Mathematically Modeling Alternans in Cardiac Myocytes

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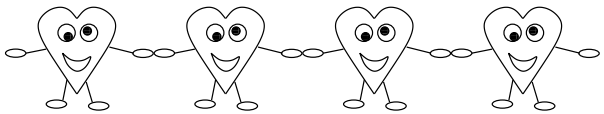
Outline

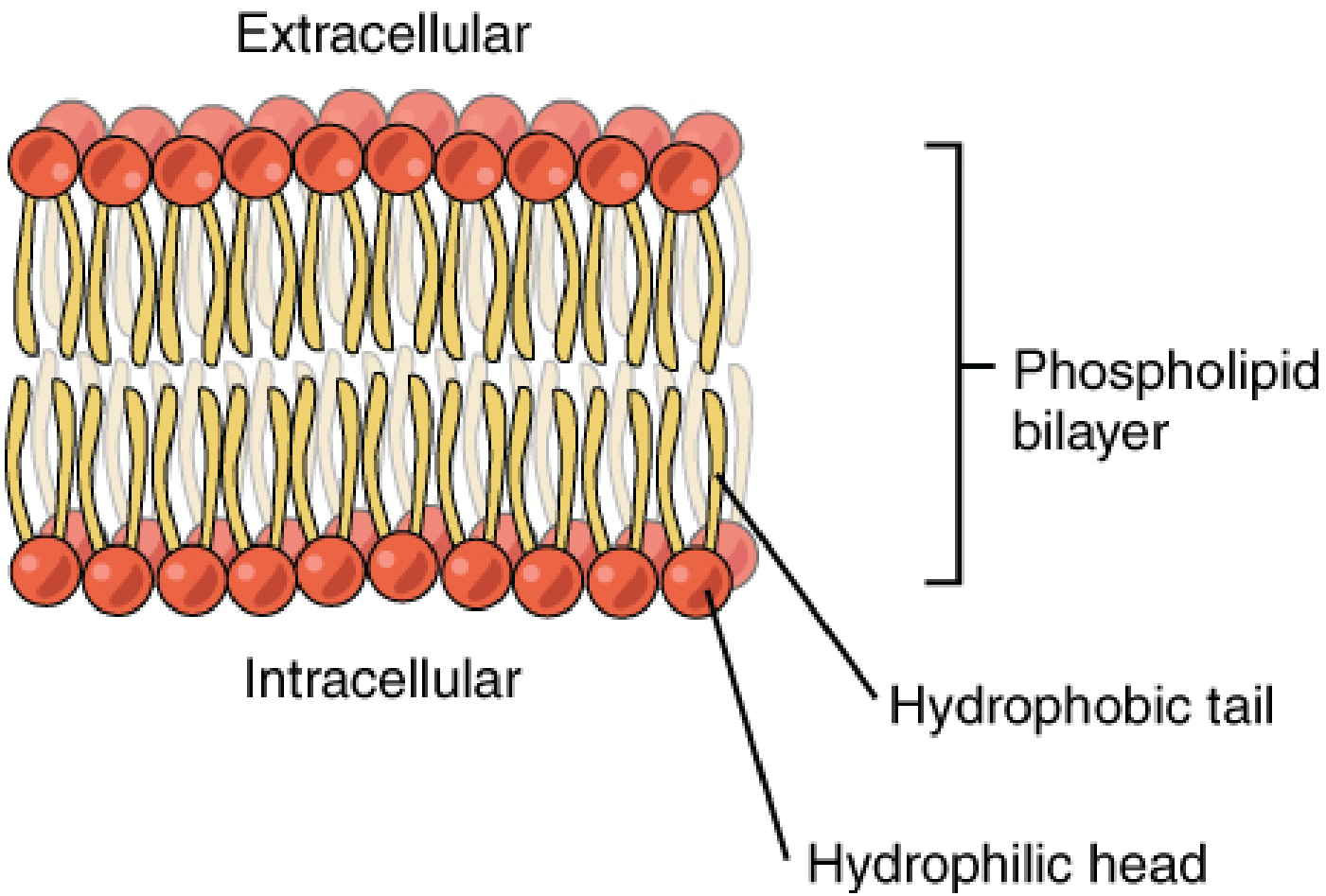
- What is mathematical modeling in biology? Why do it?
- Background on cardiac membrane models and rhythm.
- Cardiac restitution mappings and their fixed points.
- Predicting and controlling alternans.
- Discussion and interactive activities!



Mathematical Models and Why We Use Them

- A **mathematical model** is an attempt to describe a natural phenomenon quantitatively.
- Examples: Michaelis-Menten model of enzyme kinetics; Hardy-Weinberg "Law" in genetics; fruit fly population models $p_n = p_0 Q^n$; etc.
- Models are built upon assumptions and idealizations, but a good model should have some predictive power. Use models to interpolate and extrapolate beyond what is experimentally observable.
- Experiments are expensive and time-consuming! Use models to inform protocol.

The cell membrane



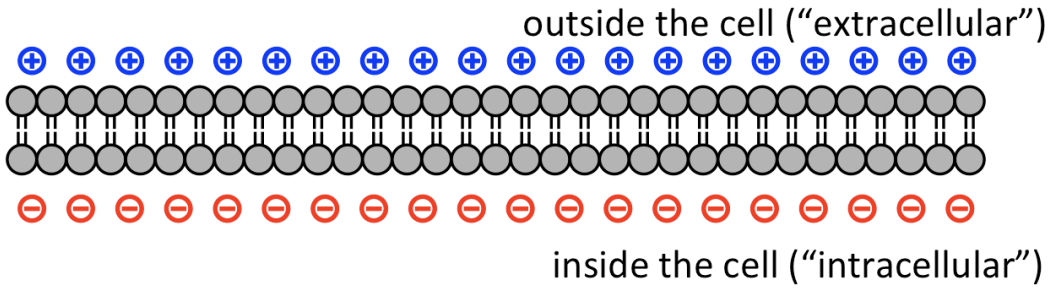
Source: OpenStax Anatomy and Physiology

Membrane potential

- "Potential" (i.e., potential energy)- energy available to do work
  - Electrical potential differences are measured in volts (V)

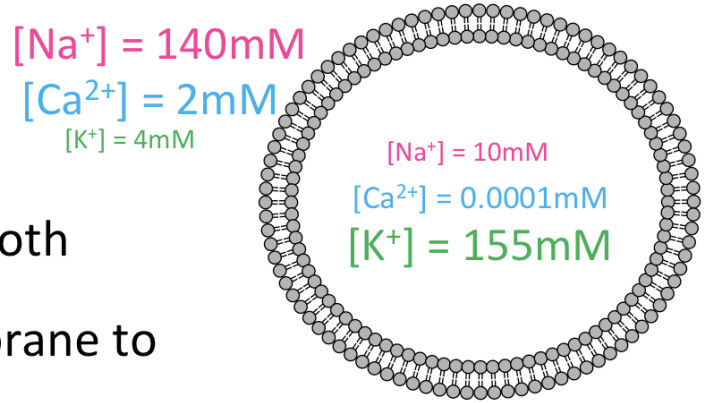
- "Membrane potential" – potential energy that develops across a biological membrane because of an asymmetric charge distribution:

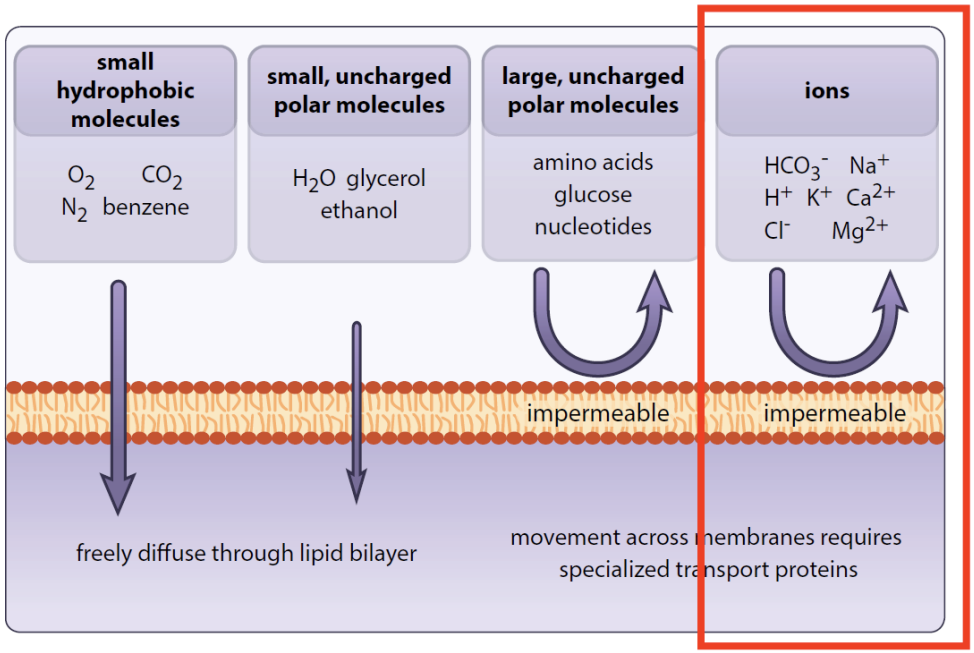
***NB*: Always read "inside with respect to outside"**

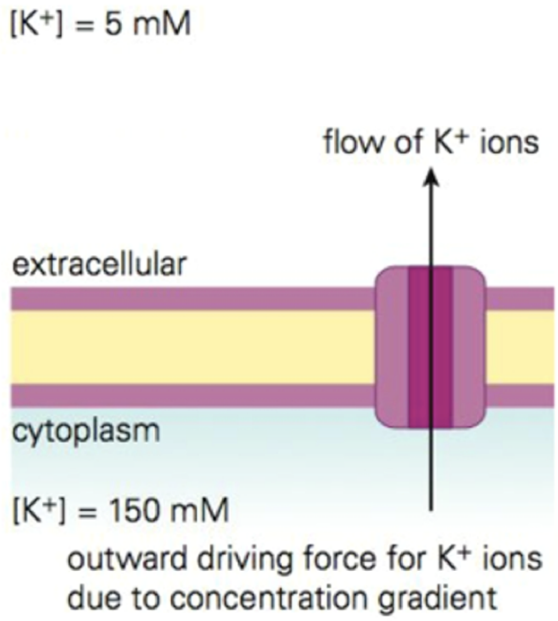


How is the membrane potential generated?

- Membrane potential relies upon two characteristics:
  - The relative concentrations of ions on both sides of the membrane
  - The selective-permeability of the membrane to the ions in question



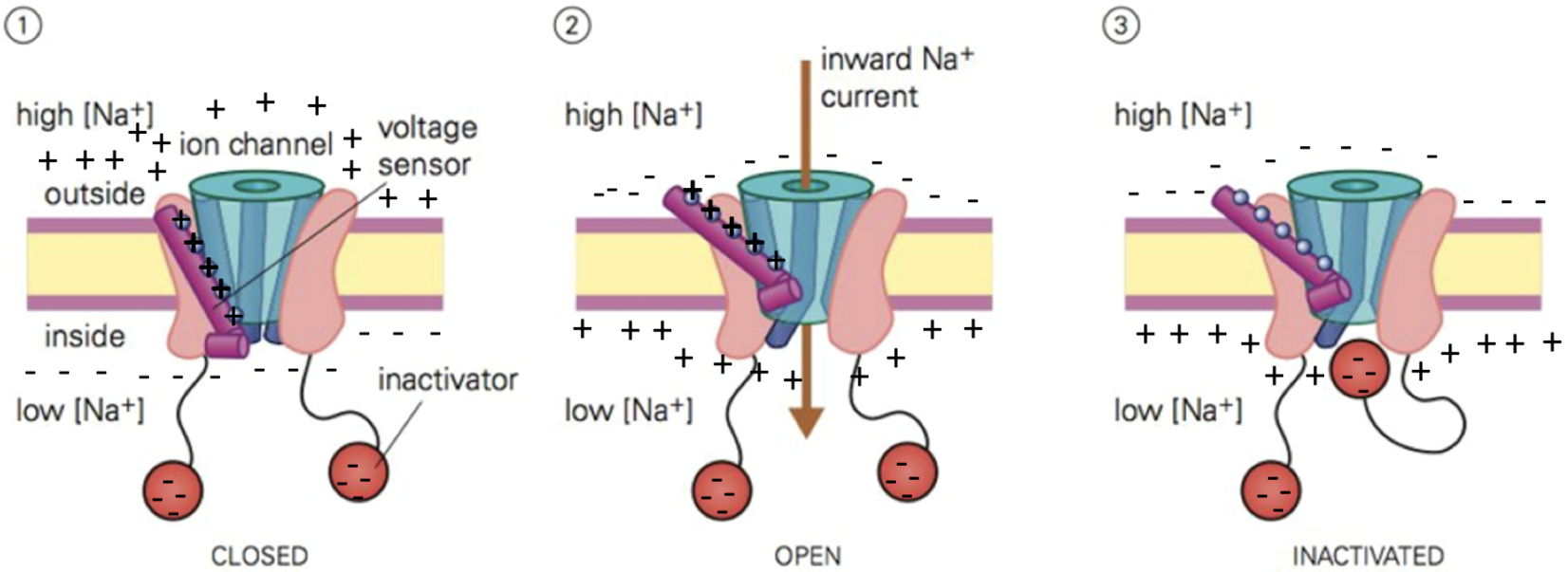




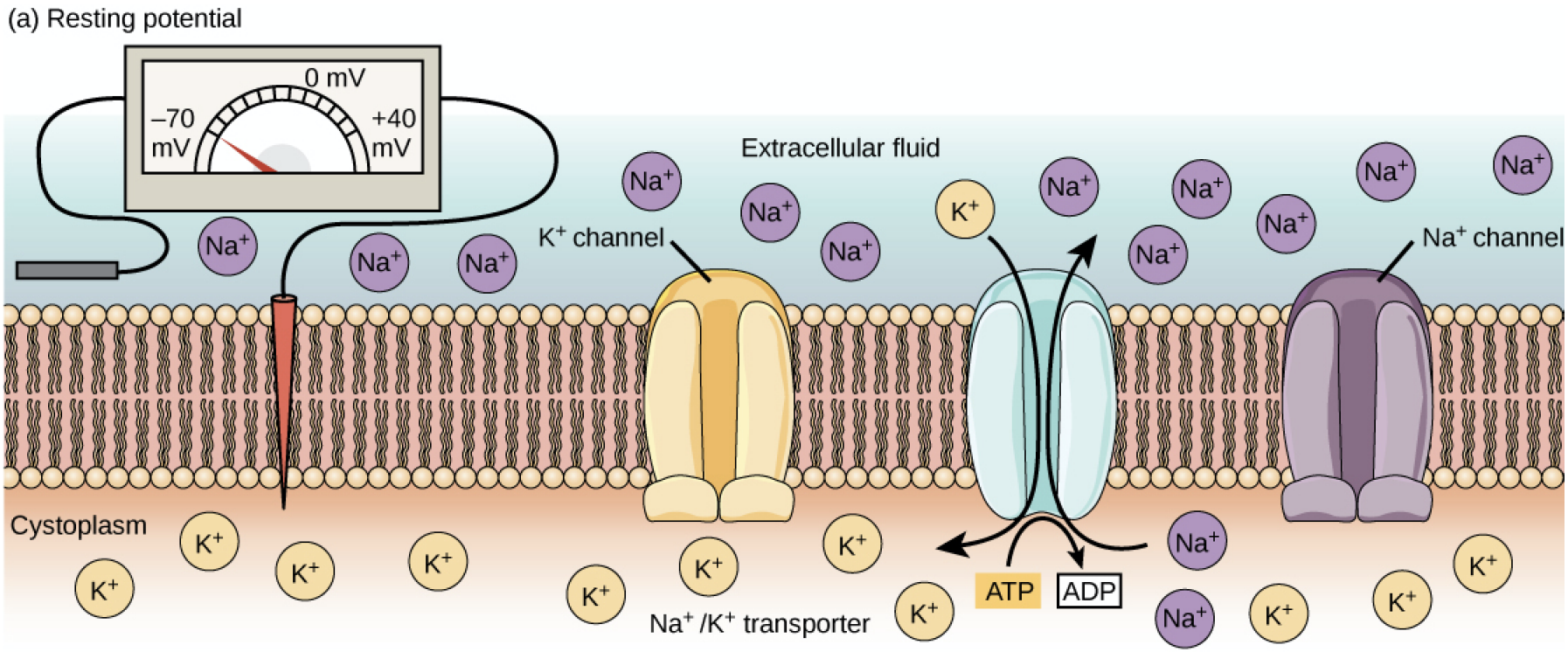
Some ion channels are voltage-gated

Voltage-Gated Channels

- Whereas "leak channels" are always open, voltage-gated channels only open in response to a change in membrane potential.
- 3 conformations: Closed, Open, and Inactivated



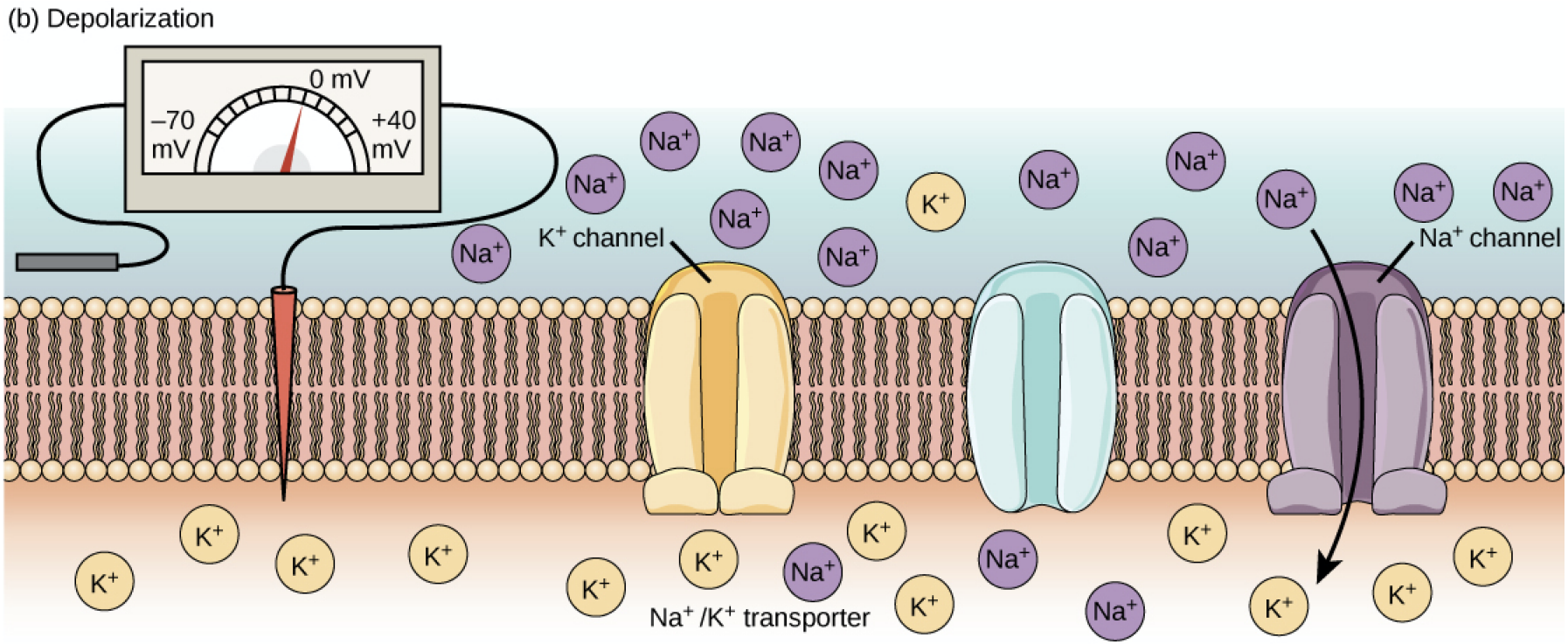
Resting potential



At the resting potential, all voltage-gated Na^+ channels and most voltage-gated K^+ channels are closed. The Na^+/K^+ transporter pumps K^+ ions into the cell and Na^+ ions out.

Source: OpenStax CNX

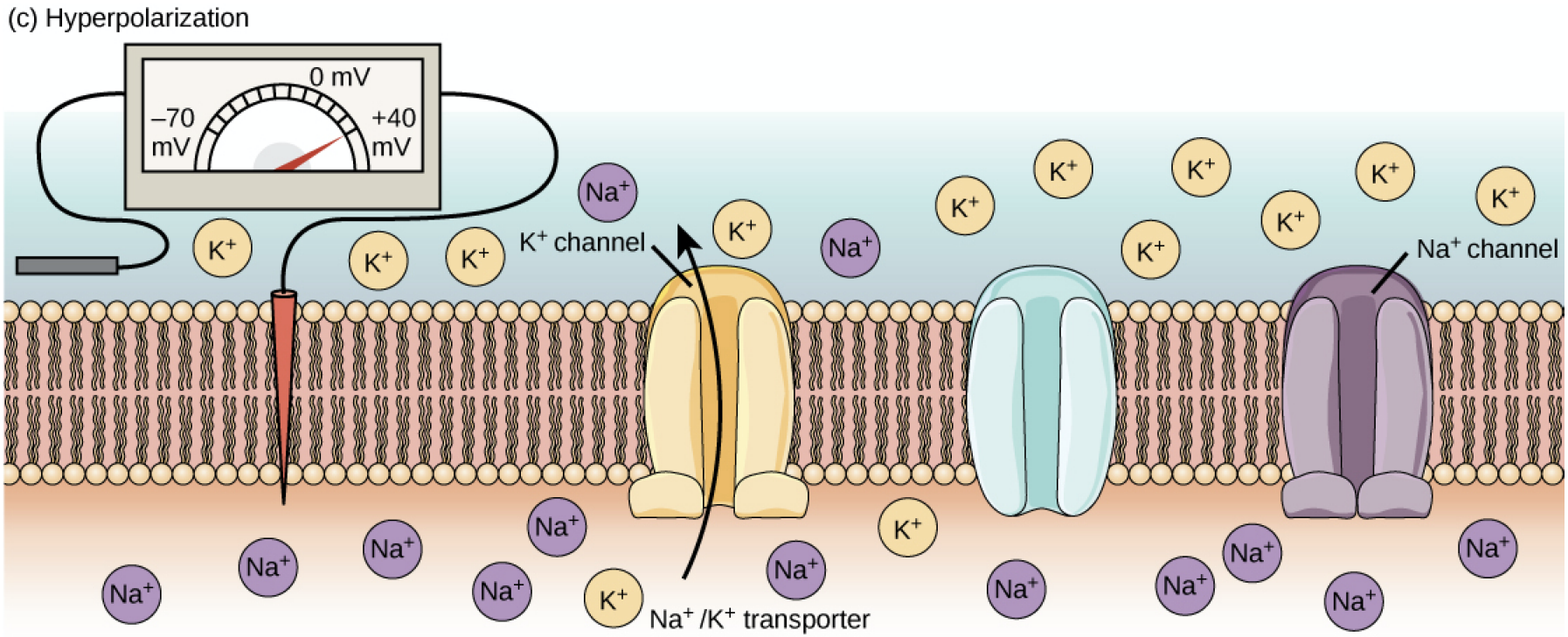
Depolarization



In response to a depolarization, some Na^+ channels open, allowing Na^+ ions to enter the cell. The membrane starts to depolarize (the charge across the membrane lessens). If the threshold of excitation is reached, all the Na^+ channels open.

Source: OpenStax CNX

Peak potential

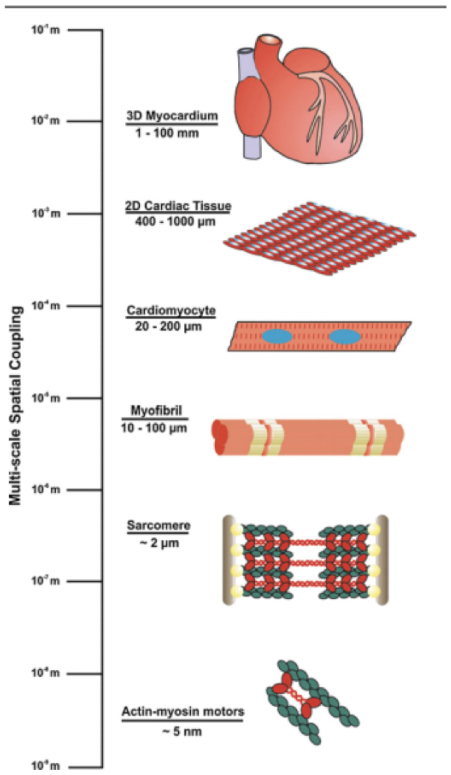


At the peak action potential, Na^+ channels close while K^+ channels open. K^+ leaves the cell, and the membrane eventually becomes hyperpolarized.

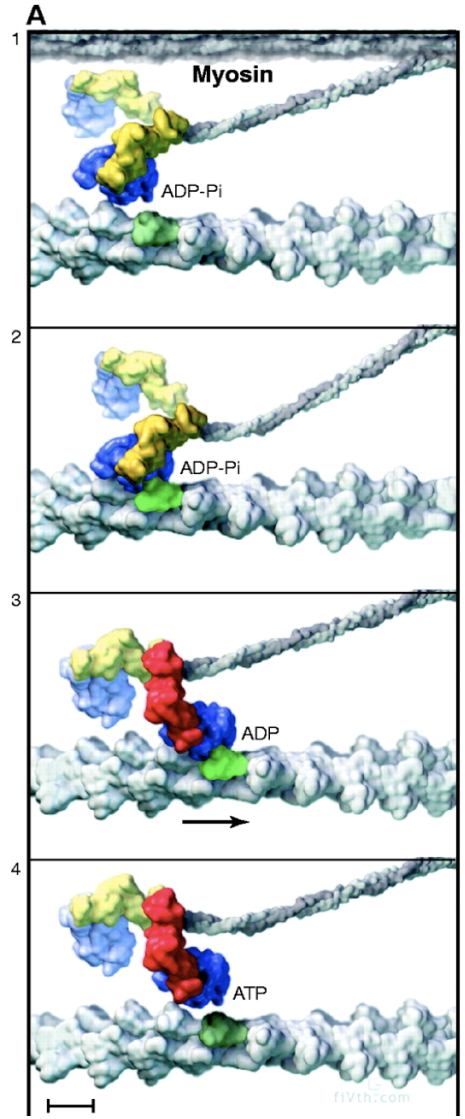
Source: OpenStax CNX

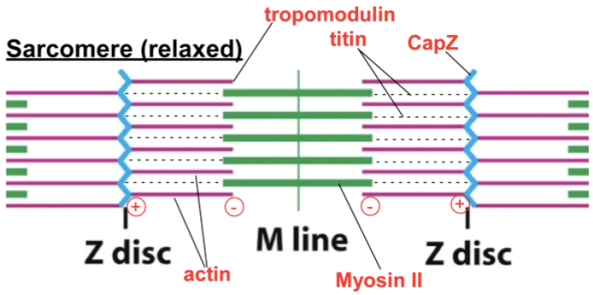
Excitation-Contraction Coupling

Muscle contractions stimulated by cardiomyocyte action potential



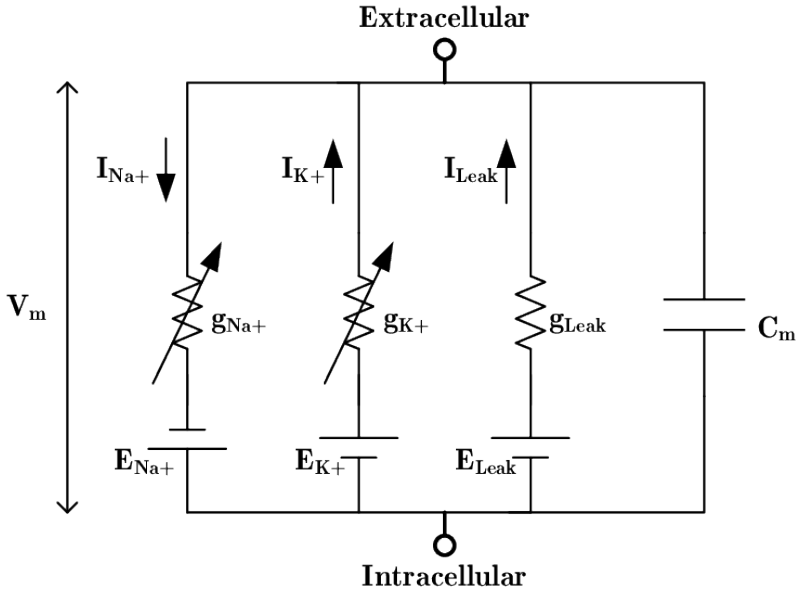
Sheehy, 2012.





Vale and Milligan, 2000.

Mathematical modeling based upon Hodgkin-Huxley-Katz



$$\begin{cases} \frac{dV_m}{dt} = \frac{I}{C_m} - \frac{\bar{g}_K n^4}{C_m}(V_m - V_K) - \frac{\bar{g}_{Na} m^3 h}{C_m}(V_m - V_{Na}) - \frac{\bar{g}_l}{C_m}(V_m - V_l) \\ \frac{dn}{dt} = \alpha_n(V_m)(1-n) - \beta_n(V_m)n \\ \frac{dm}{dt} = \alpha_m(V_m)(1-m) - \beta_m(V_m)m \\ \frac{dh}{dt} = \alpha_h(V_m)(1-h) - \beta_h(V_m)h \end{cases}$$

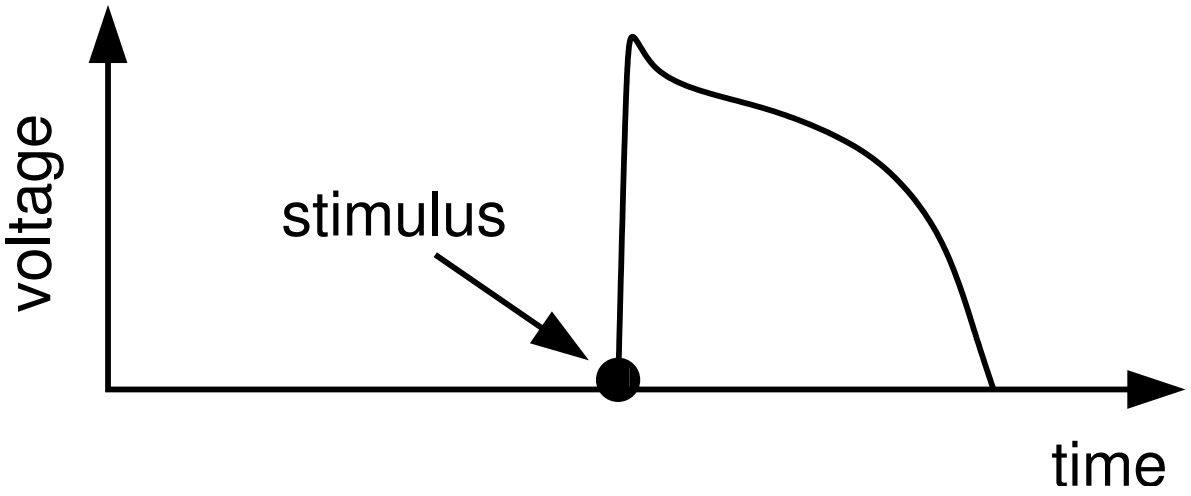
Excitability

- Cardiac tissue is an example of an excitable medium.
- A sufficiently strong electrical stimulus can cause a cell's transmembrane voltage v to experience a prolonged elevation before eventual return to rest.
- Toilet-flushing analogy[1]

[1] Fittingly, I used the TeX command *flushright* to right-justify the photo.

Action Potentials

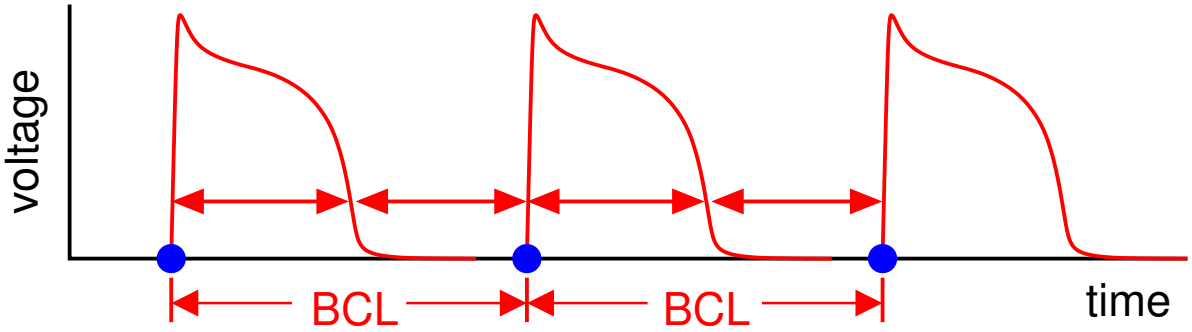
- *Action potential:* Prolonged elevation of transmembrane voltage v following a superthreshold stimulus. In the absence of subsequent stimulation, v eventually decays to the resting potential.



Pacing

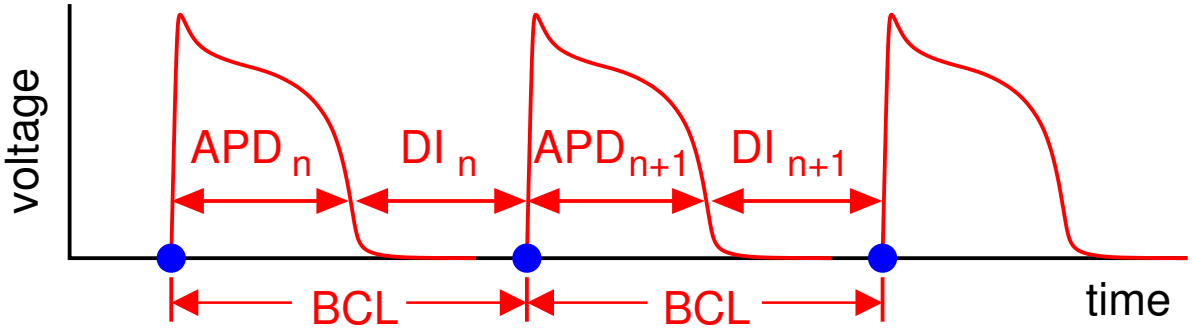
- **Pacing:** Repeated stimulation of cardiac cells.
- Useful to explore how a cell responds to *periodic* stimulation. We'll refer to the pacing period as the **basic cycle length (BCL)** (see figure).

Concept check: If a patient's heart rate is 120 beats per minute, what is their BCL?



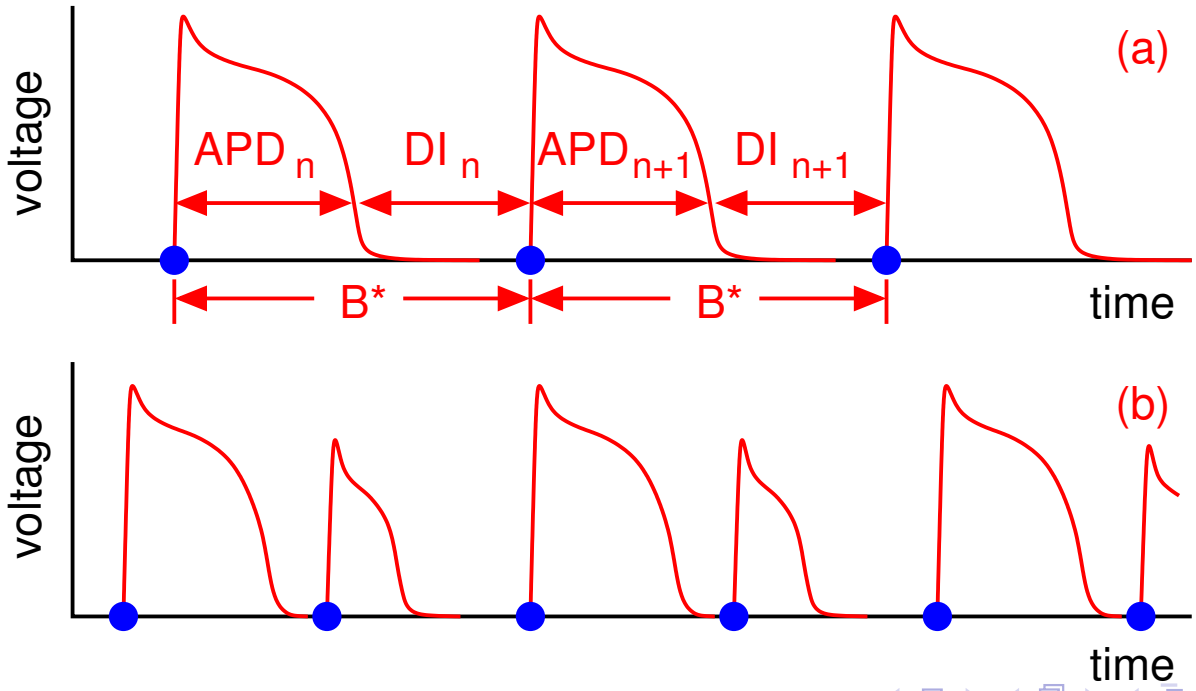
Pacing continued...

- Action potential duration (APD) and recovery time (diastolic interval, DI) can be defined relative to a threshold voltage $v = v_{\text{thr}}$.
- We'll let APD_n denote the APD which follows the nth stimulus in a paced cell, and DI_n the subsequent DI.



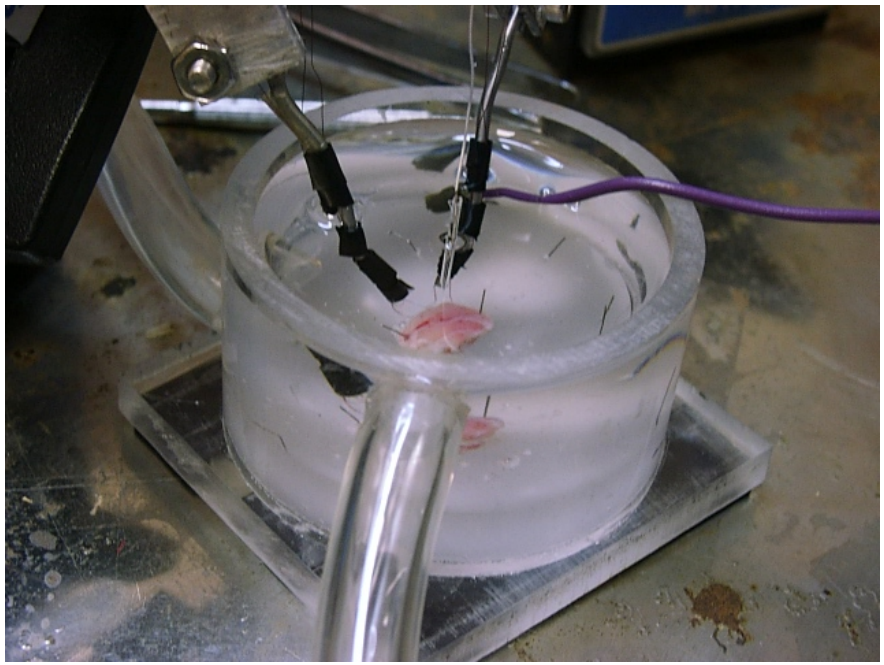
Types of rhythms

- If BCL is large, the sequence $\{\mathrm{APD}_n\}$ converges to a number APD^*.
- If BCL is decreased, the sequence $\{\mathrm{APD}_n\}$ may settle into a pattern of repeated alternation between two different numbers. This response, known as **alternans**, is abnormal.
- Further reduction of BCL may prevent cells from responding to every stimulus.



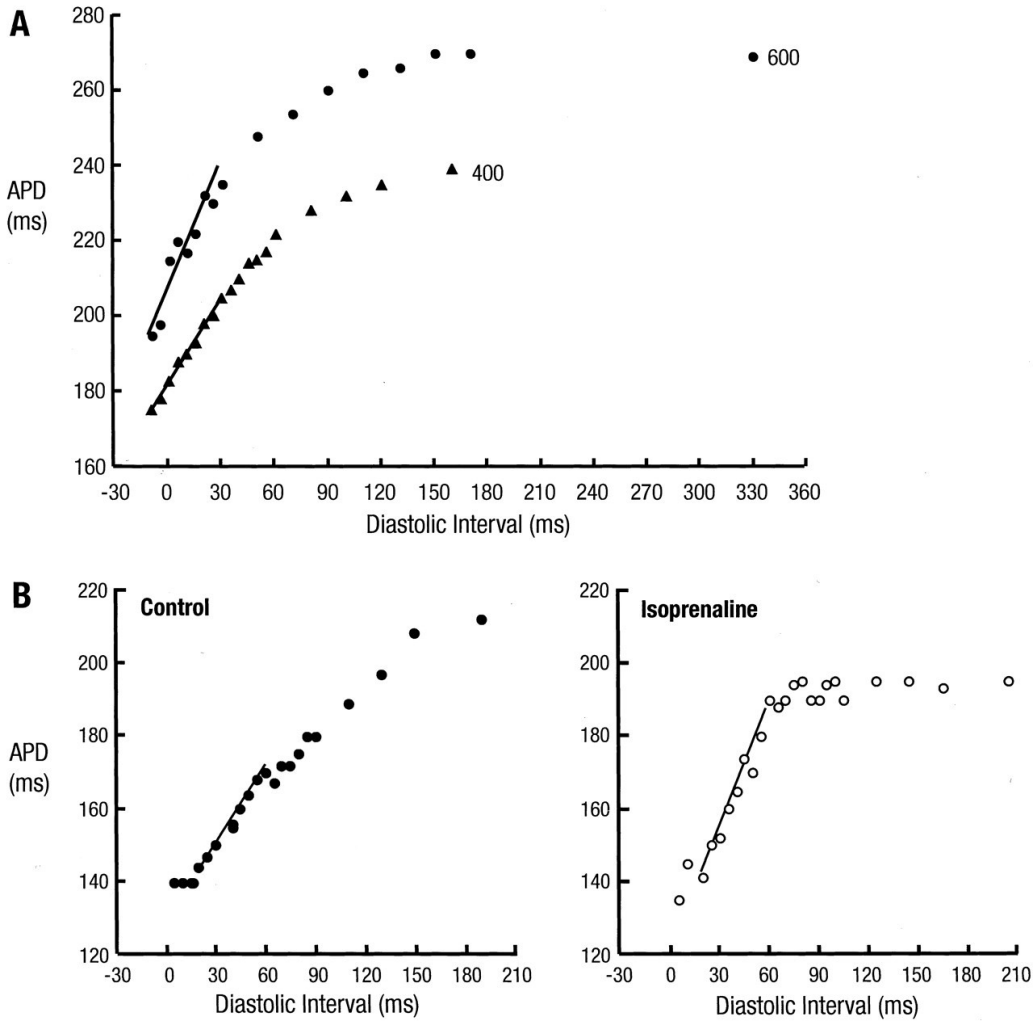
Experiment: How DI affects APD

- Shortening DI tends to shorten the subsequent APD. Why?
- Sample experiment: (1) Excise a heart, perfuse it. (2) Apply a single stimulus via an electrode to generate an AP. (3) Once AP ends, apply a 2nd stimulus after a specified DI. (4) Record resulting APD.



Source: Laboratory of Daniel J. Gauthier.

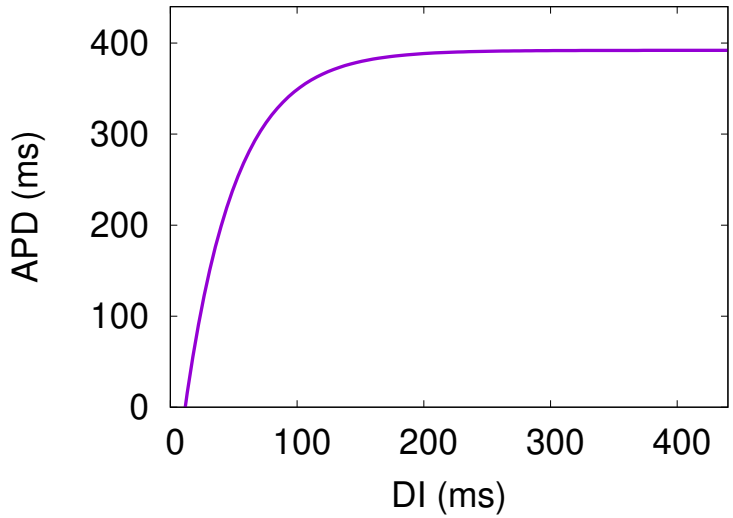
Results can be patient-specific, but same general trend



Source: Effect of Adrenergic Stimulation on Action Potential Duration Restitution in Humans, Circulation, 2003.

Restitution

- APD depends upon the preceding DI.
- Increasing DI (i.e., giving more rest) typically yields longer APD, but with diminished returns if DI is huge.
- If plot APD_{n+1} versus DI_n, data points tend to fall along a **restitution curve**: $\mathrm{APD}_{n+1} = f(DI_n)$.



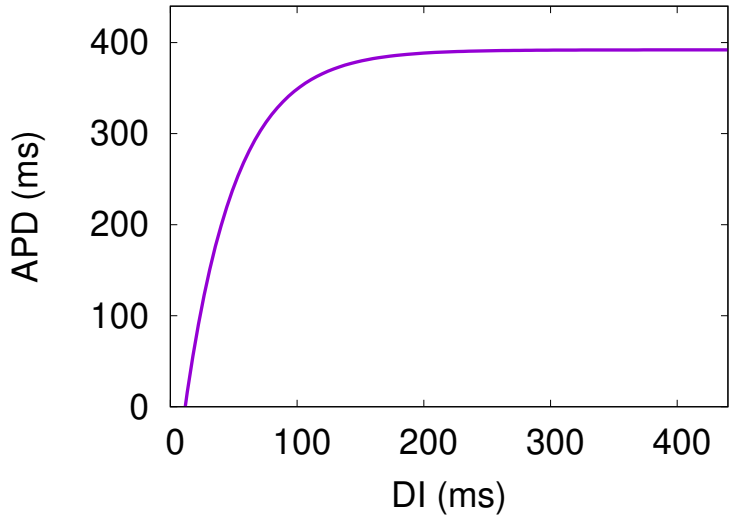
Restitution Mapping

If BCL constant, we can predict APD_{n+1} if we know APD_n:

$$\mathrm{APD}_{n+1} = f(\mathrm{DI}_n) = f(\mathrm{BCL} - \mathrm{APD}_n).$$

Concept check: If a plot of APD_{n+1} versus DI_n looks like the curve below, what would a plot of APD_{n+1} versus APD_n look like?

How can math help us understand whether alternans will occur?



Digression: One-dimensional mappings

- Suppose a sequence of numbers is defined recursively according to the rule $x_{n+1} = x_n^2$. Given x_0, all subsequent numbers in the sequence are uniquely determined.
- If $x_0 = \frac{1}{2}$, what are $x_1, x_2, \ldots$? What happens to x_n as n becomes larger and larger?
- If $x_0 = 2$, what are $x_1, x_2, \ldots$? What happens to x_n as n becomes larger and larger?
- For which special choices of x_0 does the sequence $x_1, x_2, x_3, \ldots$ remain constant?

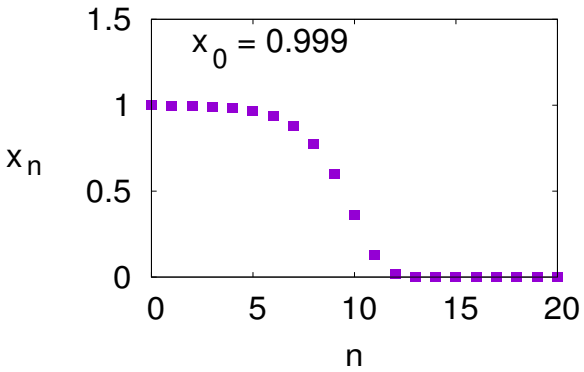
Fixed points

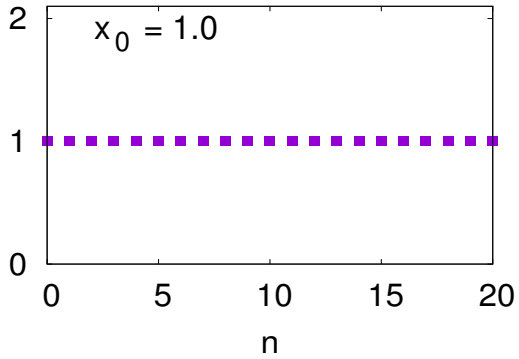
- A **fixed point** of the recurrence $x_{n+1} = f(x_n)$ is a number x such that $f(x) = x$.
- If $x_{n+1} = x_n^2$, then $f(x) = x^2$. Fixed points satisfy $f(x) = x$, which means $x^2 = x$. There are two solutions: $x = 0$ and $x = 1$ are the only fixed points.
- Fixed points can be **stable** or **unstable** depending upon what happens if we start from x_0 **near but not equal to** the fixed point.

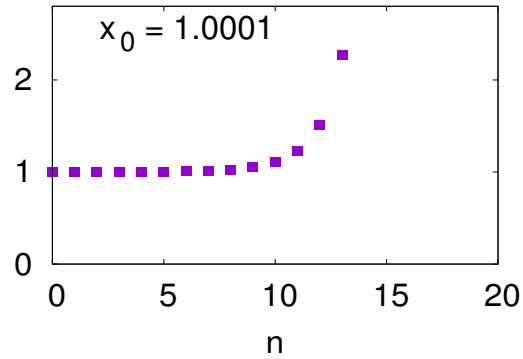
Stability of Fixed points

- Remember that $x_{n+1} = x_n^2$ has two fixed points: x = 0 and x = 1.

Concept check: Is $x = 0$ stable? Is $x = 1$ stable?







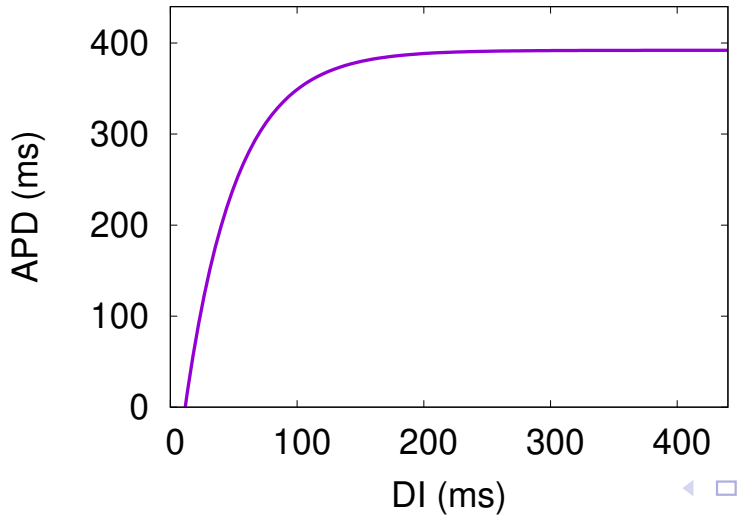
Cardiac restitution mapping

- Recall that we can predict APD_{n+1} if we know APD_n:

$$\mathrm{APD}_{n+1} = f(\mathrm{BCL} - \mathrm{APD}_n),$$

where BCL is determined from the heart rate.

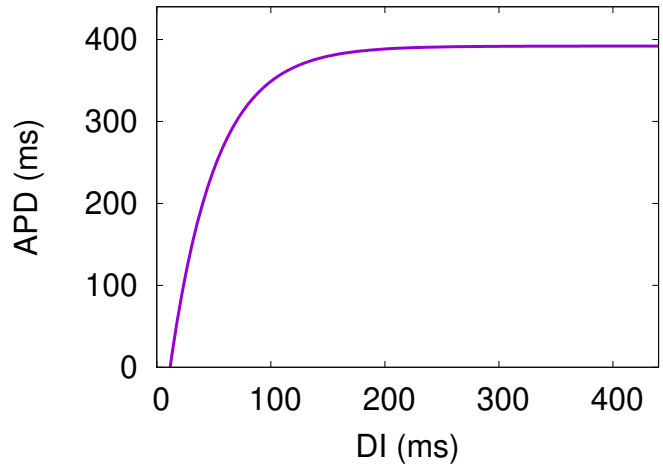
Concept check: If APD_0 were a fixed point, what would the restitution mapping $\mathrm{APD}_{n+1} = f(\mathrm{BCL} - \mathrm{APD}_n)$ predict about rhythm?



Cardiac restitution mapping

- Here is an example of a restitution function that was fit to data from bullfrog hearts, collected using the above mentioned experiment: $f(x) = 392 - 525e^{-x/40}$. The restitution mapping would be

$$\mathrm{APD}_{n+1} = 392 - 525e^{-(\mathrm{BCL}-\mathrm{APD}_n)/40}.$$



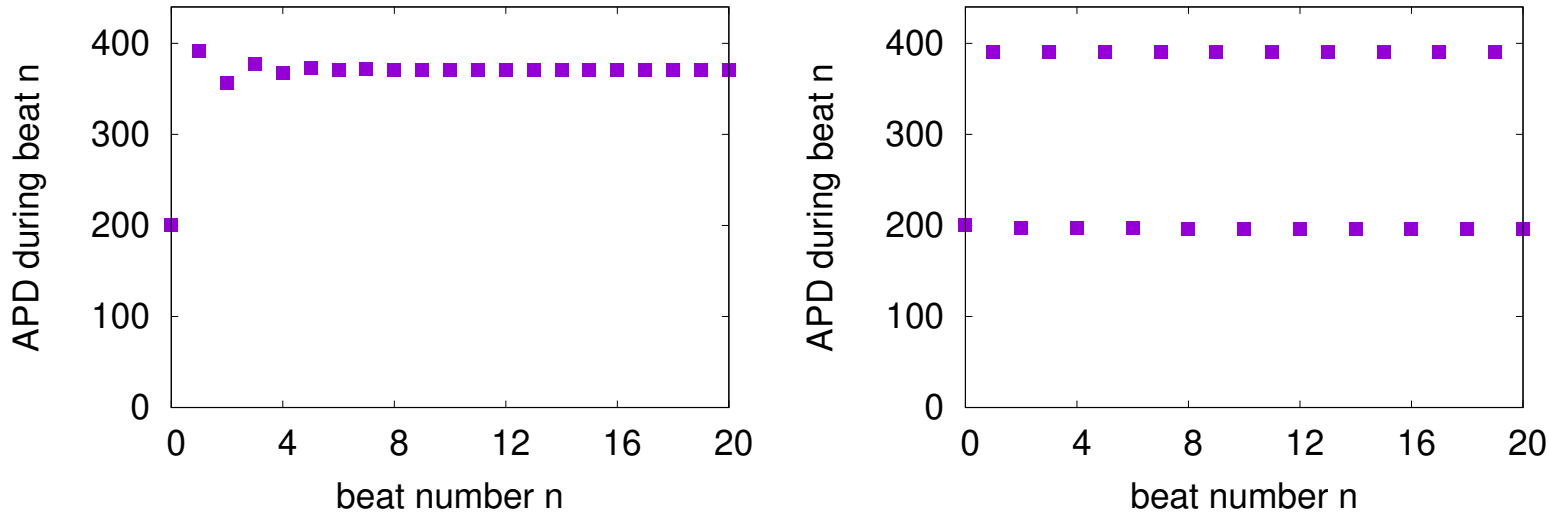
Concept check: If the bullfrog experienced alternans, what would a plot of APD_n versus n look like?

Cardiac restitution mapping

The figure below shows what happens if $\mathrm{APD}_0 = 200$ and

$$\mathrm{APD}_{n+1} = 392 - 525e^{-(\mathrm{BCL}-\mathrm{APD}_n)/40},$$

with $\mathrm{BCL} = 500$ (left panel) or $\mathrm{BCL} = 430$ (right panel).



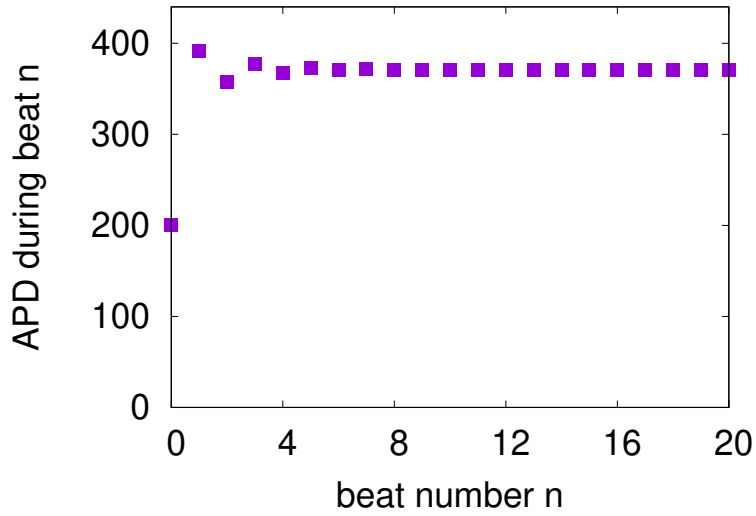
What triggers alternans

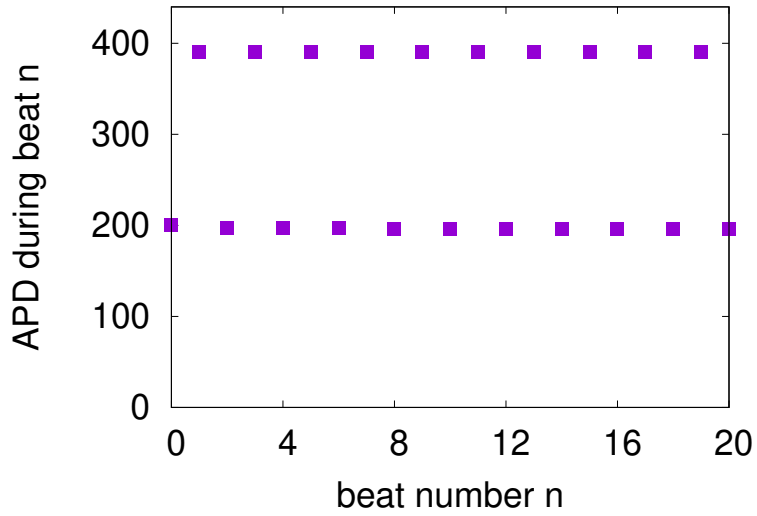
- When BCL is large enough (left panel), the restitution mapping

$$\mathrm{APD}_{n+1} = 392 - 525e^{-(\mathrm{BCL}-\mathrm{APD}_n)/40},$$

has a stable fixed point.

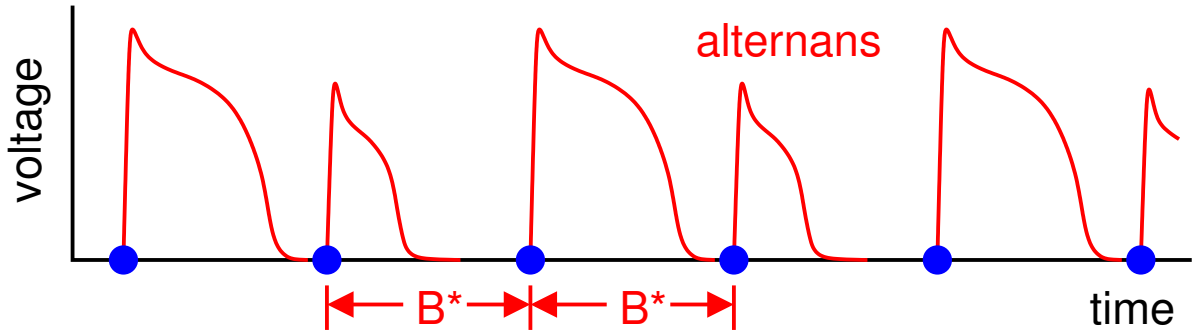
- If BCL dips below some threshold, the fixed point loses stability and alternans results. The fixed point is still there—it's just unstable!





Controlling Alternans

- It is known that APD alternans can lead to life-threatening rhythms, such as ventricular fibrillation.
- We will explain how to terminate alternans by applying small adjustments to the heart rate.
- Clinically, these adjustments can applied by an electrode attached to a surgically implanted device.



TDAS Control: Rob from the Rich, Give to the Poor

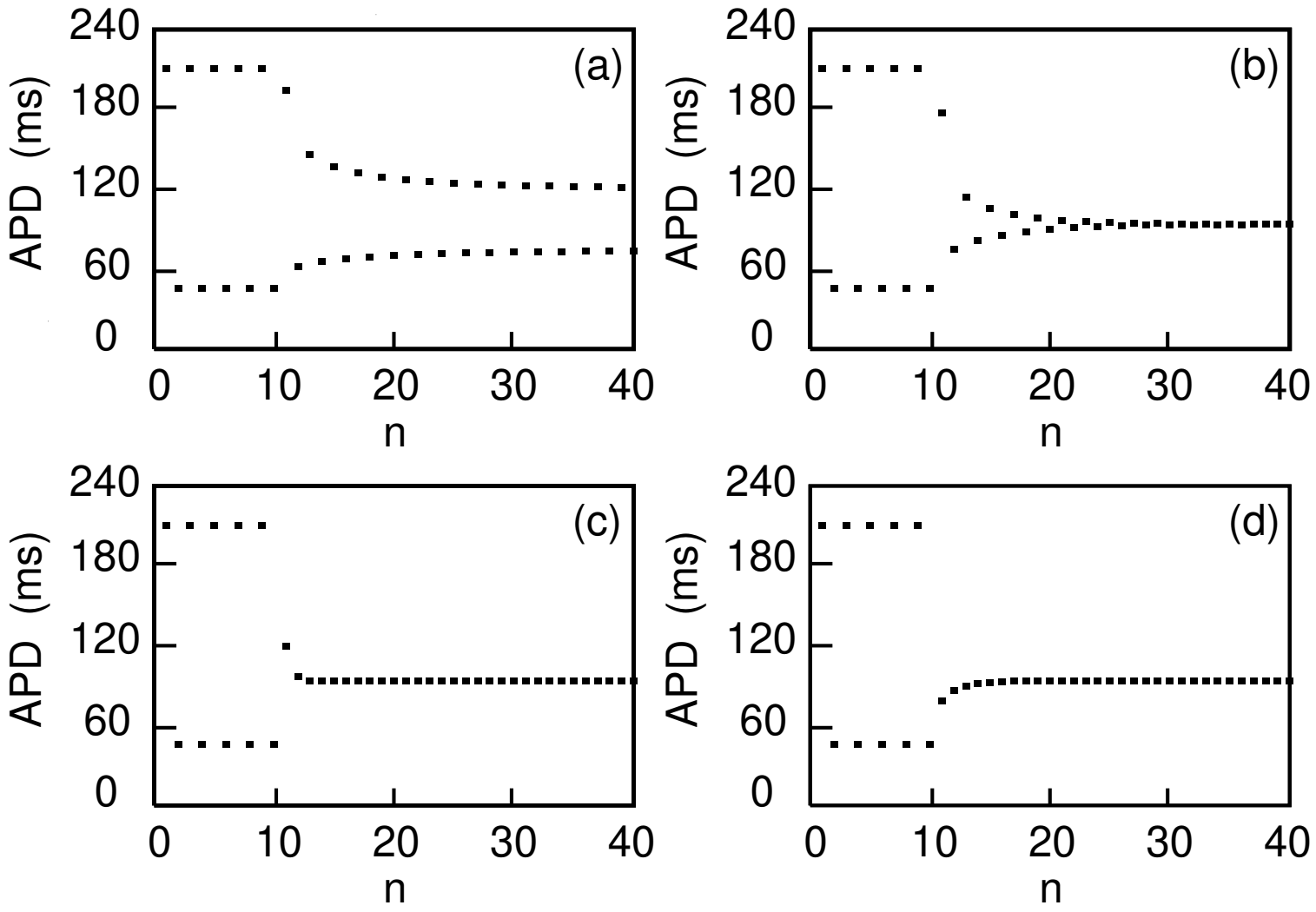
- During each beat, have the electrode fire stimuli at times that are not precisely BCL units of time apart.
- Modify BCL by an amount proportional to the difference between the two most recent APD values, replacing BCL with

$$\mathrm{BCL} + \gamma(\mathrm{APD}_n - \mathrm{APD}_{n-1}).$$

- The restitution mapping is modified accordingly:

$$\mathrm{APD}_{n+1} = f(\mathrm{BCL} + \gamma[\mathrm{APD}_n - \mathrm{APD}_{n-1}] - \mathrm{APD}_n).$$

Wow—this actually works if γ is well-chosen!



Discussion

- Using linear algebra and multivariate calculus, it's straightforward to predict which γ values will yield successful control for a given heart rate BCL.
- This has worked experimentally *in vitro*.
- There are some constraints to consider: We cannot delay the heart's native stimuli. It's difficult to achieve control over the whole heart.
- There are more sophisticated methods, such as far-field pacing, but the mathematics requires more background.

References

1. Dale Dubin, Ion Adventure in the Heartland, 2003.
2. J. Keener and J. Sneyd, Mathematical Physiology I, 2009.

Thank you!

For more information:

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