"Tutorial" on Voltage Gated Channels

Outline of basic ideas:

(0) a little history

(1) The membrane potential

Concentration differences across the membrane ➔ potential difference (in equilibrium)
[Nernst Equation]

(2) Different ionic species (Na, K, Cl, Ca) have different equilibrium potentials; different channels For each ion type.

(3) Only K and Cl have equilibrium potentials close to the actual resting potential. Generally Currents through the channels

(4) Specific pumps (Calcium pumps, and Na/K pumps) maintain concentration differences. These require energy (ATP) consumption. E.g. for the Na/K pump, transporting 3 Na (2 K) requires 1 ATP= 20 kT of energy

(5) Ion permeabilities are voltage dependent.

(6) Channels tend to have/are believed to have a single open state, and many closed state. Actual topology is not known. Hodgkin and Huxley's guess.

J. Physiol. (1952) 117, 500–544

A QUANTITATIVE DESCRIPTION OF MEMBRANE CURRENT AND ITS APPLICATION TO CONDUCTION AND EXCITATION IN NERVE

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This article concludes a series of papers concerned with the flow of electric current through the surface membrane of a giant nerve fibre (Hodgkin, Huxley & Katz, 1952; Hodgkin & Huxley, 1952 *a–c*). Its general object is to discuss the results of the preceding papers (Part I), to put them into mathematical form (Part II) and to show that they will account for conduction and excitation in quantitative terms (Part III).

PART I. DISCUSSION OF EXPERIMENTAL RESULTS

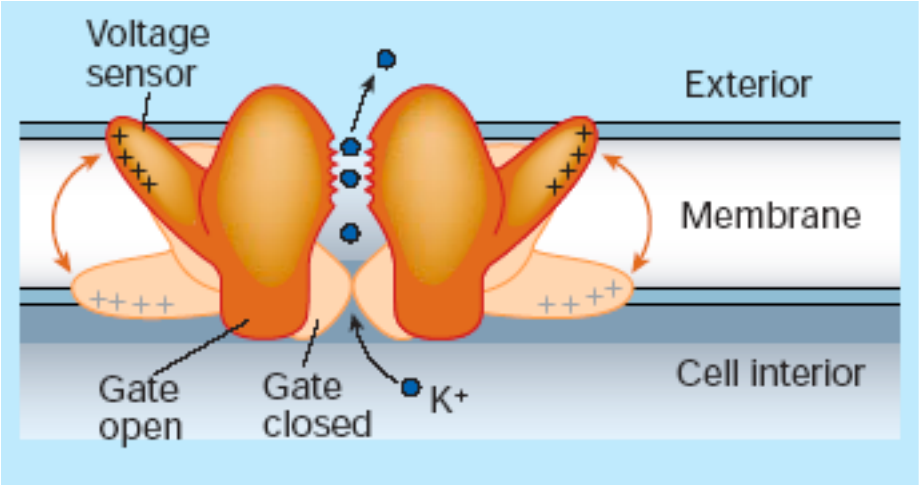
The results described in the preceding papers suggest that the electrical behaviour of the membrane may be represented by the network shown in Fig. 1. Current can be carried through the membrane either by charging the membrane capacity or by movement of ions through the resistances in parallel with the capacity. The ionic current is divided into components carried by sodium and potassium ions (I_{Na} and I_K), and a small 'leakage current' (I_l) made up by chloride and other ions. Each component of the ionic current is determined by a driving force which may conveniently be measured as an electrical potential difference and a permeability coefficient which has the dimensions of a conductance. Thus the sodium current (I_{Na}) is equal to the sodium conductance (g_{Na}) multiplied by the difference between the membrane potential (E) and the equilibrium potential for the sodium ion (E_{Na}). Similar equations apply to I_K and I_l and are collected on p. 505.

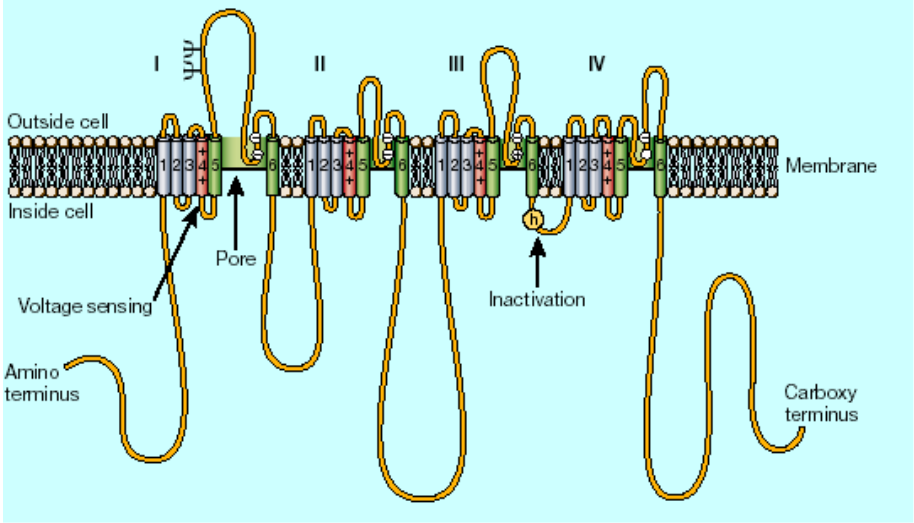
Our experiments suggest that g_{Na} and g_K are functions of time and membrane potential, but that E_{Na}, E_K, E_l, C_M and $\bar{g}_l$ may be taken as constant. The influence of membrane potential on permeability can be sum-

The nature of the permeability changes

At present the thickness and composition of the excitable membrane are unknown. Our experiments are therefore unlikely to give any certain information about the nature of the molecular events underlying changes in permeability. The object of this section is to show that certain types of theory are excluded by our experiments and that others are consistent with them.

(Voltage Gated) Ion Channels:





Sodium, Potassium, Calcium

common evolutionary history

common functions (molecular basis of nervous system)

but tremendous functional diversity

Enormous Ion Selectivityç

MacKinnon

There are other types of channels that we are not going to discuss today

Ligand Gated
Stretch Sensitive (mechanically gated)
Etc.

Overview of Molecular Relationships in the Voltage-Gated Ion Channel Superfamily

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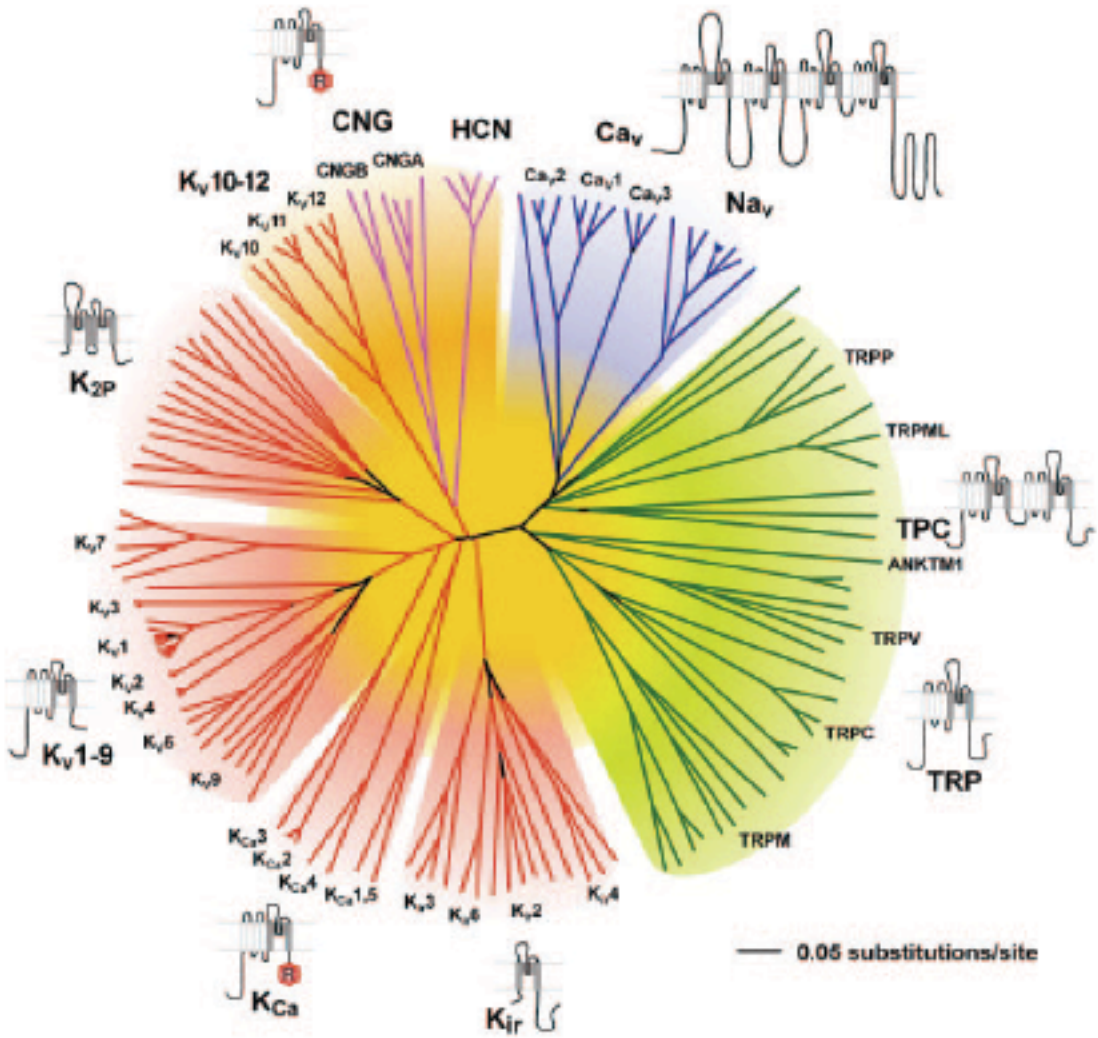
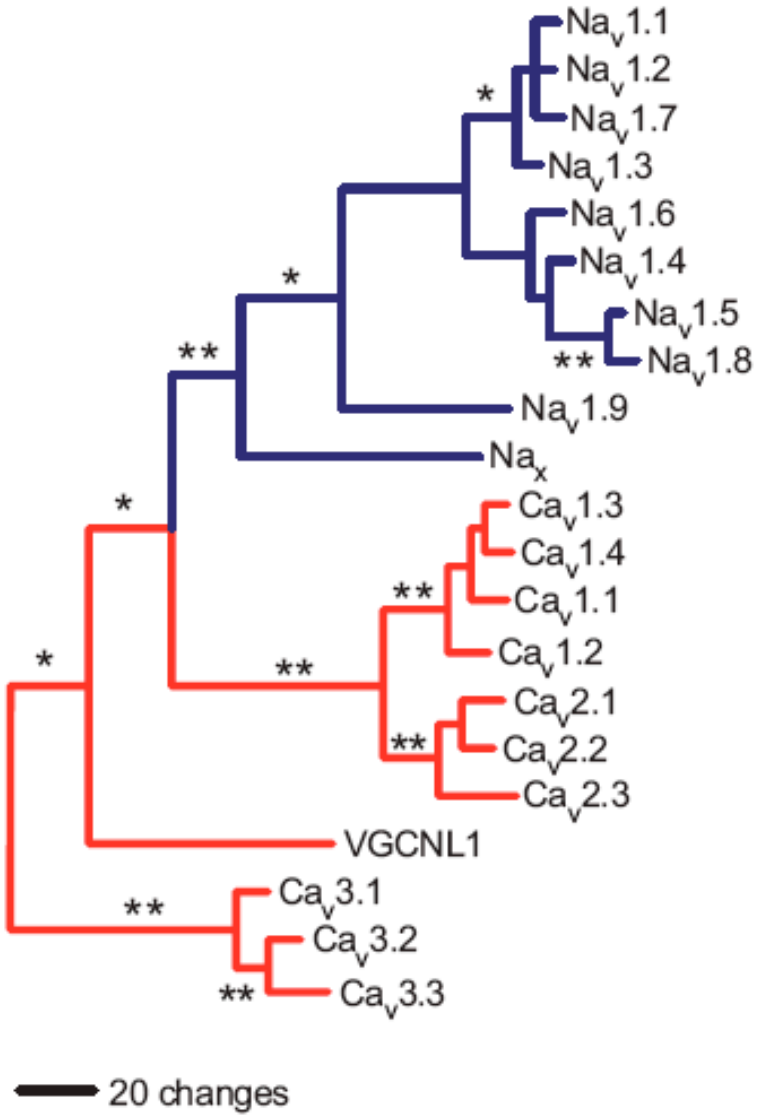
Introduction

Complex multicellular organisms require rapid and accurate transmission of information among cells and tissues and tight coordination of distant functions. In vertebrates, electrical signals and the resulting intracellular calcium transients control contraction of muscle, secretion of hormones, sensation of the environment, processing of information in the brain, and output from the brain to peripheral tissues. In nonexcitable cells, calcium transients signal many key cellular events, including secretion, gene expression, and cell division. In epithelial cells, huge ion fluxes are conducted across tissue boundaries. All of these physiological processes are mediated in part by members of the voltage-gated ion channel protein superfamily (Fig. 1) (Yu and Catterall, 2004). This protein superfamily of more than 140 members is one of the largest groups of signal transduction proteins, and many family members are the molecular targets for toxins and therapeutic agents. Here we review the molecular and evolutionary relationships among the families within the voltage-gated-like (VGL[1]) ion channel superfamily.



.. Representation of the amino acid relationships of the minimal pore regions of the voltage-gated ion channel superfamily. Thi
:3 members of the structurally related ion channel genes highlights seven groups of ion channel families and their membra
nain channels (Ca_V and Na_V) are shown as blue branches, potassium-selective channels are shown as red branches, cyclic nuc
are shown as magenta branches, and TRP and related channels are shown as green branches. Background colors separate th
into related groups: light blue, Ca_V and Na_V; light green, TRP channels; light red, potassium channels, except $K_V10–12$, which
le binding domain and are more closely related to CNG and HCN channels; light orange, $K_V10–12$ channels and cyclic nucleoti
l HCN channels. Minimal pore regions bounded by the transmembrane segments M1/S5 and M2/S6 were aligned by ClustalX (
) and refined manually. The pore regions of the fourth homologous domain of Na_V and Ca_V channels, the second domain of

143 voltage gated ion channel genes in humans



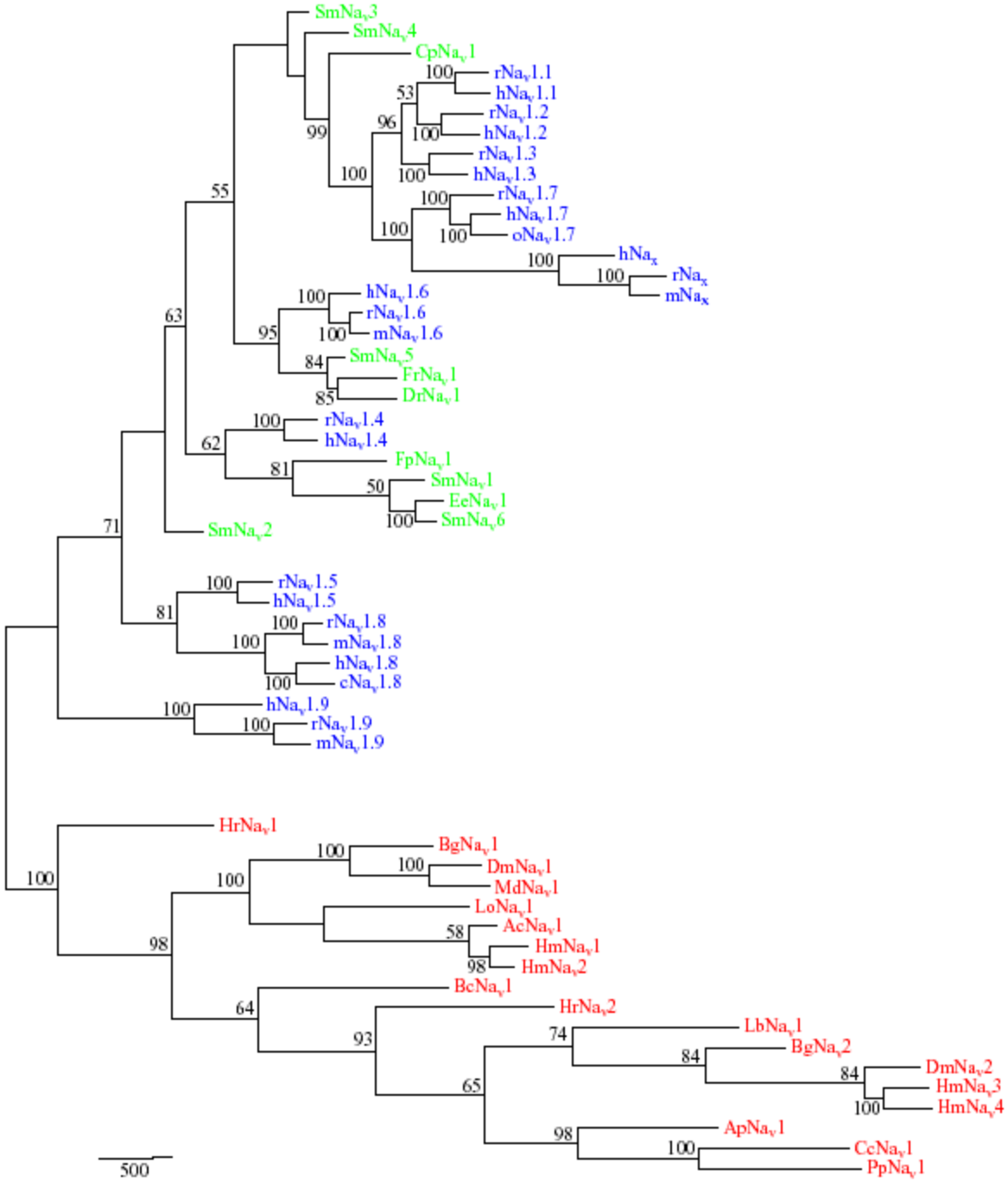
Caterall

Different channels are expressed in different places

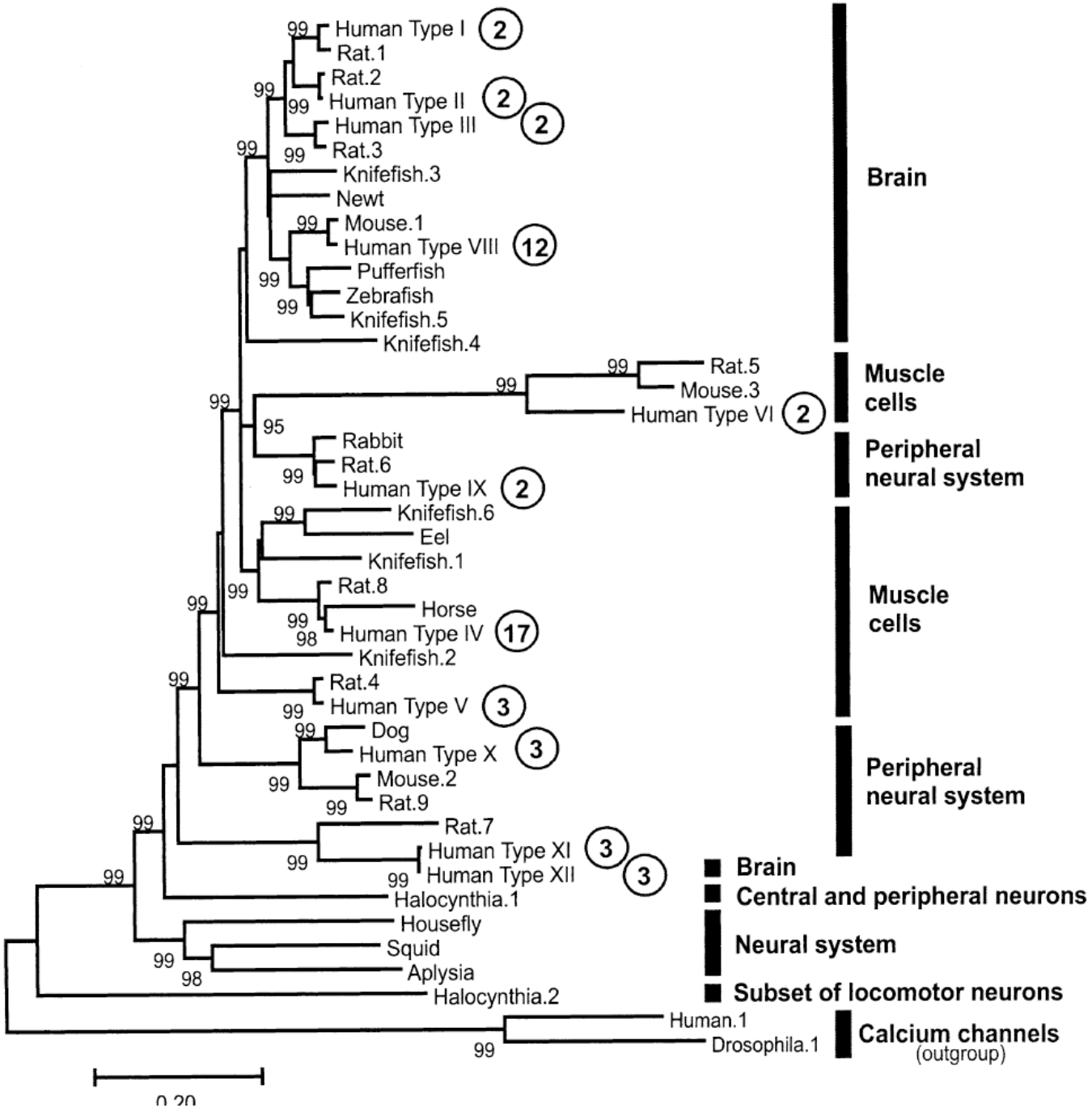
Table

Name	Original name	Species	Common name	Tissue
$rNa_v1.1$	rat I	*Rattus norvegicus*	Rat	CNS, PNS
$hNa_v1.1$	SCN1A HBSCI	*Homo sapiens*	Human	CNS
$rNa_v1.2$	rat II rat IIA	*Rattus norvegicus*	Rat	CNS
$hNa_v1.2$	HBA HBSCII	*Homo sapiens*	Human	CNS
$rNa_v1.3$	rat III	*Rattus norvegicus*	Rat	CNS
$hNa_v1.3$	type III	*Homo sapiens*	Human	CNS
$rNa_v1.4$	SkM1, μ1	*Rattus norvegicus*	Rat	Skeletal muscle
$hNa_v1.4$	SkM1	*Homo sapiens*	Human	Skeletal muscle
$rNa_v1.5$	SkM2 rH1	*Rattus norvegicus*	Rat	Denervated skeletal muscle, heart
$hNa_v1.5$	H1	*Homo sapiens*	Human	heart
$rNa_v1.6$	NaCh6 PN4	*Rattus norvegicus*	Rat	CNS, PNS
$hNa_v1.6$	Scn8a	*Homo sapiens*	Human	CNS
$mNa_v1.6$	Scn8a	*Mus musculus*	Mouse	CNS
$rNa_v1.7$	PN1	*Rattus norvegicus*	Rat	PNS
$hNa_v1.7$	hNE-Na	*Homo sapiens*	Human	Medullary thyroid Ca
$oNa_v1.7$	Nas	*Oryctolagus cuniculus*	Rabbit	Schwann cells
$rNa_v1.8$	SNS PN3	*Rattus norvegicus*	Rat	PNS (DRG)
$hNa_v1.8$	PN3	*Homo sapiens*	Human	PNS (DRG)
$mNa_v1.8$	SNS	*Mus musculus*	Mouse	PNS
$oNa_v1.8$	NaNG	*Canis familiaris*	Dog	
$rNa_v1.9$	SNS2 NaN PN5	*Rattus norvegicus*	Rat	PNS
$hNa_v1.9$	NaN SCN12A	*Homo sapiens*	Human	
$mNa_v1.9$	NaN NaT	*Mus musculus*	Mouse	
rNa_x	Na-G SCL11	*Rattus norvegicus*	Rat	Astrocytes PNS (DRG)
hNa_x	$Na_v2.1$	*Homo sapiens*	Human	Heart, uterus muscle
mNa_x	$Na_v2.3$	*Mus musculus*	Mouse	Heart, uterus muscle

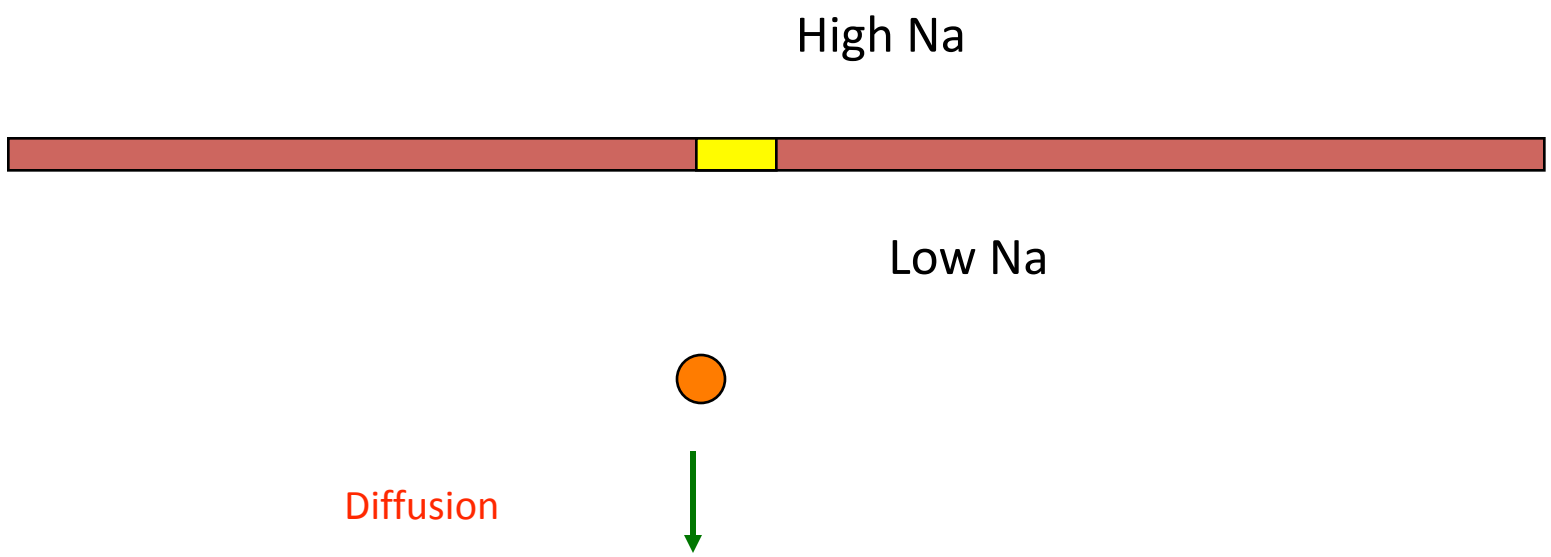
Evolutionary Stability of Channel types



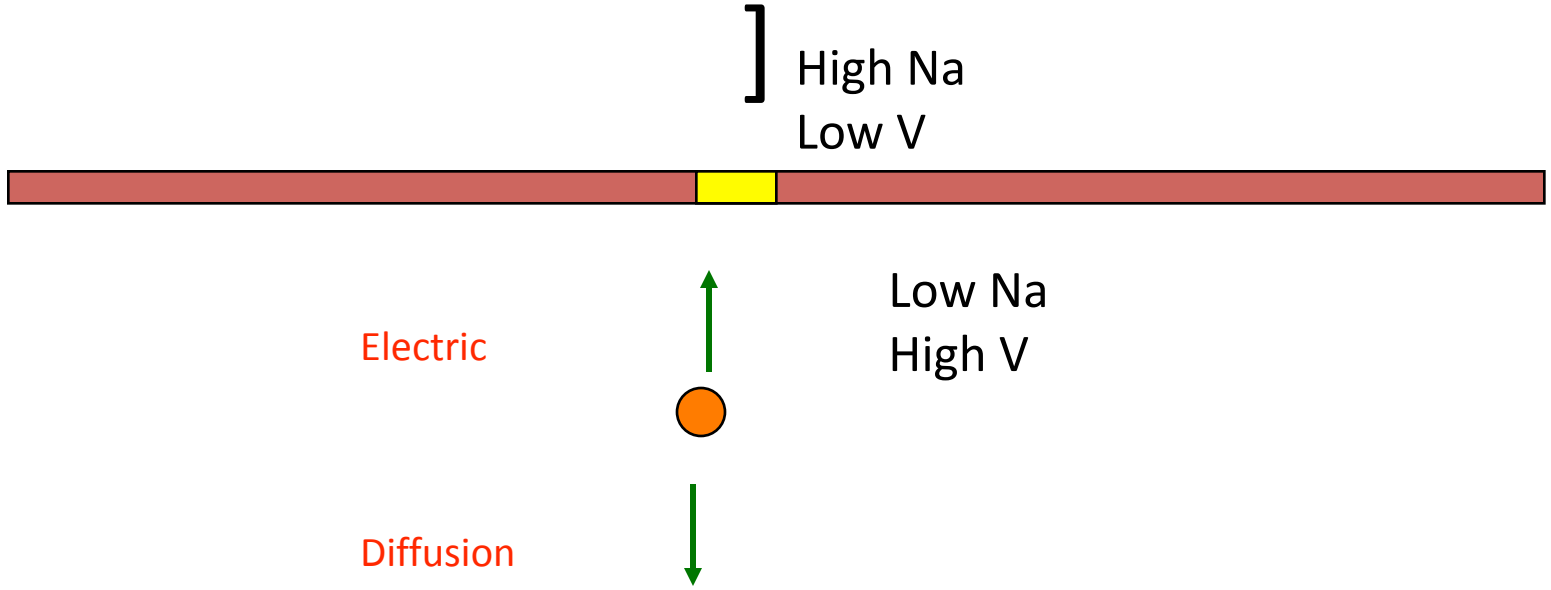
Goldin, 2002


Human Type I
Rat.1
Rat.2
Human Type II
Human Type III
Rat.3
Knifefish.3
Newt
Mouse.1
Human Type VIII
Pufferfish
Zebrafish
Knifefish.5
Knifefish.4
Rat.5
Mouse.3
Human Type VI
Rabbit
Rat.6
Human Type IX
Knifefish.6
Eel
Knifefish.1
Rat.8
Horse
Human Type IV
Knifefish.2
Rat.4
Human Type V
Dog
Human Type X
Mouse.2
Rat.9
Rat.7
Human Type XI
Human Type XII
Halocynthia.1
Housefly
Squid
Aplysia
Halocynthia.2
Human.1
Drosophila.1
2
2
2
12
2
2
17
3
3
3
3
Brain
Muscle cells
Peripheral neural system
Muscle cells
Peripheral neural system
Brain
Central and peripheral neurons
Neural system
Subset of locomotor neurons
Calcium channels
(outgroup)
0.20

Voltage Gated Ion Channel Primer



Voltage Gated Ion Channel Primer



$$V_{eq} = V_{in} - V_{out} = \underbrace{-\frac{k_B T}{e}}_{25\text{mV}} \log\left(\frac{c_{in}}{c_{out}}\right)$$

If $V \neq V_{eq}$ there is a current!

V_{na}=60mV
V_K=-70 mV

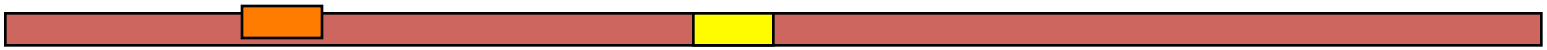
Ionic Species	Intracellular Concentration (mM)	Extracellular concentration	Nernst potential
K	155	4	-98
Na	12	145	67
Ca	0.0001	1.5	130
Cl	4	120	-90

From Phillips, Phys Bio of Cell, who got them from Hille

Note: These numbers are often quoted—but there is variability in different types of tissues And organisms. What sets the numbers?

Voltage Gated Ion Channel Primer

High Na, Low K



Low Na, High K

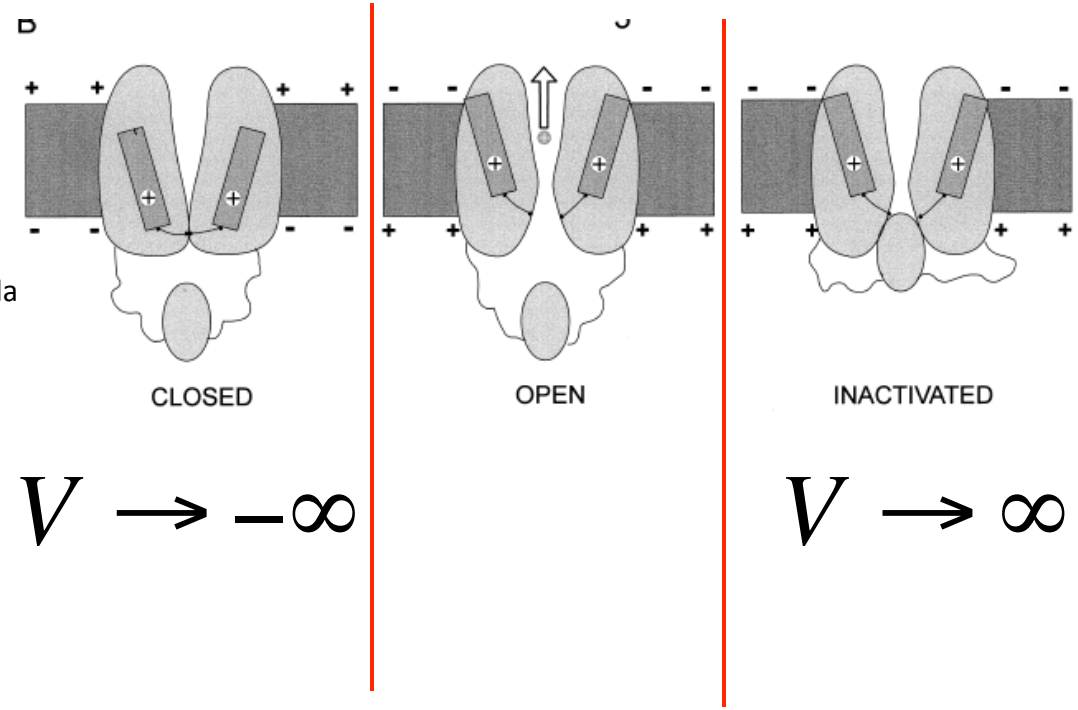
$$I = G_{Na} \boxed{P_{Na}(V)}(V - V_{Na})$$
$$+ G_{K} \boxed{P_{K}(V)}(V - V_{K})$$

conductance

open probability

Standard Picture

$$P_{Na}(V)$$



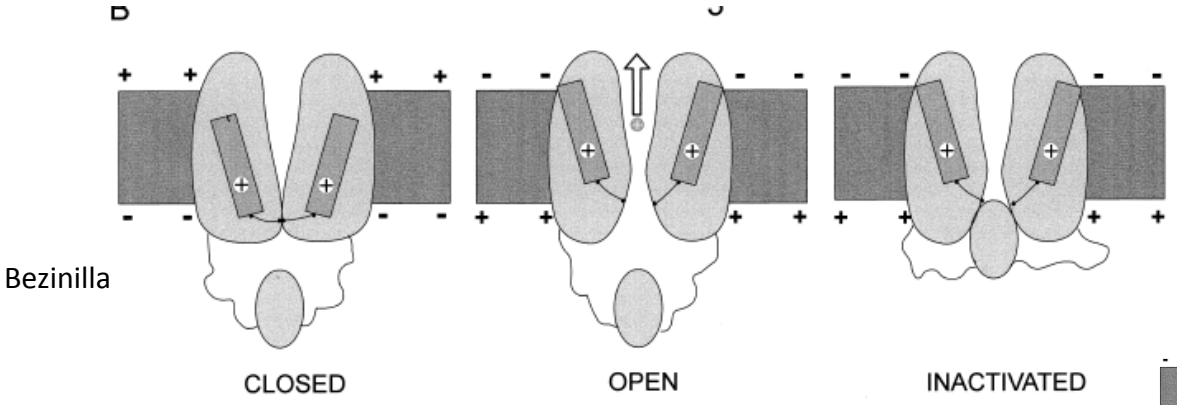
Bezinilla

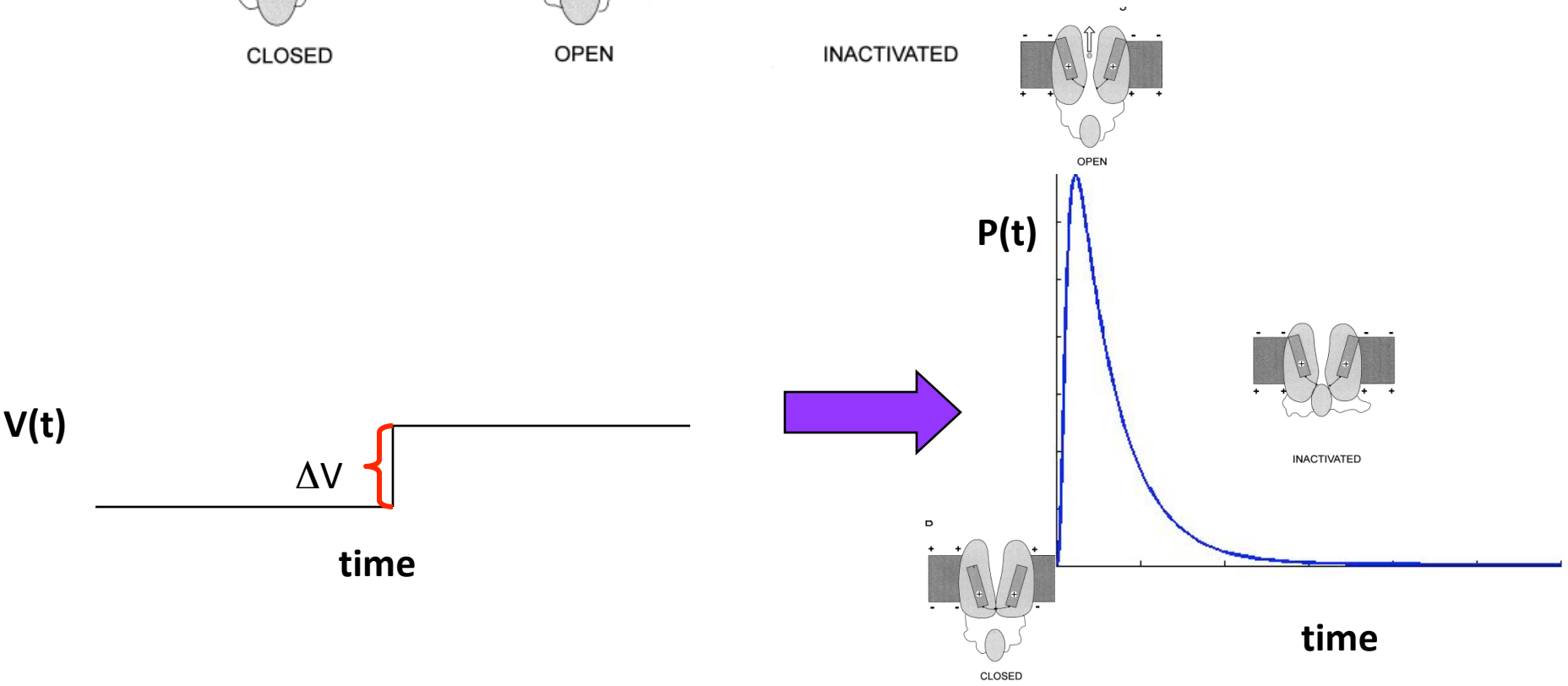
$V \to -\infty$

$V \to \infty$

Standard Picture

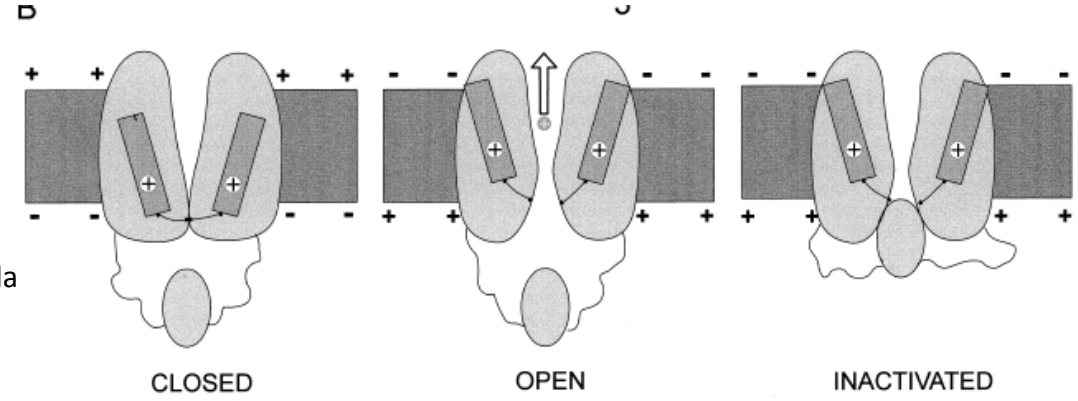
$$P_{Na}(V)$$

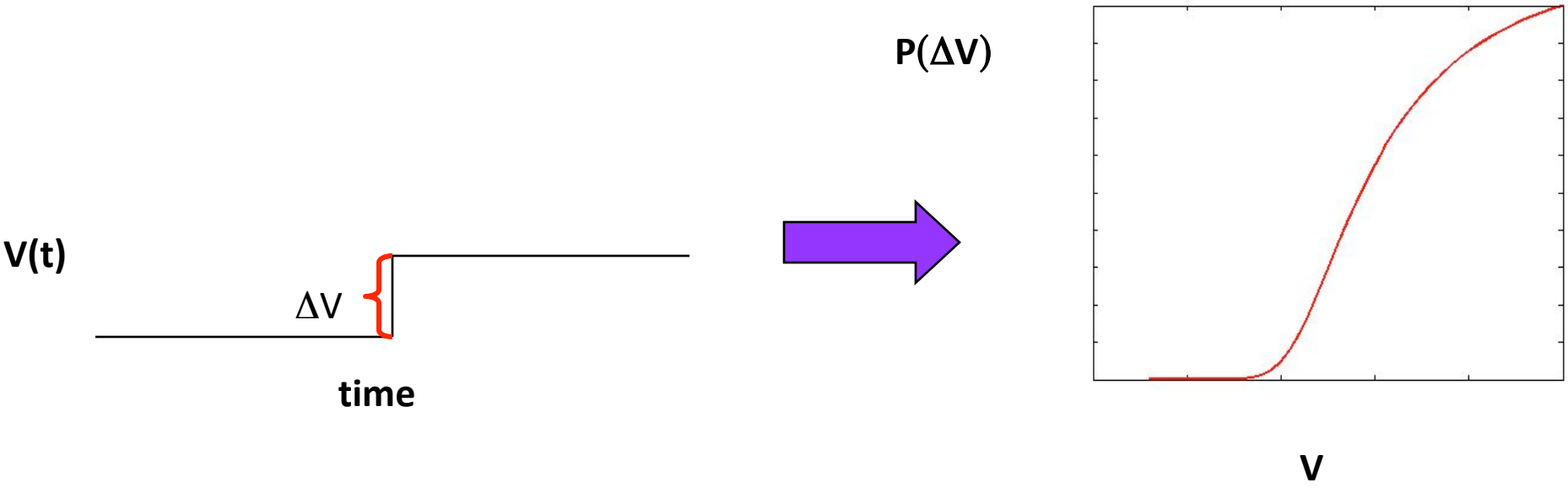




Standard Picture

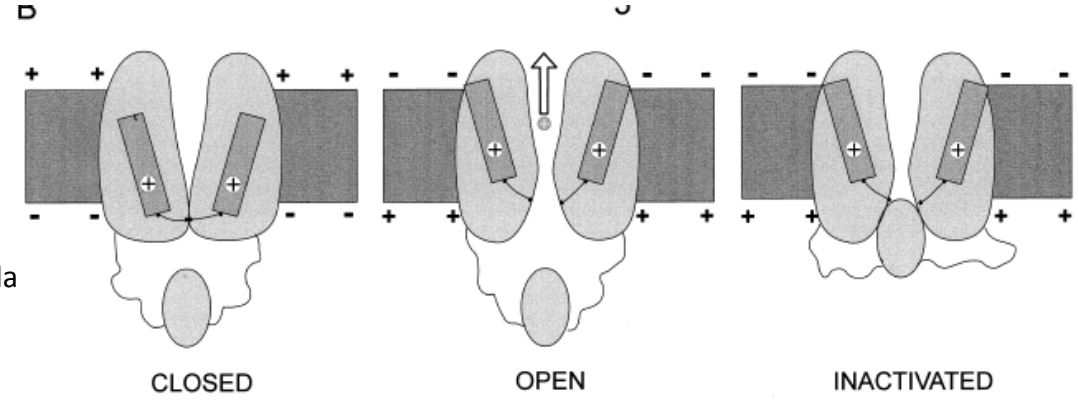
$$P_{Na}(V)$$





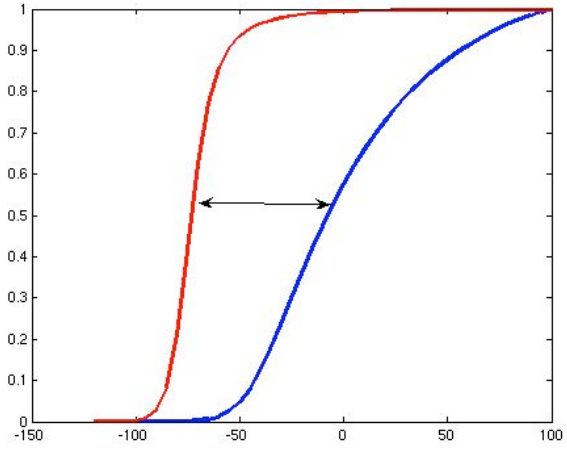
Standard Picture

$$P_{Na}(V)$$



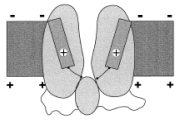
Bezinilla

P(ΔV)



V

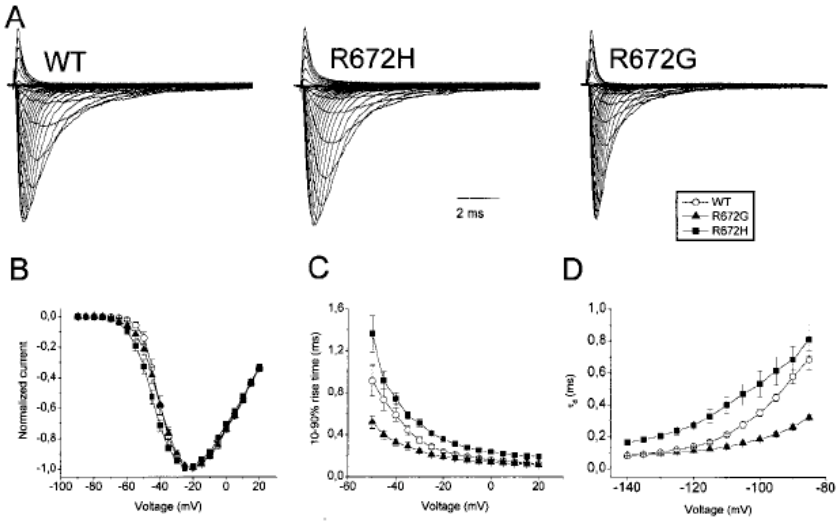
Equilibrium Probability

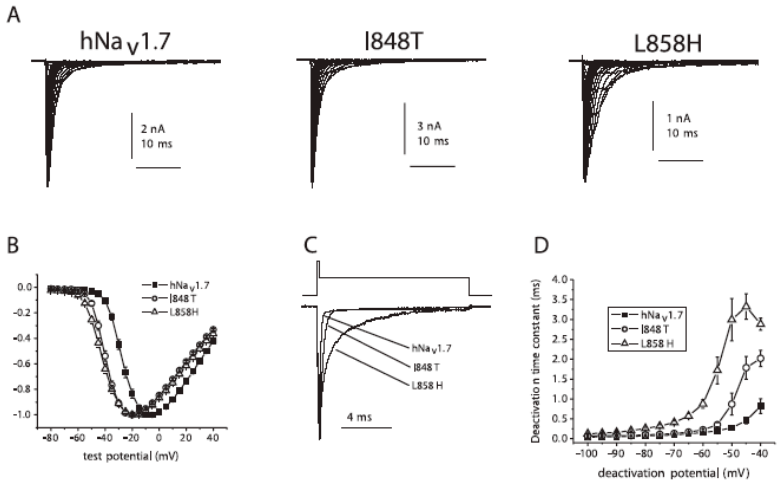


Different Channels Have Different Kinetic Properties

Nav 1.4

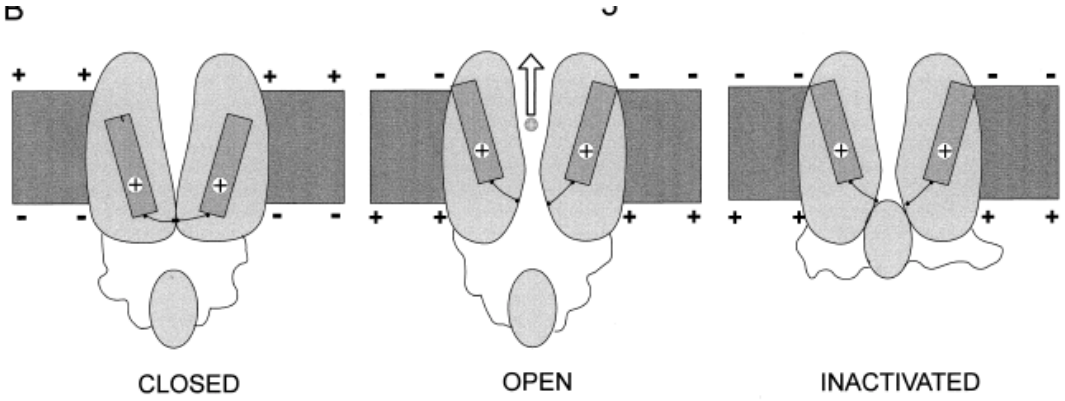
Nav 1.7





What sets the numbers? Which numbers change under evolution?

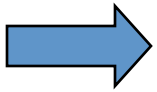
Models?



Parameters:

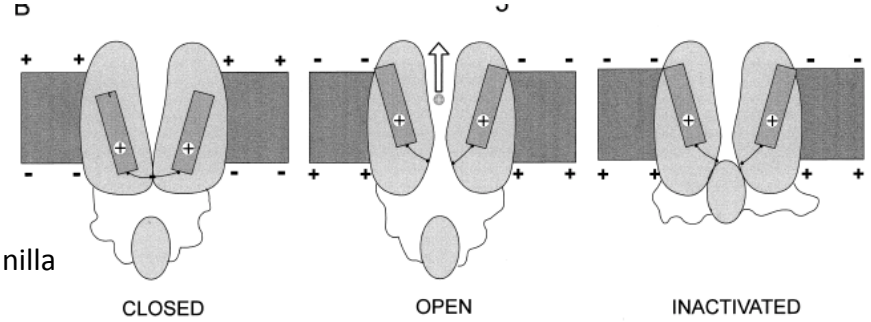
closed --> open $\quad Rate_{f,b}=c\ \exp(\Delta E_{f,b}-q_{f,b}V)$

open --> inactivated $\quad Rate^{i}_{f,b}=c\ \exp(\Delta E^{i}_{f,b}-q^{i}_{f,b}V)$



At least 8 parameters…

Hodgkin Huxley



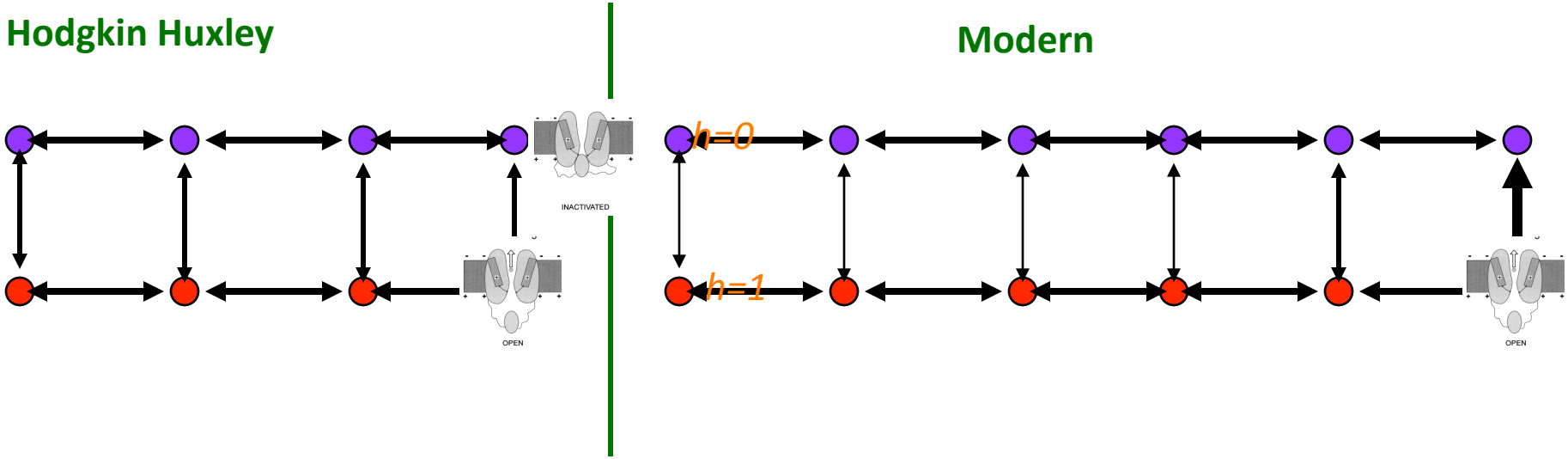
Bezinilla

$$P_{Na}(V) = m^3 h$$

m: activation
h: inactivation

$$\frac{dm}{dt} = \alpha_m(V)(1-m) - \beta_m(V)m$$

$$\alpha_m(V) = \frac{25 - V}{10\left(\exp\left(\frac{25-V}{10}\right) - 1\right)}$$



Qualitative Problems with Hodgkin/Huxley

(1) Channel has 4 domains (4 fold "symmetry")

at least 4 closed states (observations suggest 5)

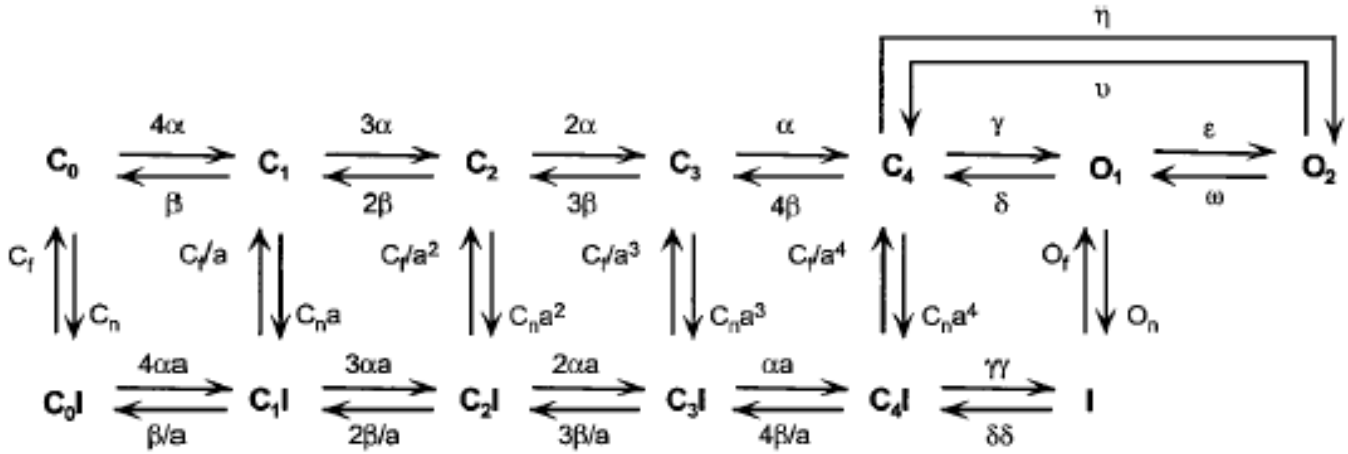
(2) Inactivation tightly coupled to activation

vertical arrows have different strengths

(4) Inactivation is voltage independent

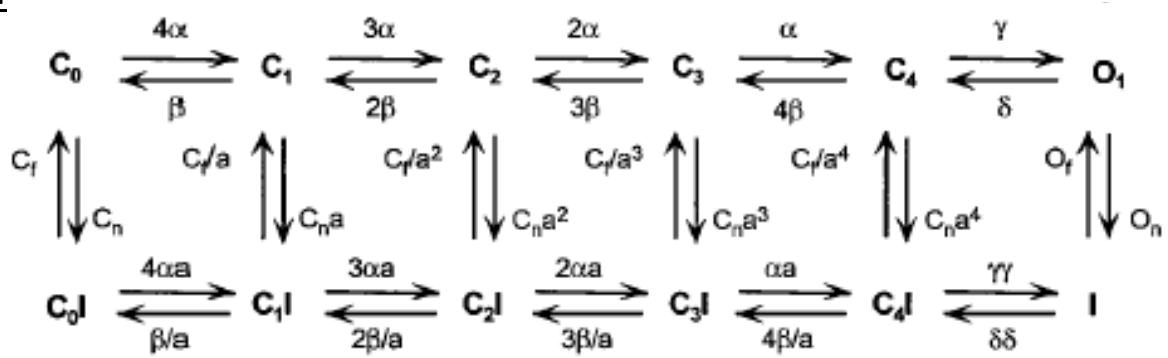
Kinetic Schemes

Cardiac



Winslow

Neuronal



Bean