ZU CHONGZHI DISTINGUISHED LECTURE SERIES

Topic

1) Sep 4: From Atoms to Axons: how a handful of atoms control signals in the 10^{20} atoms of a nerve fiber
2) Sep 11: Ion Channels and Transporters: How do they work? (1)
3) Sep 18: Ion Channels and Transporters: How do they work? (2)
4) Sep 27: Stochastic Basis of Mean Field Theories

Lecture Time

Sep 4, 11, 18 FRIDAY
Sep 27 SUNDAY
9:00-10:30 AM Kunshan Time
8:00-9:30 PM Chicago Time

Open Discussion Time

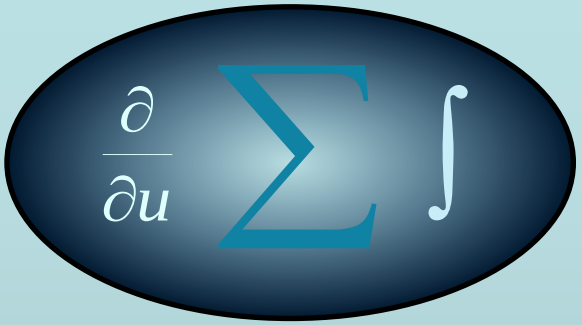
Sep 8, 15, 22, 29 TUESDAY
10:30-11:30 PM Kunshan Time
9:30-10:30 AM Chicago Time

Speaker:
Prof. Robert Eisenberg
Adjunct Professor of Applied Mathematics, Illinois Institute of Technology
Bard Professor and Chairman of Physiology and Biophysics, emeritus, Rush University

ZOOM MEETING ID:
932 7767 0707

DUKE KUNSHAN
Zu Chongzhi Center for Mathematics and Computational Sciences

First Day
September 4
2020



Special Thanks

Shixin Xu

Jian-Guo Liu

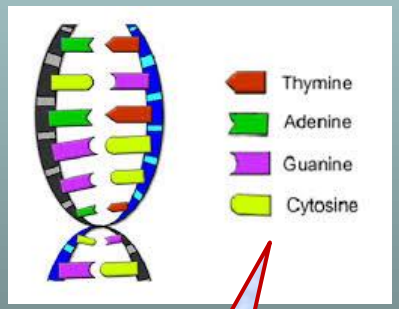
Prof. Peter Pickl

and Yiewei Xiong for her hard work!

昆山杜克大学
DUKE KUNSHAN UNIVERSITY

Life is special because it is inherited from a tiny number of atoms

How can a few thousand atoms conceivably control 10^{25} atoms?



YouTube

Vocabulary

Life extends over many Scales
with a
Hierarchy of Structures
one on top of another

So **Life Needs Many Words**
to define the Structures
And how they work

Extensive Vocabulary is Needed
Extensive Vocabulary is a Barrier for Students
I mark most of these in my lectures with
a call out YouTube

and I will provide a
Vocabulary List

Vocabulary

Extensive Vocabulary is Needed
Extensive Vocabulary is a Barrier for Students

Best Source for Vocabulary are Video Clips, often from YouTube

or from educational websites like MIT

or from Wikipedia

Or from general Internet Search

and I will provide a Vocabulary List

How can a few thousand atoms conceivably control 10^{25} atoms?

The thousand atoms of one gene occupy say 10^{-27} m^3

The volume of a person might be $1m^3$

Volume of USA *or* China 1m high is 10^{13} m^3

Fraction of space of a gene is about 10^{-27}

Fraction of Space of One Person in USA is 10^{-13}

$1\ m^3$ has no effect in USA or China

1 gene should have no effect

How can a few thousand atoms conceivably control 10^{25} atoms?

Biological Answer:

Structure: a Hierarchy of Devices

Physical Answer:

Electrodynamics: Strong and Universal

inside atoms to stars

Another talk* another day!

*Eisenberg, Oriols, and Ferry. 2017. Dynamics of Current, Charge, and Mass. Molecular Based Mathematical Biology 5:78-115 arXiv https://arxiv.org/abs/1708.07400.

Everyone knows Biology
is made of
Structures

Working hypothesis:
The Structures make Devices
that span the scales

And make biology
The ULTIMATE MULTISCALE DEVICE
Atoms to Axons to Meters

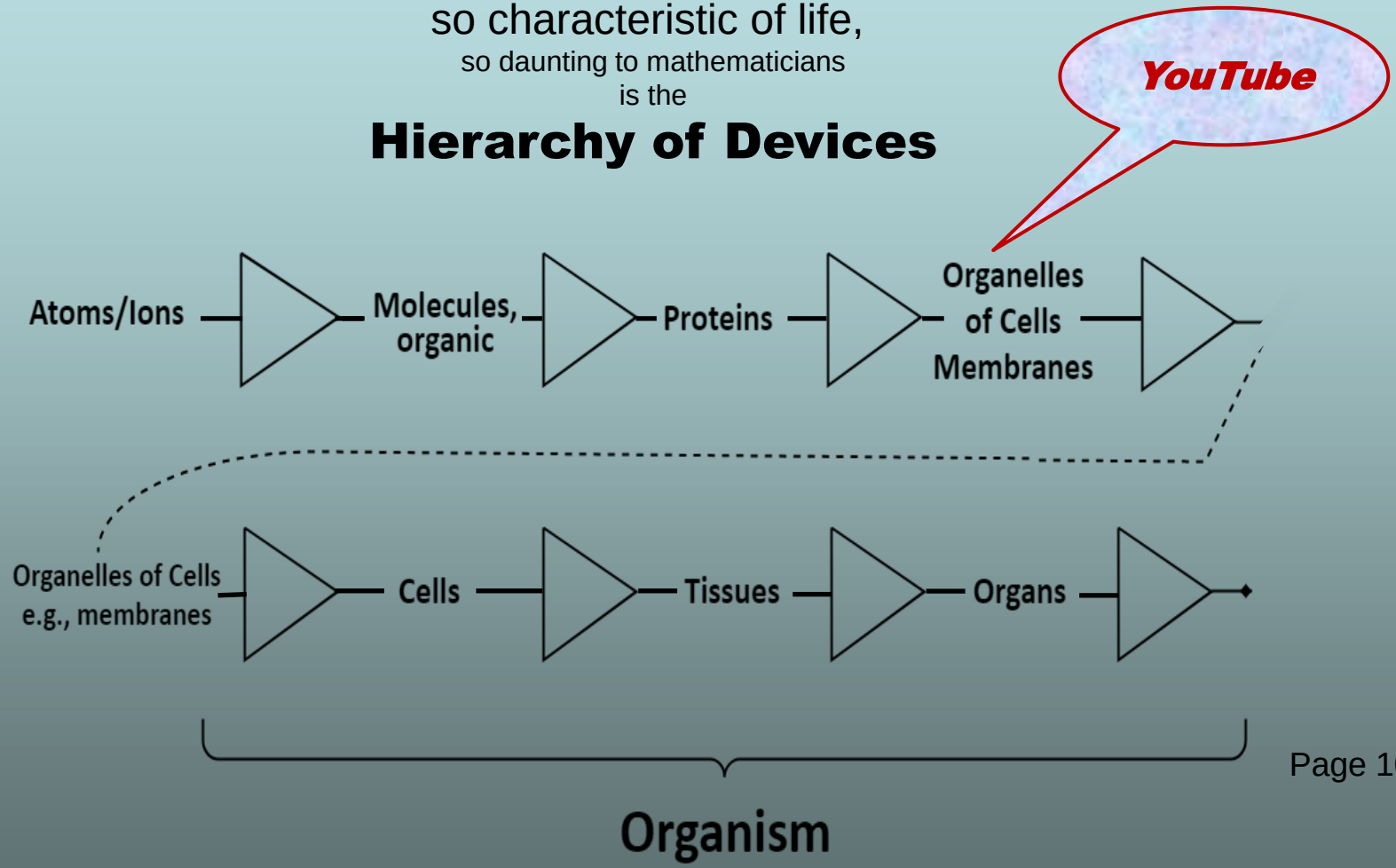
Structural Complexity

so characteristic of life,

so daunting to mathematicians

is the

Hierarchy of Devices



How can a few thousand atoms conceivably control 10^{25} atoms?

ANSWER:
by forming a
HIERARCHY of DEVICES

Working hypothesis:

The Structures of Biology

make a

Hierarchy of Devices

that span the scales

And make biology

The ULTIMATE MULTISCALE MACHINE

From

Atoms to Axons to Meters

MUST know some elementary biology

EASY to learn

Compared to the books you all had to memorize in high school, I am told.

Certainly
EASIER THAN LEARNING
AMERICAN ENGLISH

Elementary Material

I rather

patronize

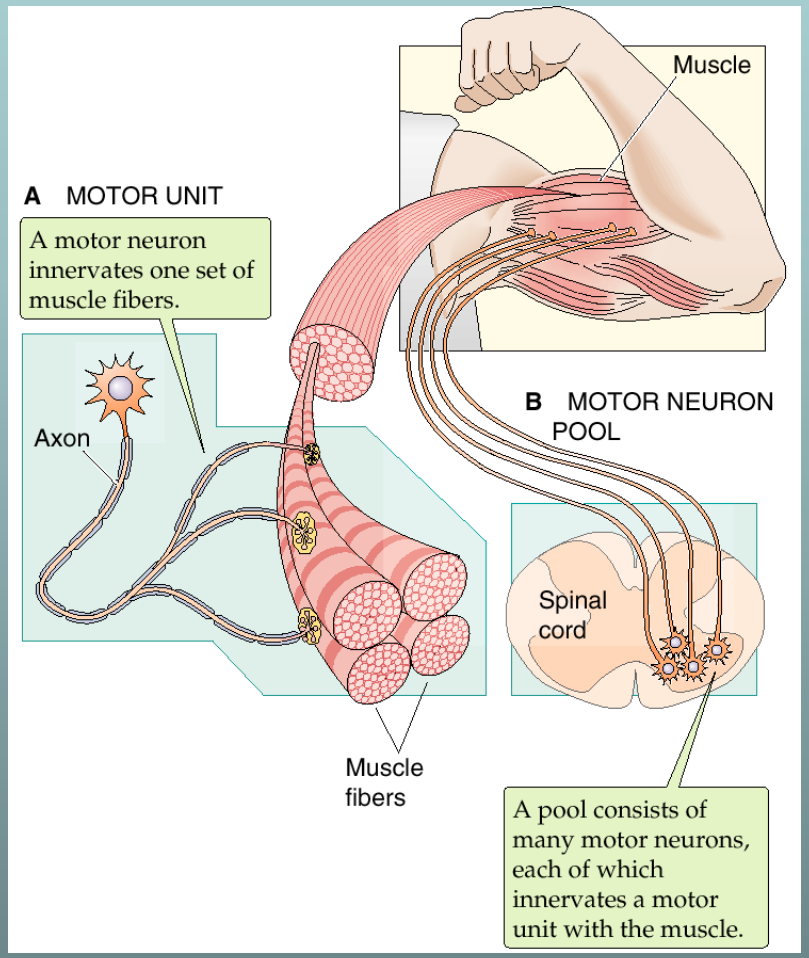
than mystify

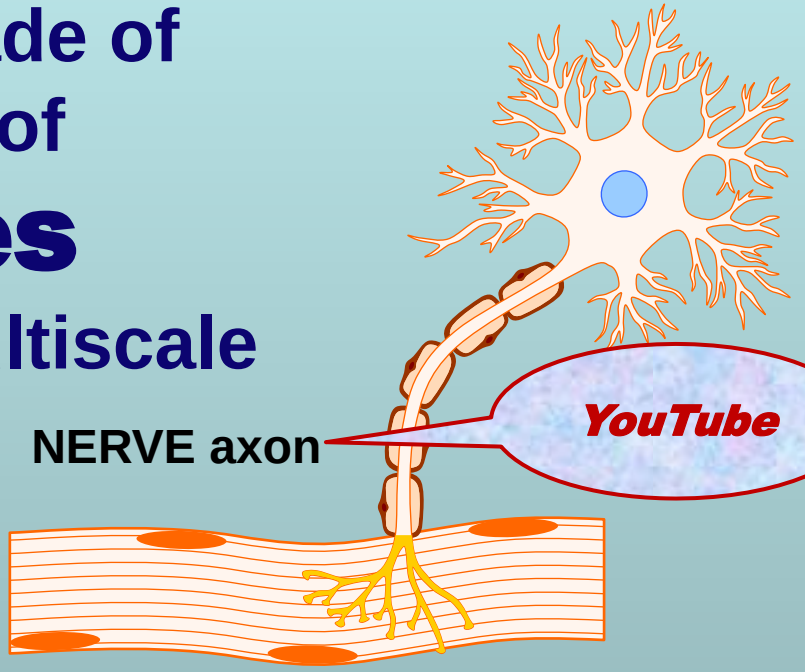
Few mathematicians know
ELEMENTARY chemistry, biochemistry or molecular biology
EASY

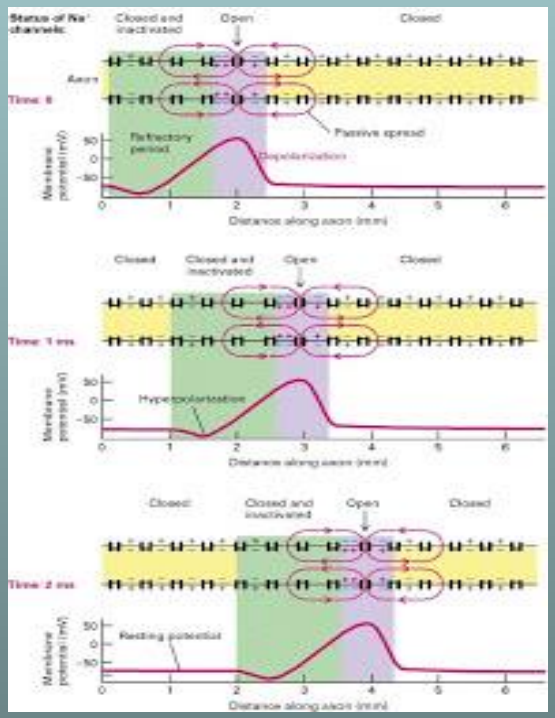
Biology is made of Hierarchy of **Devices**

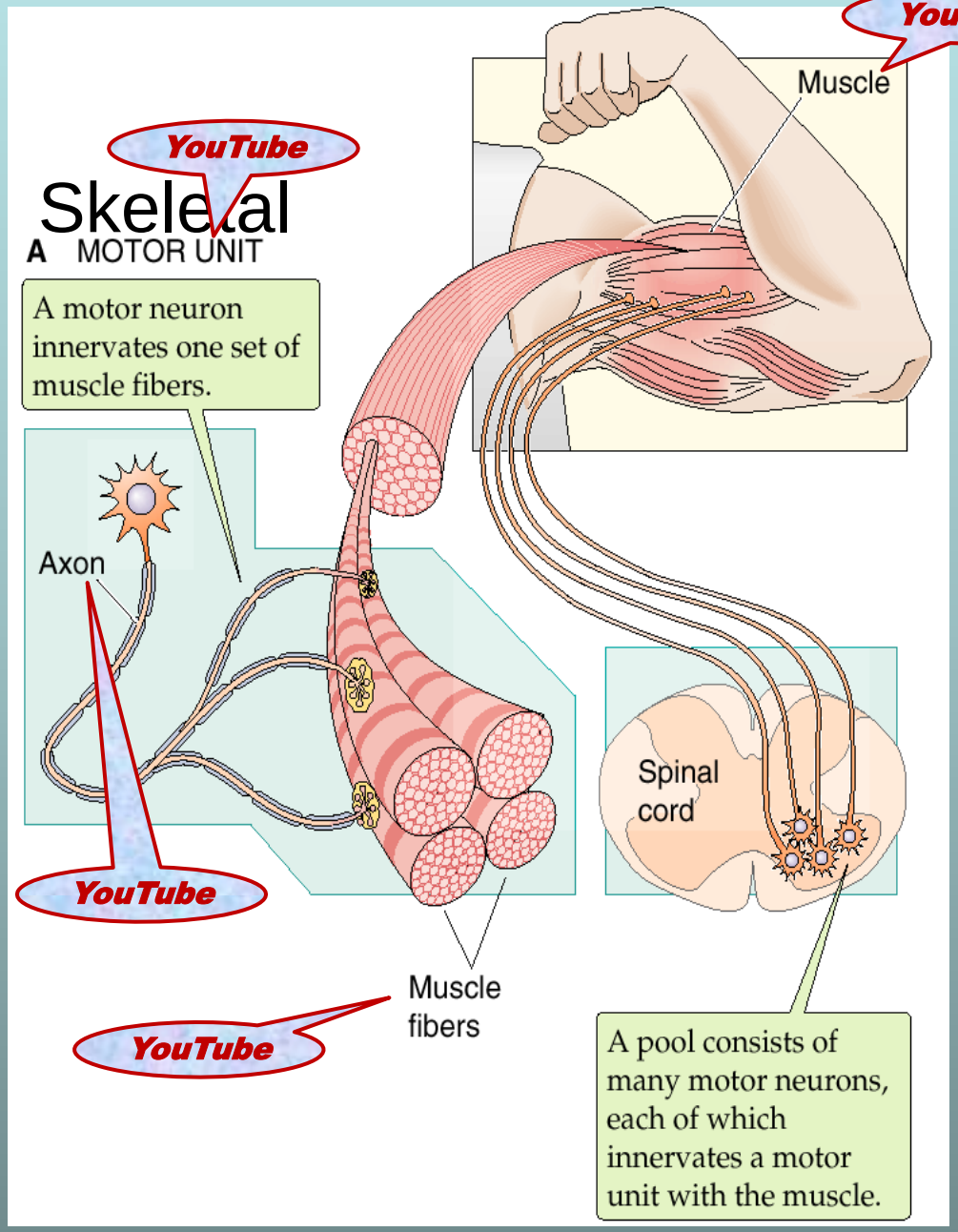
YouTube

Nerve MUSCLE and they are Multiscale





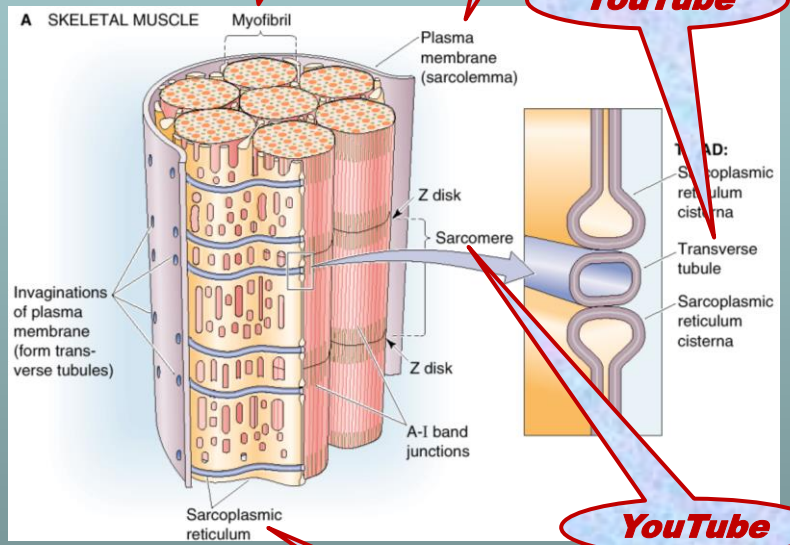




Biology is made of Hierarchy of

Devices

and they are Multiscale



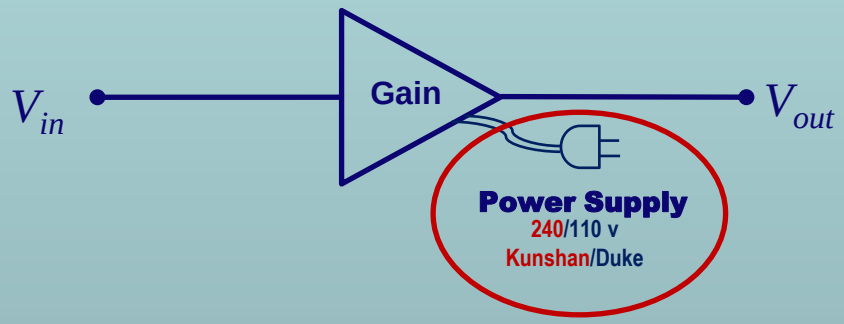
What is aDevice

YouTube

YouTube

Amplifier

Converts an Input to an Output



by a simple 'law'

an algebraic equation

$$V_{out} = g_{gain} V_{in}$$

$g_{ain} = positive\ constant, like\ 12$

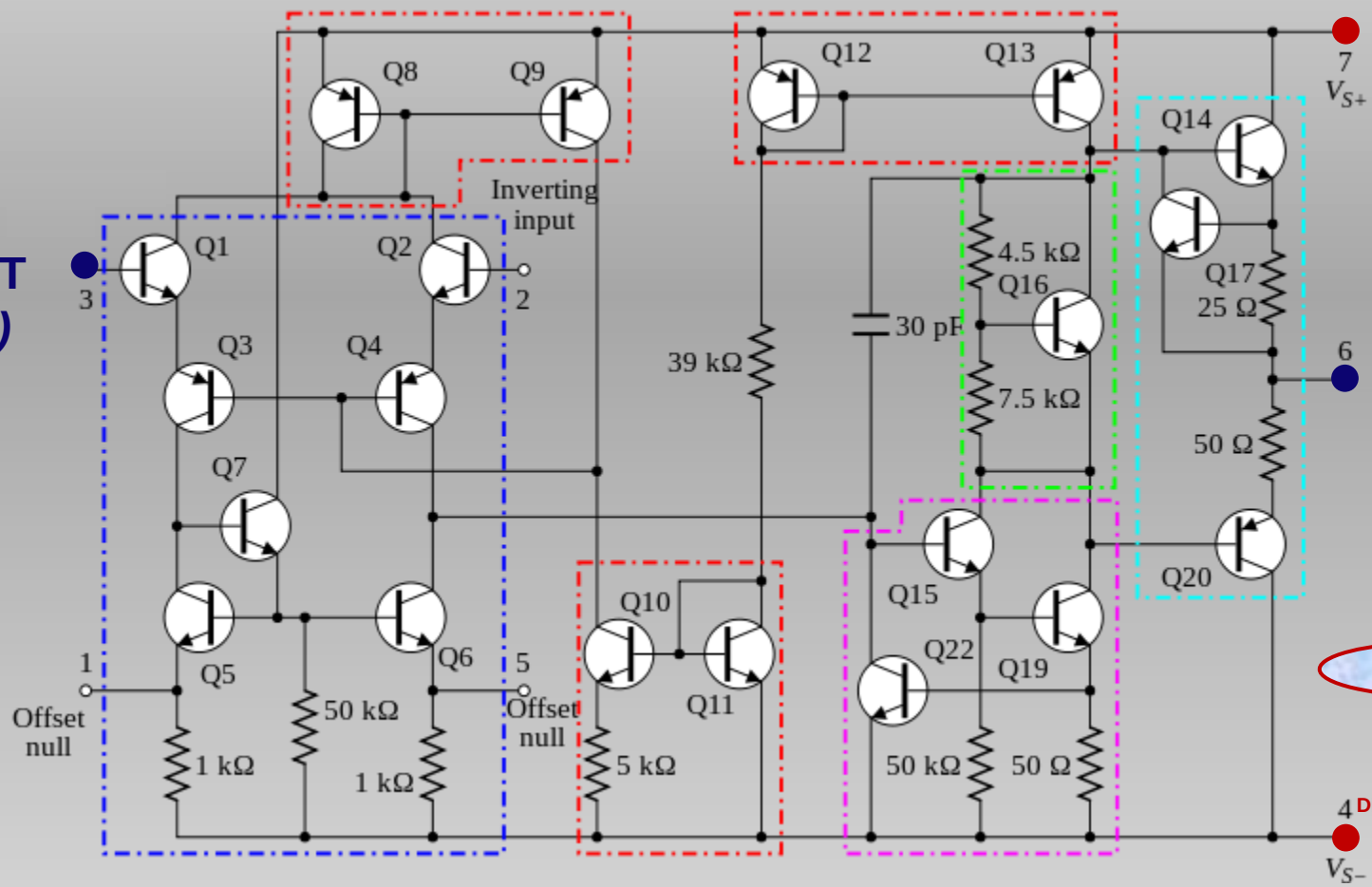
Device converts Input to Output by a simple 'law'

Device is ROBUST and TRANSFERRABLE because it uses POWER and has complexity!

YouTube

YouTube

Circuit Diagram of common 741 op-amp: Twenty transistors needed to make linear robust device



YouTube

Dotted lines outline: current mirrors (red); differential amplifiers (blue);
class A gain stage (magenta); voltage level shifter (green); output stage (cyan).

Device

converts an
Input to an Output

by a simple 'law'

$$V_{out} = g_{gain} V_{in}$$

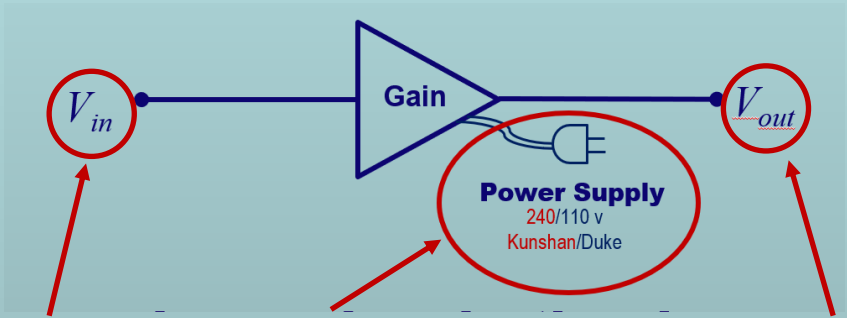
DEVICE IS USEFUL
because it is
ROBUST and TRANSFERRABLE

g_{gain} is Constant !!

Device

Amplifier

Converts an Input to an Output



Input, Power Supply, Output

are at

Different Locations

Spatially non-uniform boundary conditions

YouTube

Power is needed

Non-equilibrium, with flow

YouTube

Displaced Maxwellian

Distribution of velocities

Provides Flow

YouTube

YouTube

Input and Output are at Different Locations

YouTube

Spatially **non**-uniform boundary conditions

Power is needed

Non-equilibrium, with flow

Displaced Maxwellian

Distribution of velocities

YouTube

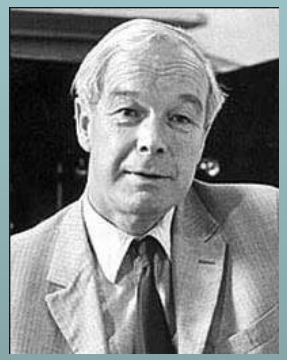
Provides Flow

VERY simple kind of nonequilibrium,

driven only by boundary conditions with trivial but essential change in distribution of velocities

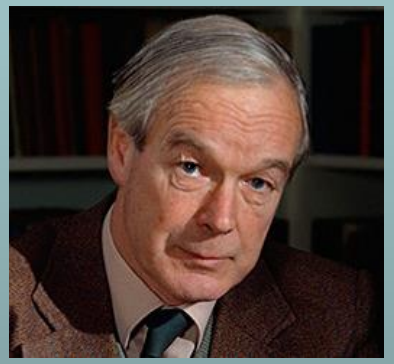
Device Approach to Biology

is a



Alan Hodgkin
friendly

Miracle



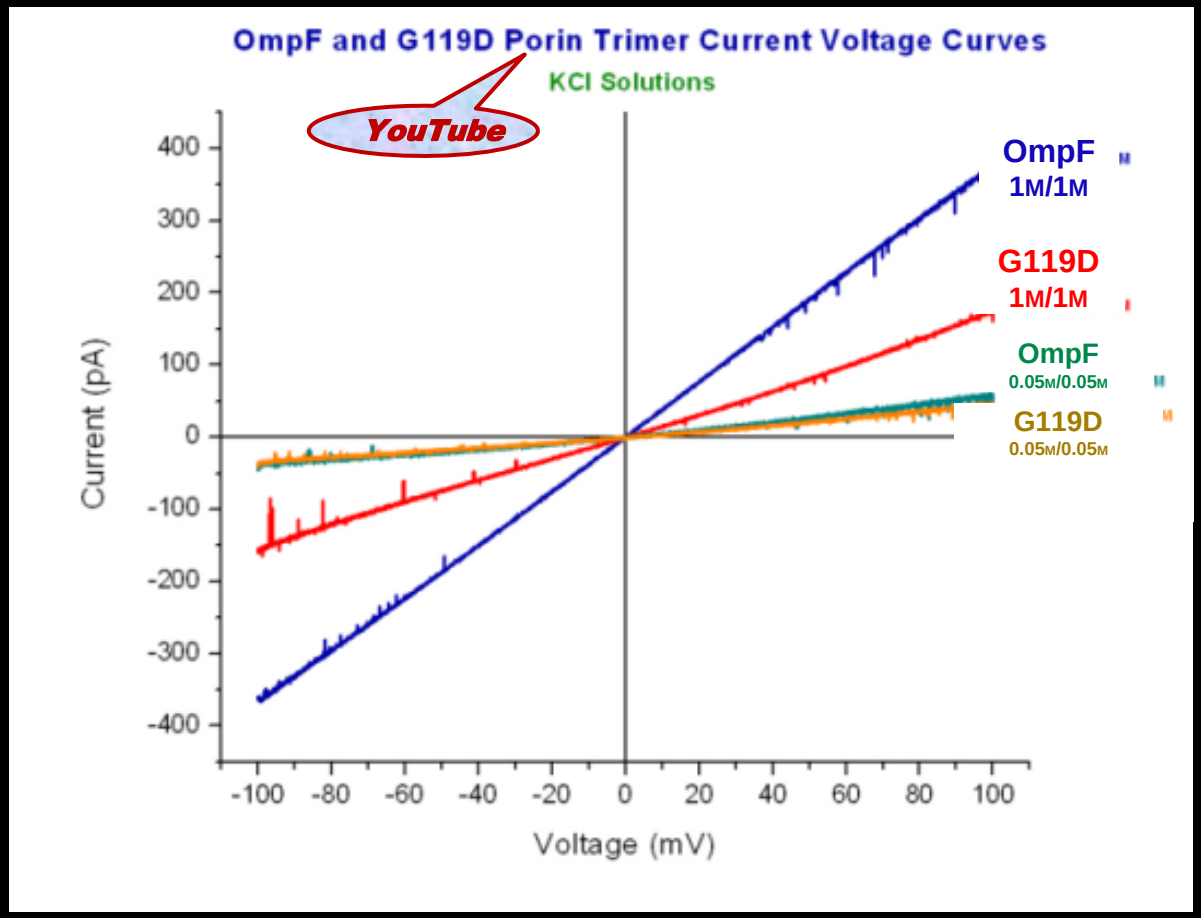
Alan Hodgkin:
“Bob, I would not put it that way”

Engineering is about Device Equations

How Describe Biological Devices?

P.S. I do not know the answer. But I know how to begin, …. I think.

A few atoms make a BIG Difference



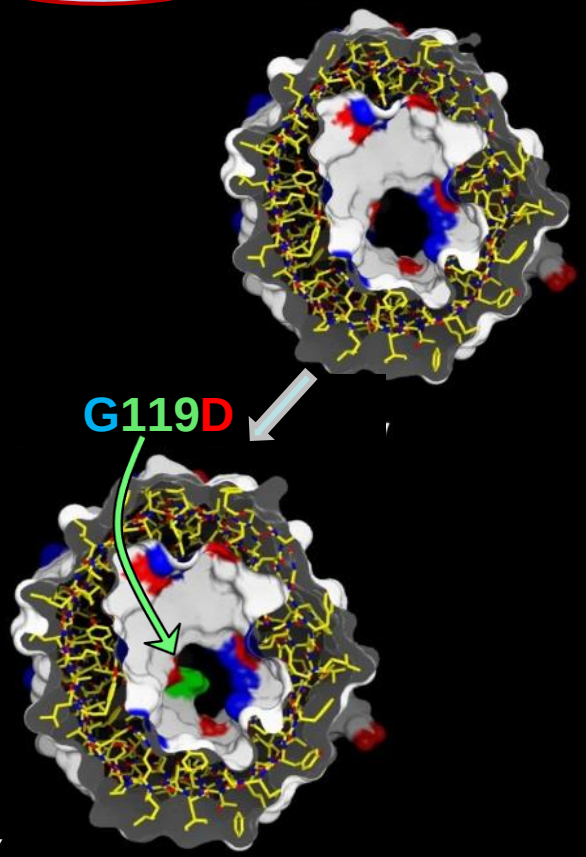
Current Voltage relation determined by
John Tang
in Bob Eisenberg's Lab

YouTube

Glycine G
replaced by
Aspartate D

YouTube

Ompf



Structure determined by
Raimund Dutzler
in Tilman Schirmer's lab

Biological Question

How do a few atoms control

(macroscopic)

Device Function ?

Mathematics of Molecular Biology
is about
How the device works

In mathspeak:
Solving Inverse Problems

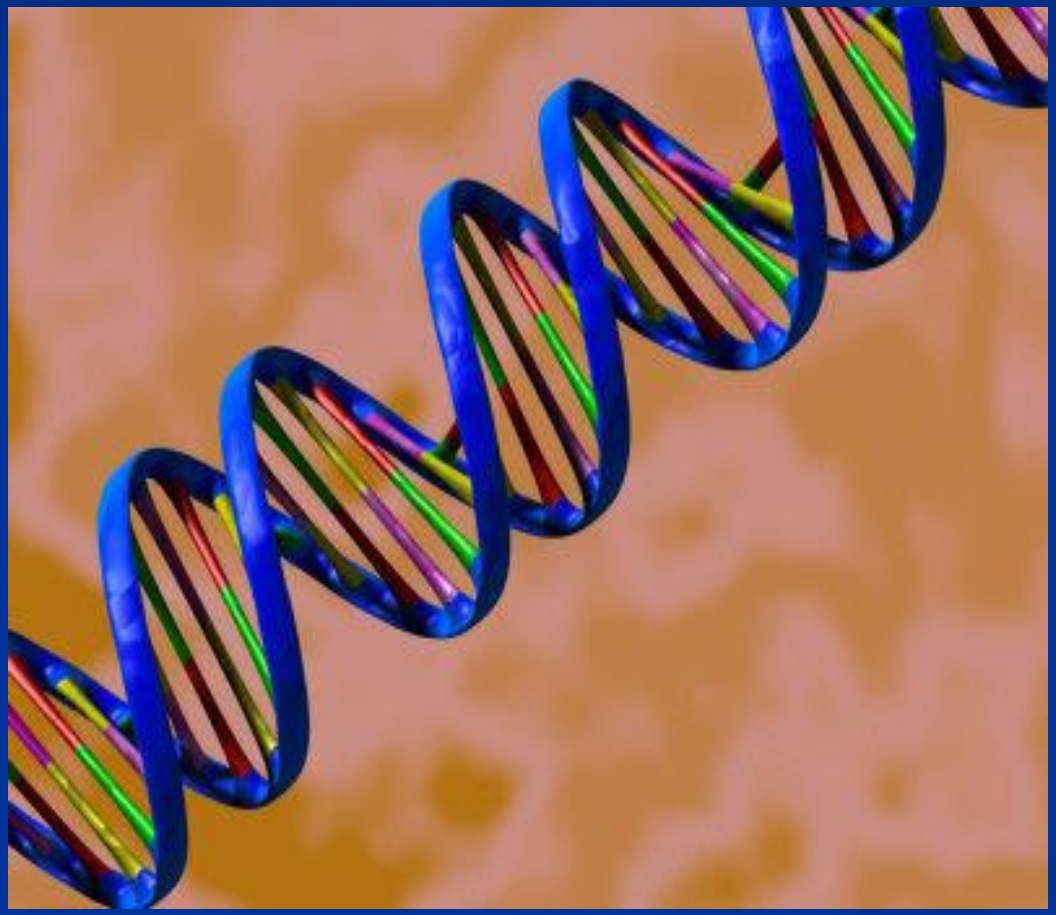
Life is different

because
it is inherited

Blueprint of Life is DNA = string of genes

ONLY the blueprint is inherited

Watson & Crick model of DNA

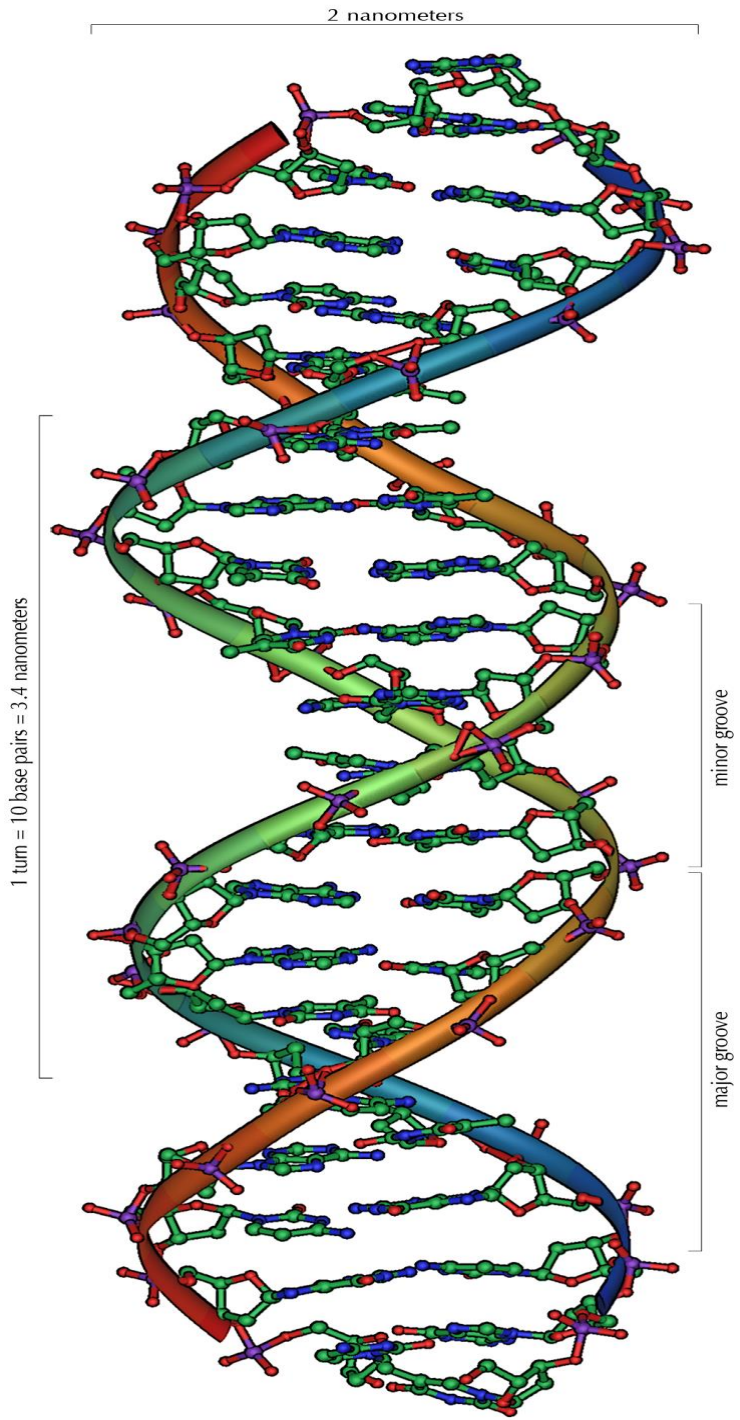


- Introduced in 1953.
- DNA is in the form of a regular helix containing two polynucleotide chains connected to each other by hydrogen bonds.

Blueprint is shown in many different ways

LEARN FROM INTERNET

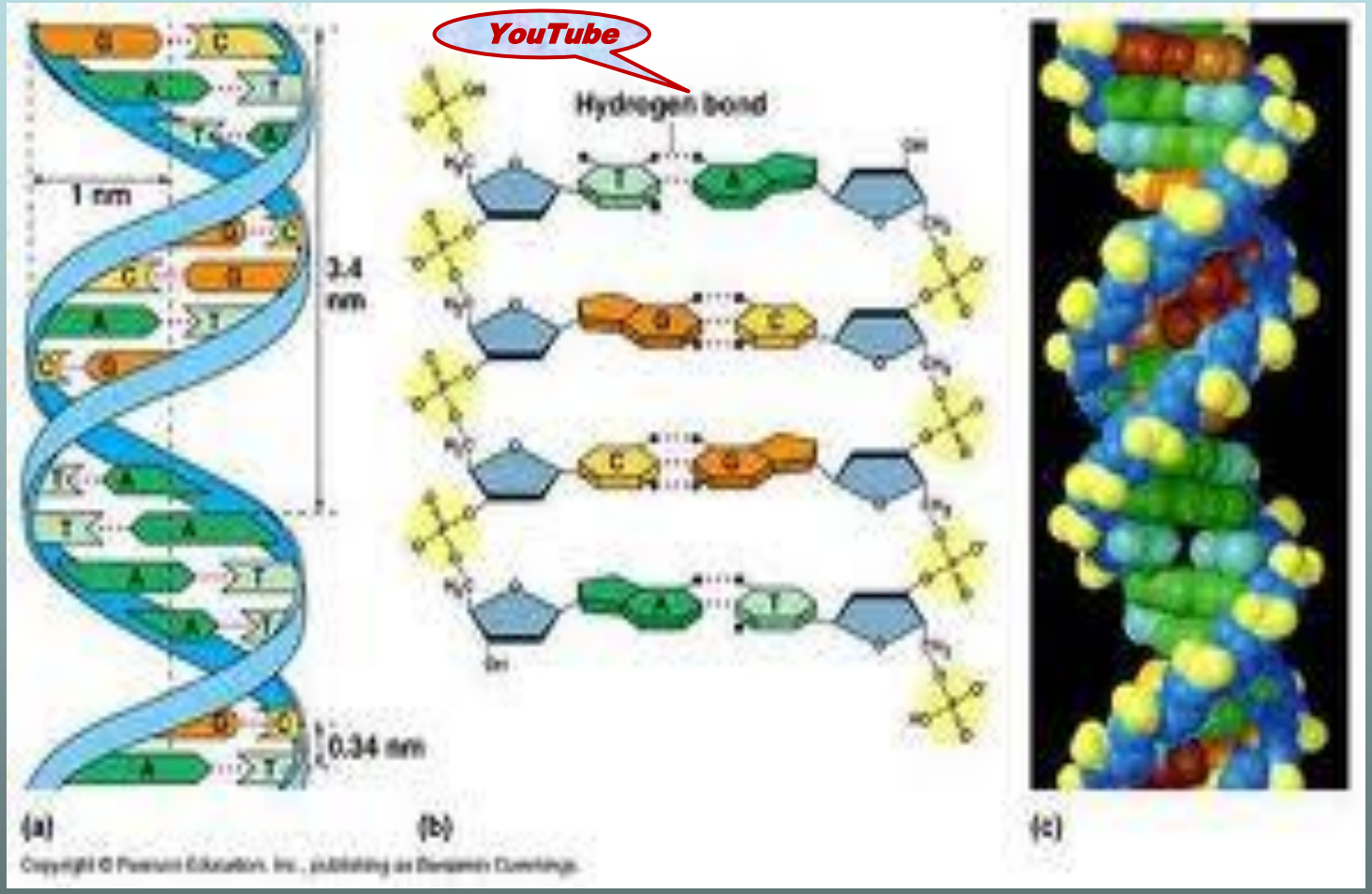
Just search for DNA, Molecular Biology, Proteins and read in Mandarin, I imagine



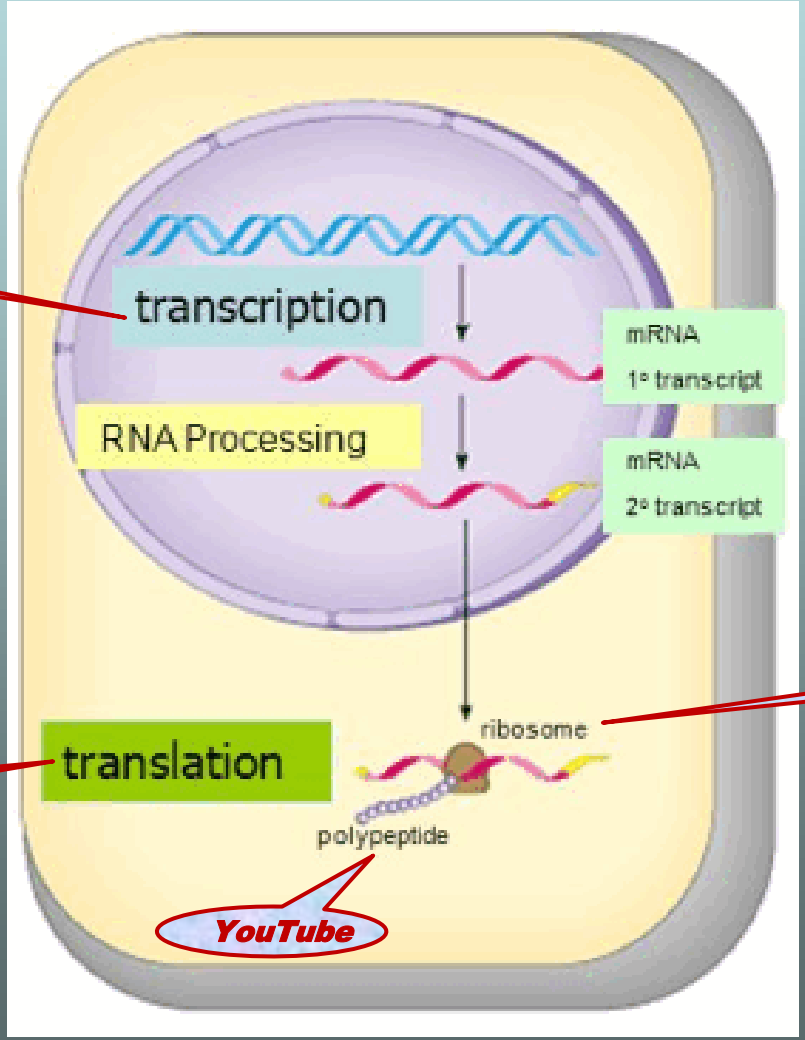
Watson & Crick Model

(DNA is polar)

- Right handed double helix.
- Chargaff's base pairing rule. YouTube
- Hydrogen bonding. YouTube
- Antiparallel.
- Each strand acts as template during replication. YouTube



Blueprint can only make PROTEINS



YouTube

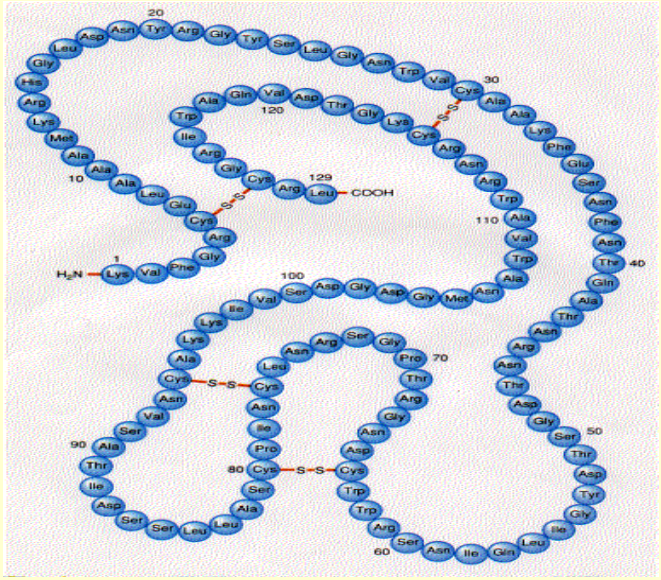
YouTube

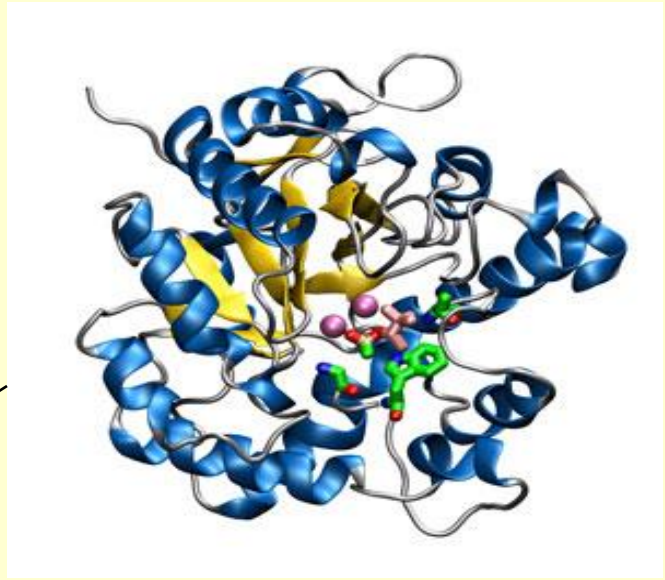
YouTube

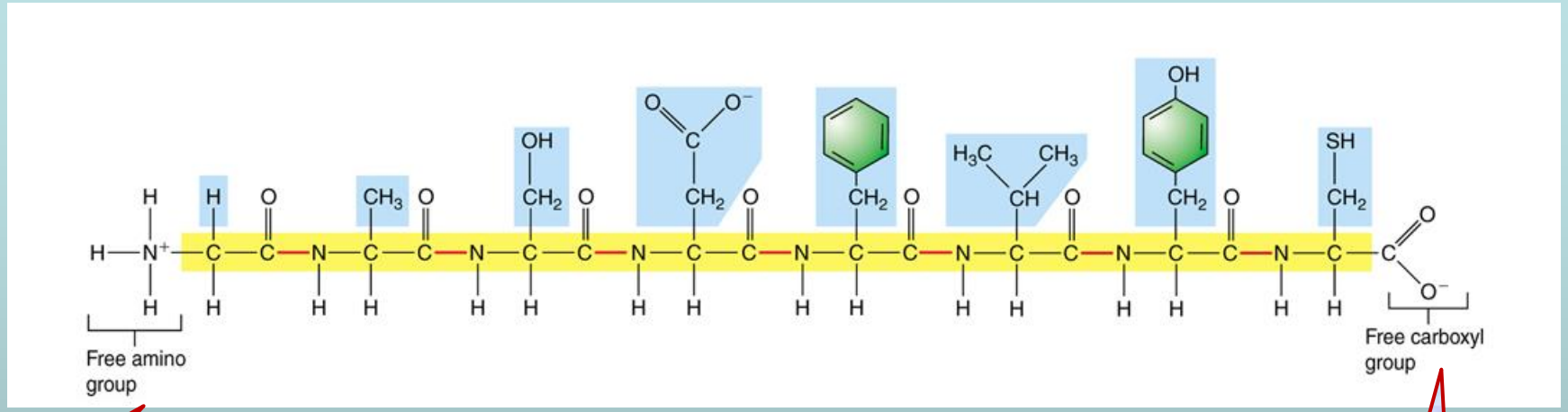
YouTube

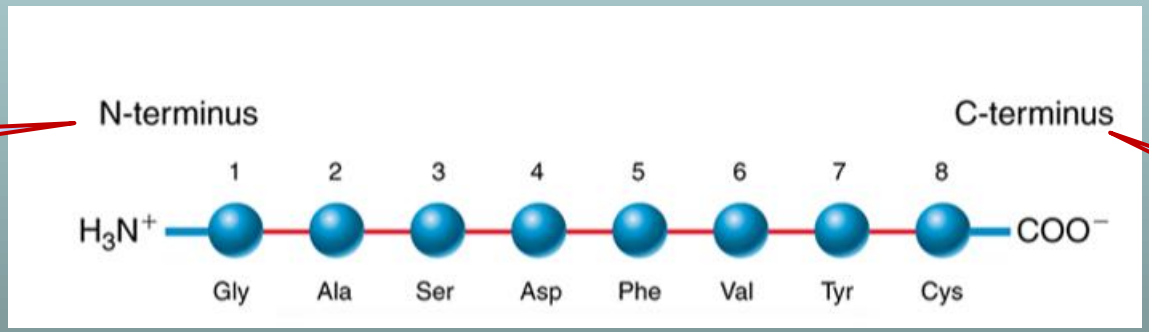
Proteins are a String of Beads that can Make ANYthing

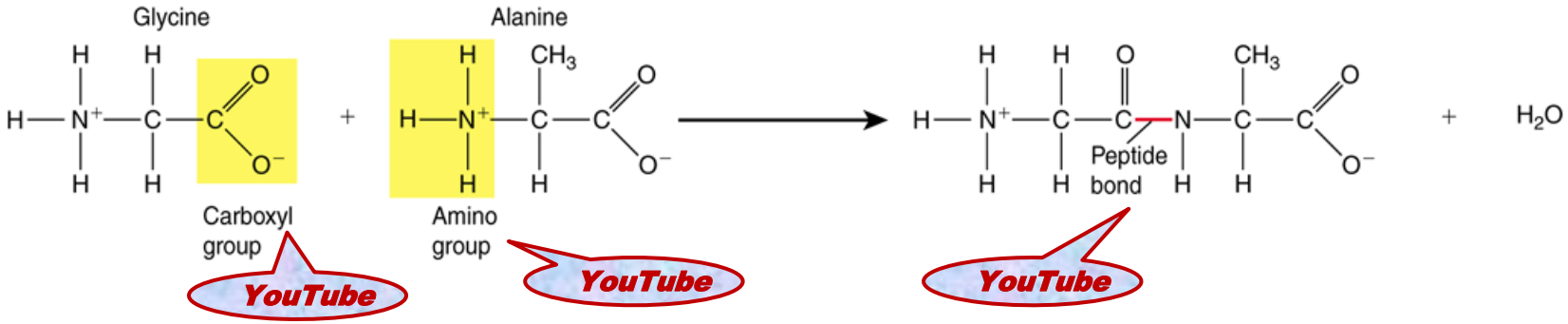
including devices and machines






Free amino group
Free carboxyl group


N-terminus
C-terminus
1 2 3 4 5 6 7 8
H_3N^+
COO^-
Gly Ala Ser Asp Phe Val Tyr Cys


Glycine
Alanine
Carboxyl group
Amino group
Peptide bond
H_2O

PRIMARY STRUCTURE

The sequence of amino acids

MIL1 sequence:

>gi|7662506|ref|NP_056182.1| MIL1 protein [Homo sapiens]

MEDCLAHLGEKVSQELKEPLHKALQMLLSQPVTYQAFRECTLETTVHASGWNKILVPLVLLRQML
LELTRLGQEPLSALLQFGVTYLEDYSAEYIIQQGGWGTVFSLESEEEEYPGITAEDSNDIYILPS
DNSGQVSPPESPTVTTSWQSESLPVSLSASQSWHTESLPVSLGPESWQQIAMDPEEVKSLDSNGA
GEKSENNSSNSDIVHVEKEEVPEGMEEAAVASVVLPARELQEALPEAPAPLLPHITATSLLGTRE
PDTEVITVEKSSPATSLFVELDEEEVKAATTEPTEVEEVVPALEPTETLLSEKEINAREESLVEE
LSPASEKKPVPPSEGKSRLSPAGEMKPMPLSEGKSILLFGGAAAVAILAVAIGVALALRKK

length: 386amino acids

PRIMARY STRUCTURE

- The numbers of amino acids vary (e.g. insulin 51, lysozyme 129, haemoglobin 574, gamma globulin 1250)
- The primary structure determines the folding of the polypeptide to give a functional protein
- **Polar amino acids** (acidic, basic and neutral) are hydrophilic and tend to be placed on the **outside** of the protein.
- **Non-polar** (hydrophobic) amino acids tend to be placed on the **inside** of the protein

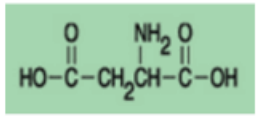
Infinite variety

- The number of possible sequences is infinite
  An average protein has 300 amino acids,
  At each position there could be one of 20 different amino acids
  = 10^{390} possible combinations
- Most are useless
  Natural selection picks out the best

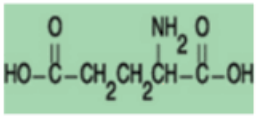
Acid = NEGATIVE (like chloride ion) like vinegar
BASE = POSITIVE (like sodium ion) like soap

YouTube

Amino Acids with Electricaly Charged Side Chains - Acidic



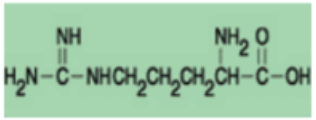
Aspartic acid, Asp, D



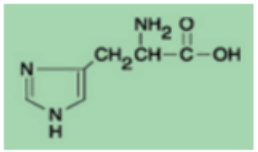
Glutamic acid, Glu, E

back to top

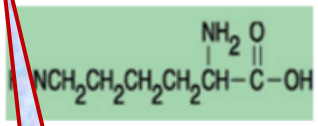
Amino Acids with Electricaly Charged Side Chains - Basic



Arginine, Arg, R



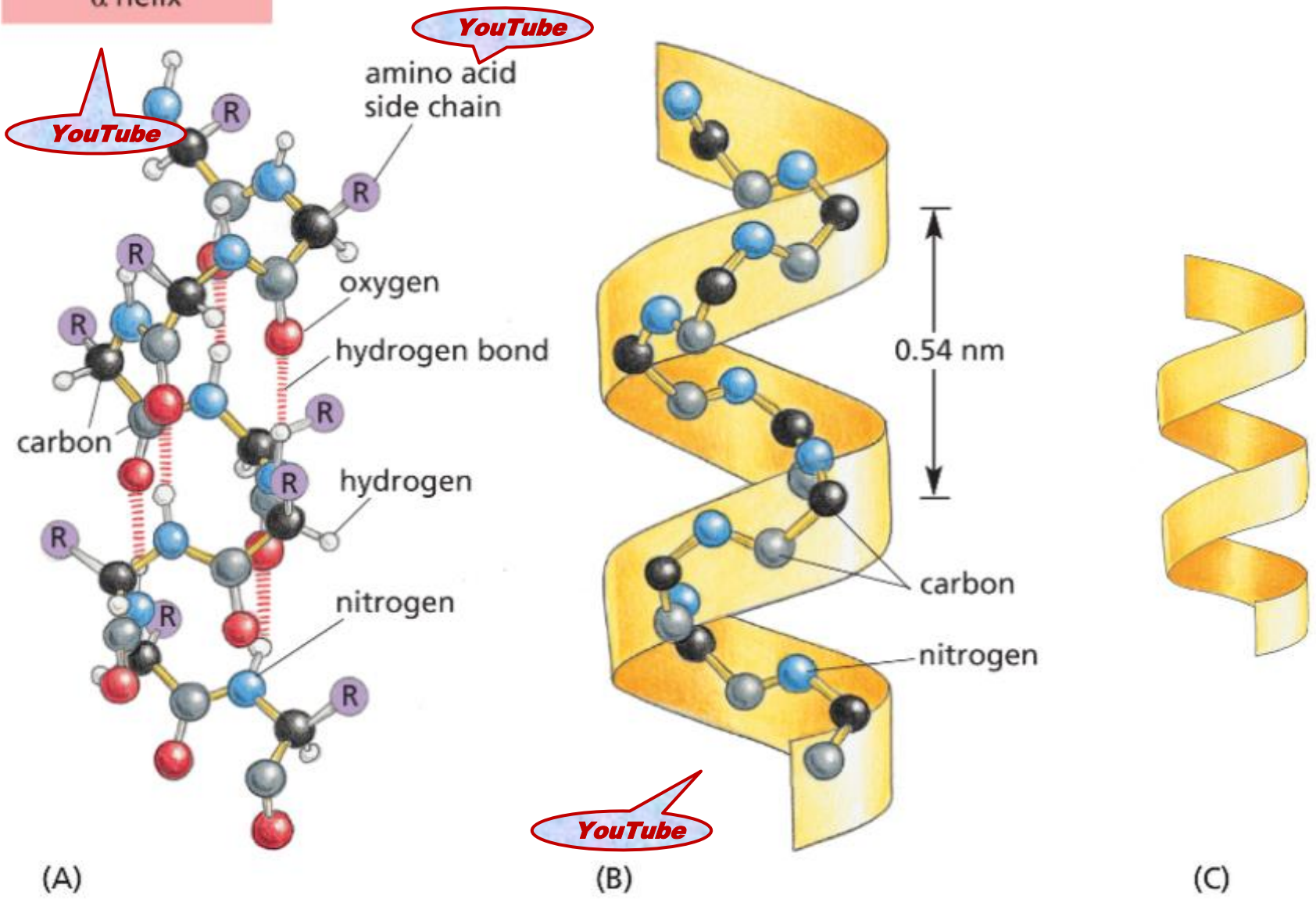
Histidine, His, H



Lysine, Lys, K

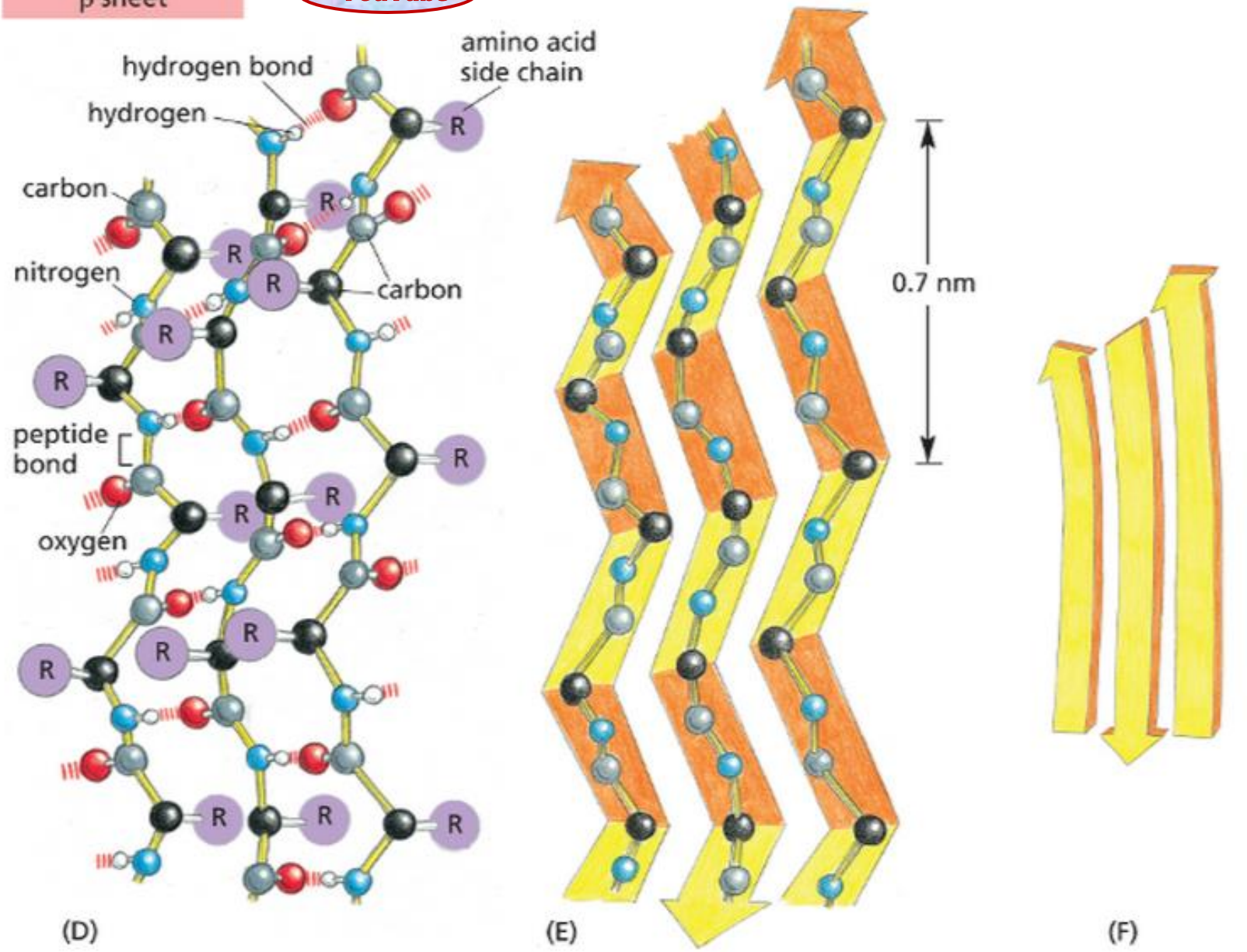
YouTube

α helix


amino acid
side chain
oxygen
hydrogen bond
carbon
hydrogen
nitrogen
R
0.54 nm
carbon
nitrogen
(A)
(B)
(C)

β sheet

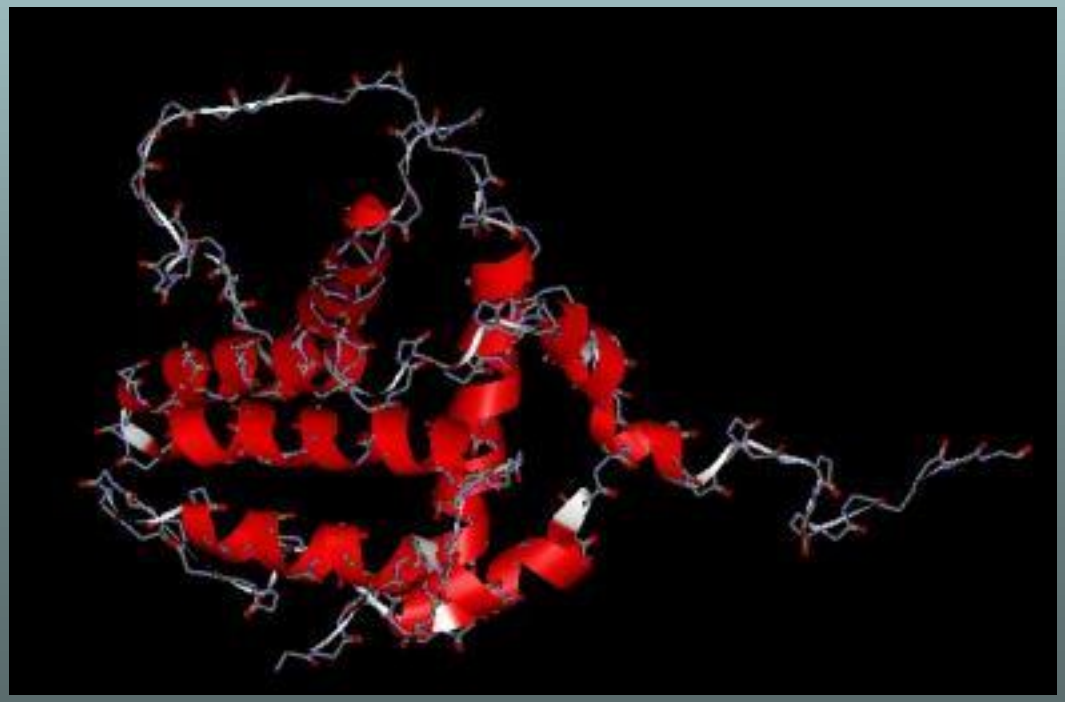
YouTube



TERTIARY STRUCTURE

YouTube

The folding of the polypeptide into domains whose chemical properties are determined by the amino acids in the chain



MIL1 protein

YouTube

Chain B of Protein Kinase C

Result

Protein structure depends upon the amino acid sequence

This, in turn, depends upon the sequence of bases in the gene

Multiscale Models
of
Nerve and Muscle

also called
Physiology
of
Nerve and Muscle

From Structure to Function using Fundamental Physical Laws

From Anatomy to Physiology using Biophysics & Biochemistry

Multiscale Analysis

is also called

Physiology

Multiscale MATHEMATICAL Analysis

has rarely been possible until now

Multiscale
MATHEMATICAL
Analysis

has rarely been possible
until now

Except for

Nerve Cells

Hodgkin, Huxley and Katz

MultiScale Analysis of Nerve Function

is more complete than of **ANY** other cell/tissue in Biology

Multiscale Mathematical Analysis is not available for any other tissue or cell,

although many are working to change this!

MultiScale Analysis of Nerve Function

Multiscale Analysis is Structural.

(Almost) all Structures are known and can be described on all scales.

MultiScale Analysis of Nerve Function

Multiscale Analysis is physical,
as well as mathematical.

Physical variables and equations can be used in almost all steps.

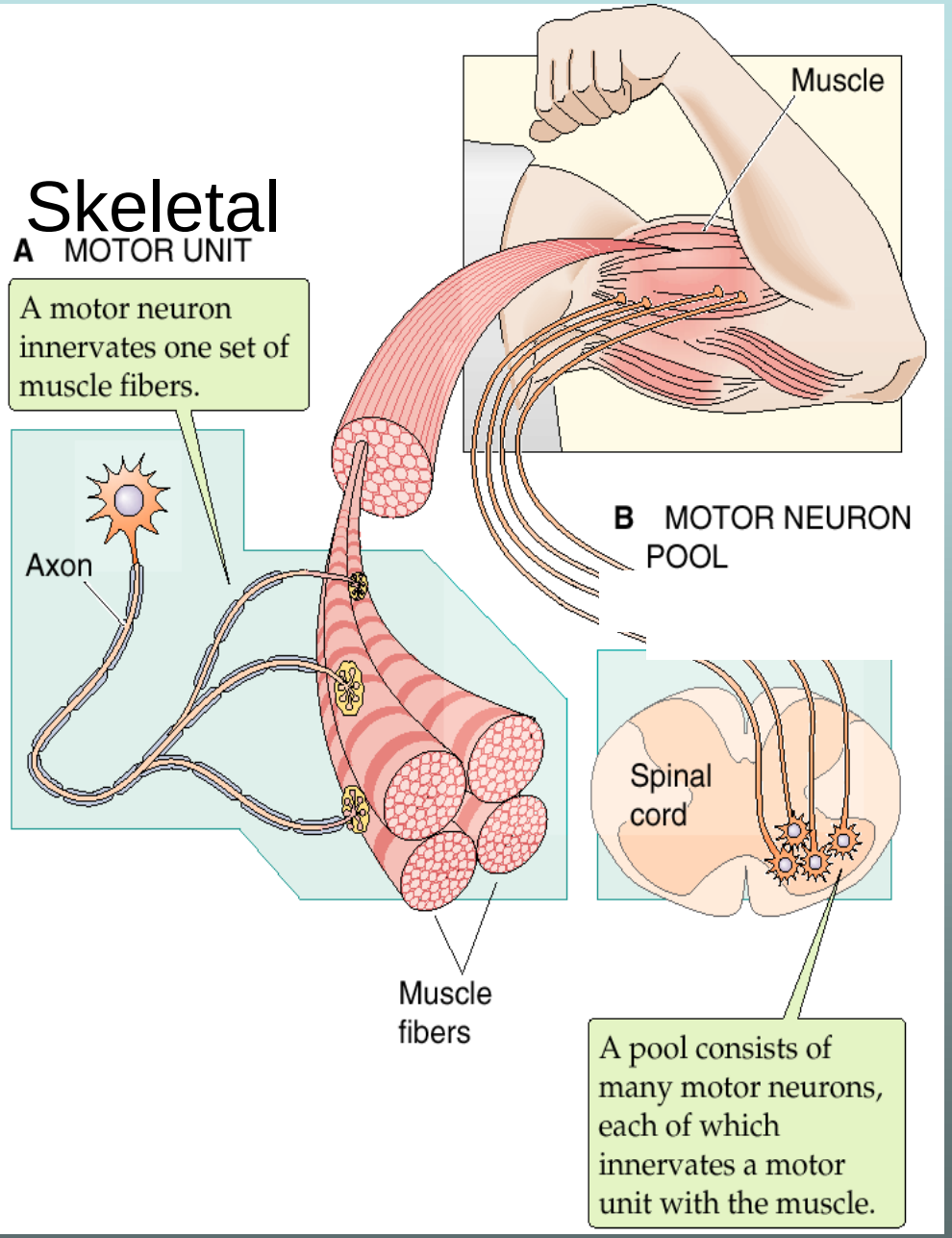
Description is needed only in one important case, namely gating.

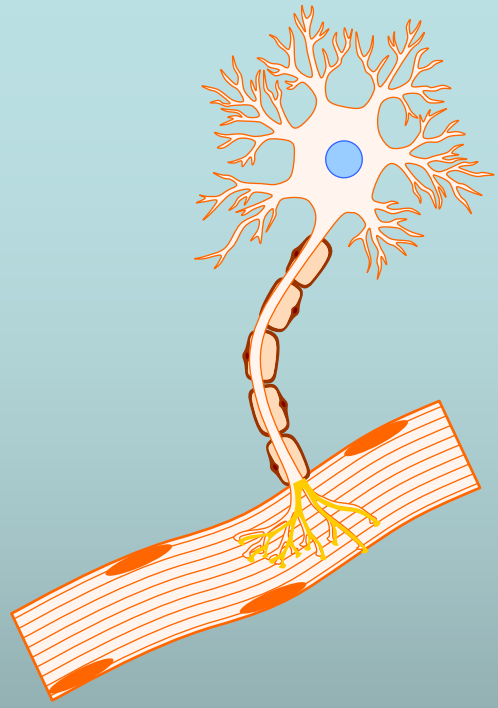
From Structure to Function using Fundamental Physical Laws

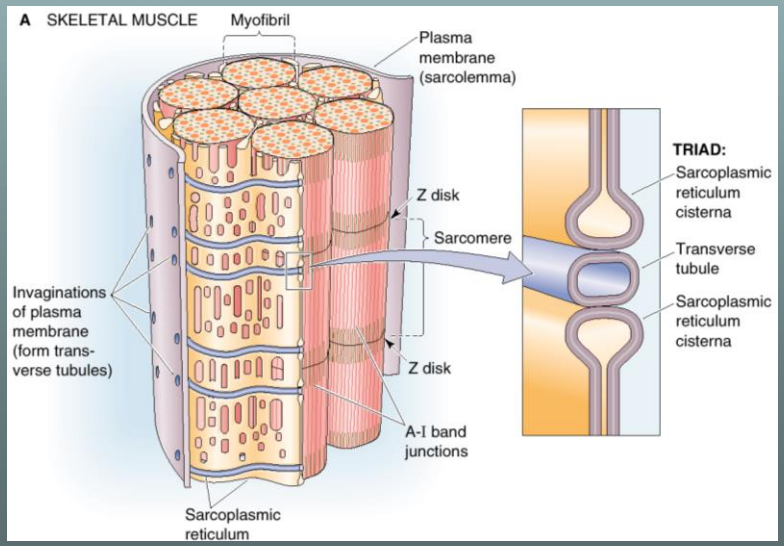
From Anatomy to Physiology using Biophysics & Biochemistry

PHYSIOLOGY of Nerve and Skeletal Muscle

Skeletal


A MOTOR UNIT
A motor neuron innervates one set of muscle fibers.
Muscle
B MOTOR NEURON POOL
Axon
Spinal cord
Muscle fibers
A pool consists of many motor neurons, each of which innervates a motor unit with the muscle.



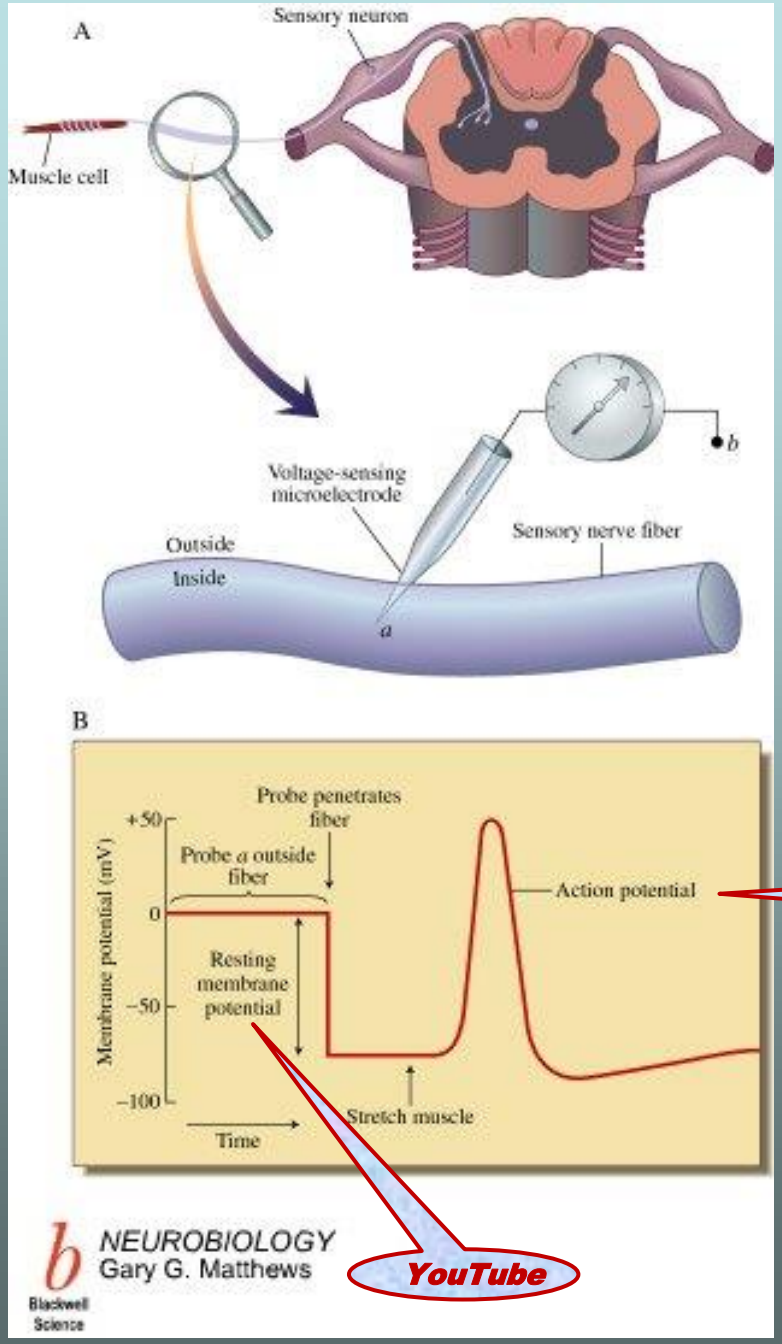

A SKELETAL MUSCLE
Myofibril
Plasma membrane (sarcolemma)
Z disk
Sarcomere
Z disk
A-I band junctions
Invaginations of plasma membrane (form transverse tubules)
Sarcoplasmic reticulum
TRIAD:
Sarcoplasmic reticulum cisterna
Transverse tubule
Sarcoplasmic reticulum cisterna

Nerve Conduction

- What is the information signal of a nerve?
- How does that signal move down a nerve fiber?
- What are the molecular mechanisms involved?
- Completely solved in outline
- Mathematics available
  - Many IMPORTANT problems unsolved

Optimization of function

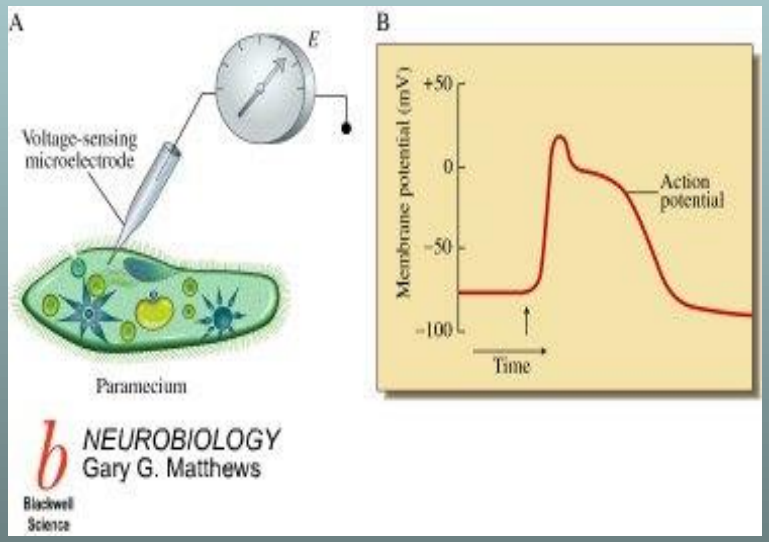
Neuronal Signal



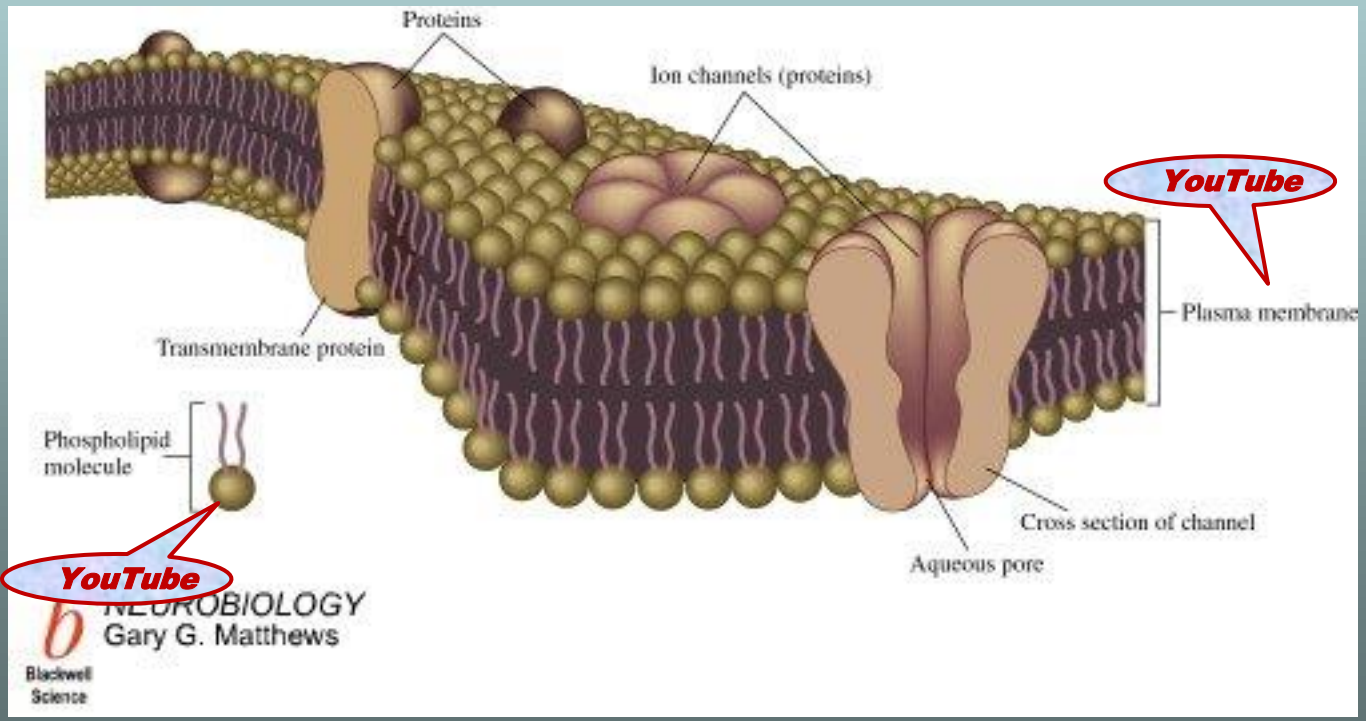
YouTube

YouTube

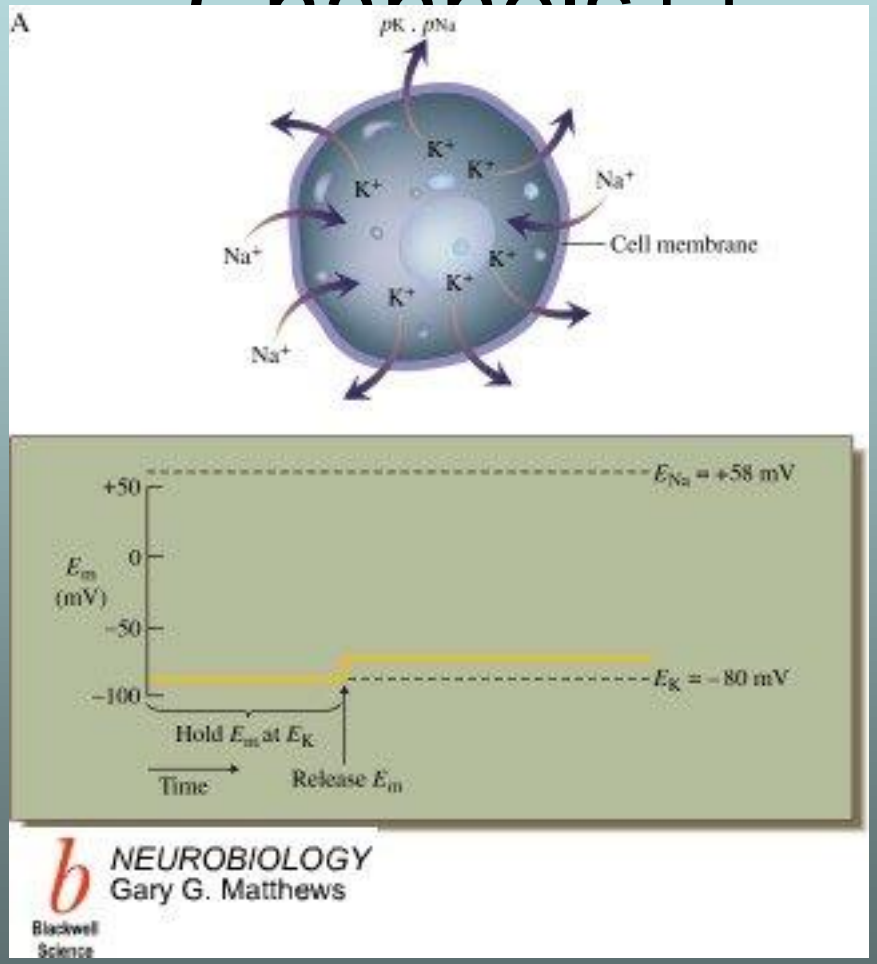
Voltage Signals are Found Throughout Life



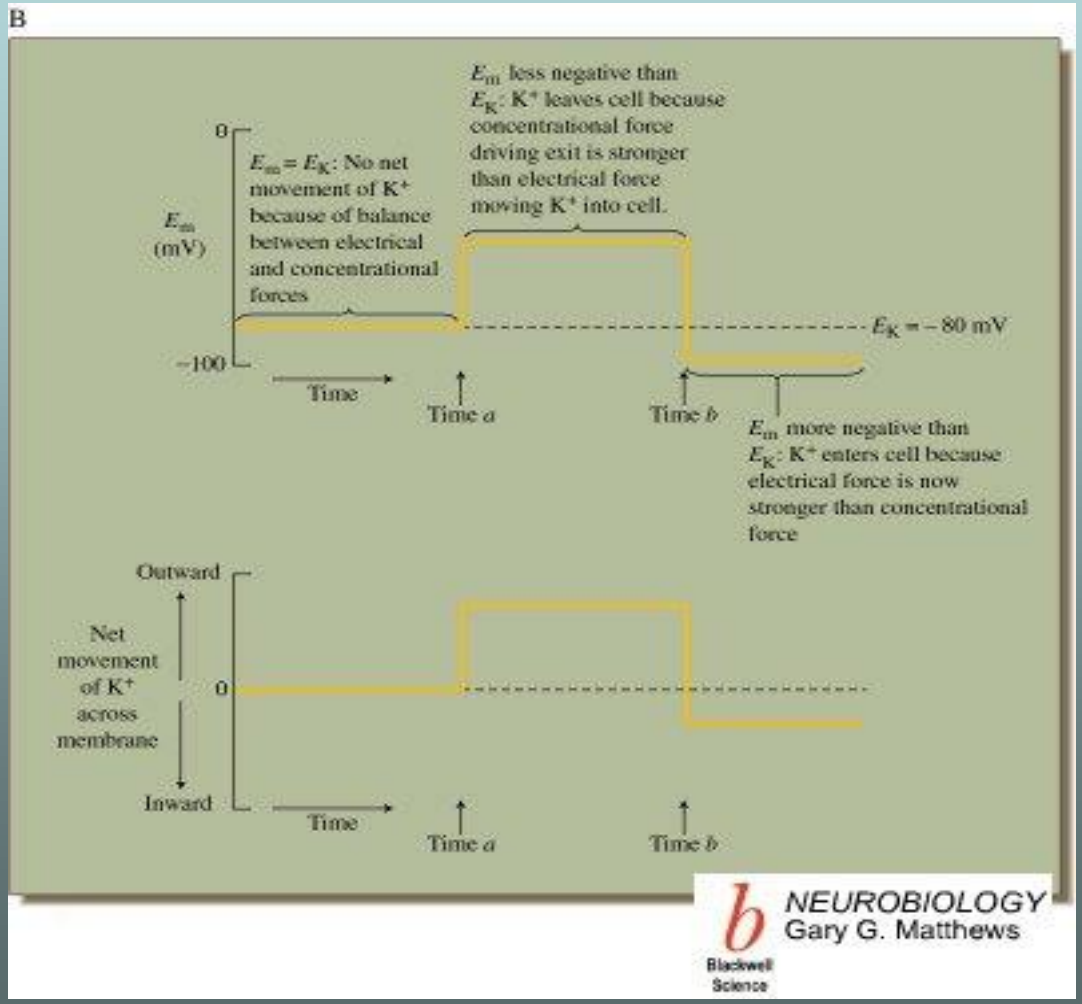
Channels Determine Electrical Properties



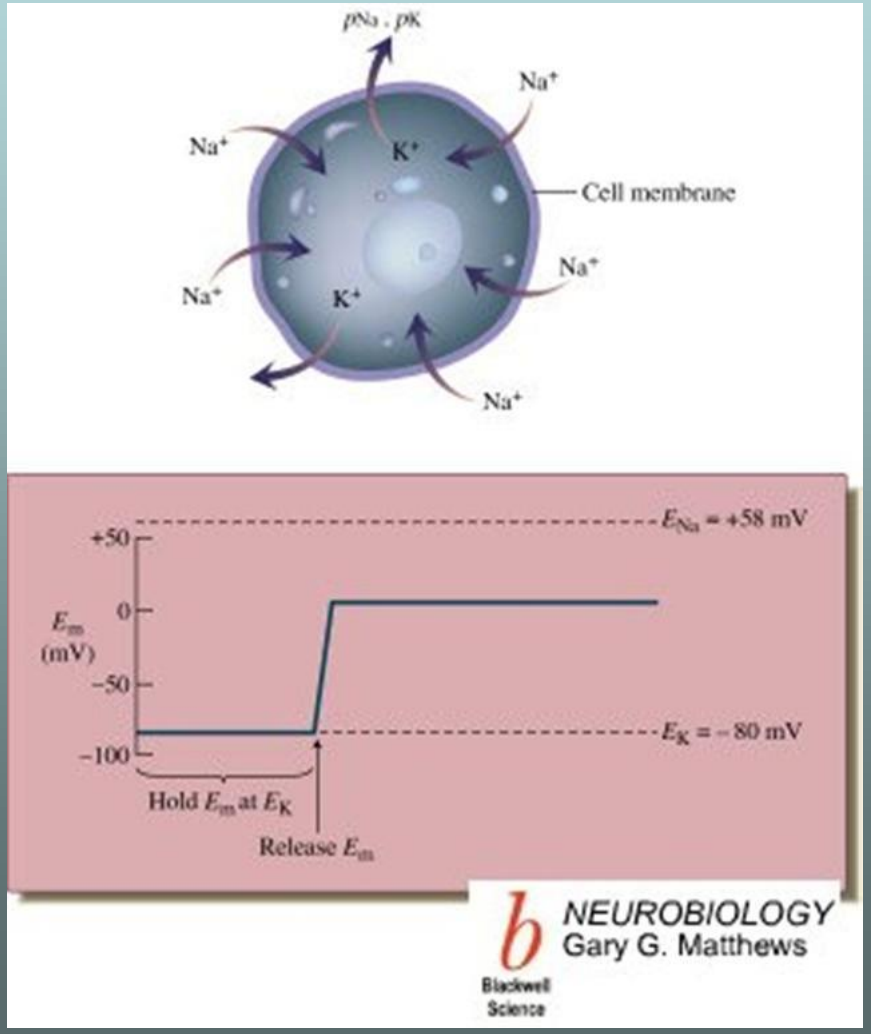
Resting Potential Set by K Channels



Potential Determined by the Ion with the greatest Conductance

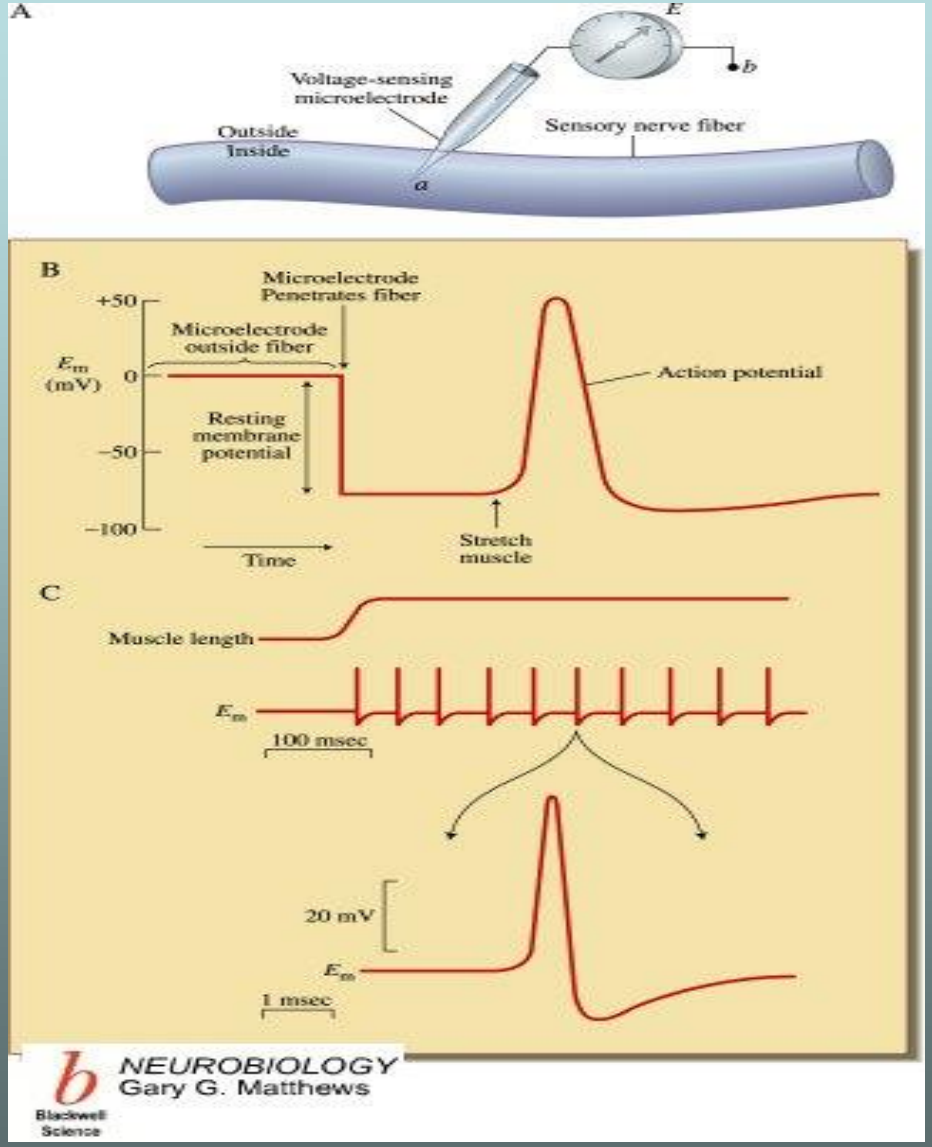


Potential Determined by the Ion with the greatest Conductance

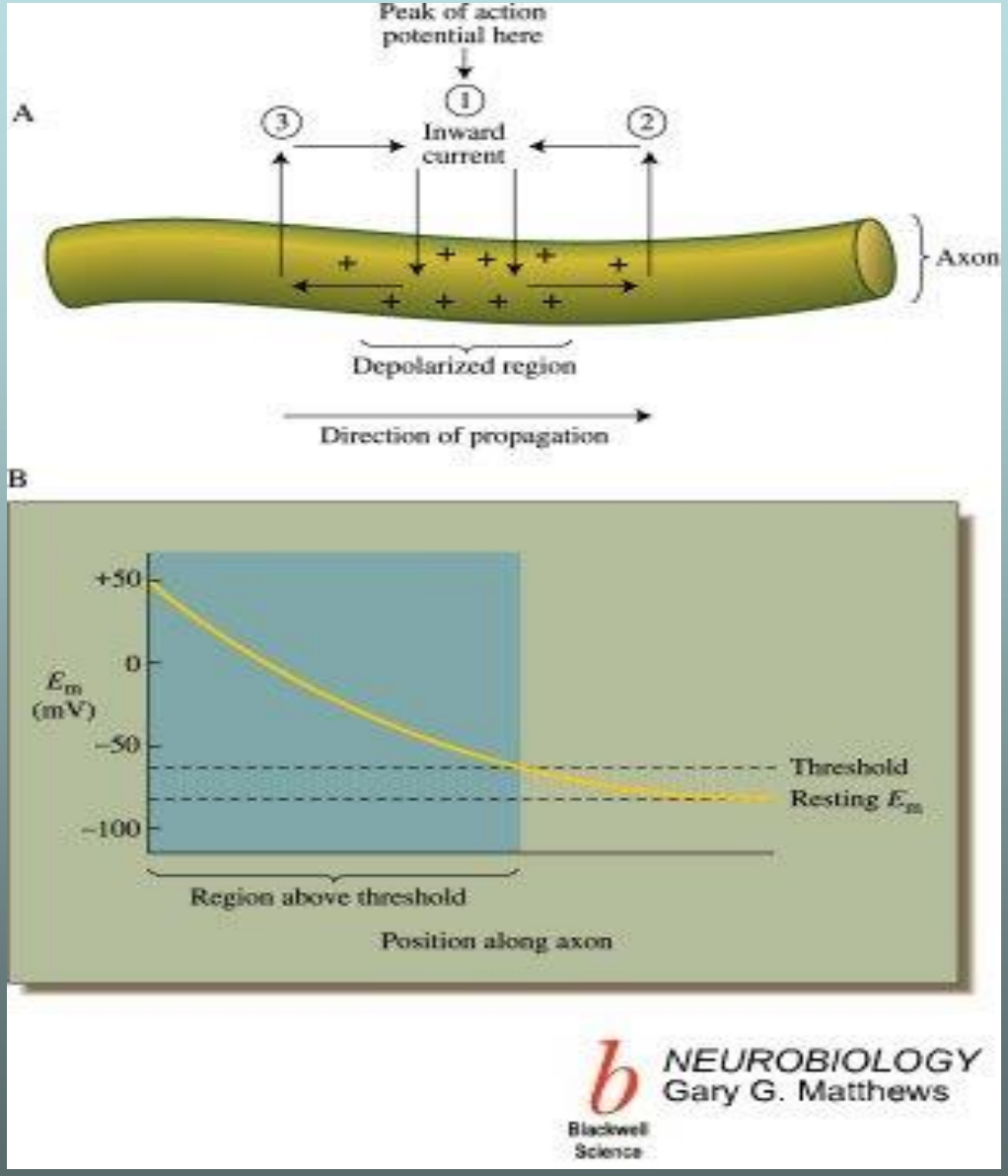


Action Potential

[Gating Animation Action Potential]

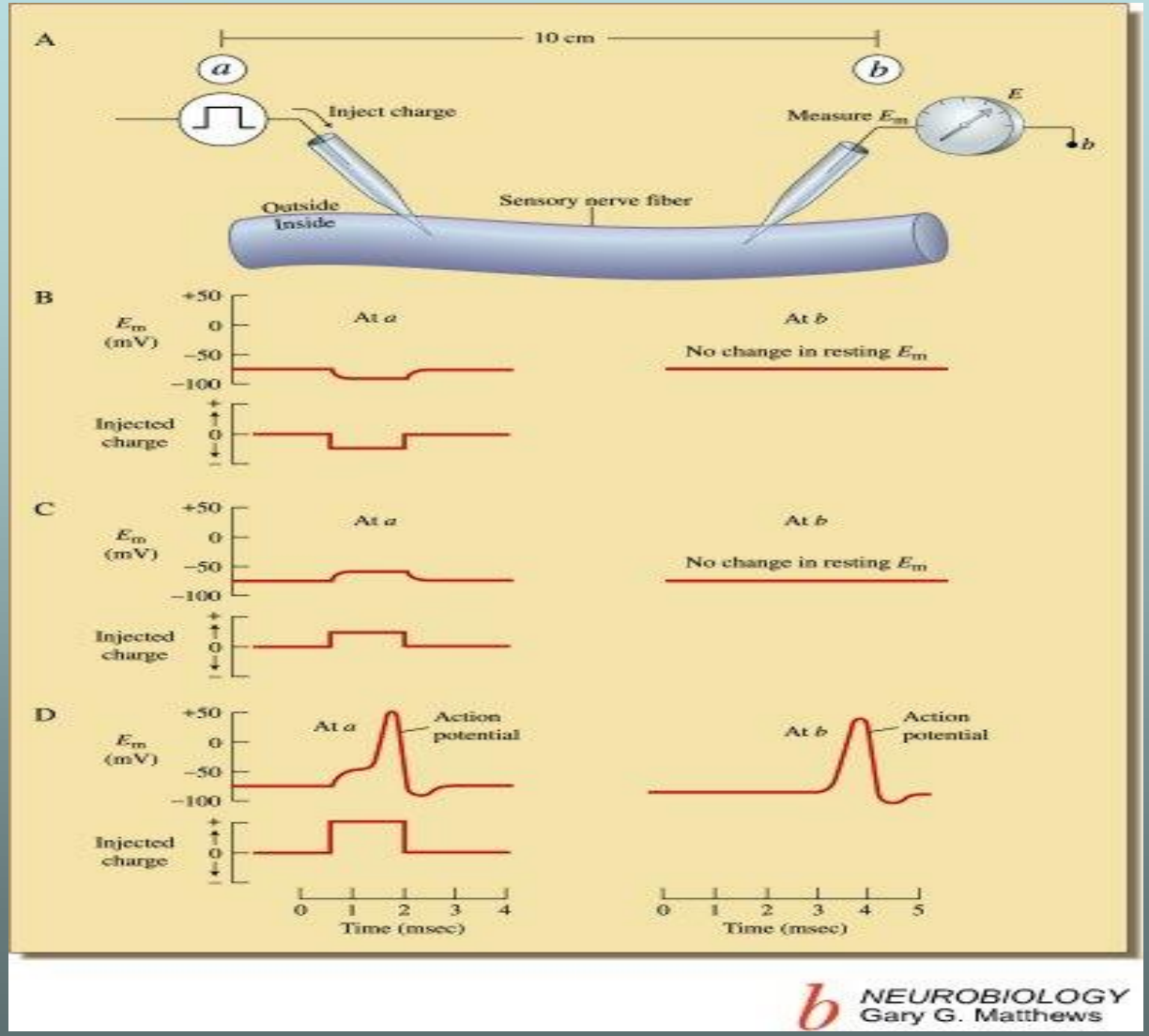


Propagation

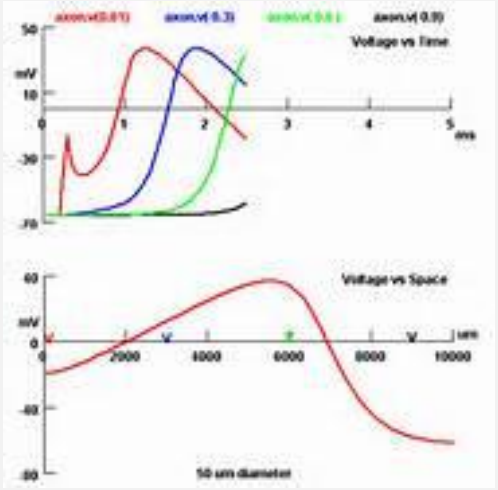


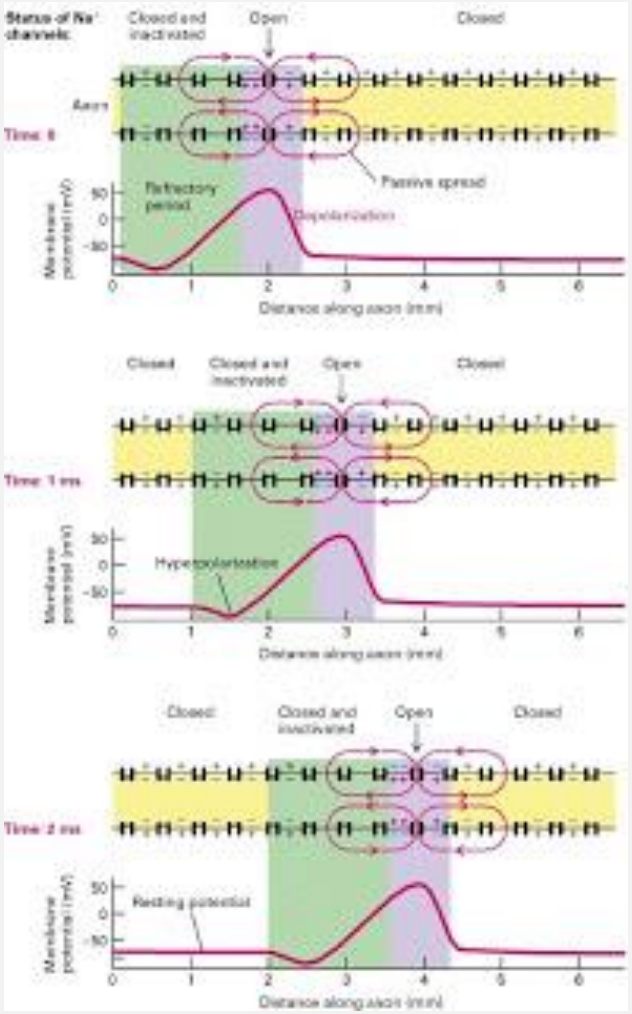
Propagation

Action Potential Propagation



Propagation
of
Action Potential

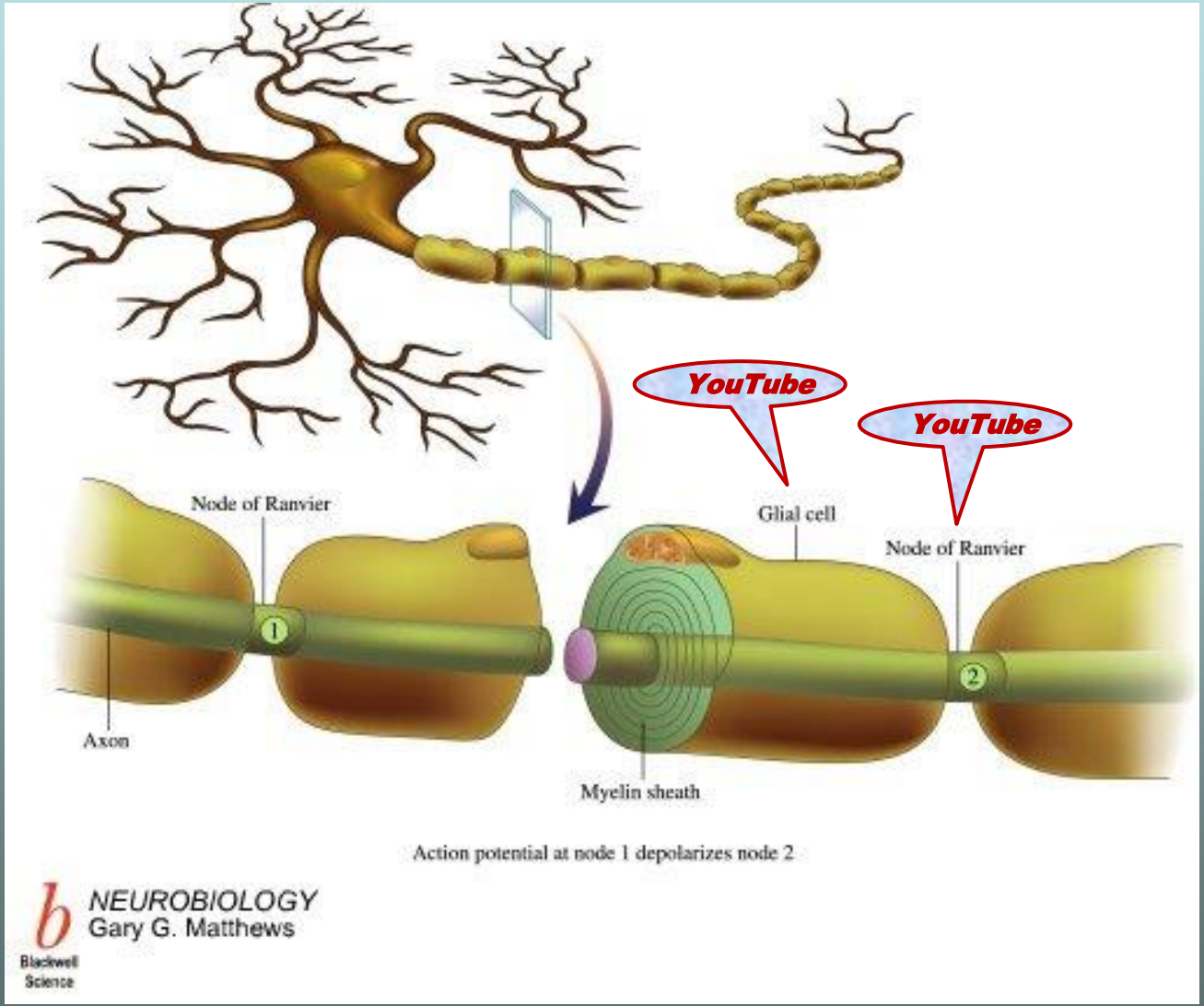




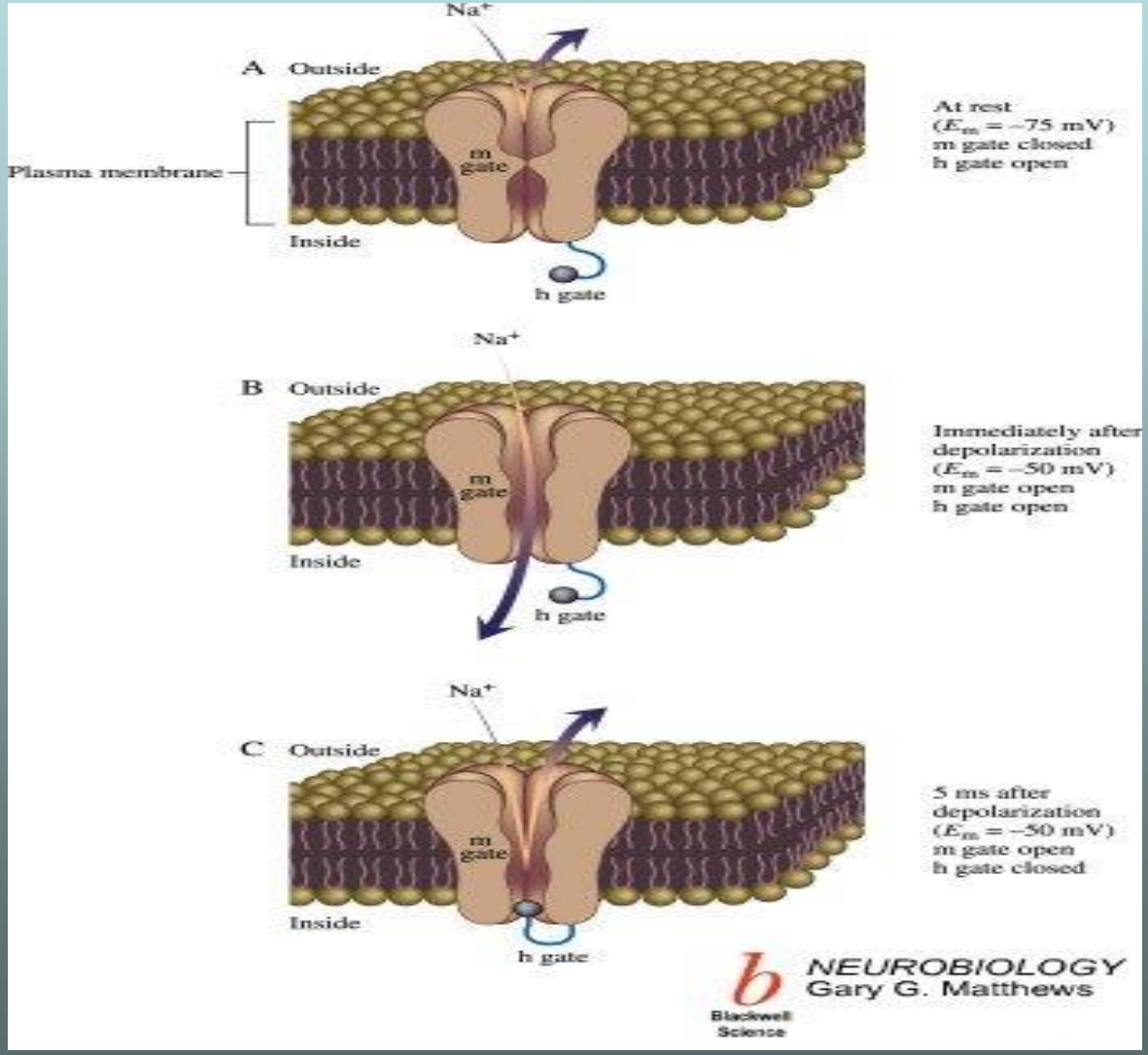
Myelinated Nerve Propagation

YouTube

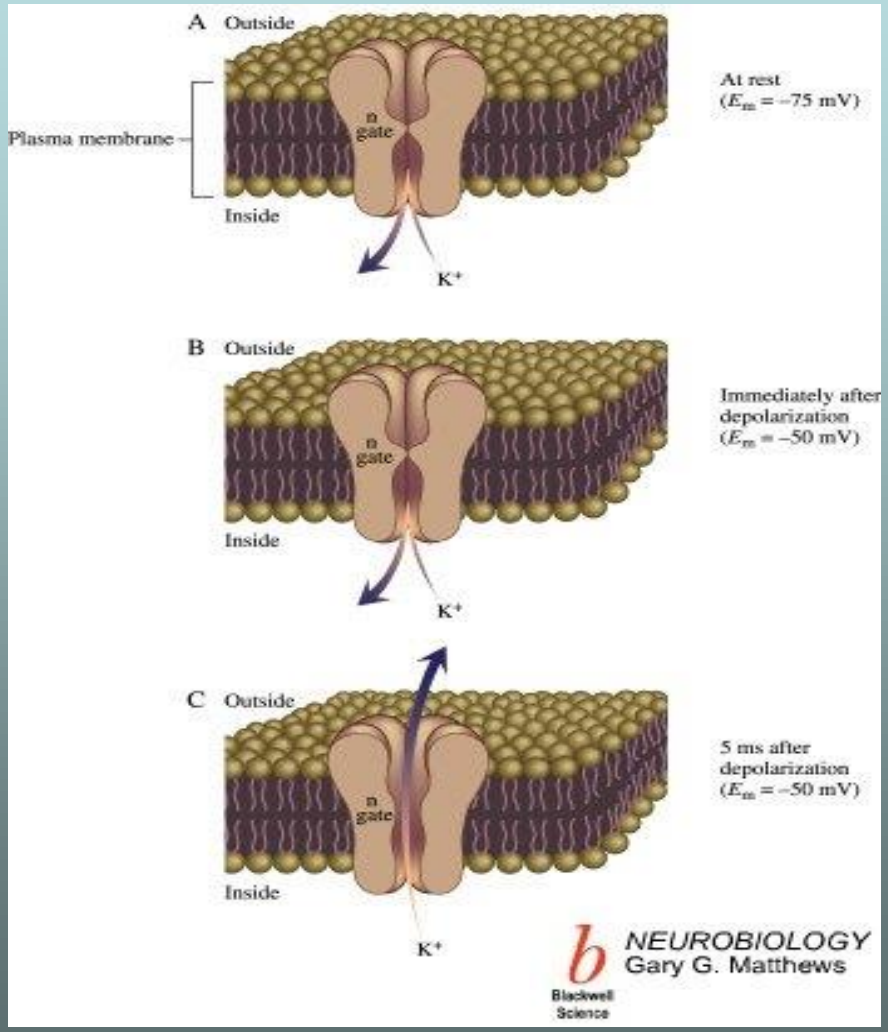
Action Potential Propagation



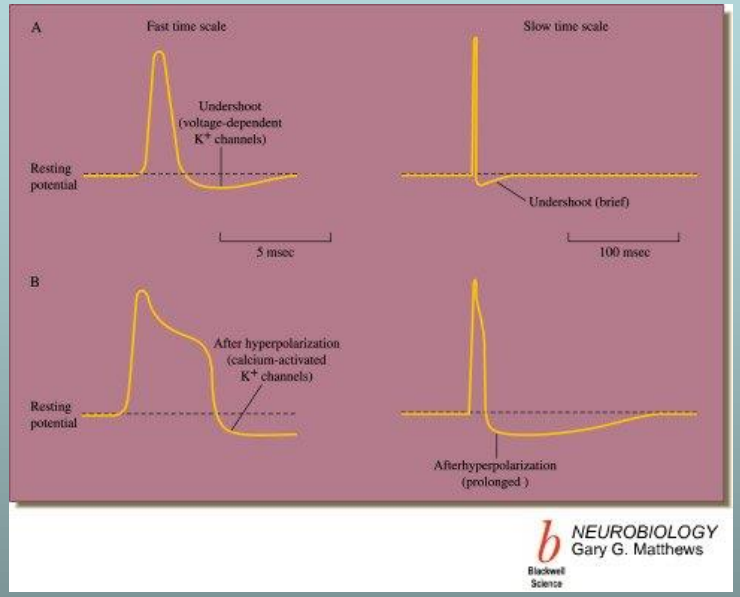
Na Channel

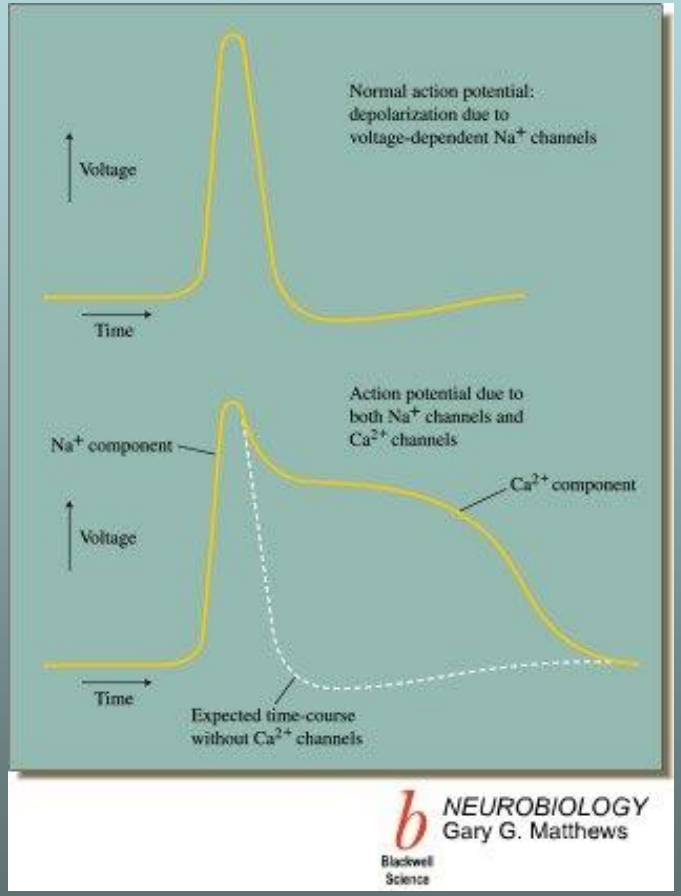

Na+
A
Outside
Plasma membrane
m gate
Inside
h gate
At rest
(E_m = −75 mV)
m gate closed
h gate open
Na+
B
Outside
m gate
Inside
h gate
Immediately after depolarization
(E_m = −50 mV)
m gate open
h gate open
Na+
C
Outside
m gate
Inside
h gate
5 ms after depolarization
(E_m = −50 mV)
m gate open
h gate closed
NEUROBIOLOGY
Gary G. Matthews
Blackwell Science

K channel


A Outside
Plasma membrane
n gate
Inside
K+
At rest
(E_m = –75 mV)
B Outside
n gate
Inside
K+
Immediately after depolarization
(E_m = –50 mV)
C Outside
n gate
Inside
K+
5 ms after depolarization
(E_m = –50 mV)
NEUROBIOLOGY
Gary G. Matthews
Blackwell Science

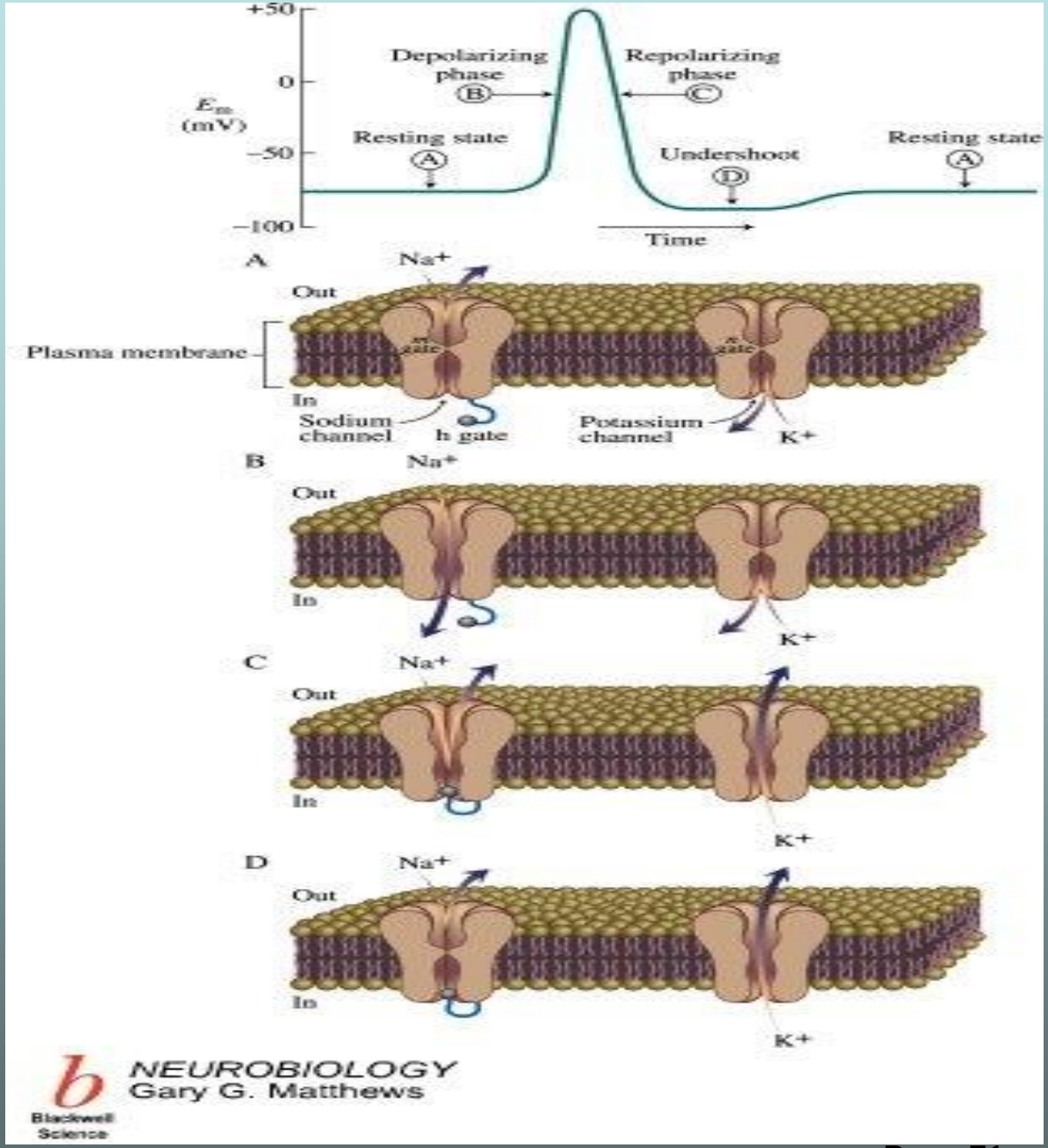
Reminder: the Action Potential



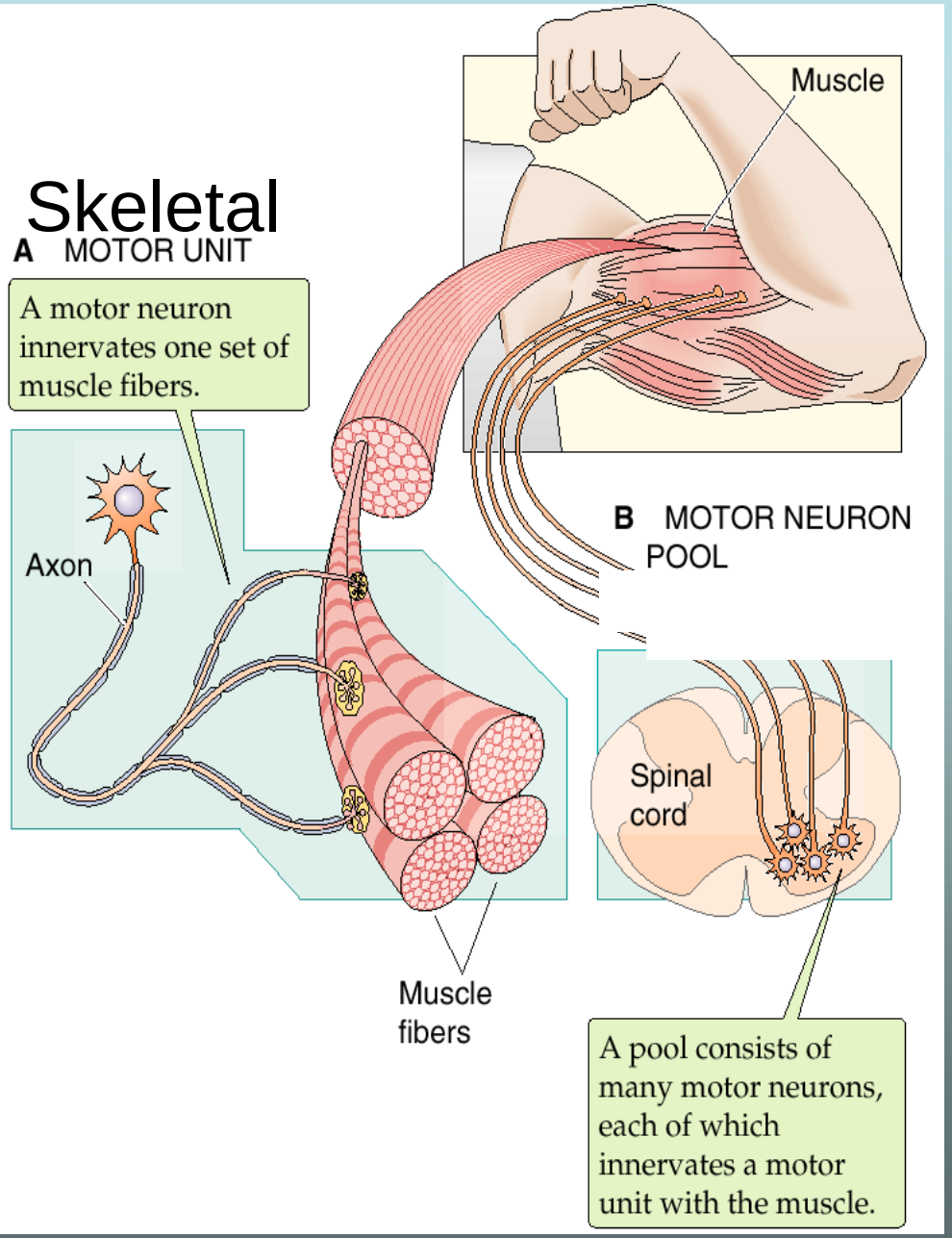


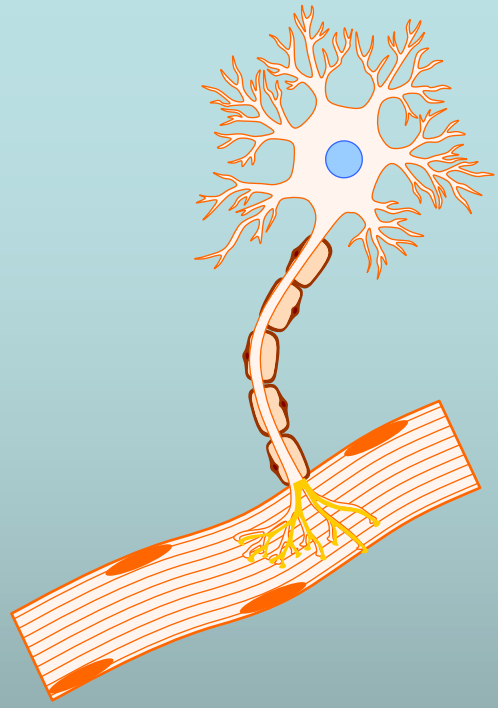
Na & K channels

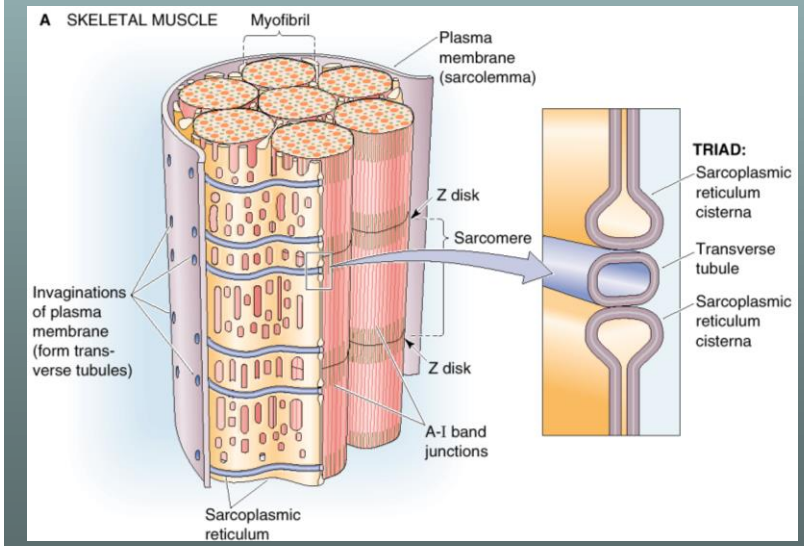
[Gating Animation Action Potential]



Skeletal


A MOTOR UNIT
A motor neuron innervates one set of muscle fibers.
Muscle
B MOTOR NEURON POOL
Axon
Spinal cord
Muscle fibers
A pool consists of many motor neurons, each of which innervates a motor unit with the muscle.




A SKELETAL MUSCLE
Myofibril
Plasma membrane (sarcolemma)
Z disk
Sarcomere
Z disk
A-I band junctions
Invaginations of plasma membrane (form transverse tubules)
Sarcoplasmic reticulum
TRIAD:
Sarcoplasmic reticulum cisterna
Transverse tubule
Sarcoplasmic reticulum cisterna