
SNAP tag
α_{2A}-AR
G_i protein
Gβγ
CLIP tag
$G\alpha_i$
SiR-BC
α_{2A}-AR
$G\alpha_i$
Interaction
2 µm
2 µm
c
S1
S3

Lohse 2018

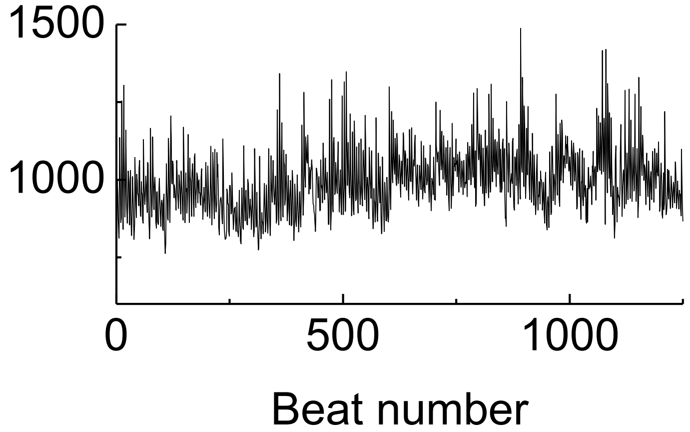

Extracellular Fluid
a
Plasma Membrane
d
e
c
b
Cytosol
1)
2)
3)
4)
Action potential
+40
0
-55
-70
Voltage (mV)
Depolarization
Repolarization
Threshold
Failed initiations
Resting state
Stimulus
Refractory period
0
1
2
3
4
5
Time (ms)

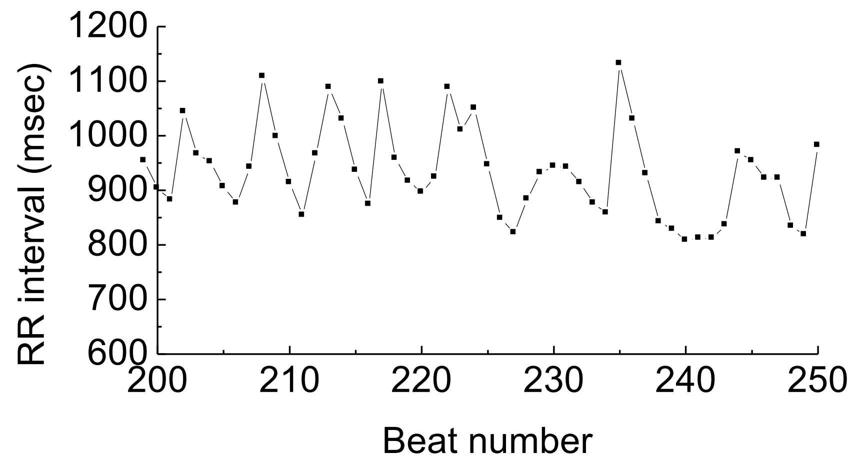


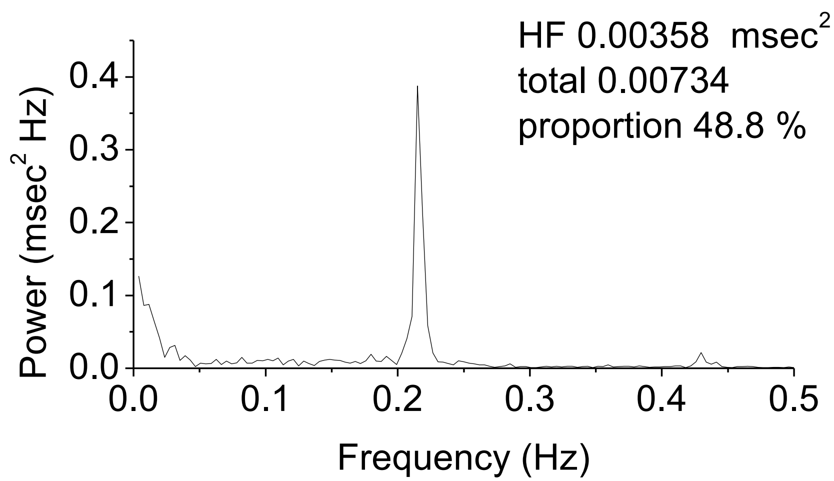
(There are multiple ion channel types in SA node cells)

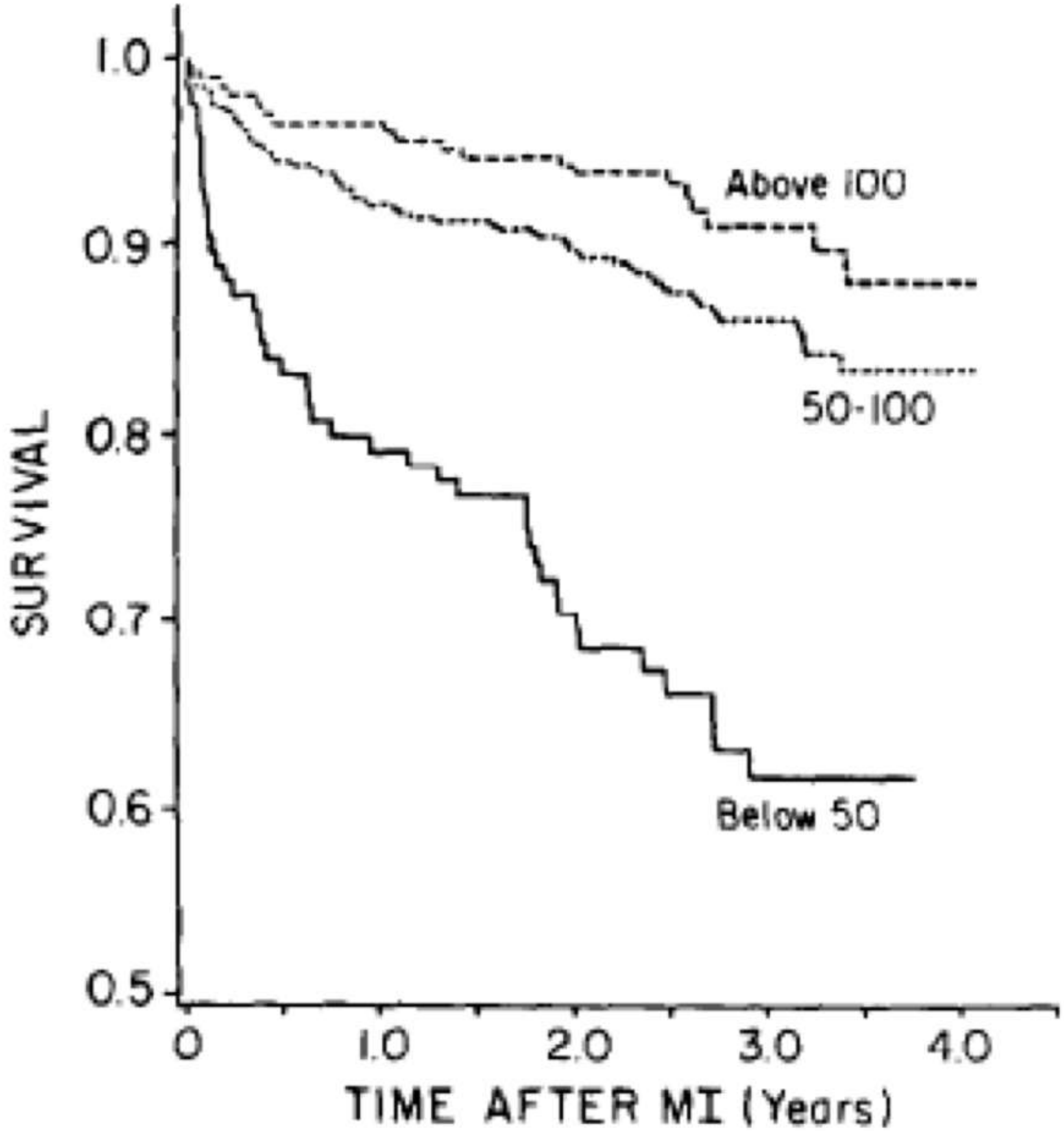
Lakatta 2012

Normal HRV=
f (Respiratory Sinus Arrhythmia, RSA) =
entrainment of heart and lungs=



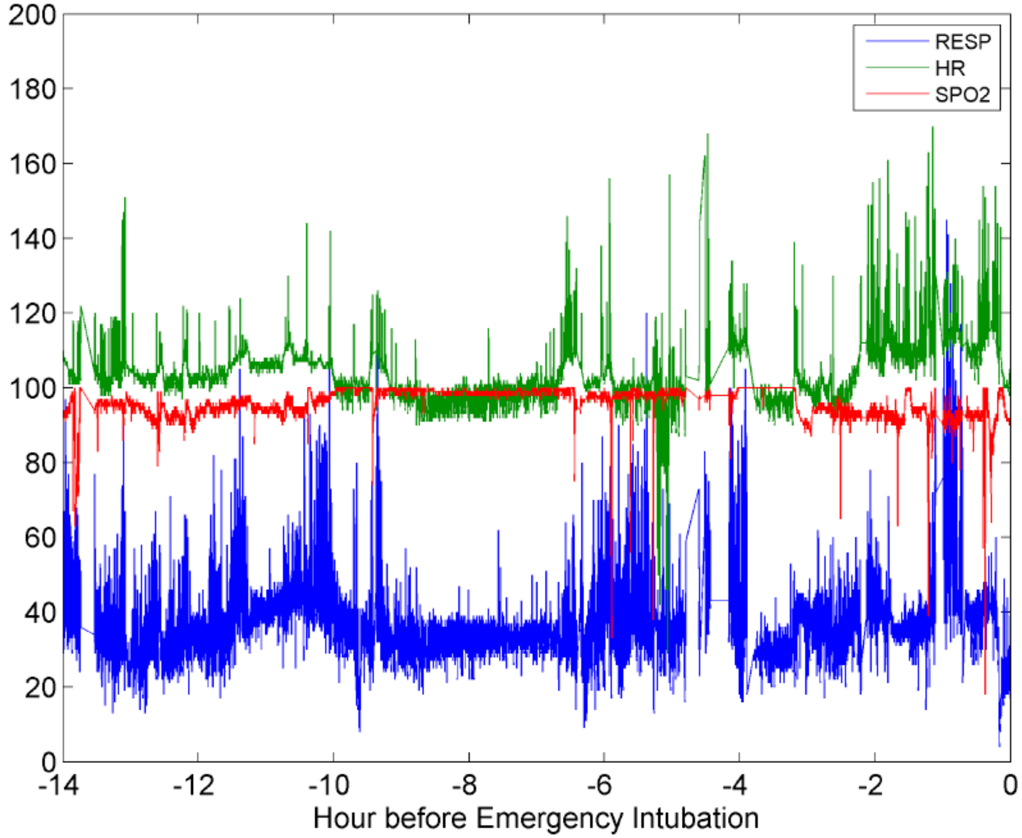




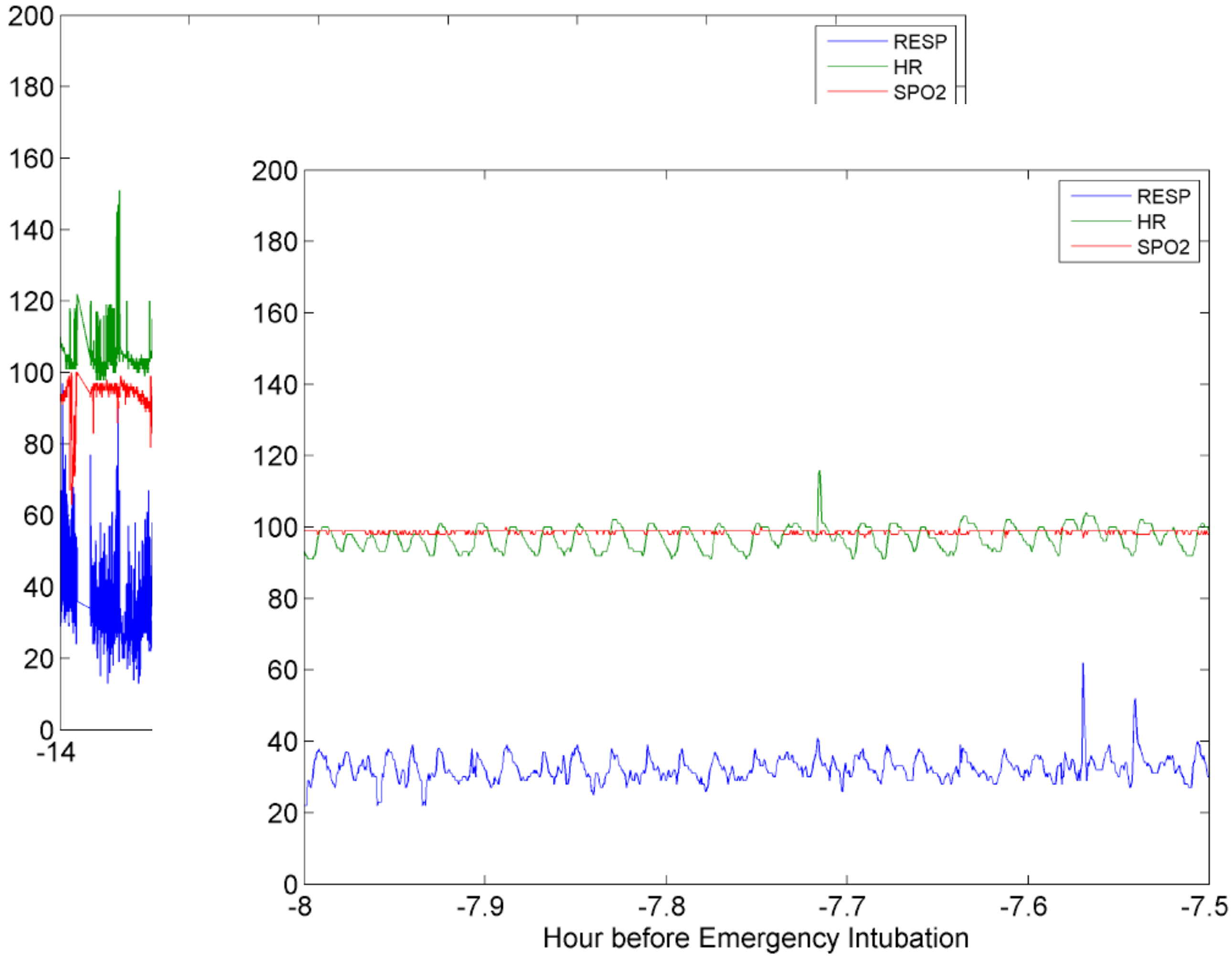


Kleiger 1986

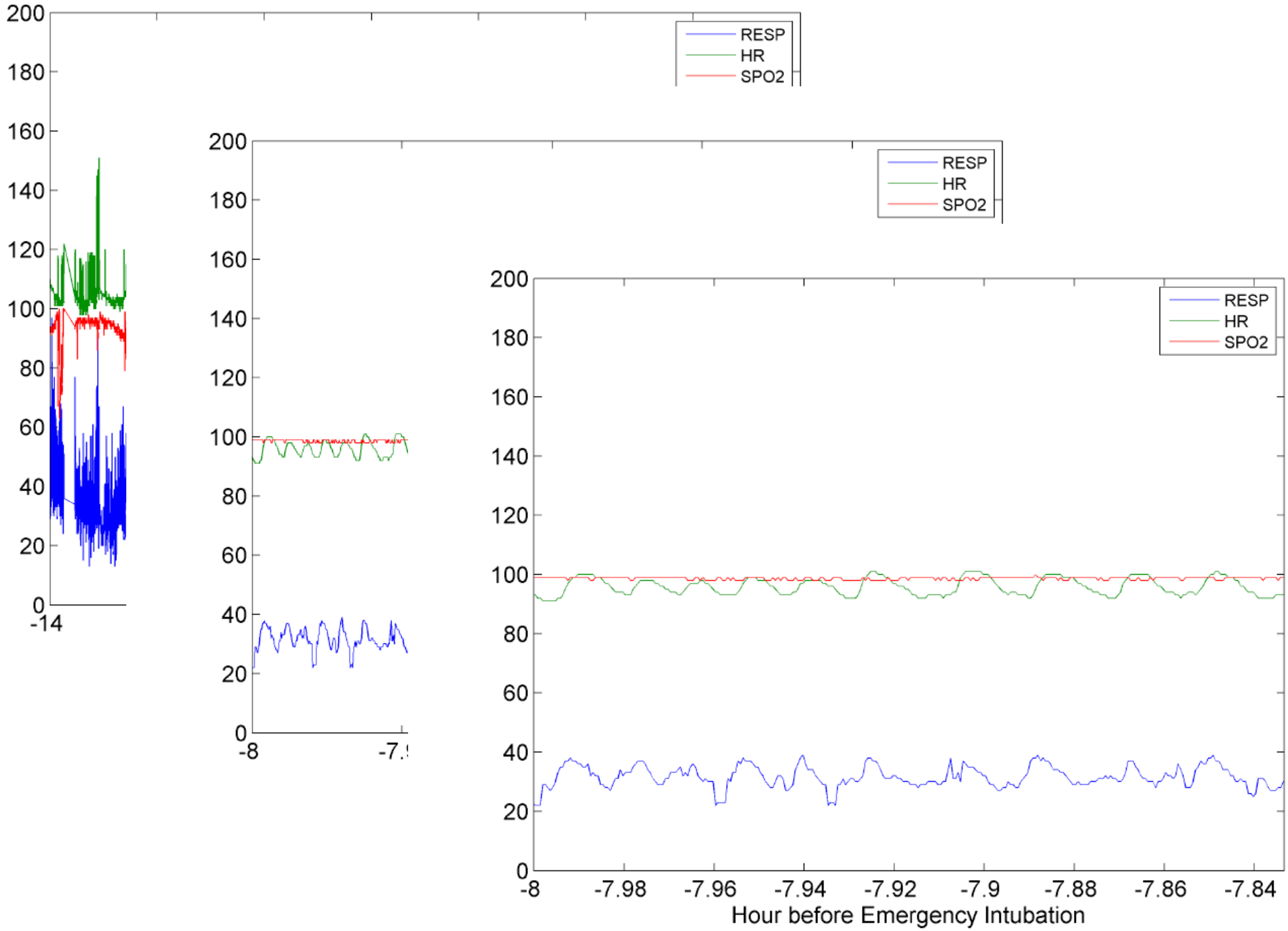
Too much of a good thing: MICU



Too much of a good thing: MICU

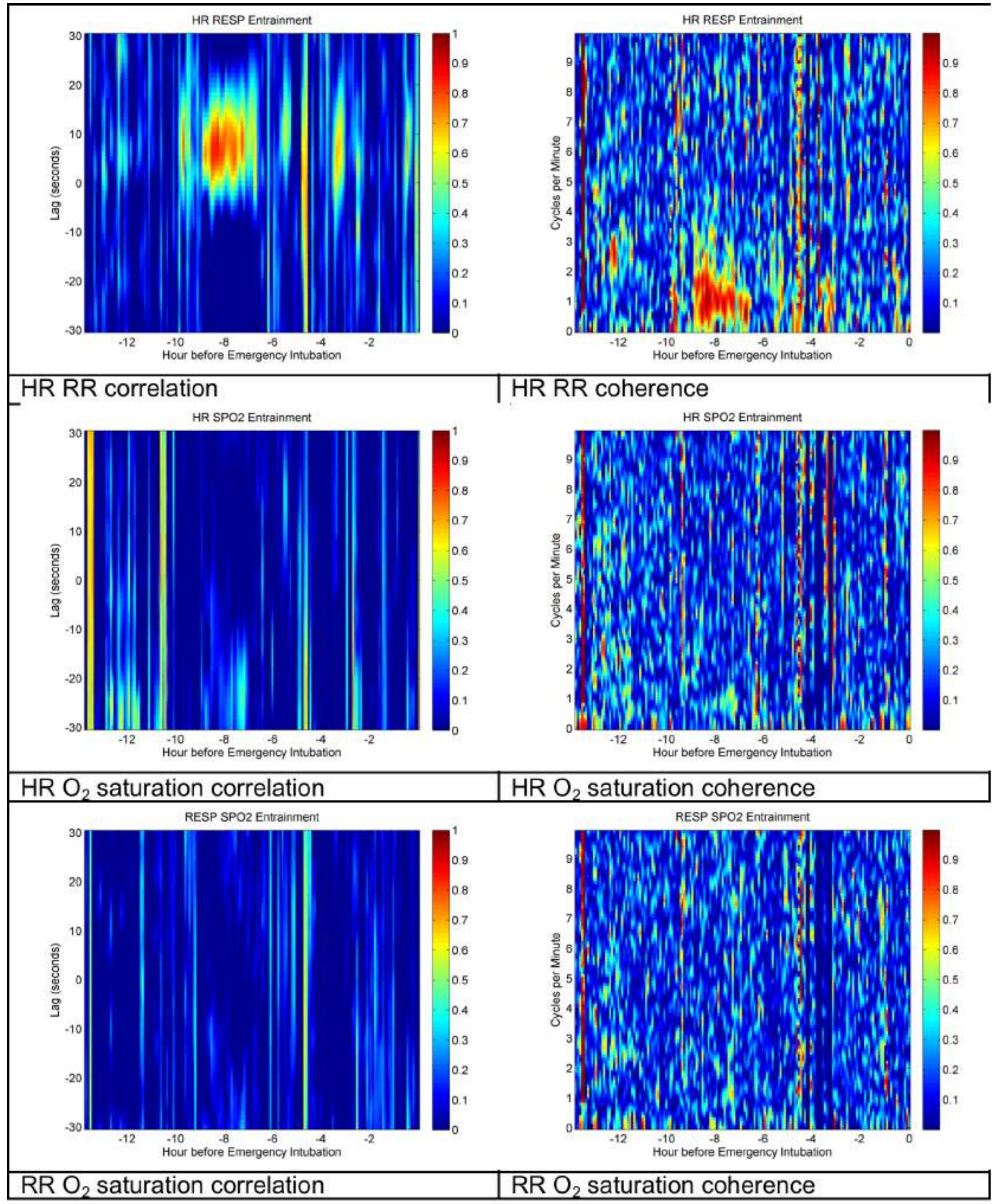


Too much of a good thing: MICU

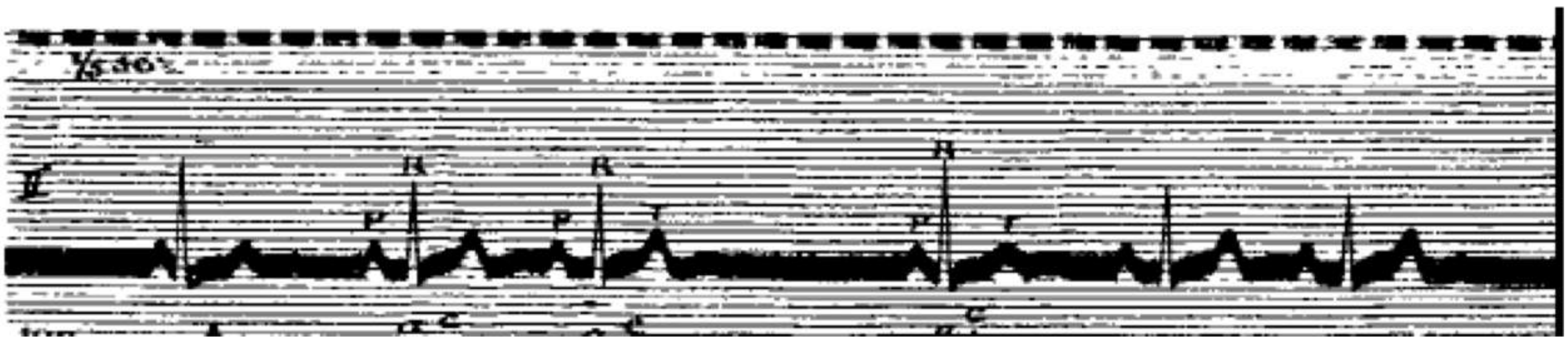


Entrainment

The entrainment of HR and RR in this adult with respiratory decompensation leading to urgent unplanned intubation occurred at lag 0 to +10 seconds, and at frequency about 1 per minute.
The entrainment was brief – about an hour – and was manifest only in the HR and RR analysis.



Counter-example 1:
No 1:1 correspondence of trigger and response



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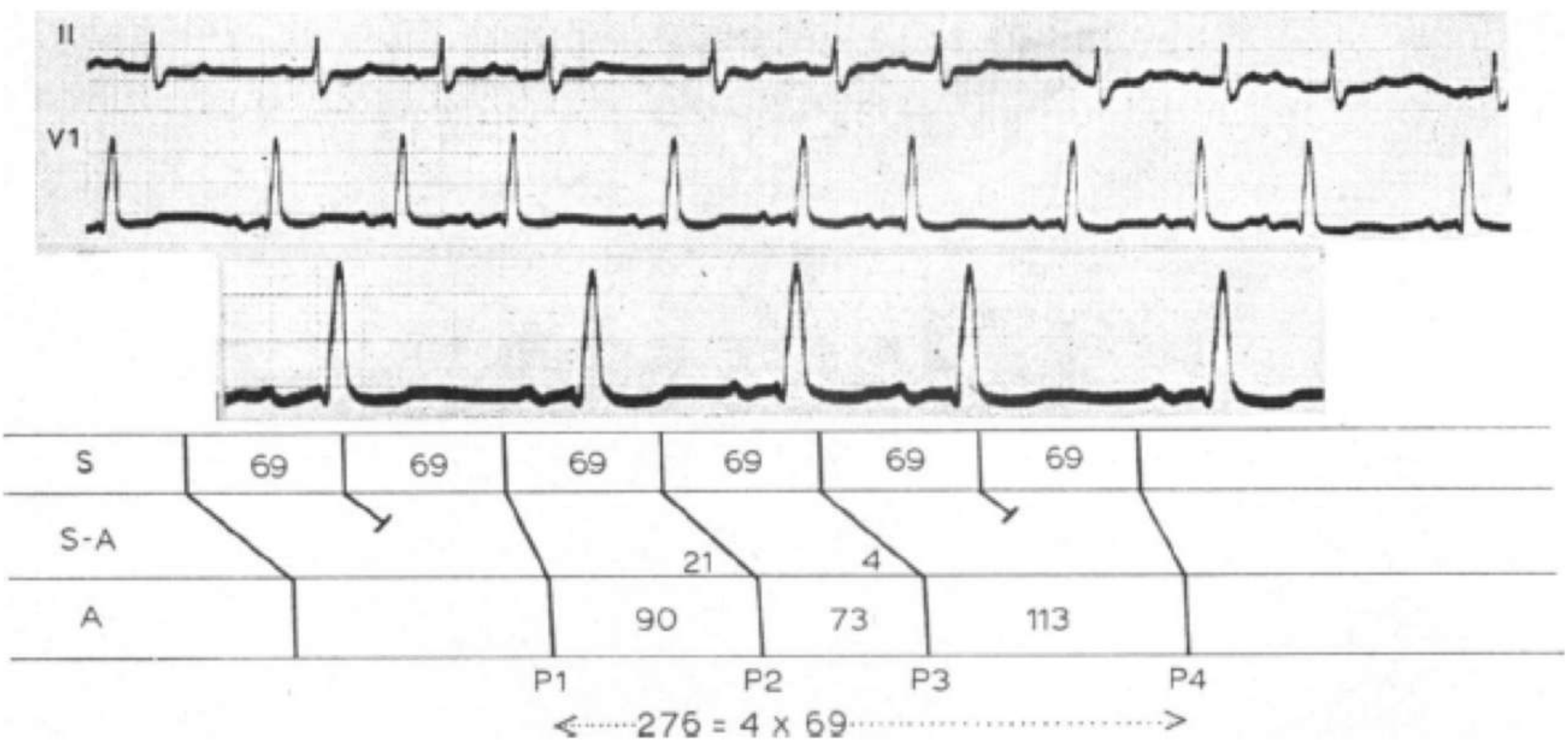
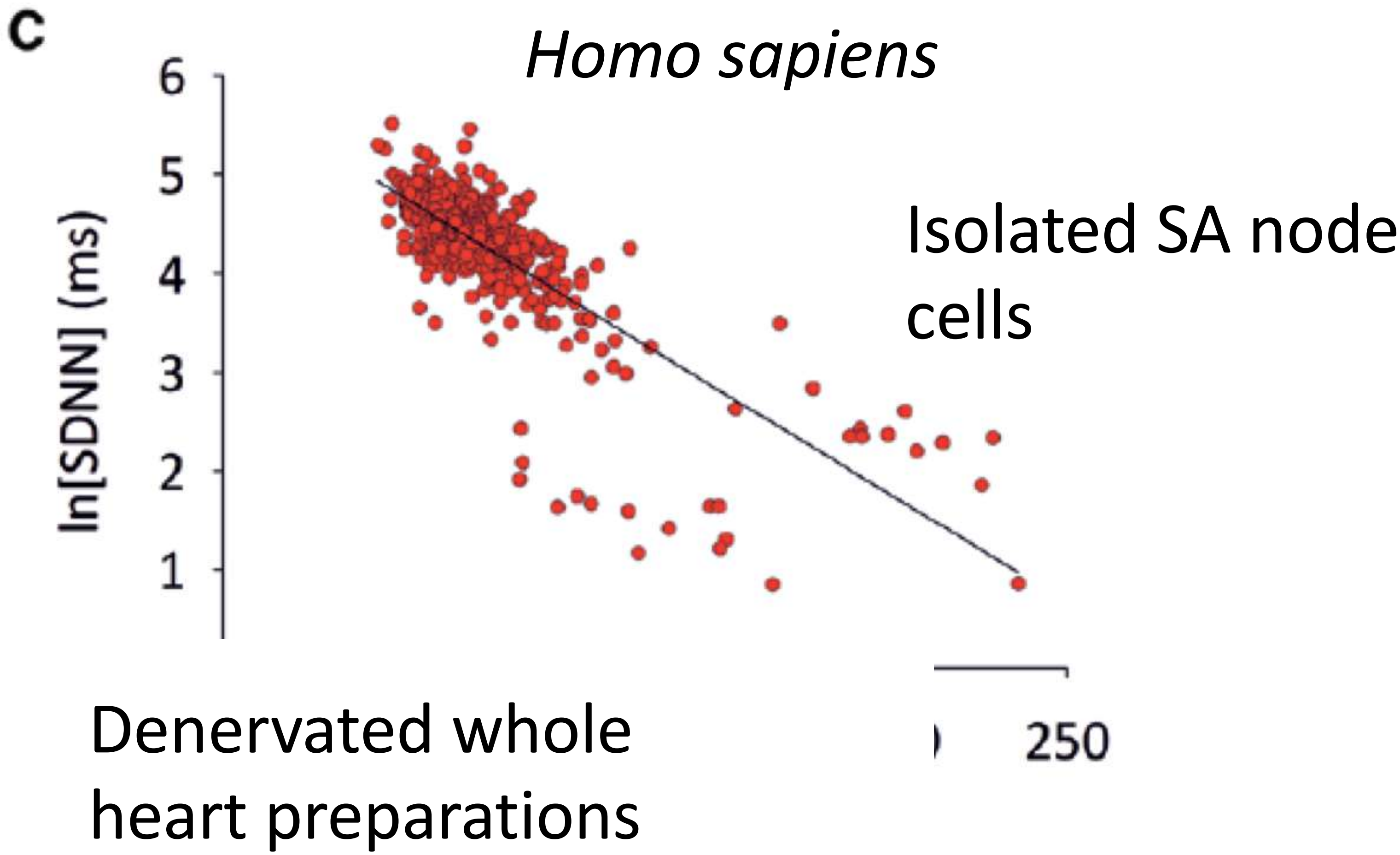


Schamroth 1966

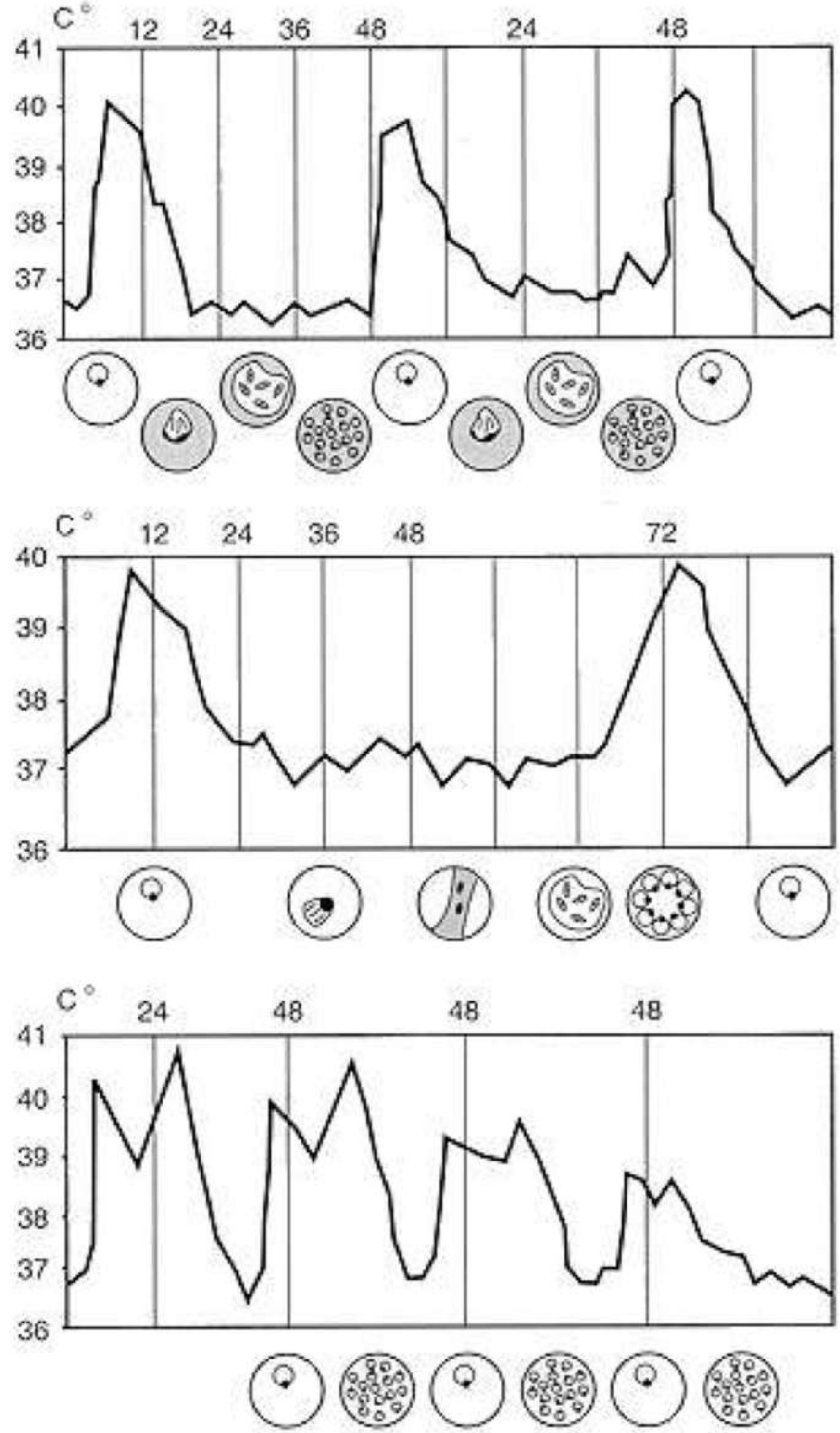
Counter-example 2:
$\sigma = f(\text{rate})$



Counter-example 3: Entrainment by another clock

Higgins, John R., 1947: The heart rate in malaria; a review of ninety cases. Ann Internal Med: 433-440

85 patients with Plasmodium vivax infestations, 2 with P. falciparum and 3 with P. malariae are reviewed with respect to the relationship between pulse rate and fever. Approx. 25% had pulse rates below 101 when the temp. was above 102.9F by mouth. The remainder of the cases exhibited a wide range of tachycardia. The wide variation in cardiac acceleration was not a function of the resting pulse rate in afebrile periods.



Summary

- Network Physiology leads to entrainment of heartbeats and breaths
- For respiratory sinus arrhythmia in adults, the mechanism is known to the Angstrom level
- Detection and interpretation requires fidelity between triggers and responses

Questions for the field

- What are the common physiological mechanisms of Network Physiology at the level of regulation of membrane excitability – the autonomic nervous system, synaptic transmission, neurotransmitters, cytokines, ligands, receptors, signal transduction, ion channels – and how do their kinetics, which are generally stochastic, sum to the observed behaviors?
- What experiments can be designed?
- Which signals are triggers and which are responses; that is, what is entraining which? Is there confusion when the rates are fast compared to the delays in coupling?
- How is fidelity ensured?