Lecture #6: Mechanotransduction

What is mechanotransduction?

- the process of converting physical forces → biochemical signals → cellular response
- need to understand how externally applied forces are transmitted into & throughout the cell
  → various techniques developed to probe mechanotransduction

What questions do we answer when we study mechanotransduction?

① How do cells respond to mechanical force? How does this translate into a signal?
② How can we strengthen bone? muscle?
③ How can we improve cardiac contractility?
④ How can we engineer tissue for artificial organs?

Disease	Dysfunctional Cell Type
Deafness	Hair cells in the inner ear
Glaucoma (Loss of Vision)	Optical neurons
Muscular Dystrophy	Myocytes, Endothelial Cells, Fibroblasts
Cardiomyopathy	Cardiomyocytes
Osteoporosis	Bone Cells
Arteriosclerosis	Endothelial Cells, Smooth Muscle Cells
Immune System Disorders	White Blood Cells
Central Nervous System Disorders	Neurons

Example: Skin Growth

Three Stages of Mechanotransduction

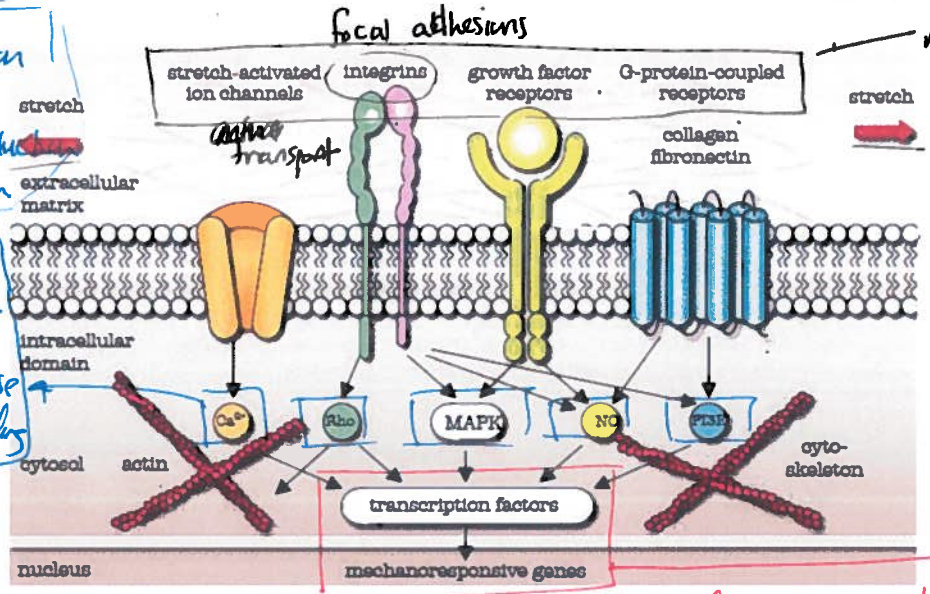
(i.) Mechanoreception – detection of stimulus and transmission of the signal from outside → in cell
↓
stretch beyond the physiological limit for skin growth

(ii.) Intracellular Signal Transduction
– transduction of the stimulus to location in the cell where a molecular response forms.
↳ nucleus.

(iii.) Target Activation – activation of proteins that cause alterations in cell behaviour through different mechanisms → FOR SKIN: ↑ mitotic activity and ↑ collagen synthesis

physical transduction
the cytoskeleton is a scaffold for the transduction of mechanical → biochem

Biochemical transduction
Signaling molecules from activation cause a cascade of signaling



mechanoreceptors → transmembrane proteins

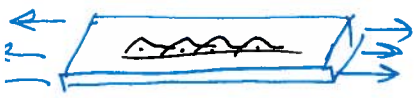
these mechanisms will lead to ↑ skin surface area

all these signals converge to activate transcription factors, which stimulate gene expression and other nuclear events

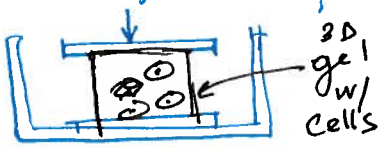
Probing Mechanotranduction

- Mechanotransduction probed in living cells in three major ways:

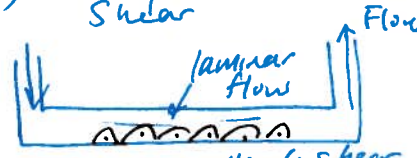
(i.) Uniaxial/Biaxial Tension



(ii) Uniaxial or Hydrostatic compression



(iii) Uniaxial/Circumferential Shear

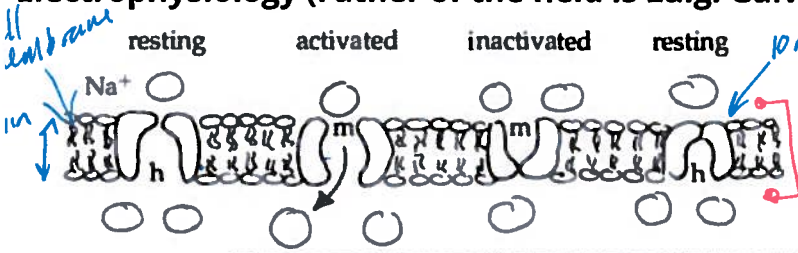


expose cells to s.s heer flow.

Some history...

- From 1948-1952: Hodkin and Huxley conducted patch clamp experiments on a giant squid axon and used this to develop a model.
  - They manipulated ionic concentration and controlled membrane potential
- From the mid-1950s: FitzHugh simplified Hodkin-Huxley work to a two variable model.

Electrophysiology (Father of the field is Luigi Galvani)



mechanisms of transport
- passive vs. active

$\phi = \phi^{int} - \phi^{ext}$ ... membrane potential due to concentration differences

Patch Clamp Expt. Measurements

Cell	Na^+_{int} (mM)	Na^+_{ext} (mM)	K^+_{int} (mM)	K^+_{ext} (mM)	Cl^-_{int} (mM)	Cl^-_{ext} (mM)	Resting pot. (mV)
Nerve	50	437	397	20	40	556	-65
Skeletal Muscle	13	110	138	2.5	3	90	-99
Cardiac Muscle	10	145	135	4	25	140	-90
Red Blood	19	155	136	5	78	112	-8

virtually all cells are negatively charged

Why?

① Discontinuous Passive Transport (ion channels)

② Continuous active transport (ion pump)

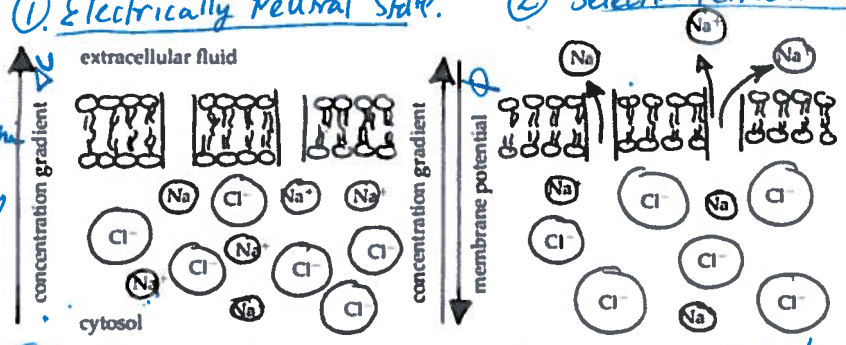
① Electrically Neutral State.

Each (+) has a (−) ion and each side is neutral locally but vary in concentration

② Selective Permeability

membrane permeable only for Na^+ so ∇C drives transport $\Rightarrow \phi$

only need a few ions for large ϕ. Thus ∇C doesn't change while ϕ does.

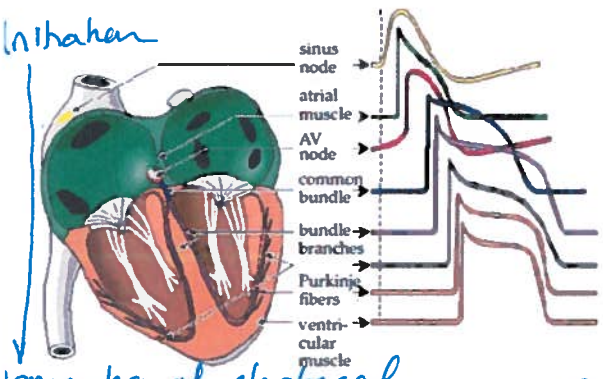


③ Resting State

conc gradient driven diffusion = membrane potential driven forces

resting potential (equilibrium)

Problem: Cardiomyocyte [Heart cell] and Neuron action potential upstroke



Initiation

Propogation of electrical signals: controlled by opening/closing of ion channels

understand this is important

↳ Self Generating Pulse like wave of electrochemical activity

"Sudden $\Delta\phi$"

When a cell produces an action potential → "Cell fires": all or nothing response.

Note: action potential is not a function of stimuli.

There are two different categories for models: ionic and phenomenological models. We will focus on the later – specifically: **FitzHugh-Nagumo Model** → Key Q: What is the total ion flux that drives the evolution of ϕ?

We start with the following:

$$\ddot{\phi} + k\dot{\phi} + \phi = 0$$

damping $k = c[\phi^2 - 1]$

$$\Rightarrow \ddot{\phi} + c[\phi^2 - 1]\dot{\phi} + \phi = 0$$

where $\phi = \phi(t)$ and $\dot{\phi} = \frac{d\phi}{dt}$

With the help of Lienard's transformation, you state

$$r = -\frac{1}{c}\dot{\phi} - \frac{1}{3}\phi^3 + \phi$$

r: "recovery variable"

ϕ: ~~membrane~~ potential

so

$$\dot{r} = -\frac{1}{c}\ddot{\phi} - [\phi^2 - 1]\dot{\phi}$$

and use this to turn our original 2[nd] order differential equation into two 1[st] order equations.

$$\dot{\phi} = c[-\tfrac{1}{3}\phi^3 + \phi - r] \qquad \dot{r} = \phi/c$$

allows for regenerative self excitation through fast positive feed back

slow variable ⇒ slow negative feedback

What is r? It is something like a phenomenological representation of the influences of all ionic fluxes. We now want to add some sort of stimulus and this will result in the classical FitzHugh-Nagumo model.

$$\dot{\phi} = c[-\tfrac{1}{3}\phi^3 + \phi - r + I]$$

$$\dot{r} = \frac{1}{c}[\phi - br - a]$$

Note: I = stimulus; a & b: additional constants.

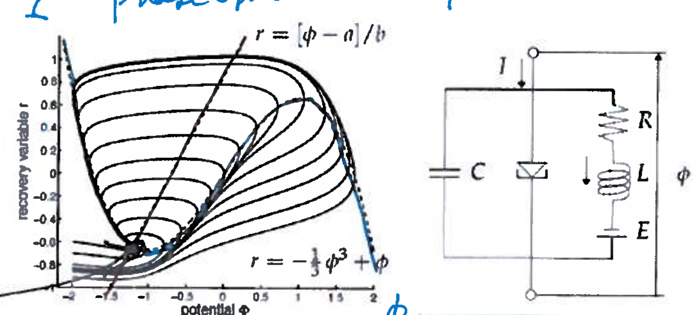
Now, FitzHugh did this entire math part of this model but Nagumo's contribution was creating an electrical circuit interpretation. Additionally, when you plot these two equations, you can create a 2-d phase space plot as shown below. For homework 3, I have given you code for coupled neurons and you will play around with the parameters.

$$\dot{\phi} = 0 \rightarrow r = -\frac{1}{3}\phi^3 + \phi + I$$

$$\dot{r} = 0 \rightarrow r = \frac{\phi - a}{b}$$

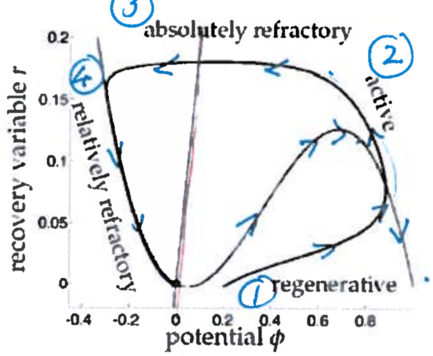
} plot to get dotted line

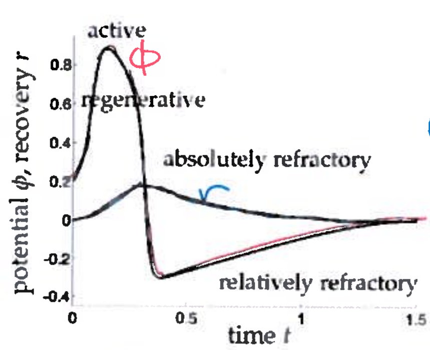
Phase space for multiple I



there is a single point of intersection that represents steady state aka $\dot{r} = \dot{\phi} = 0$

Now what do these results exactly mean?





1. Excitation begins with rapid cell depolarization through a fast upstroke ϕ → opening of ion channel
2. Permeability maximized at this point and Na^+ channels close as K^+ open.
3. ϕ decreases smoothly while r is const. The cell "recovering" b/c it cannot generate an immediate new action potential
4. ↓ r as solution slowly returns to resting state.