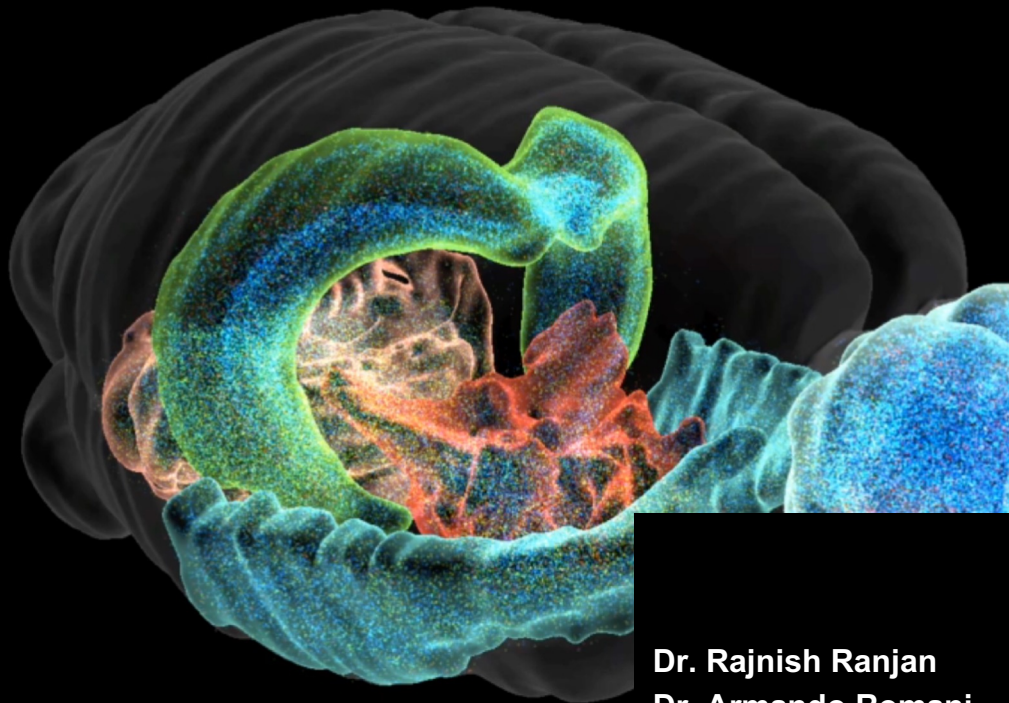




Computational neuroscience: biophysics - Lecture 4

**Dr. Rajnish Ranjan
Dr. Armando Romani**

Ion channels

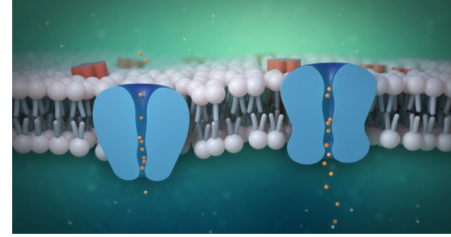
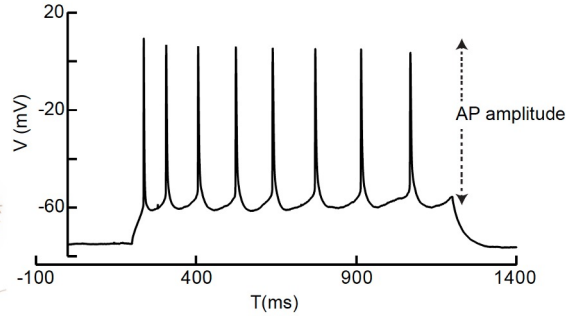
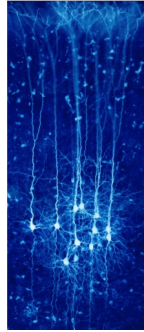
Lecture Overview

- Scope
- Approaches
- Applications

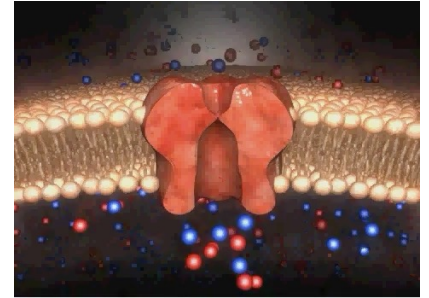
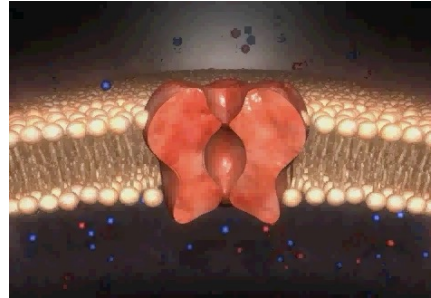
Lecture Overview

- **Scope**
 - **Why ion channels exist ?**
 - **What is an ion channel ?**
 - **How does it function**
- **Approaches**
 - How do we study ion channels
 - How do we model and simulate ion channel
- **Applications**
 - Areas of research in ion channels
 - Channelopathies
 - Automated ion channel characterization
 - Web resources

Why ion channels ?

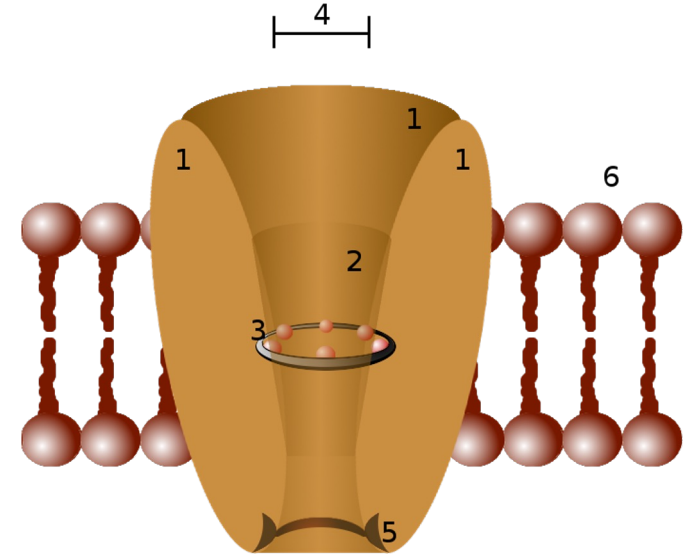


The function of the brain depends on the ability of neurons to transmit electrochemical signals to other cells, and their ability to respond appropriately to electrochemical signals received from other cells.



What is an ion channel ?

- Membrane proteins
- Water-filled pore
- Permeable to ions
- Specificity
- The pore can be opened or closed by electrical, mechanical, or chemical signals

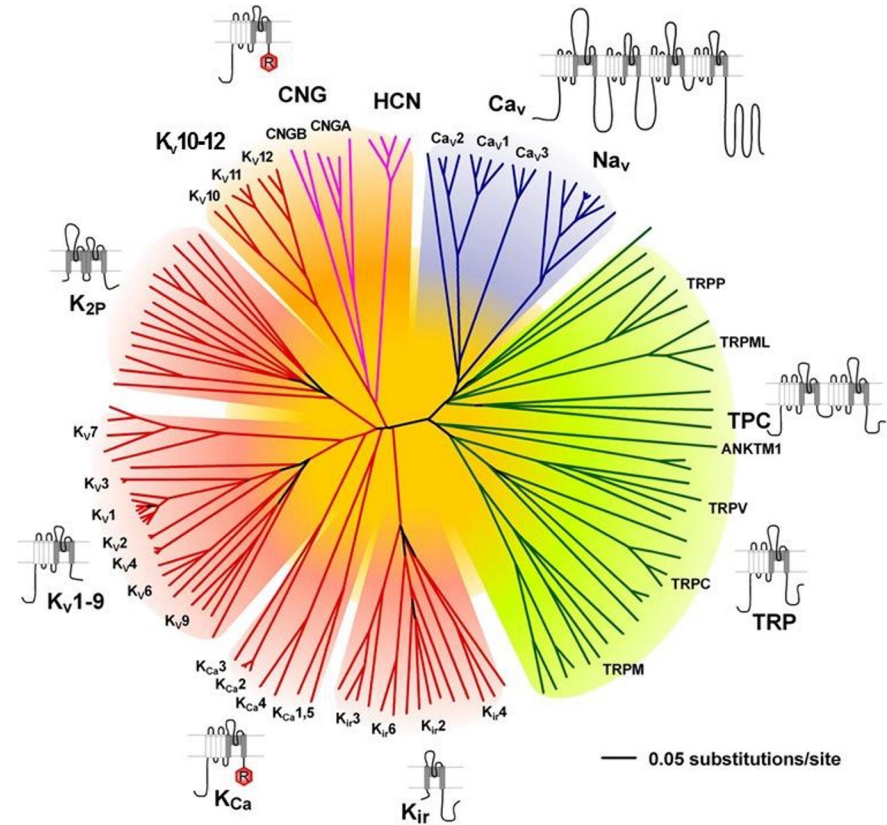


Schematic diagram of an ion channel. 1 - channel domains (typically four per channel), 2 - outer vestibule, 3 - selectivity filter, 4 - diameter of selectivity filter, 5 - phosphorylation site, 6 - cell membrane.

https://en.wikipedia.org/wiki/Ion_channel

Classification

- Classification by gating
 - Voltage-gated, ligand-gated, ...
- Classification by the main ion
 - K^+ , Na^+ , Ca^{2+} , Cl^- , ...
- IUPHAR International Union of Basic and Clinical Pharmacology
- Around 350 ion channel types known in mammals (most of them expressed in the brain)
 - ~150 voltage gated
 - ~90 ligand gated
 - >100 others

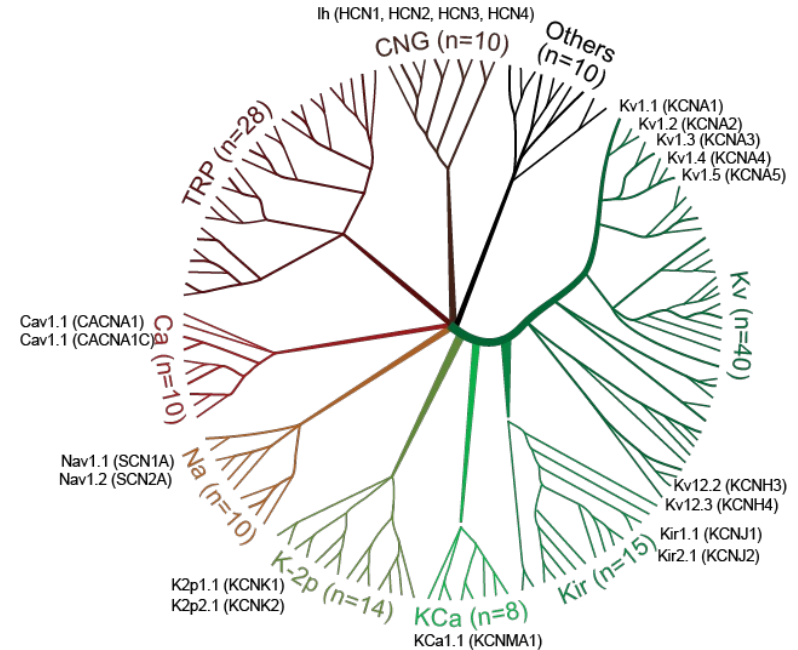


Classification

Drosophila naming (old)

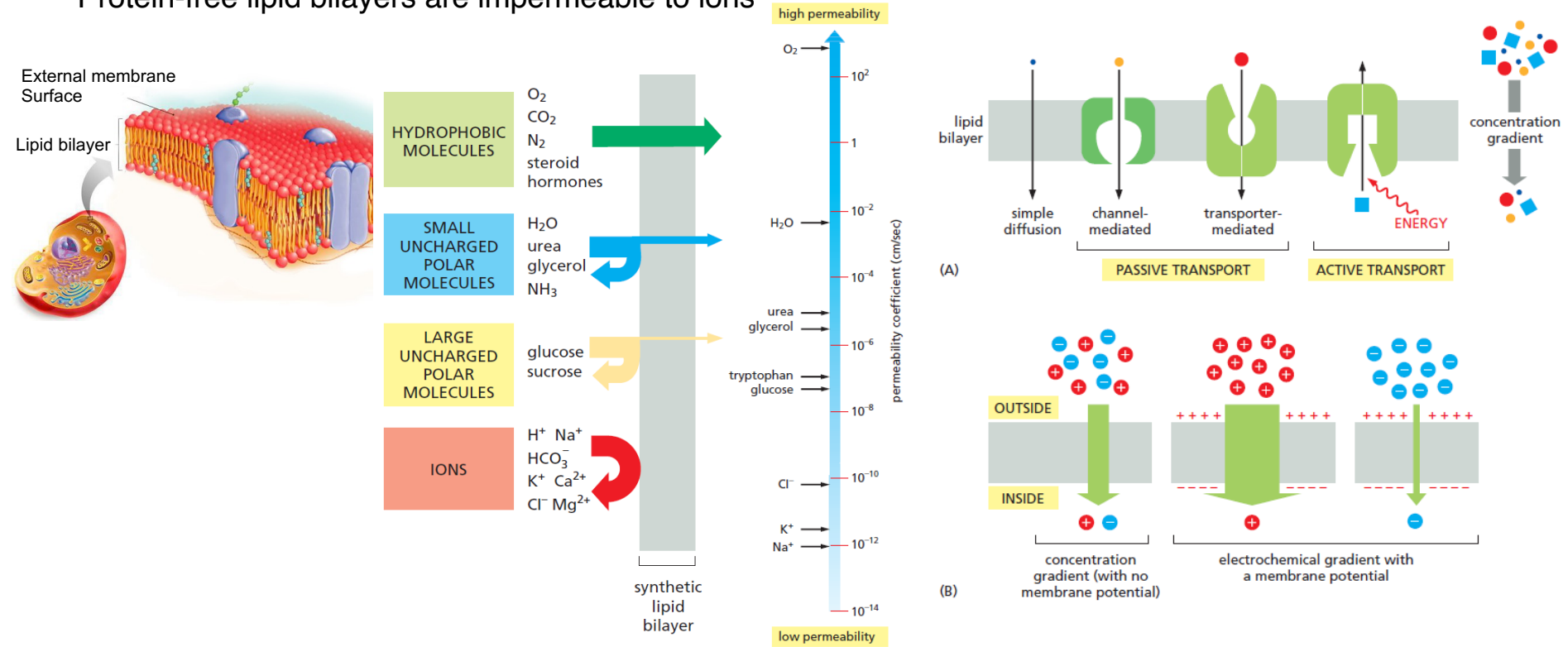
- **Shaker (Kv1)** Leg-shaking behavior when flies were anesthetized. Ref - PMID :20636, Proc R Soc Lond B Biol Sci, 1977
- **Shab (Kv2)** Ref - PMID :2493160, Science, 1989
- **Shaw (Kv3)** Ref - PMID :2493160, Science, 1989
- **Shal (Kv4)** Ref - PMID :2493160, Science, 1989
- **Erg (Kv10)** Ether-a-go-go related genes. Leg shaking behavior when flies were anesthetized with ether. Ref - PMID :5807804, Genetics, 1969
- **Elk (Kv12)** Ether-a-go-go-like
- **Eag (Kv11)** Ether-a-go-go

Current naming



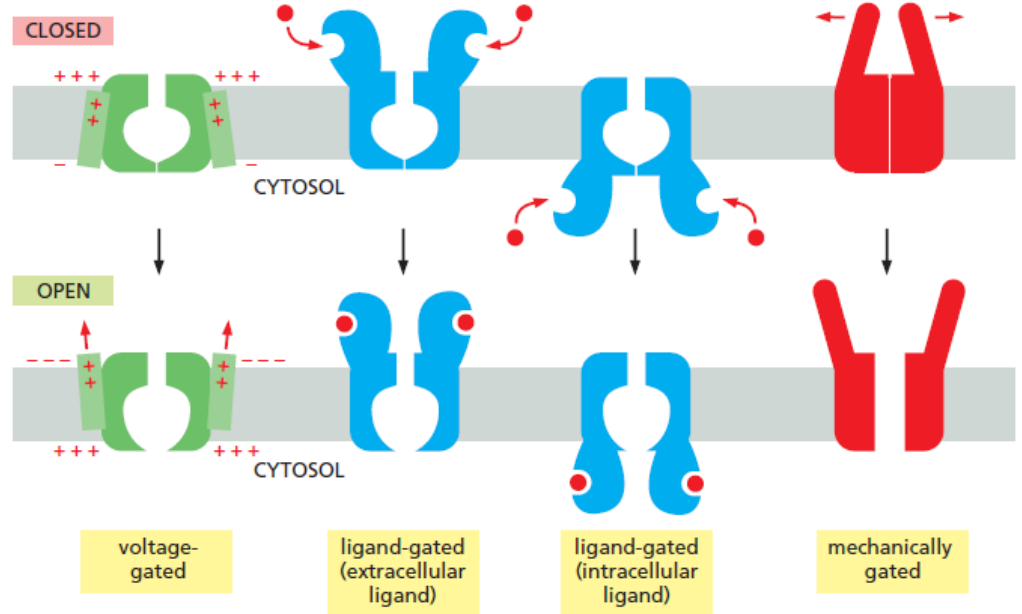
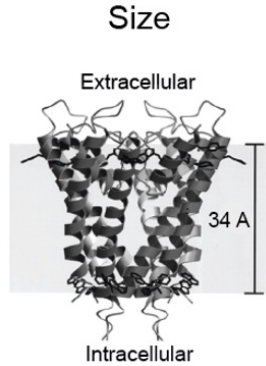
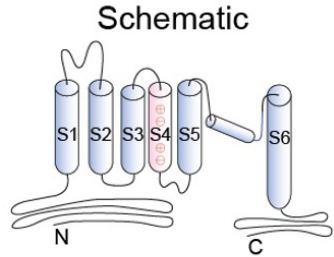
Membrane permeability

Protein-free lipid bilayers are impermeable to ions

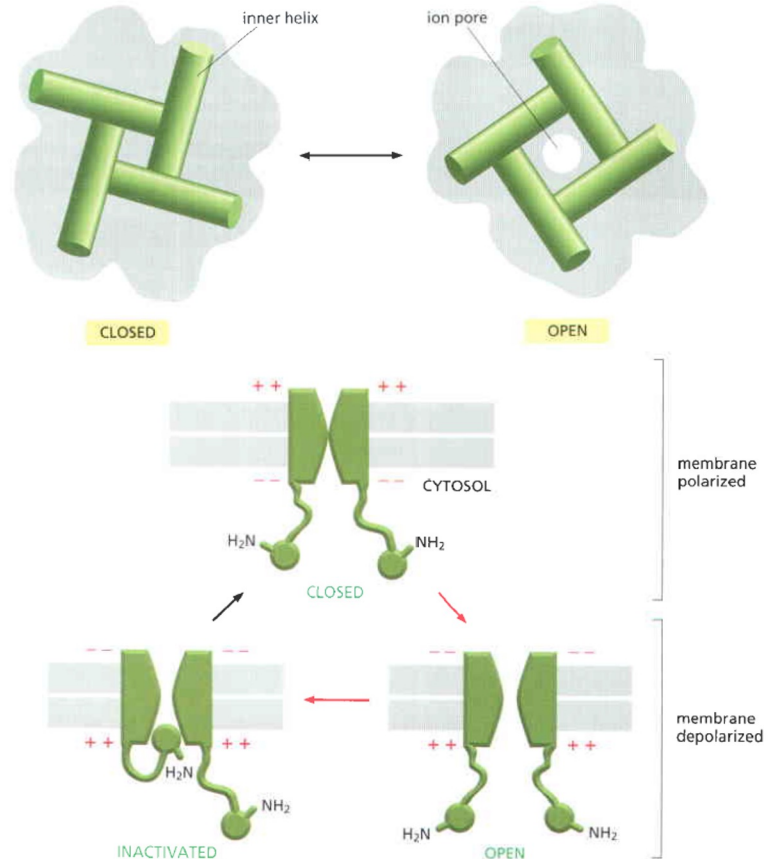
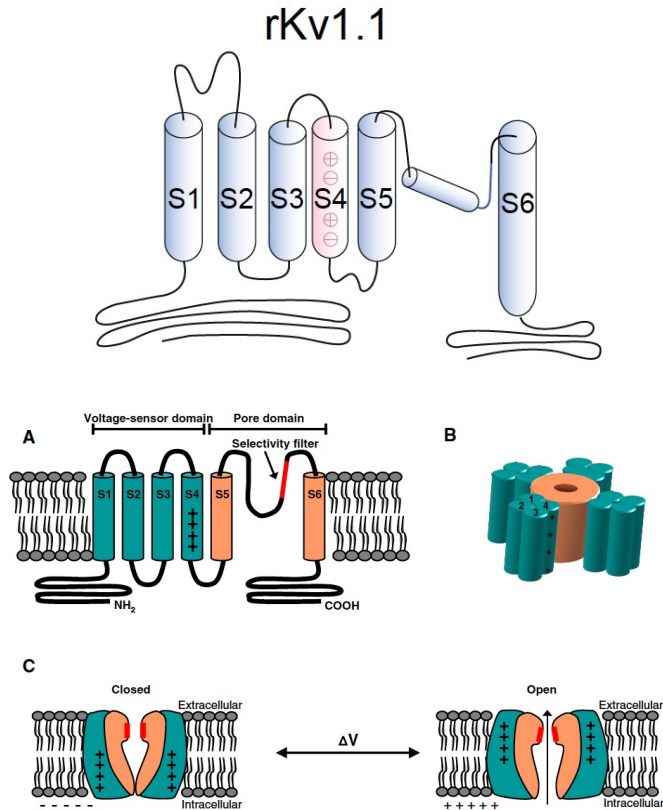


How does it function ?

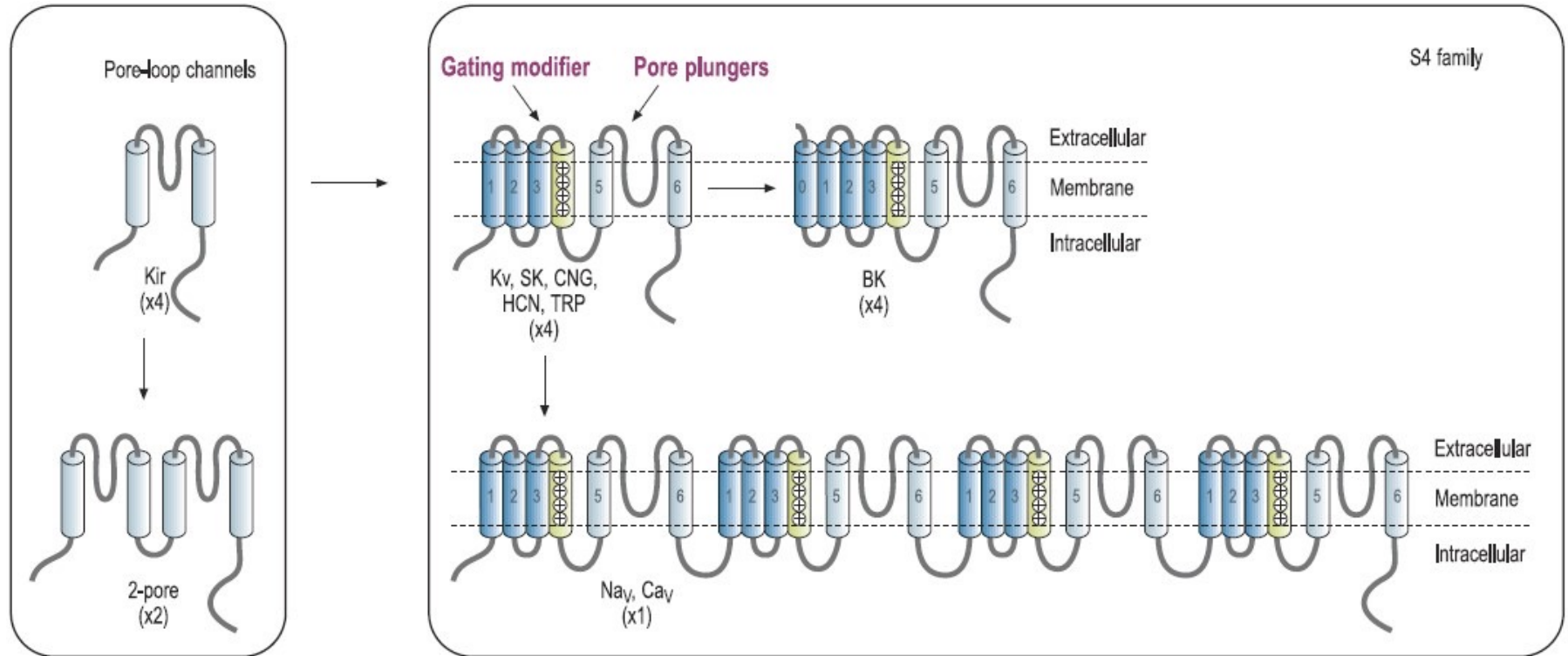
- Voltage-gated ion channels
- Ligand-gated
- Mechanically gated



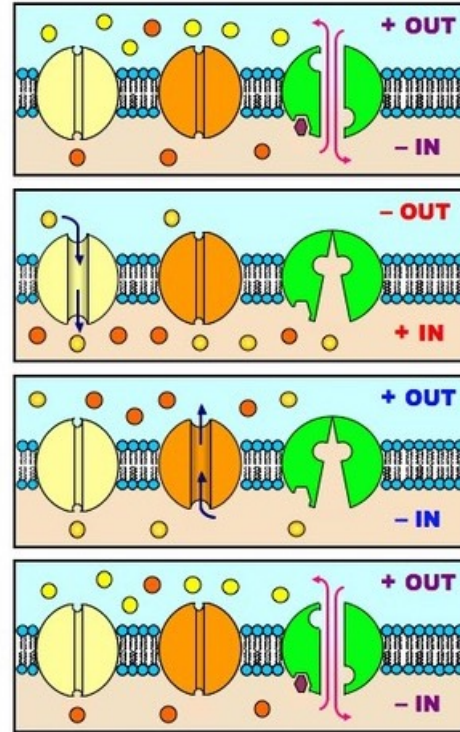
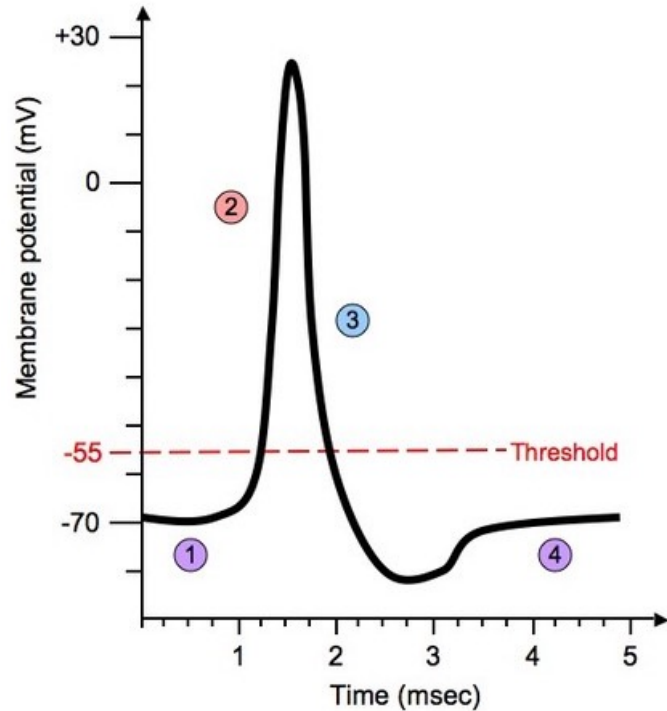
How does ion channel function ?



Ion channel structure



Role of ion channels in single cell



① **Resting Potential**
Na⁺/K⁺ pump

② **Depolarisation**
Voltage-gated Na⁺ channel

③ **Repolarisation**
Voltage-gated K⁺ channel

④ **Resting Potential**
Na⁺/K⁺ pump

<http://www.vce.bioninja.com.au/aos-2-detecting-and-respond/coordination--regulation/nervous-system.html>

Role of ion channels

Ion channels and transporters save our cells from osmotic death

No cell could exist without ion channels

(Differentiation, proliferation, secretion, apoptosis, migration, adhesion, invasion, excitability etc.)

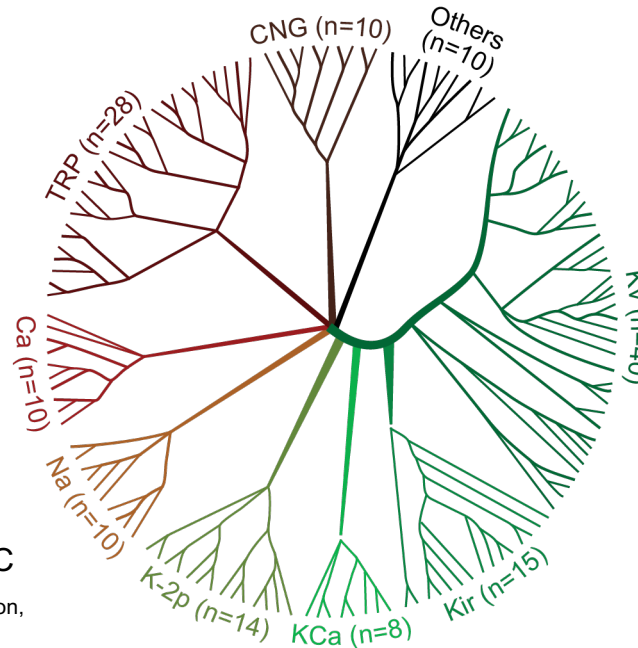
Ion channels make cells electrically active

Heartbeat is controlled by specific electrical impulses – Cardiac action potential, the direct result of cardiac ion channel function.

Ion channels/receptors transduce light into electrical signals. (TRP, CNG)

Auditory system has to convert sound waves into electrical signals. MET, TMC channels

Mechanoelectrical transduction,
Transmembrane channel like



Odor perception is a result of electrical signals generated by olfactory neurons. (CNG channels, Nav1.7)

Food and taste – Otopetrin (sour taste), TRP (cold, hot, bitter, sweet), ENaC (salty taste)

Touch – Mechanosensitive ion channels, Piezo channels

Pain sensation – Nav, Kir, ASIC, TRP, P2X channels

Muscle movements are controlled by electrical impulses, dependent on ion channel function

Toxins

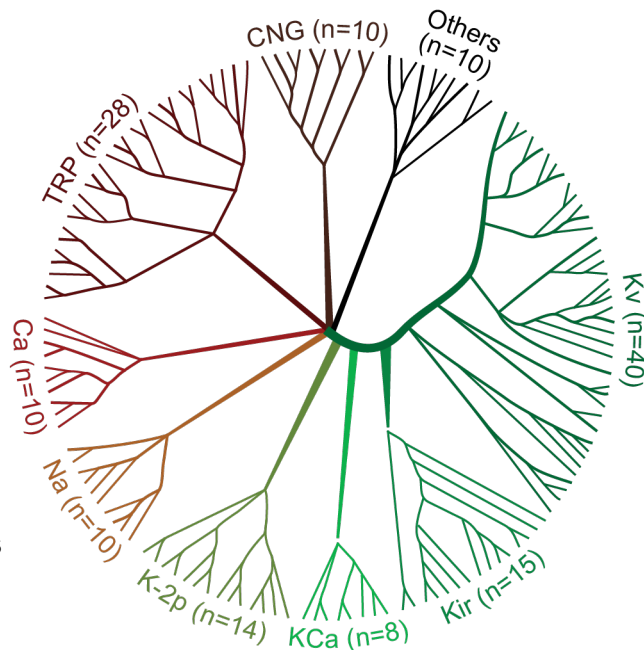
TTX



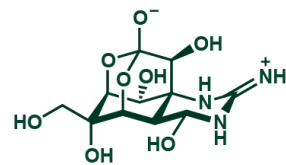
Fugu/puffer fish



Blue-ringed octopus



FUGU & TETRODOTOXIN



TETRODOTOXIN

MAIN LOCATIONS



liver

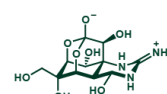


skin



sex organs

Tetrodotoxin is produced by bacteria that live in pufferfish. The parts of the fish which contain high levels of the toxin must be skillfully removed before eating. Tetrodotoxin is heat stable so can't be broken down by cooking.



blocks nervous system messages



causes loss of sensation, paralysis, respiratory arrest, and death.

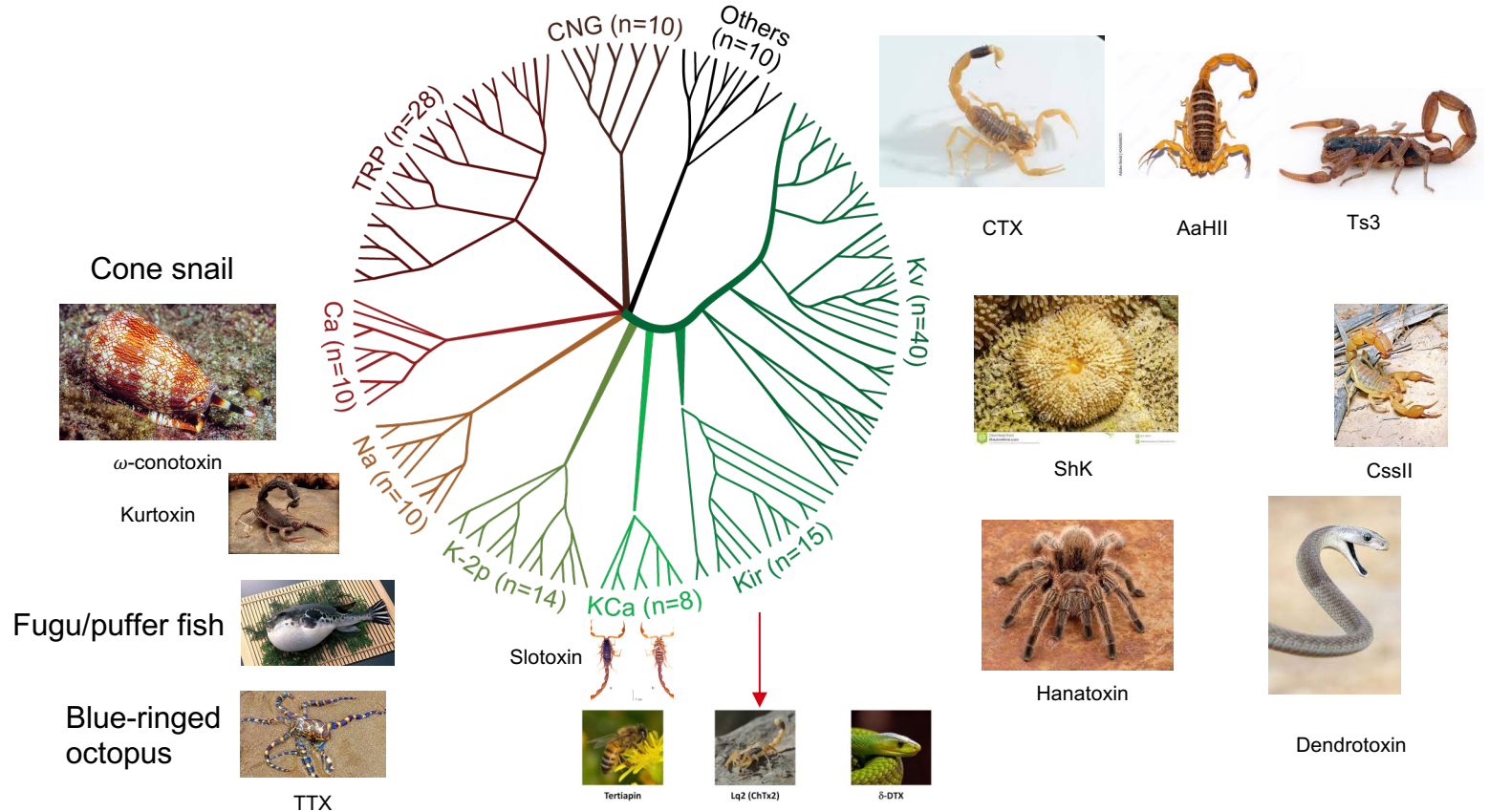
The estimated median lethal dose of tetrodotoxin is 0.33 milligrams per kilogram of body weight. There is no known antidote for the toxin.



© Andy Brunning/Compound Interest 2018 - www.compoundchem.com | Twitter: @compoundchem
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Toxins

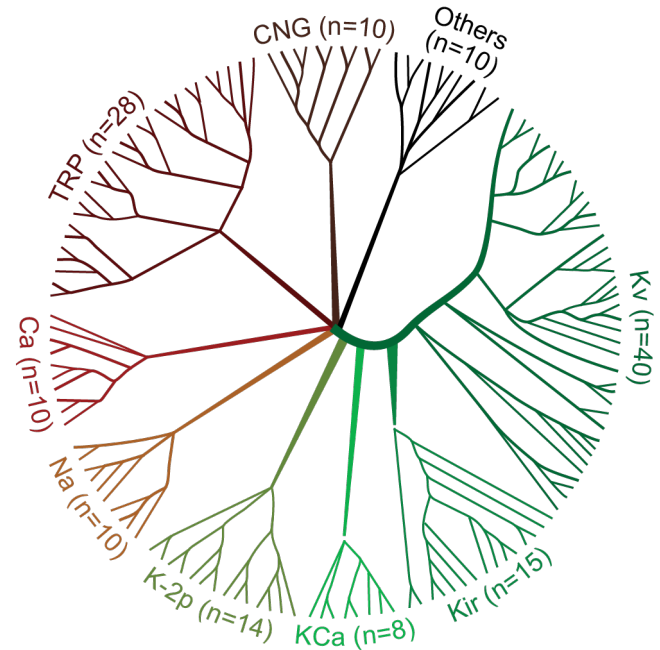


Summary

- Ion channels are protein molecules that allow ions to pass through the membrane
- Ion channels can be specific to cation or anion (Na^+ , K^+ , Ca^{2+} , Cl^-)
- Two main groups of ion channels are voltage-gated and ligand-gated ion channels
- Voltage-gated ion channels have fundamental interactive role in cell signalling
- Most common K^+ channels are tetramers
- Na/Ca channel alpha subunit is a single peptide of four homologous domains

Lecture Overview

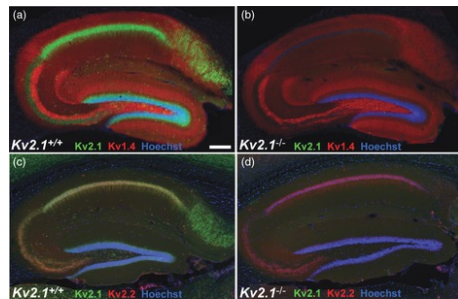
- Scope
- **Approaches**
 - How do we study ion channels ?
 - How do we model/simulate ion channels ?
- Applications



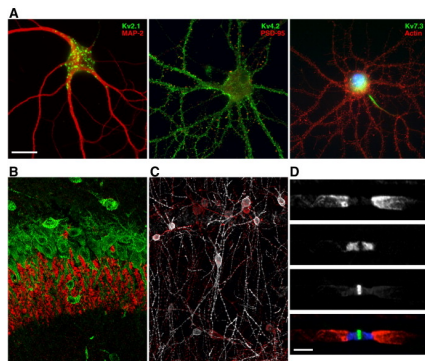
Approach

Protein expression

Immunohistochemistry



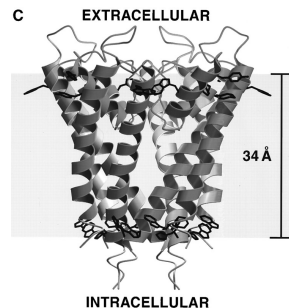
Specia D. et.al.; Deletion of the Kv2.1 delayed rectifier potassium channel leads to neuronal and behavioral hyperexcitability. *Genes Brain Behav.* 2014



Jensen CS, et.al.; Neuronal trafficking of voltage-gated potassium channels. *Mol Cell Neurosci.* 2011

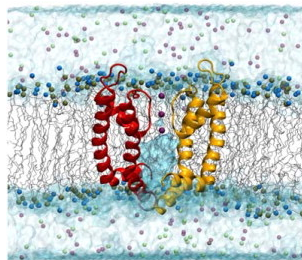
Protein structure

X-ray crystallography



Doyle DA, MacKinnon R. et.al.; The structure of the potassium channel: molecular basis of K⁺ conduction and selectivity. *Science.* 1998

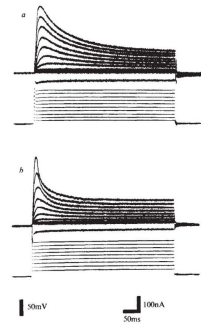
Protein modelling



Khalili-Araghi F, et.al.; Dynamics of K⁺ ion conduction through Kv1.2. *Biophys J.* 2006

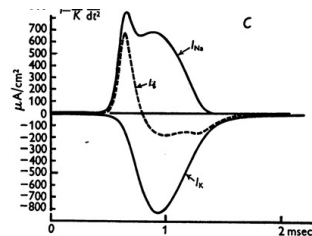
Protein Kinetics

Electrophysiology



Salkoff, L., Wyman, R. Genetic modification of potassium channels in *Drosophila* Shaker mutants. *Nature* 293, 228–230 (1981)

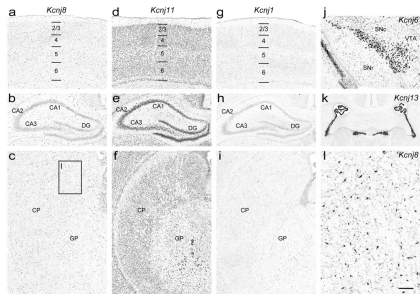
Conductance modelling



HODGKIN AL, HUXLEY AF. A quantitative description of membrane current and its application to conduction and excitation in nerve. *J Physiol.* 1952

Gene expression

In-situ hybridization



Shcherbaty V, et.al.; A digital atlas of ion channel expression patterns in the two-week-old rat brain. *Neuroinformatics.* 2015

Awards, Discoveries, Nobel Prize



Sir Alan Hodgkin, 1949



Sir Andrew Huxley, 1974

The Nobel Prize in Physiology or Medicine 1963

Sir John Carew Eccles, Alan Lloyd Hodgkin and Andrew Fielding Huxley “for their discoveries concerning the ionic mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane”



The Nobel Prize in Physiology or Medicine 1991

Erwin Neher and Bert Sakmann “for their discoveries concerning the function of single ion channels in cells”



The Nobel Prize in Chemistry 2003

“for discoveries concerning channels in cell membranes”

Peter Agre “for the discovery of water channels”

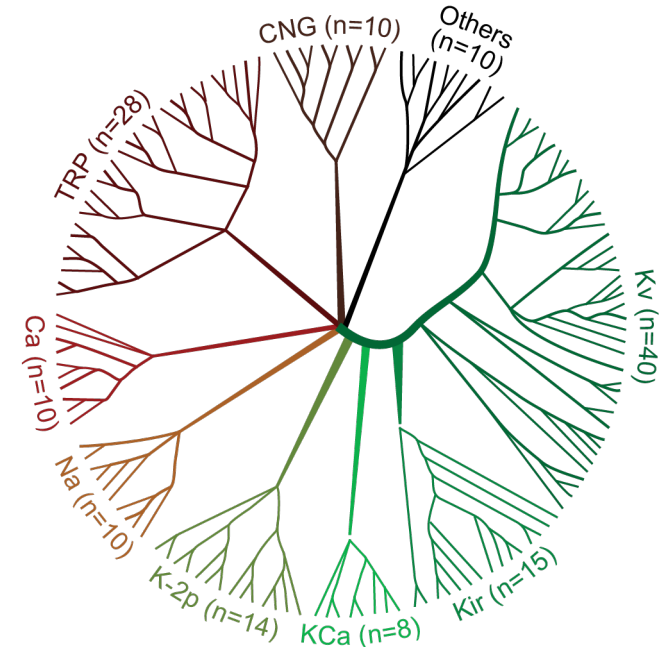
Roderick MacKinnon “for structural and mechanistic studies of ion channels”



The Nobel Prize in Physiology or Medicine 2021

David Julius and Ardem Patapoutian “for their discoveries of receptors for temperature and touch”.

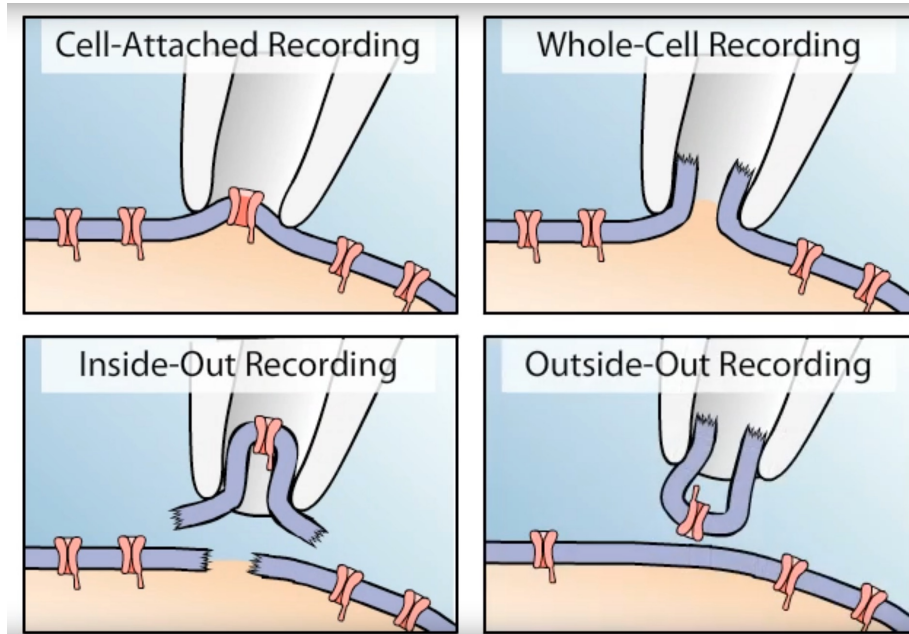
David discovered TRPV1 receptor that detects pain and heat
Ardem discovered Piezo1 and Piezo2, essential for sensing mechanical stimuli such as pressure and touch



Approach

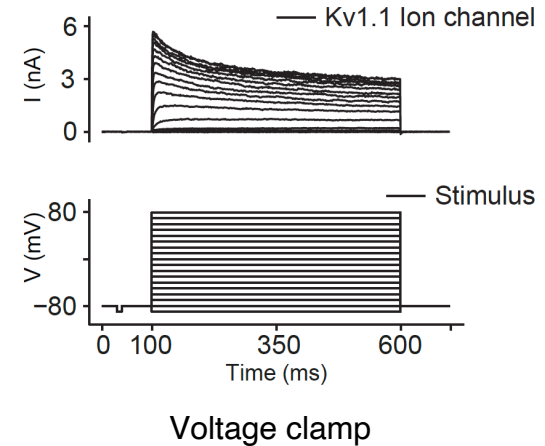
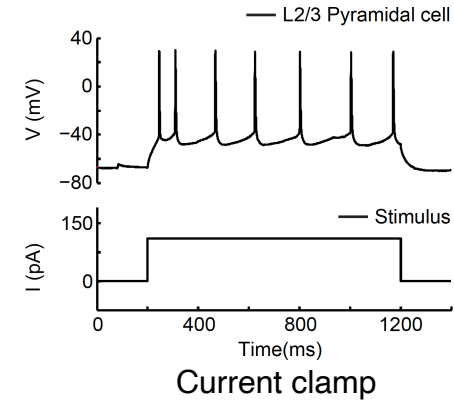
To study ion channels

Patch clamp



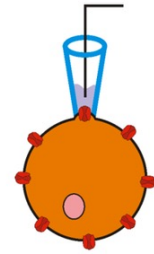
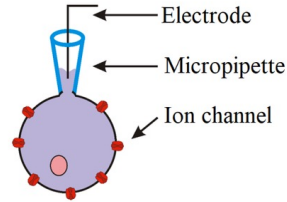
<https://www.youtube.com/watch?v=mVbkSD5FHOw>

Erwin Neher and Bert Sakmann were awarded Nobel Prize in 1991

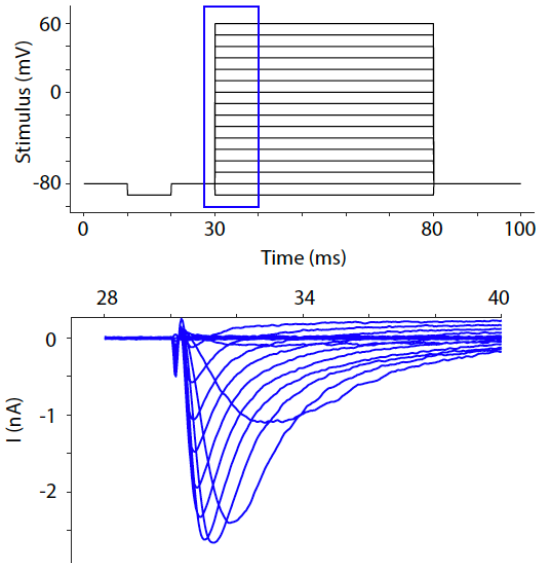


Experiments

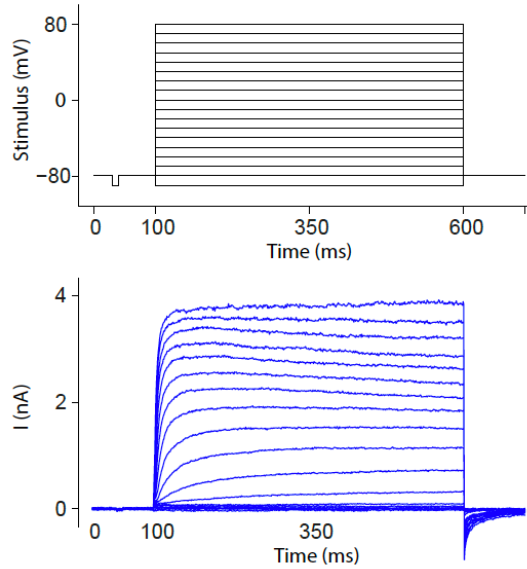
Whole cell Vs Single channel recording



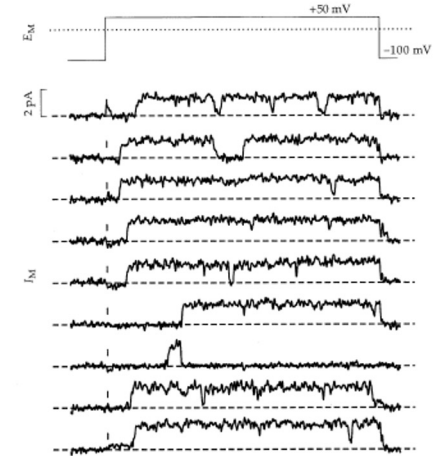
Nav 1.5



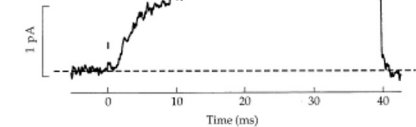
Kv 1.1



(A) UNITARY K^+ CURRENTS

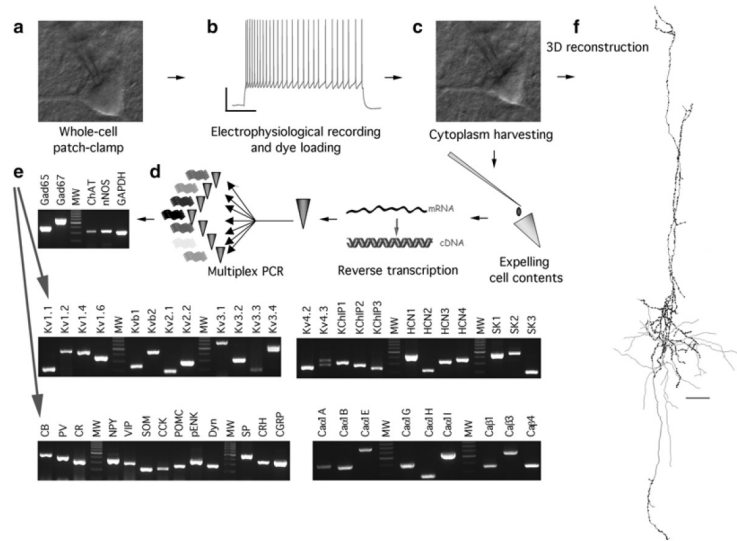


(B) ENSEMBLE AVERAGE



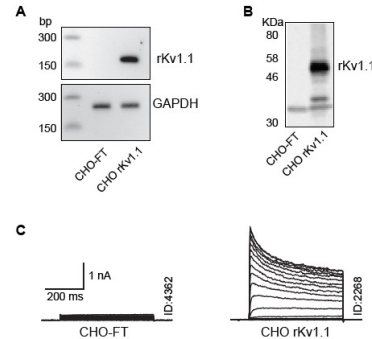
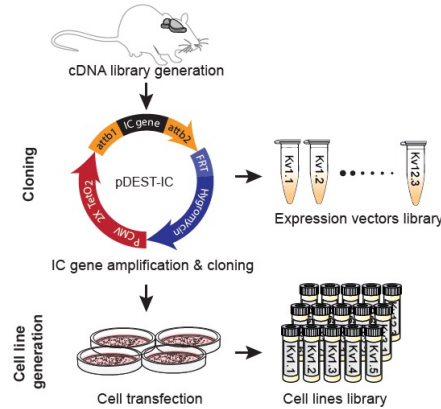
Ion channel experiments

Neurons

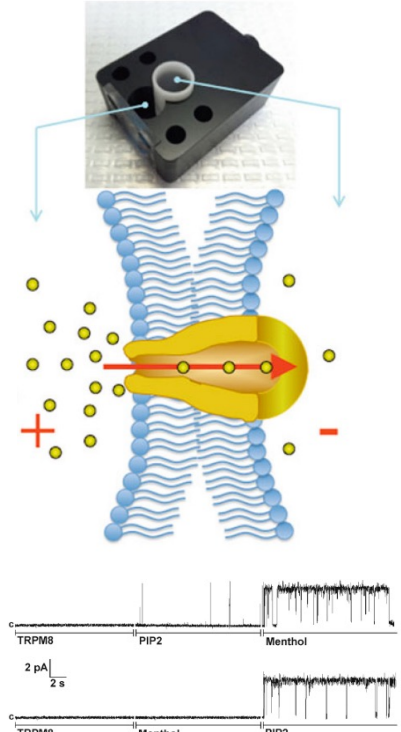


- Toledo-Rodriguez and Markram, Single-Cell RT-PCR, a Technique to Decipher the Electrical, Anatomical, and Genetic Determinants of Neuronal Diversity. *Methods in molecular biology*. 2014;1183:143-158
- Korngreen A, Sakmann B. Voltage-gated K⁺ channels in layer 5 neocortical pyramidal neurones from young rats: subtypes and gradients. *J Physiol*. 2000;525 Pt 3(Pt 3):621–639.

Cell lines



Lipid bilayers



Zakharian E. Recording of ion channel activity in planar lipid bilayer experiments. *Methods Mol Biol*. 2013;998:109–118.

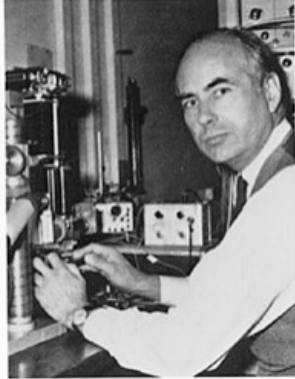
Ranjan R, Logette E, Marani M, et al. A Kinetic Map of the Homomeric Voltage-Gated Potassium Channel (Kv) Family. *Front Cell Neurosci*. 2019;13:358.

Biophysical model of ionic currents



Sir Alan Hodgkin, 1949

The Journal of Physiology, Vol. 263, No. 1 Frontispiece



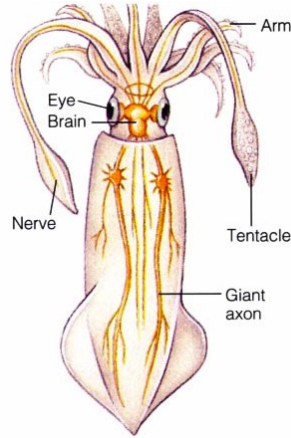
Sir Andrew Huxley, 1974

J. Physiol. (1976), 263, pp. 1–21
With 7 text-figures
Printed in Great Britain

CHANCE AND DESIGN IN ELECTROPHYSIOLOGY:
AN INFORMAL ACCOUNT OF CERTAIN EXPERIMENTS
ON NERVE CARRIED OUT BETWEEN 1934 AND 1952

By A. L. HODGKIN

*From the Physiological Laboratory, University of Cambridge,
Downing Street, Cambridge CB2 3EG*



1

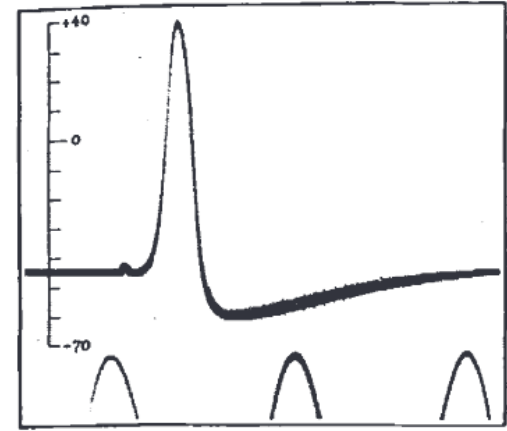


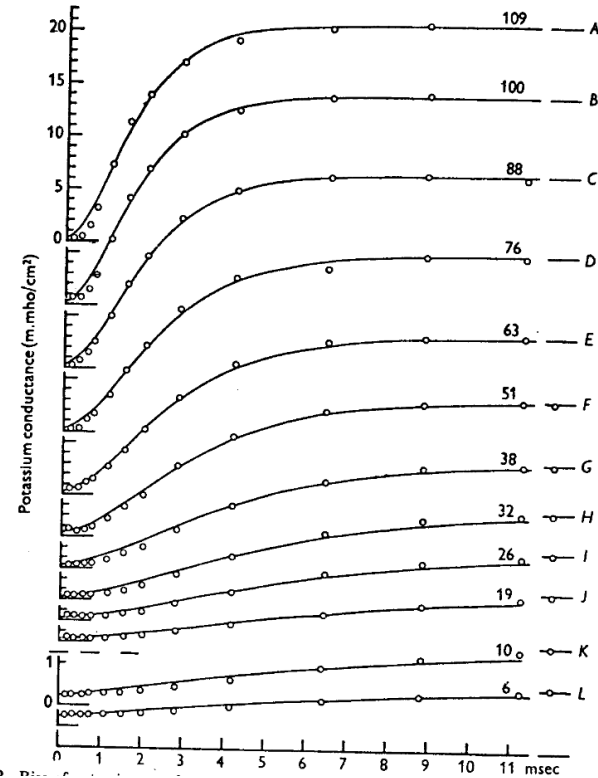
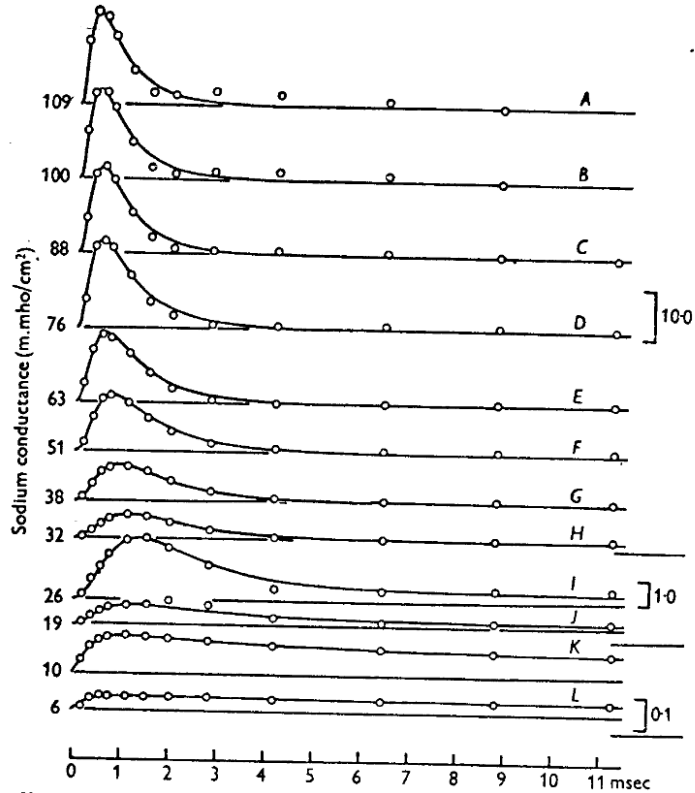
Fig. 2.

ACTION POTENTIAL RECORDED BETWEEN INSIDE AND OUTSIDE OF AXON. TIME MARKER, 500 CYCLES/SEC. THE VERTICAL SCALE INDICATES THE POTENTIAL OF THE INTERNAL ELECTRODE IN MILLIVOLTS, THE SEA WATER OUTSIDE BEING TAKEN AT ZERO POTENTIAL.

HODGKIN, A., HUXLEY, A. Action Potentials Recorded from Inside a Nerve Fibre. *Nature* 144, (1939)

Hodgkin AL & Huxley AF (1952) A Quantitative Description of Membrane Current and its Application to Conduction and Excitation in Nerve. *J Physiol* 117: 500–544.

Biophysical model of ionic currents



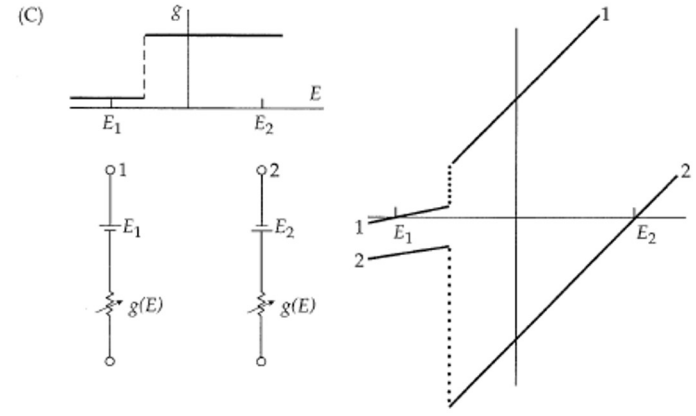
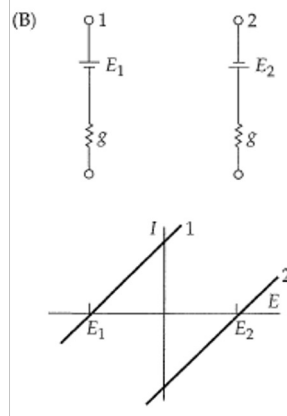
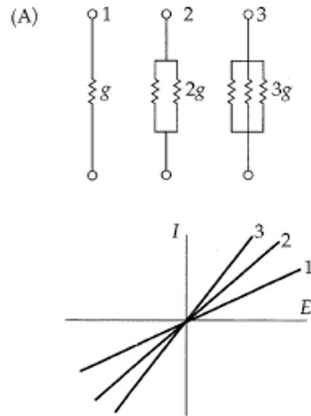
Hodgkin AL & Huxley AF (1952) A Quantitative Description of Membrane Current and its Application to Conduction and Excitation in Nerve. J Physiol 117: 500–544.

Ion channel conductance

Ohm's law

$$E = I * R$$

$$E = I * \frac{1}{g} \quad I = g * E$$



E potential difference (volts, V)

I current (amperes, A)

R resistance (ohms, Ω)

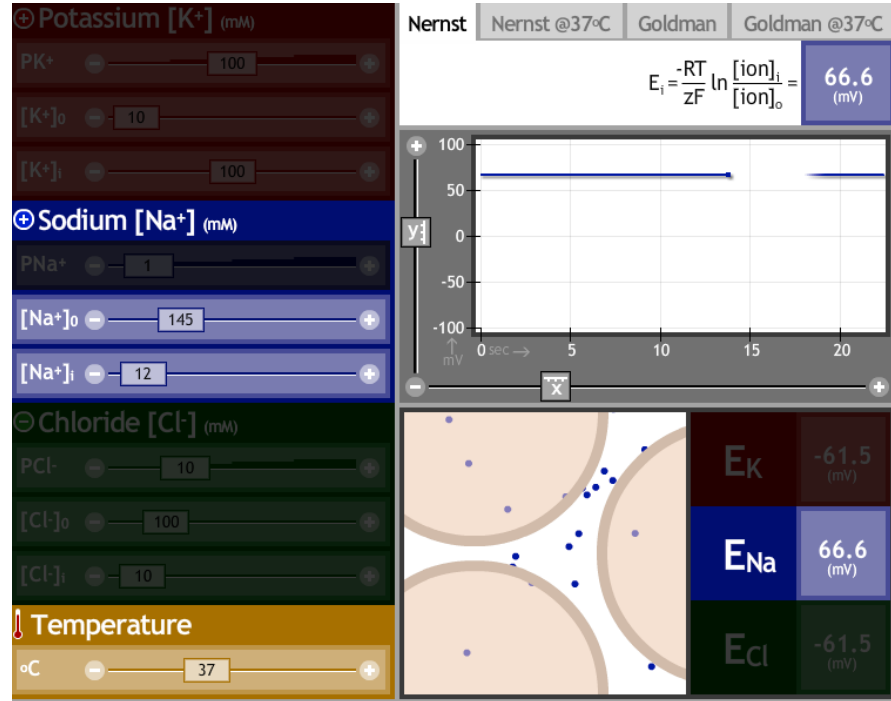
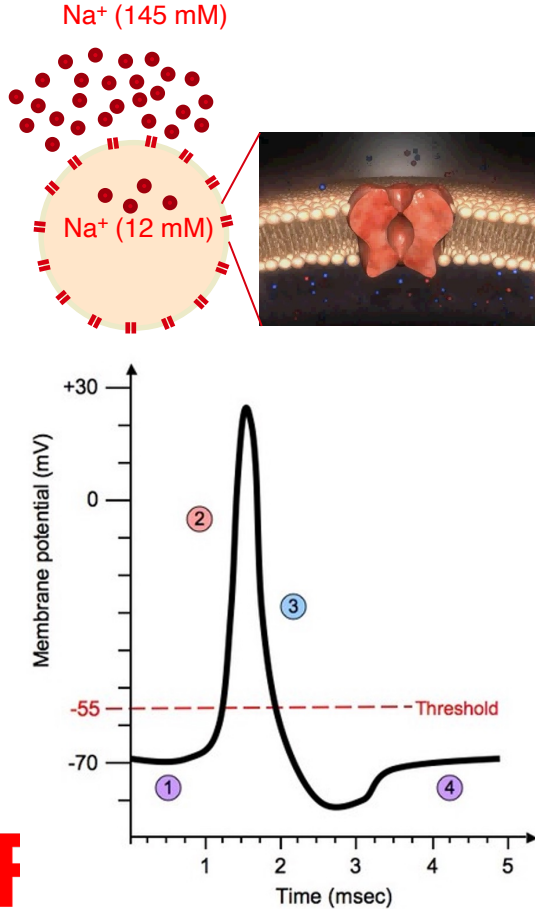
g conductance (siemens, S)

$$I_{Na} = g_{Na}(E) * (E - E_{Na})$$

$$I_k = g_k(E) * (E - E_k)$$

Nernst potential

Nernst equation



<https://www.azps.life/home/2016/4/28/teaching-spotlight-nernstgoldman-simulator>

<https://www.azps.life/s/ngswin.zip>

Standalone app still works on Windows

Nernst potential

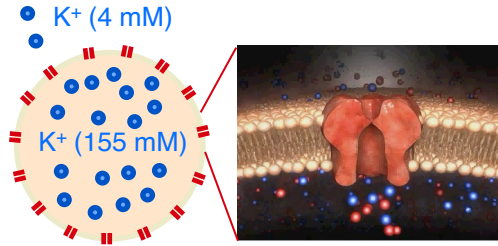


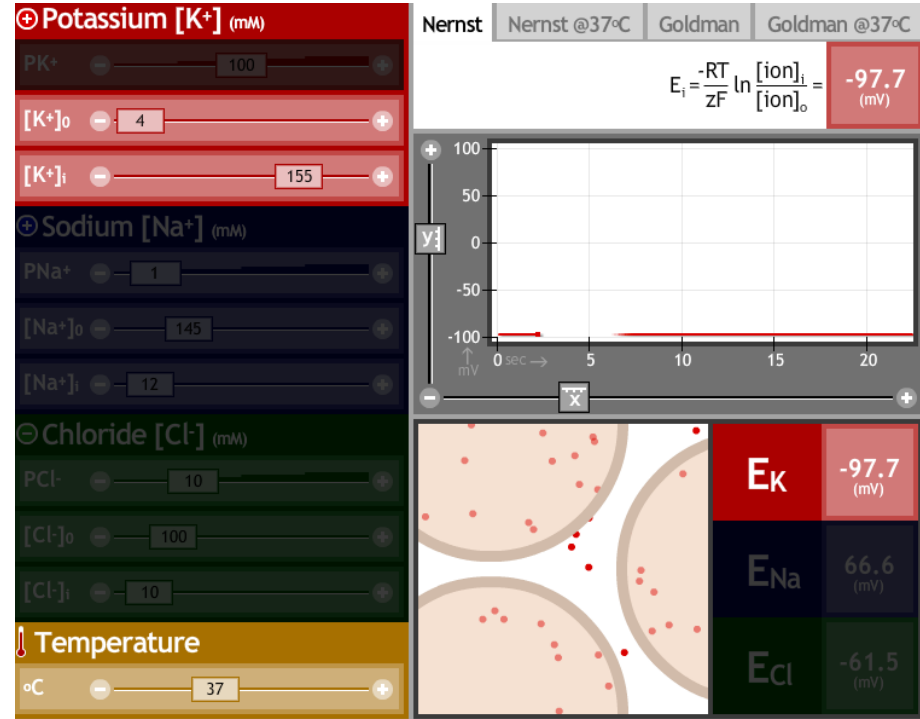
TABLE 1.3 Free Ion Concentrations and Equilibrium Potentials for Mammalian Skeletal Muscle

Ion	Extracellular concentration (mM)	Intracellular concentration (mM)	$\frac{[\text{ion}]_o}{[\text{ion}]_i}$	Equilibrium potential ^a (mV)
Na ⁺	145	12	12	+67
K ⁺	4	155	0.026	-98
Ca ²⁺	1.5	100 nM	15,000	+129
Cl ⁻	123	4.2 ^b	29 ^b	-90 ^b

^aCalculated from Equation 1.11 at 37°C.

^bCalculated assuming a -90-mV resting potential for the muscle membrane and that Cl⁻ ions are at equilibrium at rest.

Nernst equation



<https://www.azps.life/s/ngswin.zip>

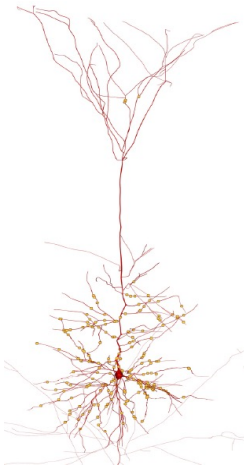
Goldman-Hodgkin-Katz equation

TABLE 1.3 Free Ion Concentrations and Equilibrium Potentials for Mammalian Skeletal Muscle

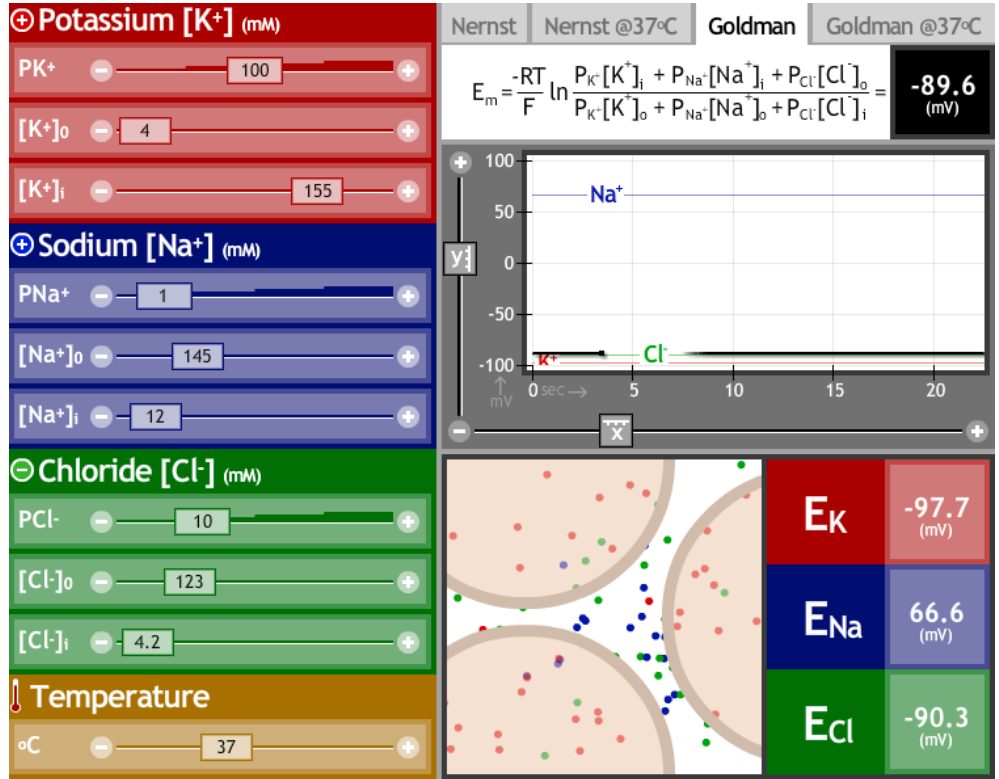
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K ⁺	4	155	0.026	-98
Ca ²⁺	1.5	100 nM	15,000	+129
Cl ⁻	123	4.2 ^b	29 ^b	-90 ^b

^a Calculated from Equation 1.11 at 37°C.

^b Calculated assuming a -90-mV resting potential for the muscle membrane and that Cl⁻ ions are at equilibrium at rest.

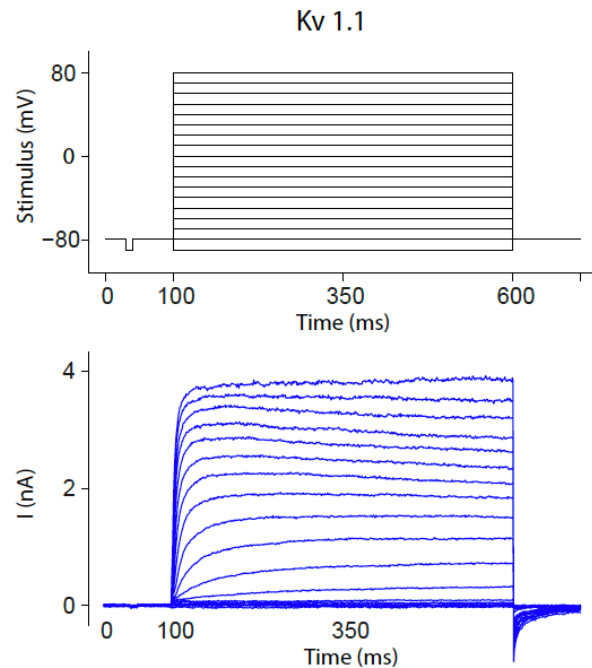
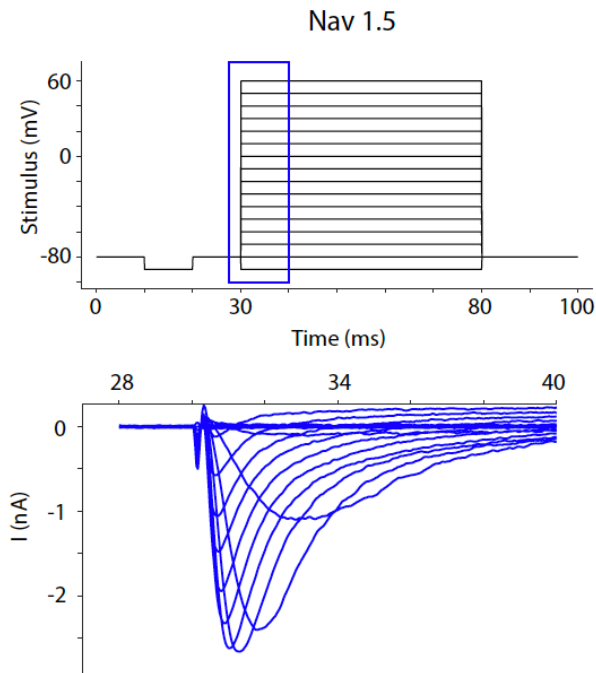
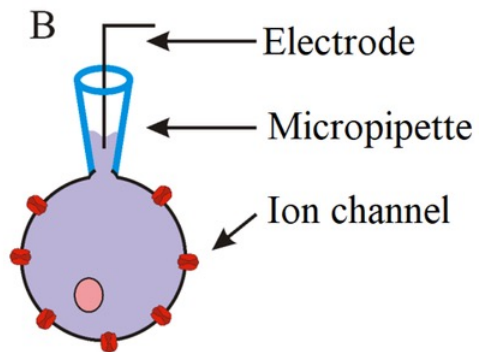


Goldman-Hodgkin-Katz equation

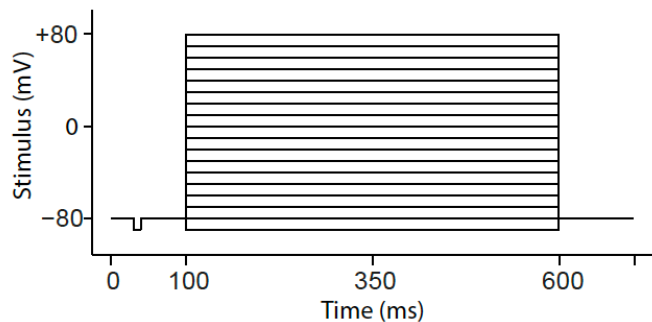
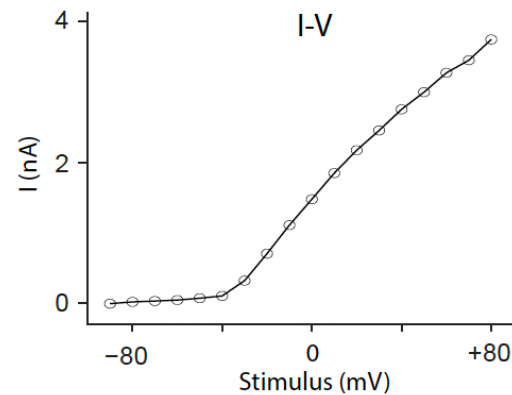
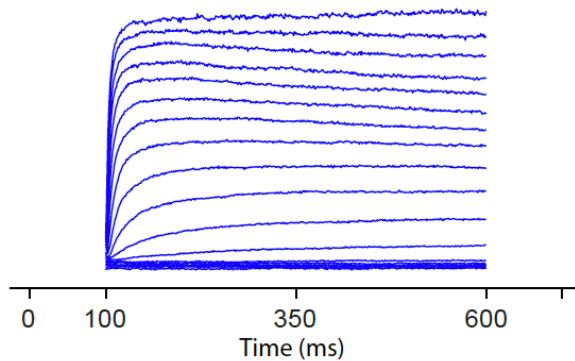
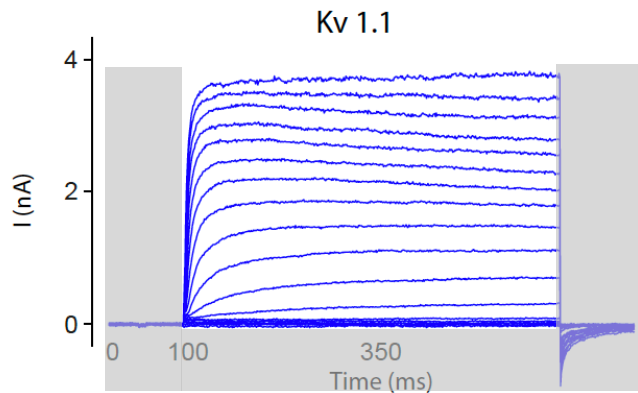


<https://www.azps.life/s/ngswin.zip>

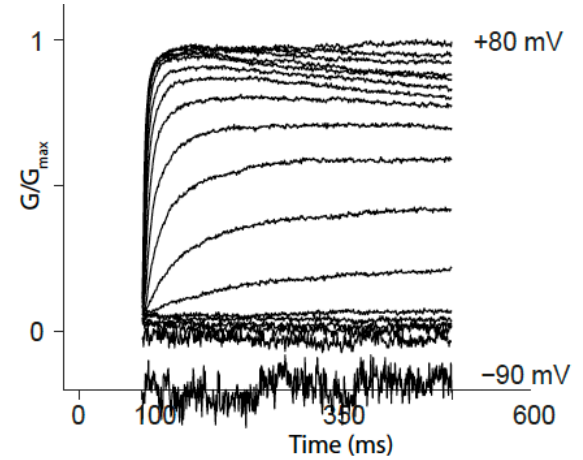
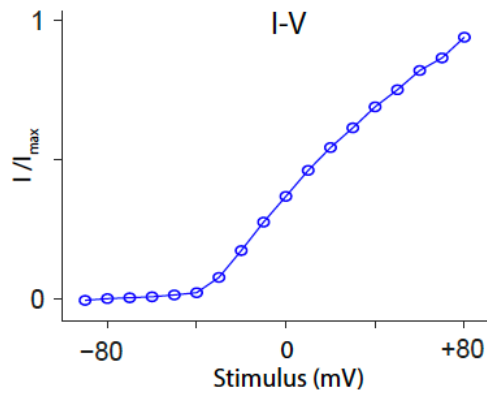
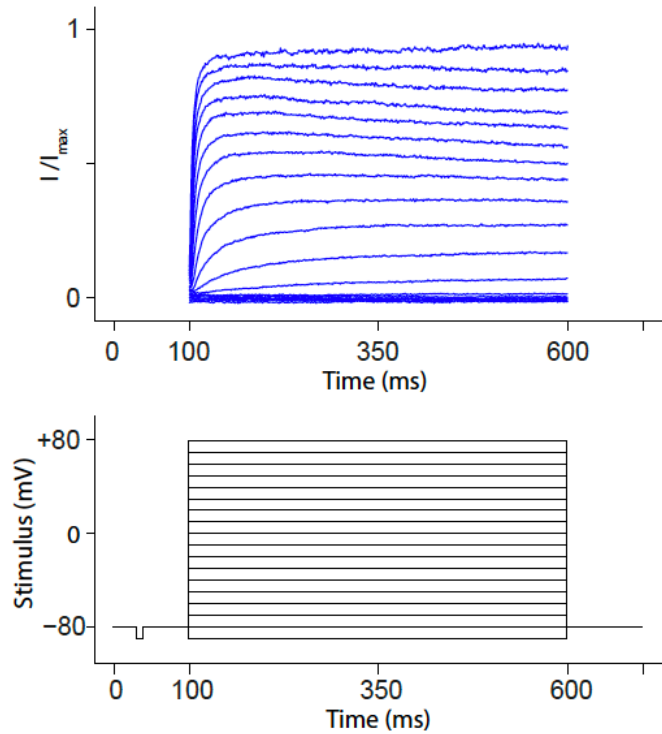
Experiments



Ion channel experiment



Ion channel experiment



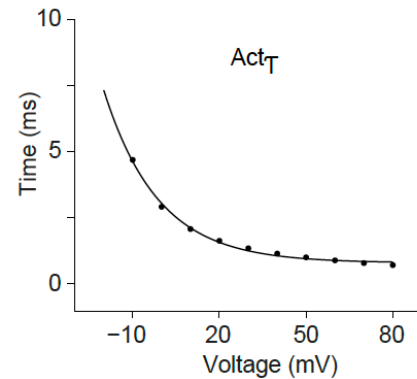
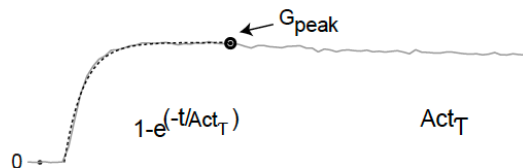
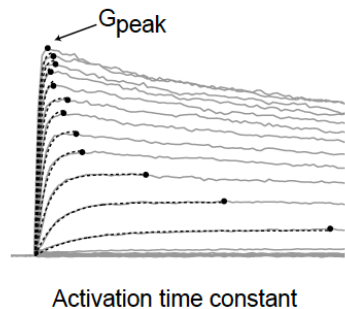
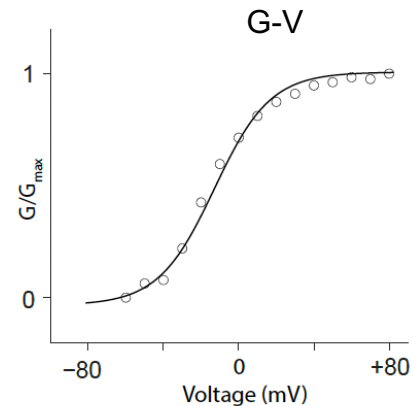
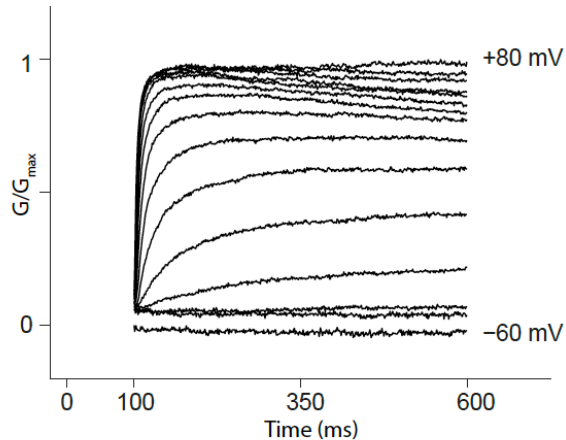
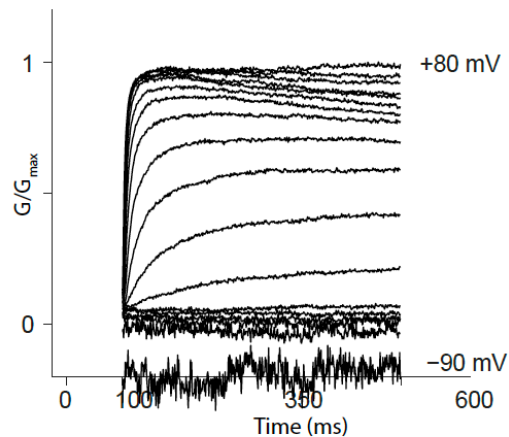
$$I_k = g_k * (V_m - E_k)$$

$$g_k = \frac{I_k}{(V_m - E_k)}$$

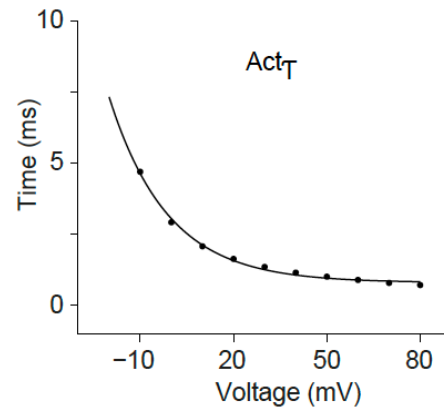
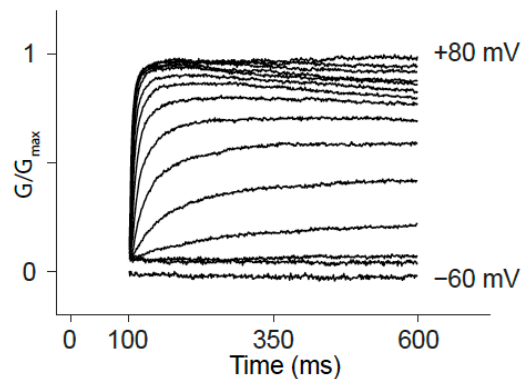
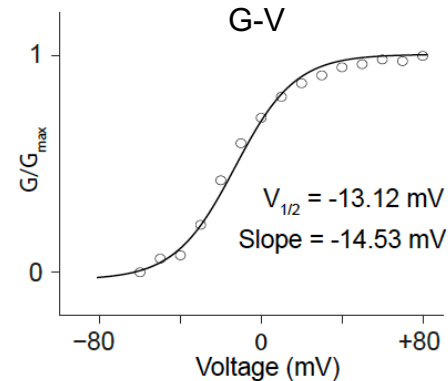
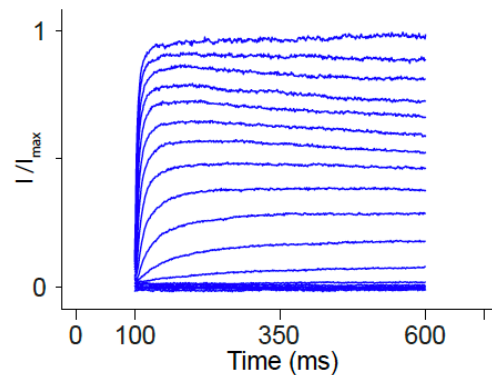
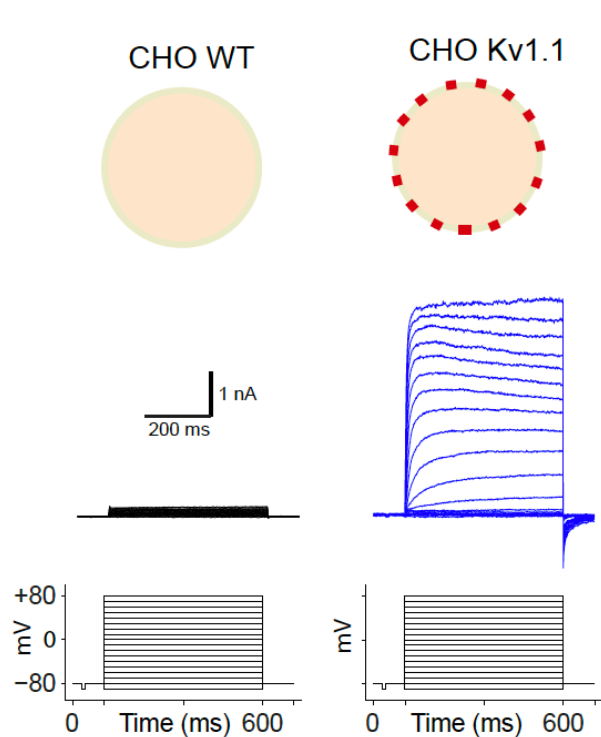
$$G_{k(v=-90)} = \frac{I_{k(v=-90)}}{(-90 - (-98))}$$

$$G_{k(v=+80)} = \frac{I_{k(v=+80)}}{(+80 - (-98))}$$

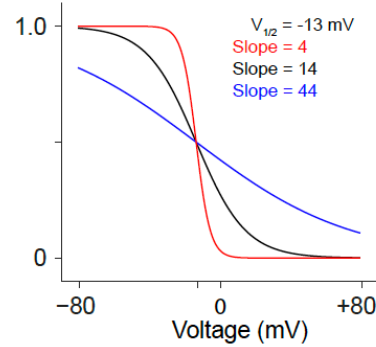
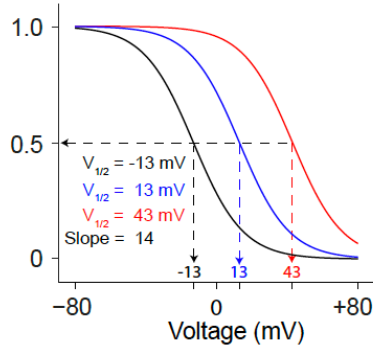
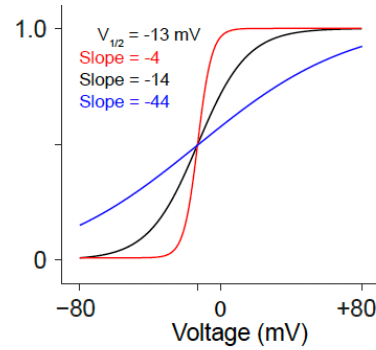
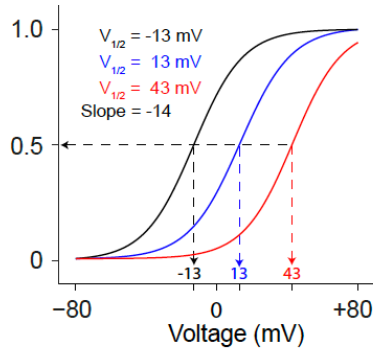
Kinetic characterization



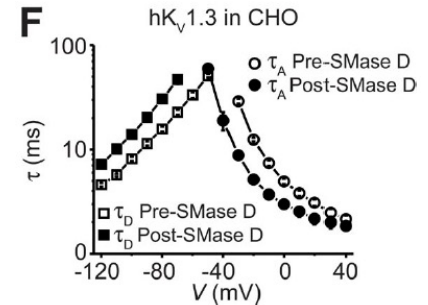
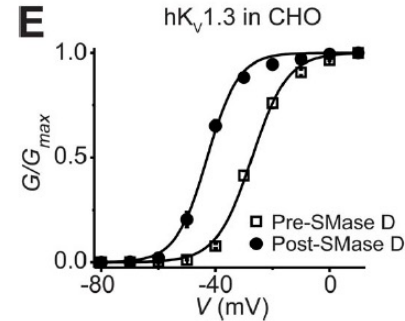
Kinetic characterization



Boltzmann sigmoid function

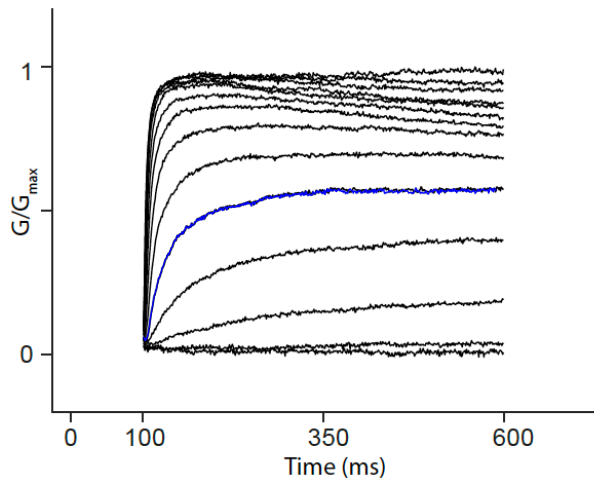


$$G/G_{max}(V) = \frac{1.0}{1.0 + e^{\left(\frac{V-V_{1/2}}{\text{Slope}}\right)}}$$



Combs DJ, Shin HG, Xu Y, Ramu Y, Lu Z. Tuning voltage-gated channel activity and cellular excitability with a sphingomyelinase. *J Gen Physiol.* 2013;142(4):367–380.

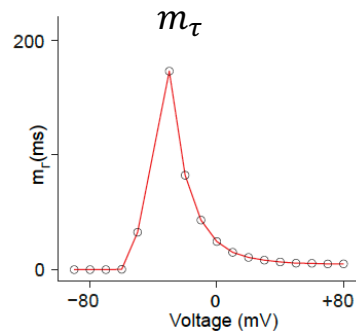
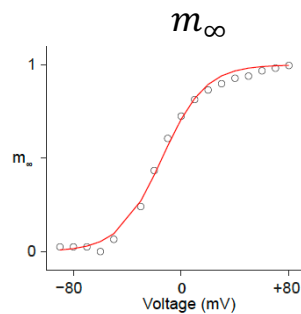
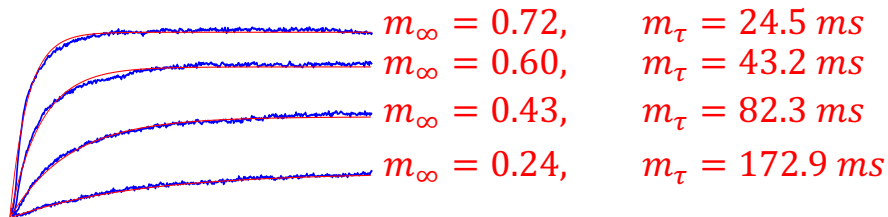
H-H model



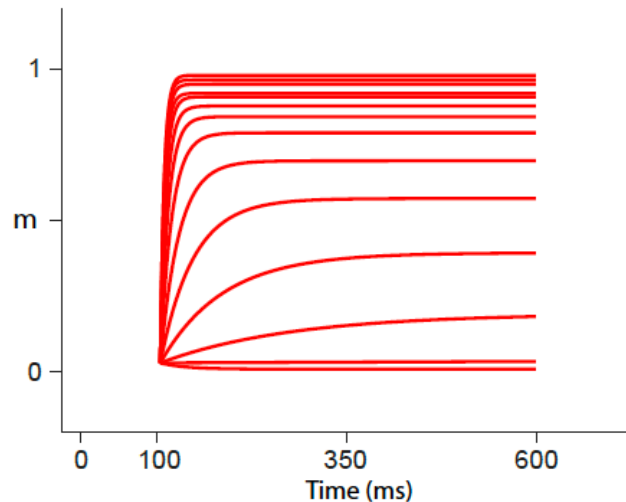
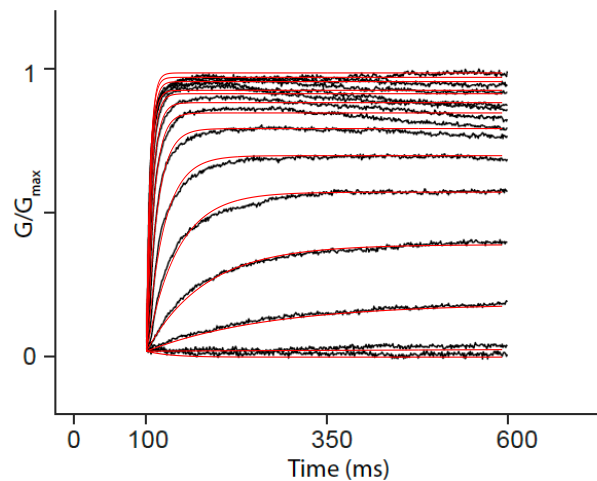
$$m_0 = 0$$

$$\frac{dm}{dt} = \frac{m_{\infty} - m}{m_{\tau}}$$

$$m = m_{\infty} - (m_{\infty} - m_0)e^{-\frac{t}{m_{\tau}}}$$

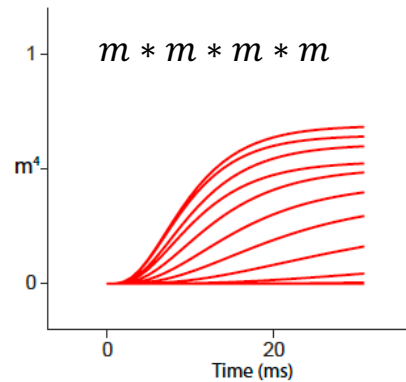
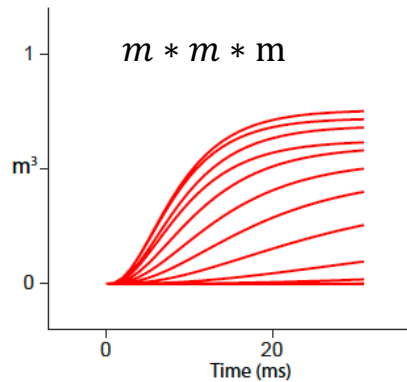
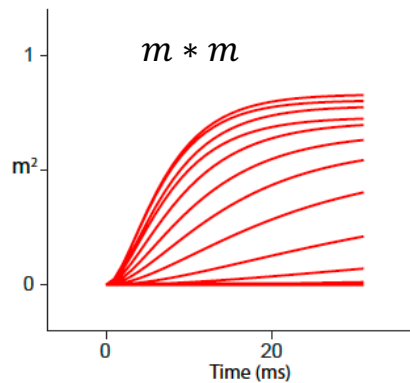
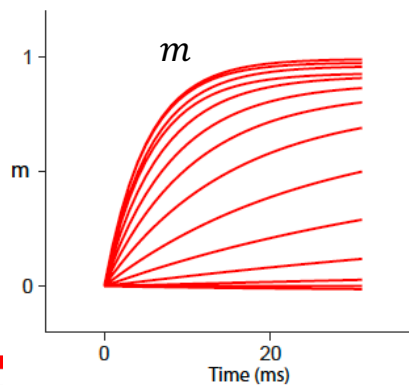
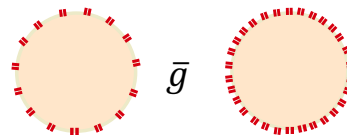


H-H model

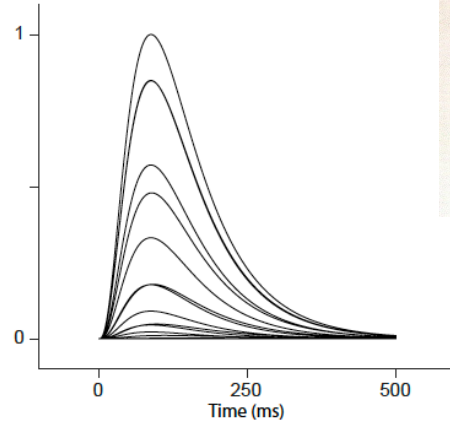
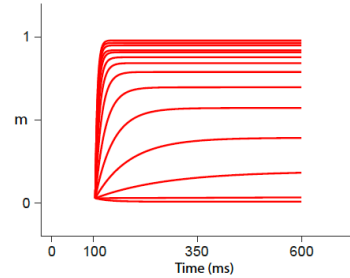
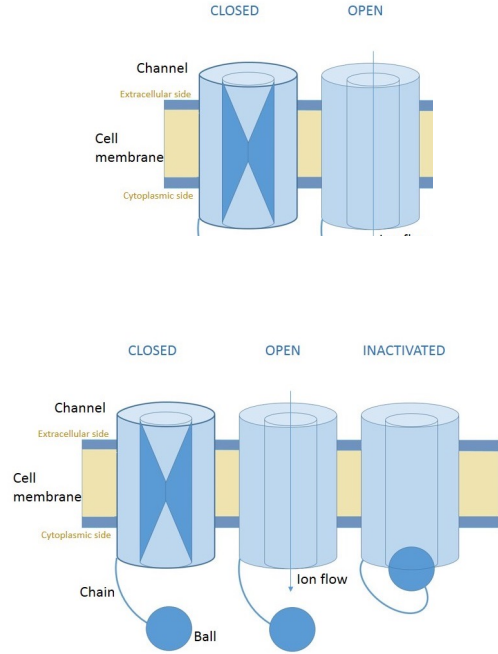


$$\frac{dm}{dt} = \frac{m_{\infty} - m}{m_{\tau}}$$

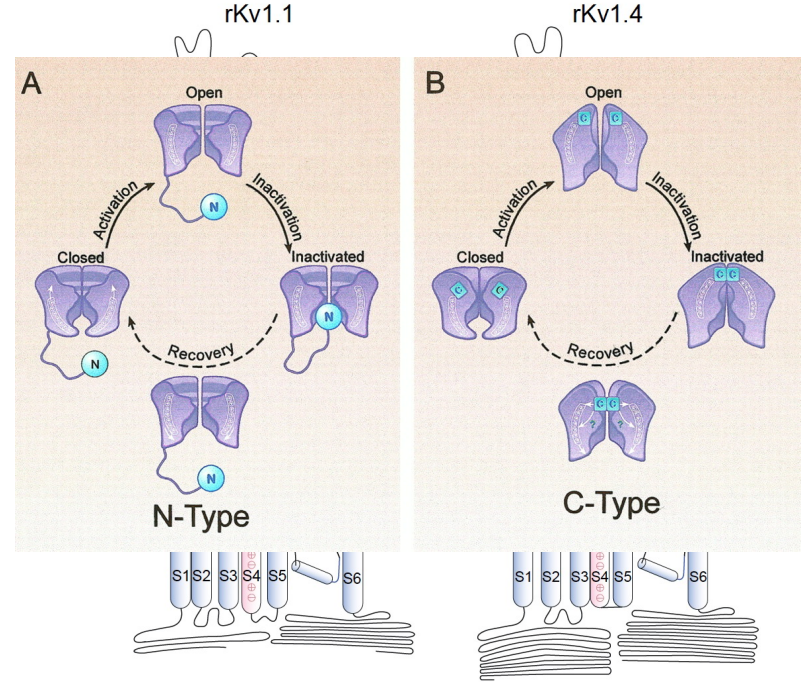
$$g_k = \bar{g} * m$$



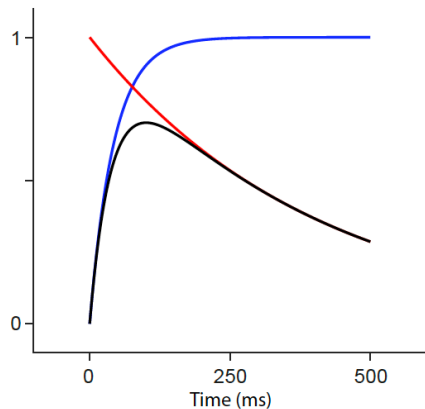
Ion channel inactivation



https://en.wikipedia.org/wiki/Ball_and_chain_inactivation



Ion channel model with inactivation gate



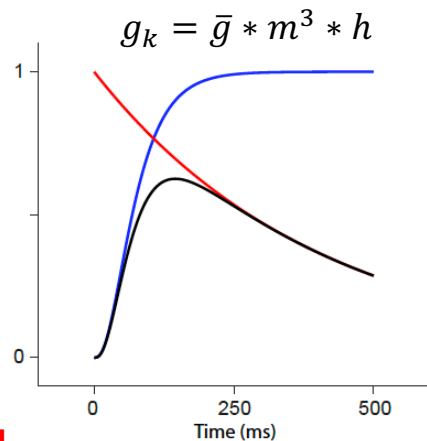
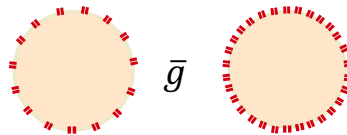
$$\frac{dm}{dt} = \frac{m_{\infty} - m}{m_{\tau}}$$

$$\frac{dh}{dt} = \frac{h_{\infty} - h}{h_{\tau}}$$

$$g_k = \bar{g} * m * h$$

$$m_0 = 0, m_{\infty} = 1.0, m_{\tau} = 43.2 \text{ ms}$$

$$h_0 = 1, h_{\infty} = 0, h_{\tau} = 400 \text{ ms}$$



$$g_k = \bar{g} * m^3 * h$$

$$m_0 = 0 \quad h_0 = 1$$

$$m_{\infty} = 1.0$$

$$m_{\tau} = 43.2 \text{ ms}$$

$$h_{\infty} = 0$$

$$h_{\tau} = 400 \text{ ms}$$

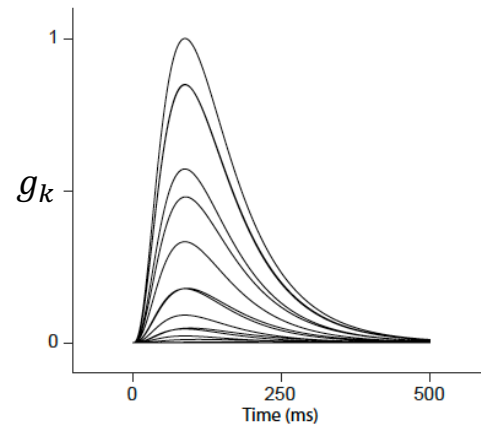
$$m_0 = 0 \quad h_0 = 1$$

$$m_{\infty} = f1(v)$$

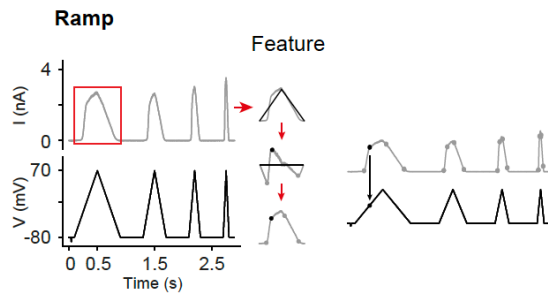
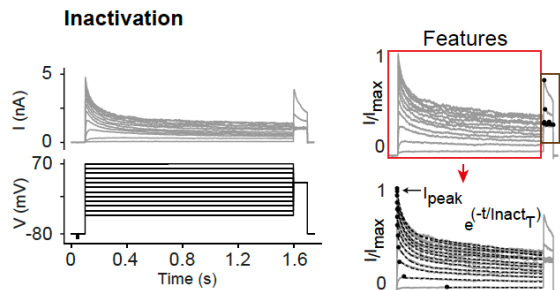
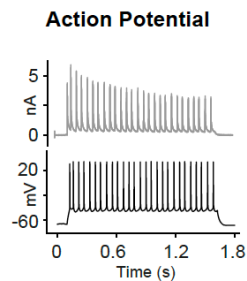
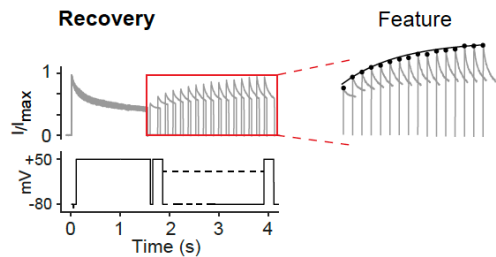
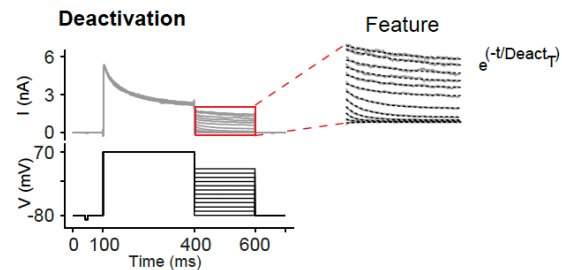
$$m_{\tau} = f2(v)$$

$$h_{\infty} = f3(v)$$

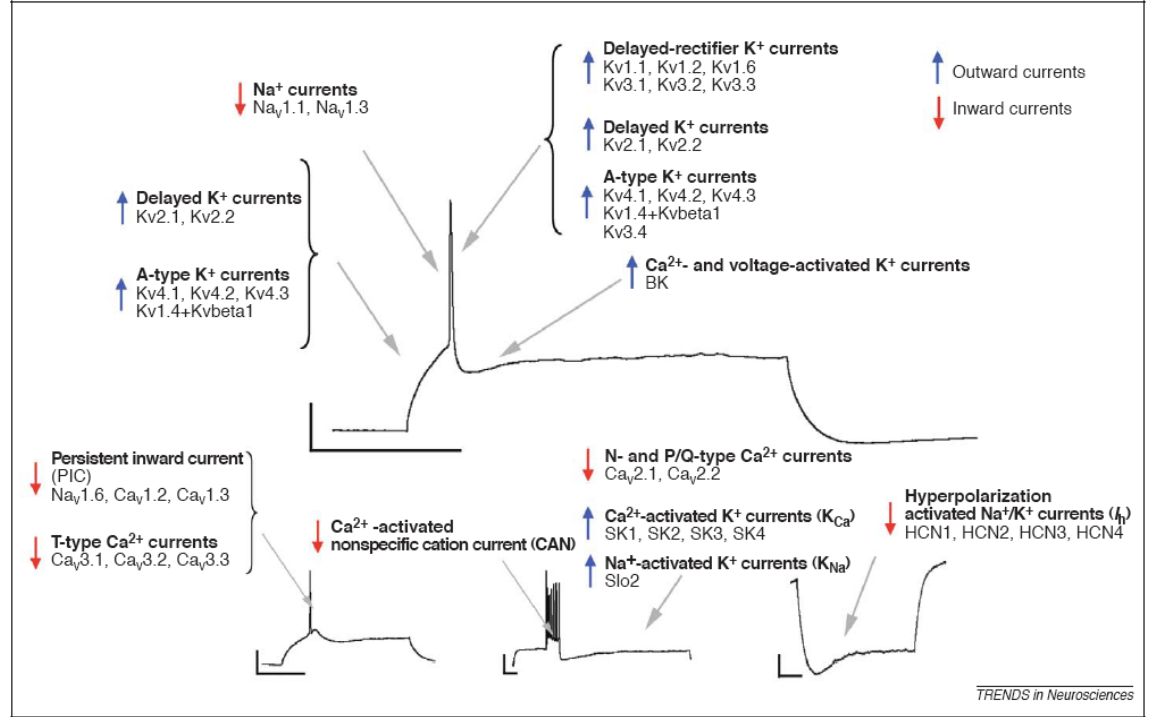
$$h_{\tau} = f4(v)$$



Detailed kinetic characterization



Ion channels in Neurons



Toledo-Rodriguez, M. Cellular signalling properties in microcircuits (2005) Trends in Neurosciences

Passive cell model

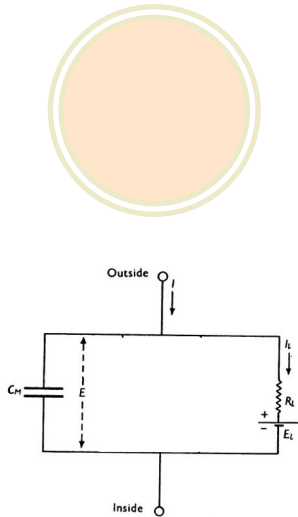


Fig. 1. Electrical circuit representing membrane.

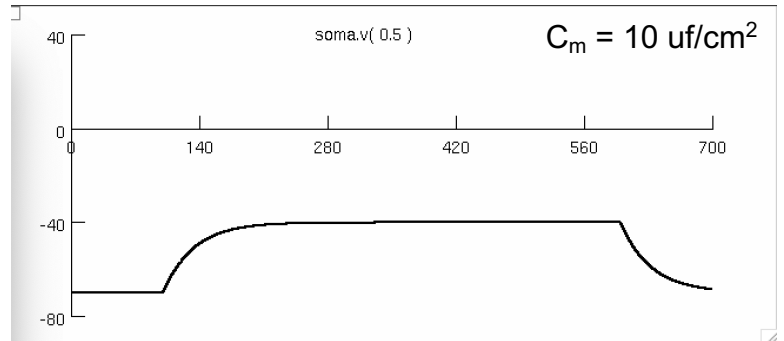
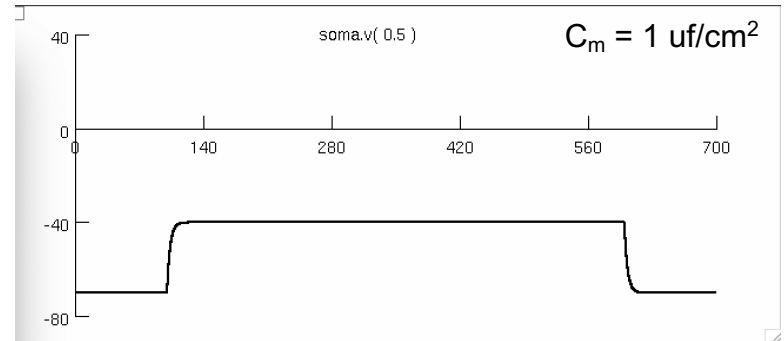
```
{load_file("nrngui.hoc")}
/*****
This function is used for voltage plot
Required Inputs : 1. what to plot like soma.v(0.5)
                  2. Color (0..9)
                  3. Brush (1..4)
*****/
obfunc plotVoltage(){ localobj grph
    grph = new Graph(0)
    grph.addexpr("", $s1, $2, $3)
    graphList[0].append(grph)
    grph.view(0, -80, tstop, 120, 300, 75, 800, 325)
    grph.label(0.4, 0.9, $s1)
    grph.label(0.9, 0.55, "Time(ms)")
    grph.label(0.1, 0.9, "V(mV)")
    return grph
}

create soma
access soma
L=18.8
nseg=1
diam=18.8
Ra = 123.0
cm = 1.0
v_init = -70
insert pas
g_pas=0.003
e_pas=-70

objectvar stim
stim = new IClamp(0.5)
stim.del = 100
stim.dur = 500
stim.amp = 0.1
tstop = 700

plotVoltage("soma.v( 0.5 )", 1, 2)
init()
run()
```

Passive cell



Active cell model with H-H channels

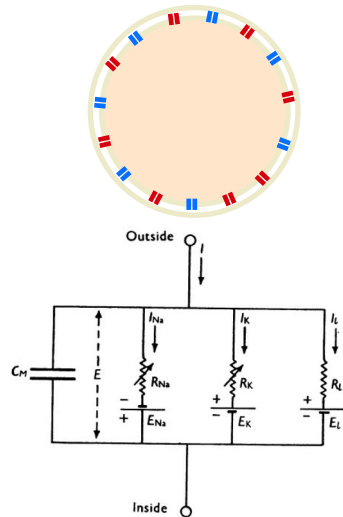
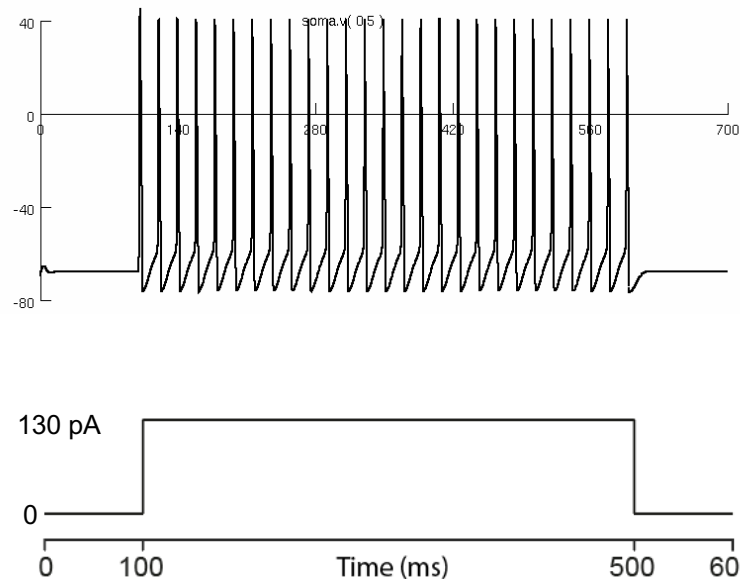


Fig. 1. Electrical circuit representing membrane.

Hodgkin AL & Huxley AF (1952)
A Quantitative Description of
Membrane Current and its
Application to Conduction and
Excitation in Nerve. J Physiol
117: 500–544.

```
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    grph = new Graph(0)  
    grph.addexpr("","$s1,$2,$3)  
    graphList[0].append(grph)  
    grph.view(0, -80, tstop, 120,300, 75, 800, 325)  
    grph.label(0.4,0.9,$s1)  
    grph.label(0.9,0.55,"Time(ms)")  
    grph.label(0.1,0.9,"V(mV)")  
    return grph  
}  
  
create soma  
access soma  
L=18.8  
diam=18.8  
Ra = 123.0  
v_init = -70  
insert pas  
g_pas=.0003 |  
e_pas=-70  
  
insert hh  
gnabar_hh = 0.4  
gkbar_hh = 0.1  
  
objectvar stim  
stim = new IClamp(0.5)  
stim.del = 100  
stim.dur = 500  
stim.amp = 0.127  
tstop = 700  
  
plotVoltage("soma.v( 0.5 )",1, 2)  
init()  
run()
```

Passive cell + H-H channels



Active cell model with H-H channels (Mod files)

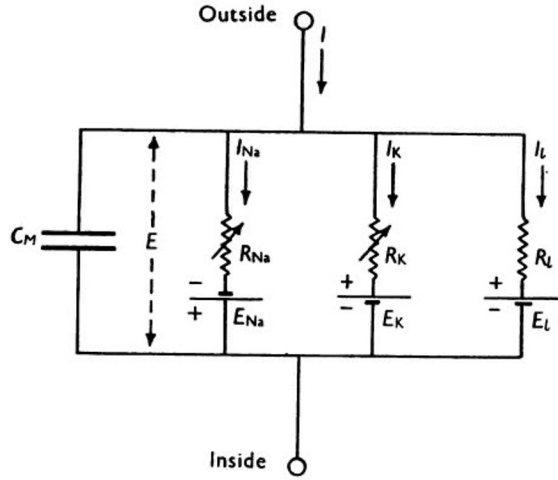
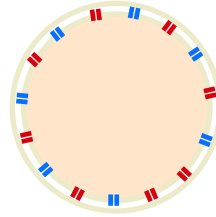
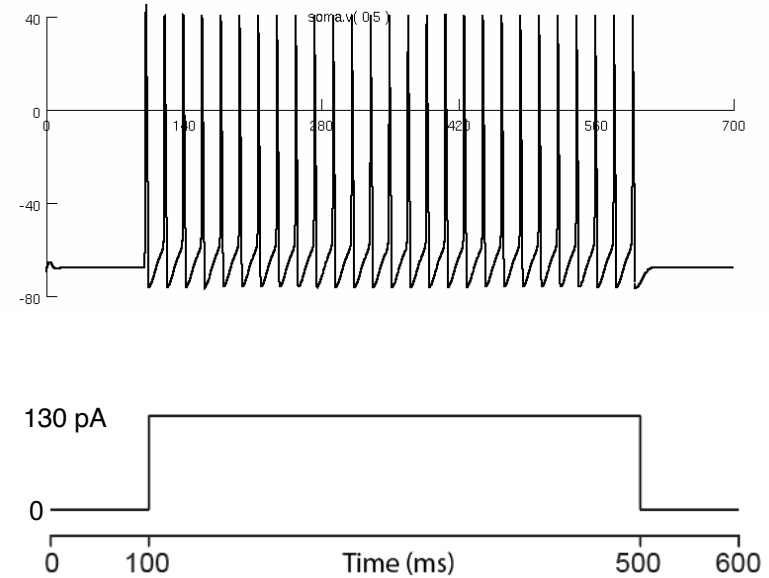


Fig. 1. Electrical circuit representing membrane.

Hodgkin AL & Huxley AF (1952) A Quantitative Description of Membrane Current and its Application to Conduction and Excitation in Nerve. J Physiol 117: 500–544.



Passive cell + H-H Mod files



Lecture Overview

K Channel

```
STATE {
    m
}

BREAKPOINT {
    SOLVE states METHOD cnexp
    gKv3 = gKv3bar*m
    ik = gKv3*(v-ek)
}

DERIVATIVE states {
    rates()
    m' = (mInf-m)/mTau
}

INITIAL{
    rates()
    m = mInf
}

PROCEDURE rates(){
    UNITSOFF
        mInf = 1/(1+exp(((v -(18.700))/(-9.700))))
        mTau = 20.000/(1+exp(((v -(-46.560))/(-44.140))))
    UNITSON
}
```

Na Channel

```
STATE {
    m
    h
}

BREAKPOINT {
    SOLVE states METHOD cnexp
    gNa_S = gNa_Sbar*m*m*h
    ina = gNa_S*(v-ena)
}

DERIVATIVE states {
    rates()
    m' = (mInf-m)/mTau
    h' = (hInf-h)/hTau
}

INITIAL{
    rates()
    m = mInf
    h = hInf
}

PROCEDURE rates(){
    UNITSOFF
        if(v == -25.0){
            v = v + 0.000001
        }
        mAlpha = (0.182 * ((v-10) - -35))/(1-(exp(-(v-10) - -35)/9)))
        if(v == -25.0){
            v = v + 0.000001
        }
        mBeta = (0.124 * ((v-10) - -35))/(1-(exp(-(v-10) - -35)/9)))
        mInf = mAlpha/(mAlpha + mBeta)
        mTau = 1/(mAlpha + mBeta)
        hInf = 1.0/(1+exp((v - -65-10)/6.2))
        if(v == -40.0){
            v = v + 0.000001
        }
        hTau = 1/((0.024 * ((v-10) - -50))/(1-(exp(-(v-10) - -50)/5))) + (0.0091 * ((v-10) - -75.000123))/(1-(exp(-(v-10) - -75.000123)/5)))
    UNITSON
}
```

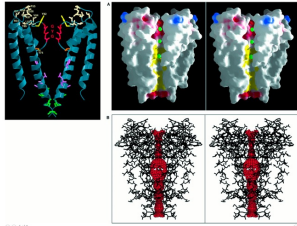
Summary

- Patch clamp experiment
- Voltage/Current clamp
- Whole cell, Single channel recordings
- Ion channel experiment in Neuron/Cell line
- Hodgkin-Huxley modelling
- Neuron simulation (Single cell)
- Neuron simulation with H-H channels
- Neuron simulation with mod files

Lecture Overview

- Scope
- Approaches
- **Applications**

Key areas of ion channel research



Doyle DA, Morais Cabral J, Pfuetzner RA, Kuo A, Gulbis JM, Cohen SL, Chait BT, MacKinnon R. The structure of the potassium channel: molecular basis of K^+ conduction and selectivity. *Science*. 1998;280(5360):69–77

Neuron 50, 89–100, April 6, 2006 ©2006 Elsevier Inc. DOI 10.1016/j.neuron.2006.03.010

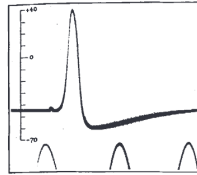
The Kv4.2 Potassium Channel Subunit Is Required for Pain Plasticity

Up-regulation of the Kv3.4 potassium channel subunit in early stages of Alzheimer's disease

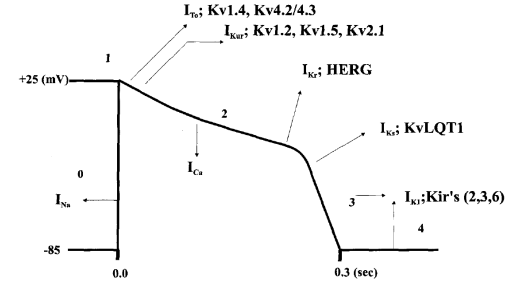
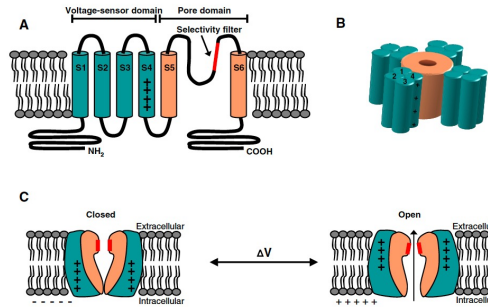
Ester Angulo,* Véronique Noé,† Vicent Casadó,* Josefa Mallol,* Teresa Gomez-Isla,‡ Carmen Lluís,* Isidre Ferrer,§¹ Carlos J. Ciudad†¹ and Rafael Franco*¹

Voltage-gated K^+ channels in layer 5 neocortical pyramidal neurones from young rats: subtypes and gradients

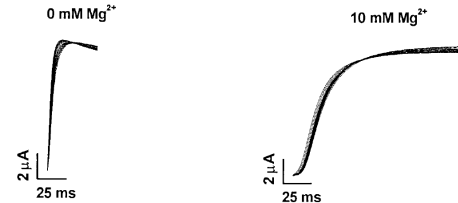
Alon Kornegreen and Bert Sakmann



HODGKIN AL, HUXLEY AF. A quantitative description of membrane current and its application to conduction and excitation in nerve. *J Physiol*. 1952;117(4):500–544. doi:10.1113/jphysiol.1952.sp004764

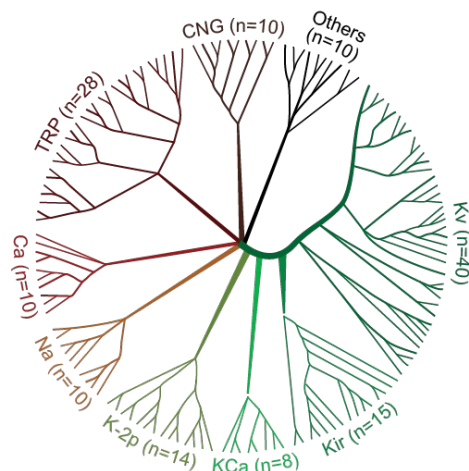


Brown, A. M. "Cardiac Potassium Channels in Health and Disease." *Trends in Cardiovascular Medicine* 7, no. 4 (May 1997): 118–24.



Silverman WR, Tang CY, Mock AF, Huh KB, Papazian DM. Mg^{2+} modulates voltage-dependent activation in ether-à-go-go potassium channels by binding between transmembrane segments S2 and S3. *J Gen Physiol*. 2000;116(5):663–678.

Channelopathies



CNS diseases	Potassium	Sodium	Calcium	Chloride
Epileptic syndromes	KCNA1 KCNA2 KCNQ2/3 KCNA1 KCNT1 KCND2 KCNH5 KCNJ10 KCNJ11	SCN1A SCN1B SCN2A SCN3A SCN8A	CACNA1H	CLCN2 GLIALCAM
Ataxia syndromes	KCNA1 KCNK3 KCND3		CACNA1A	
Familial Hemiplegic Migraine		SCN1A	CACNA1A	

PNS diseases	Sodium	Potassium	Calcium
Pain syndromes and neuropathies	SCN9A SCN10A SCN11A	KCNQ2	TRPA1

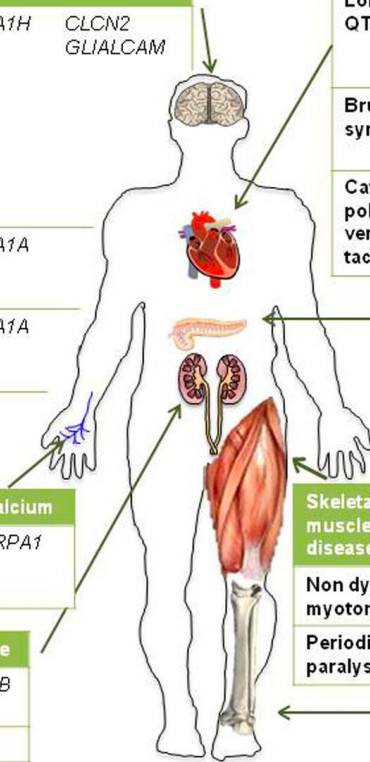
Kidney diseases	Potassium	Chloride
Bartter's syndrome	ROMK1	CLCNKB BSDN
Dent disease		CLCN5
EAST/SESAME syndrome	KCNJ11	

Heart diseases	Potassium	Sodium	Calcium
Long QT and Short QT syndromes	KCNQ1 KCNH2 KCNE1 KCNJ2	SCN5A	CACNA1C
Brugada syndromes	KCNE3 HCN4	SCN5A SCN1B SCN3B	CACNA1C
Catecholaminergic polymorphic ventricular tachycardia			RYR2

Pancreas diseases	Potassium
Familial Congenital hyperinsulinism and neonatal diabetes mellitus	KCNJ11 ABCC8

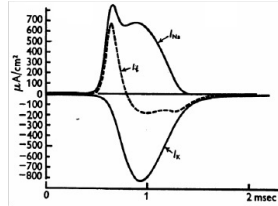
Skeletal muscle diseases	Potassium	Sodium	Calcium	Chloride
Non dystrophic myotonias		SCN4A		CLCN1
Periodic paralysis	KCNJ2 KCNJ18	SCN4A	CACNA1S	

Bone diseases	Chloride
Osteopetrosis	CLCN7 OSTM1

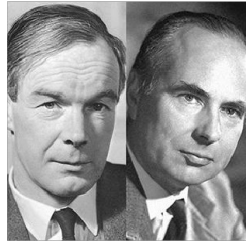


Neuron modeling timeline

Single compartment model

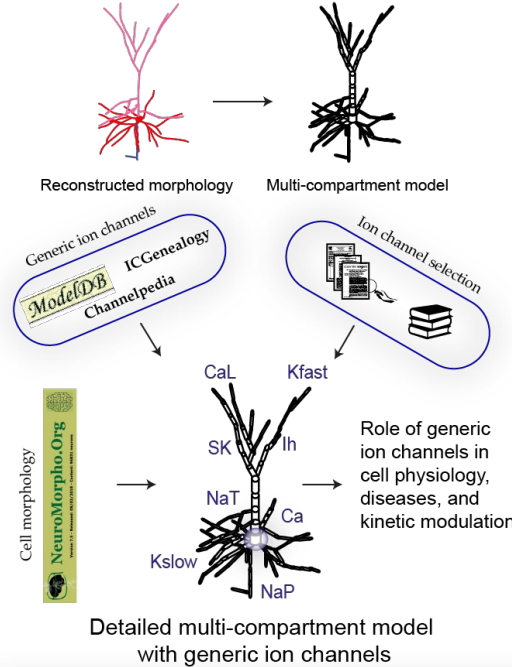


First mathematical model of action potential initiation with Na^+ and K^+ conductances



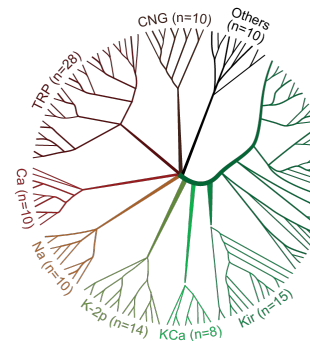
Hodgkin & Huxley 1952

Past



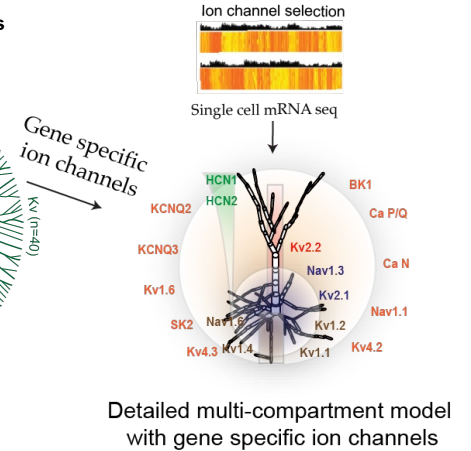
Present

Voltage-gated ion channels



Ion channel database

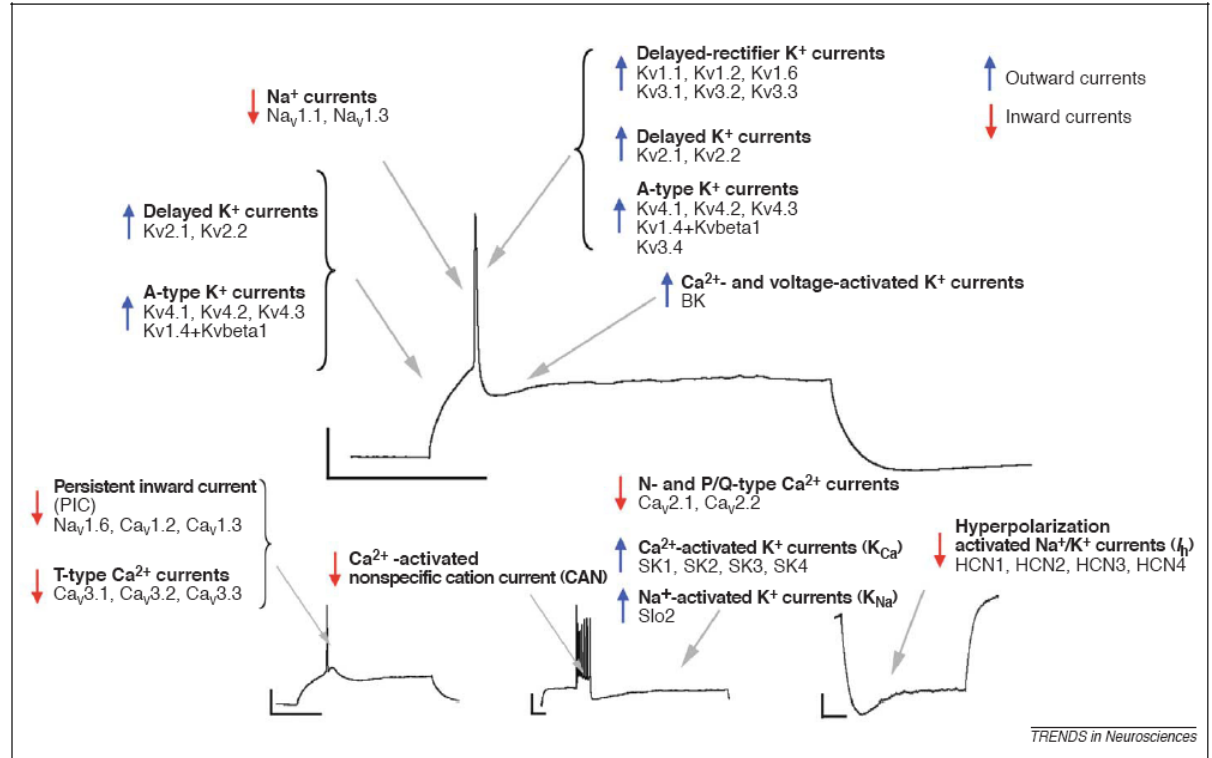
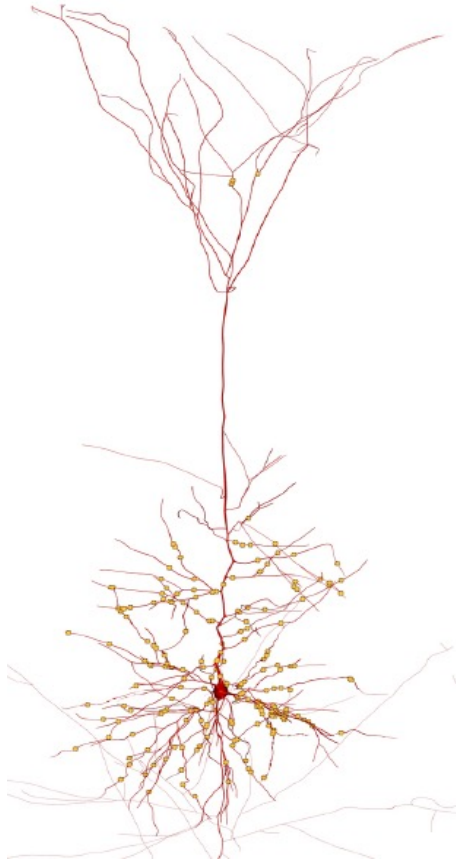
Role of **gene specific** ion channels in cell physiology, disease simulation, neuro modulation and in-silico drug screening



Future

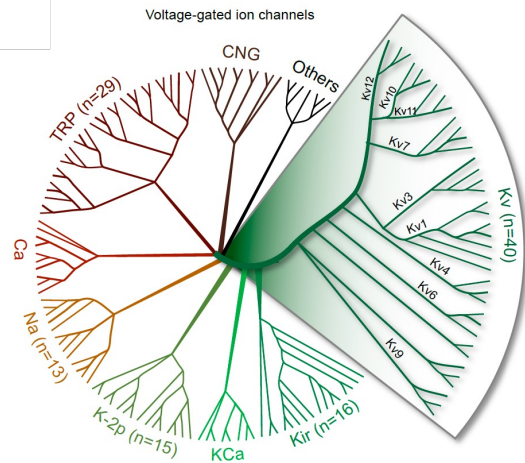
Image credits : www.nobelprize.org, The journal of physiology, ModelDB, NeuroMorpho.Org

Ion channels in Neuron



Toledo-Rodriguez, M. Cellular signalling properties in microcircuits (2005) Trends in Neurosciences

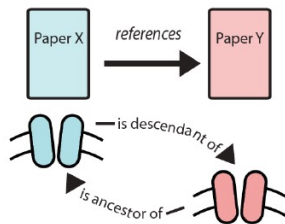
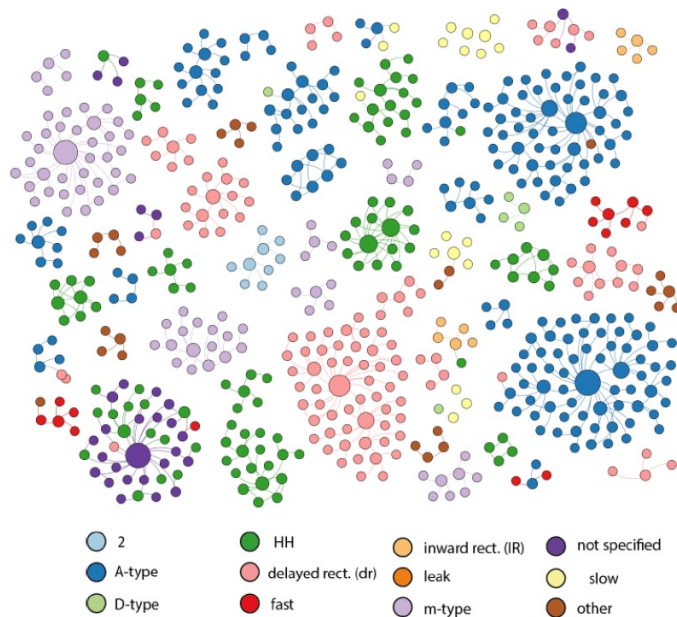
Literature overview



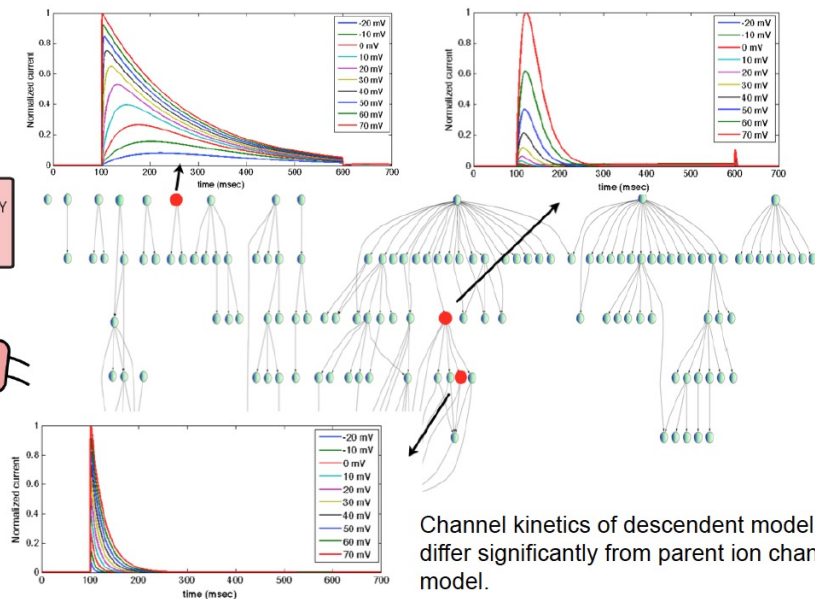
	Common knowledge	Physiological Temperature		Common knowledge	Physiological Temperature
Kv1.1 Publications n = 967	Biochem Biophys Res Commun, 1995 [PMID: 759905] 16°C, 26°C Rat Kv1.1, HEK J Membr Biol, 2003 [PMID: 1272673] RT(22 - 29°C) Rat Kv1.1, CHO Biochem J, 2013 [PMID: 2372533] RT Rat Kv1.1, HEK	No Data	Kv3.2 n = 85	J Biol Chem, 1998 [PMID: 950008] +30 mV RT(21-22 °C) Rat Kv3.2, Oocytes J Neurophysiol, 1999 [PMID: 1050708] +40 mV (21 - 25°C) Rat Kv3.2, CHO J Biol Chem, 2004 [PMID: 1557258] +40 mV RT(°C) Rat Kv3.2, CHO	No Data
Kv1.2 n = 878	Brain Res, 2007 [PMID: 173384] +50 mV RT(22 - 29°C) Rat Kv1.2, CHO Eur J Pharmacol, 2011 [PMID: 2155973] +40 mV RT(°C) Human Kv1.2, Oocytes J Gen Physiol, 2012 [PMID: 2207099] +70 mV RT(°C) Kv1.2, Oocytes	J Physiol, 1994 [PMID: 173226] 23°C 32°C Human Kv1.2, Oocytes	Kv3.3 n = 118	Ann NY Acad Sci, 1999 [PMID: 1045433] +40 mV (°C) Kv3.3, HEK 293 J Biol Chem, 2008 [PMID: 18535959] +70 mV °C Mouse Kv3.3, CHO Biophys J, 2011 [PMID: 2253433] +60 mV (°C) Rat Kv3.3, CHO	No Data
Kv1.3 n = 1037	AJP Cell Physiol, 2000 [PMID: 10759567] +80 mV RT(22 - 27°C) Mouse Kv1.3, Oocytes Br J Pharmacol, 2002 [PMID: 1261534] +70 mV RT(°C) Human Kv1.3, MEL cell line J Immunol, 2007 [PMID: 1730535] +70 mV (°C) Kv1.3, T cell	Eur Biophys J, 1997 [PMID: 945036] +40 mV 30.7 °C 9.9 - 30.7°C Drosophila Shaker B, Oocytes	Kv3.4 n = 150	Proc Biol Sci, 1992 [PMID: 1219595] +40 mV RT(20-22°C) Kv3.4, Oocytes FEBS Lett, 1996 [PMID: 895959] +60 mV RT(25-26°C) Rat Kv3.4, MEL cells Eur J Neurosci, 1997 [PMID: 935959] 0 mV RT(22 ± 1 °C) Rat Kv3.4, Oocytes	No Data
Kv1.4 n = 577	J Neurosci, 1997 [PMID: 910384] +80 mV (°C) Rat Kv1.4, HEK 293 Biochemistry, 1999 [PMID: 10528180] +50 mV RT(22 - 24°C) Rat Kv1.4, Oocytes J Gen Physiol, 1999 [PMID: 10528180] +50 mV RT(22 ± 1°C) Human Kv1.4, Oocytes	No Data	Kv4.1 n = 72	J Gen Physiol, 1999 [PMID: 10528180] +50 mV (22 ± 1°C) Mouse Kv4.1, Oocytes Folia Lett, 2001 [PMID: 11528180] +40 mV (20 ± 2°C) Kv4.1, Oocytes J Physiol, 2002 [PMID: 121528180] +50 mV RT(22 ± 1°C) Mouse Kv4.1, Oocytes	No Data
Kv1.5 n = 963	J Biol Chem, 1998 [PMID: 950008] +70 mV RT(°C) Rat Kv1.5, Oocytes AJP Cell Physiol, 2001 [PMID: 11559567] +80 mV RT(°C) Rat Kv1.5, Oocytes BB Res Commun, 2007 [PMID: 1735034] +120 mV (21-22°C) Rat Kv1.5, COS-7	Curr Opin Pharmacol, 2014 [PMID: 2462225] 37°C Human Kv1.5, L8 cells PLoS One, 2014 [PMID: 2462225] 28°C Human Kv1.5, CHO Biophys J, 1998 [PMID: 950008] +70 mV RT(°C) Human Kv1.5, CHO	Kv4.2 n = 651	Am J Physiol, 1997 [PMID: 9252225] +50 mV RT(20 ± 2°C) Rat Kv4.2, Oocytes Biophys J, 2004 [PMID: 1555433] +75 mV RT(22 - 23°C) Kv4.2, Oocytes PLoS One, 2014 [PMID: 2462225] +10 mV RT(22 ± 2°C) Mouse Kv4.2, HEK 293	No Data
Kv1.6 n = 161	Toxicon, 2004 [PMID: 1522225] +40 mV (°C) Rat Kv1.6, Oocytes Eur Biophys J, 1994 [PMID: 1735032] +20 mV (20 - 27°C) Rat Kv1.6, Oocytes Nature, 1998 [PMID: 1557258] +40 mV (°C) Rat Kv1.6, CHO	Biochem Biophys Res Commun, 2003 [PMID: 1272533] +50 mV 35°C Human Kv1.6, COS-7	Kv4.3 n = 618	J Neurophysiol, 1996 [PMID: 8752225] +50 mV RT(20 - 23°C) Rat Kv4.3, Oocytes J Physiol, 2002 [PMID: 121528180] +50 mV (23 ± 1°C) Rat Kv4.3, Oocytes Br J Pharmacol, 2011 [PMID: 2155973] +60 mV RT(22 - 24°C) Rat Kv4.3, CHO	Elife, 2014 [PMID: 2500000] Kv4.3 23-39°C Mouse Kv4.3, HEK
			Kv5.1 n = 25	No Data	No Data

Ion channel models in literature

~ 900 Kv ion channel models in ModelDB



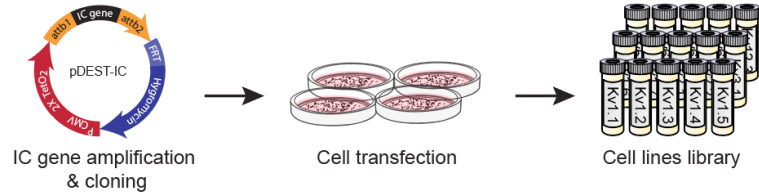
Models (A-type potassium current)



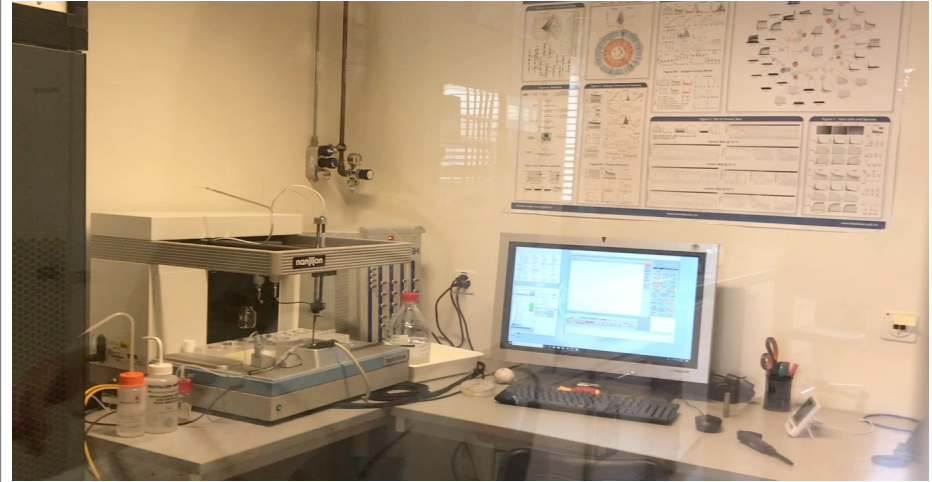
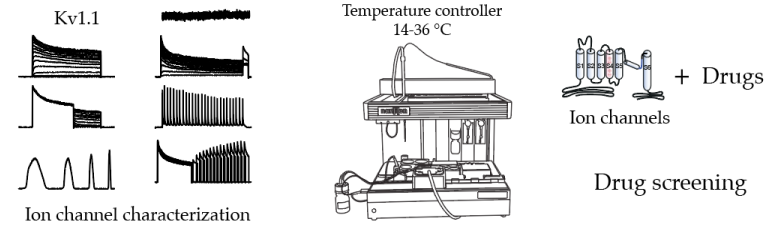
Podlaski, W.F., Seeholzer, A., Groschner, L.N., Miesenböck, G., Ranjan, R., and Vogels, T.P. (2017). Mapping the function of neuronal ion channels in model and experiment. *ELife* 6.

Automated ion channel characterization

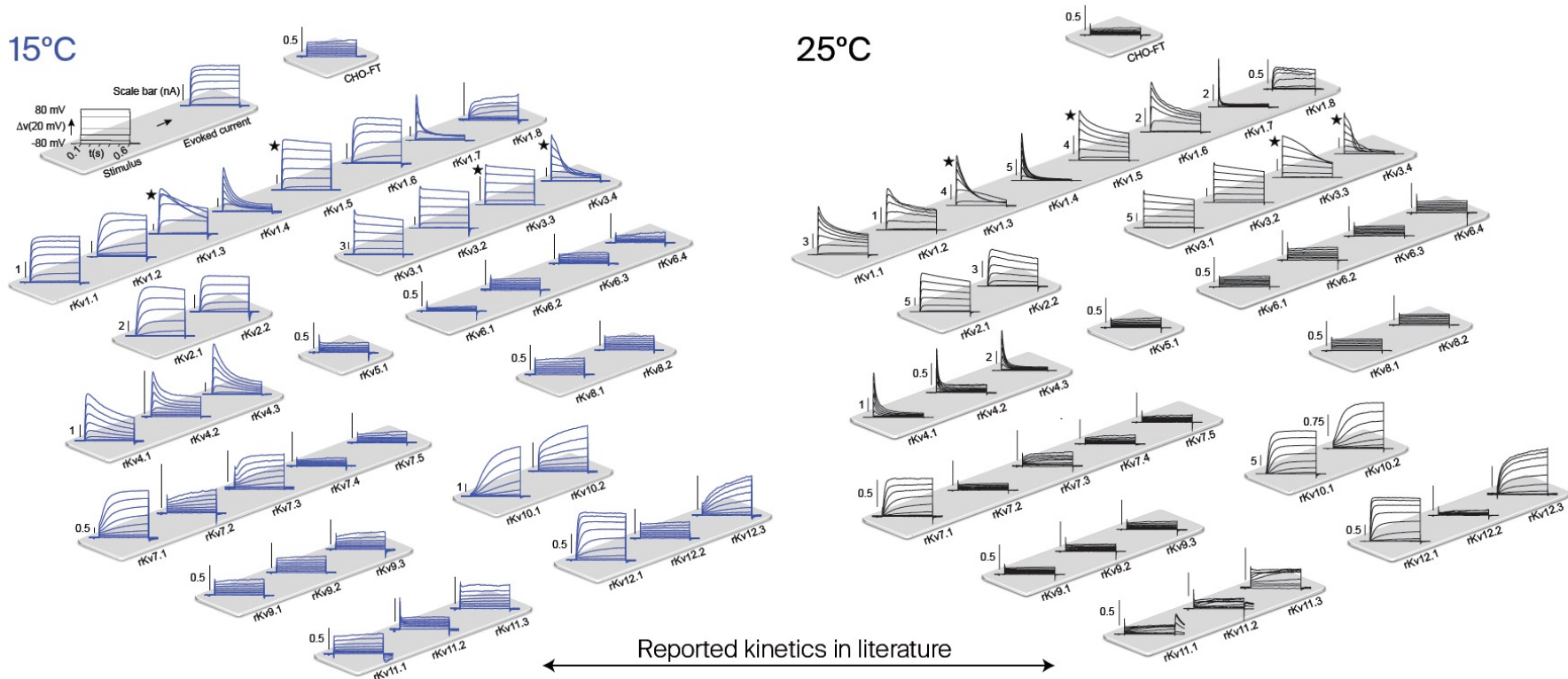
Cell culture platform & cell line generation



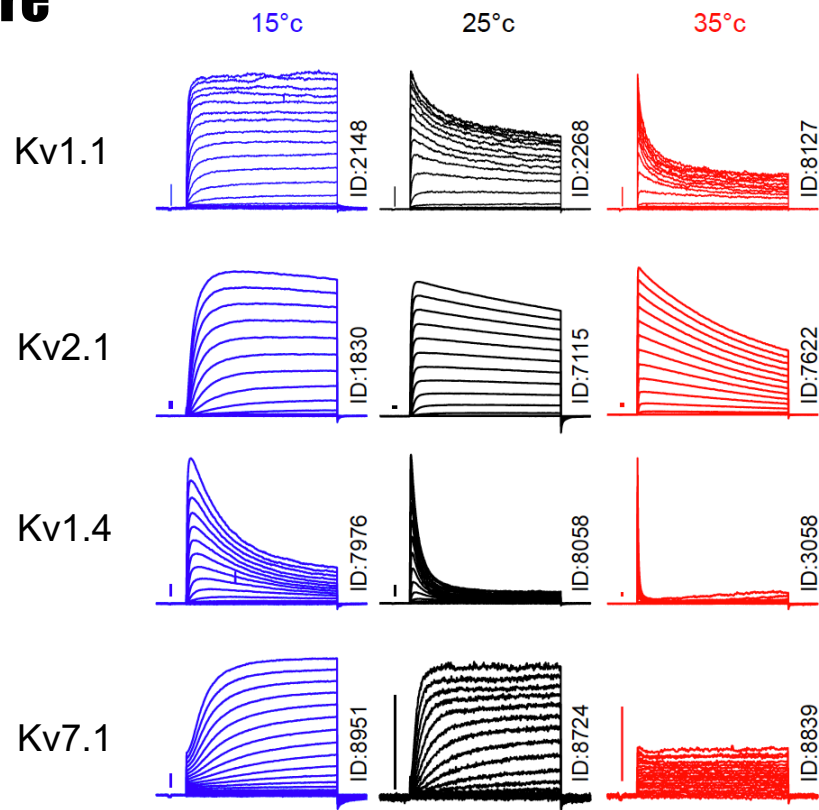
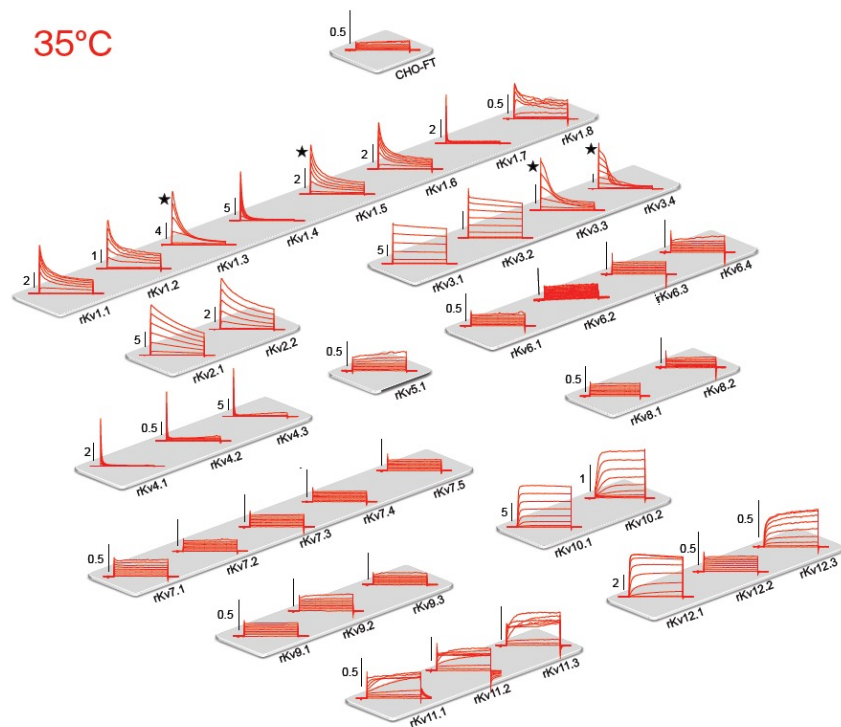
Automated patchclamp



Kinetics comparison



Kinetics near physiological temperature



New findings

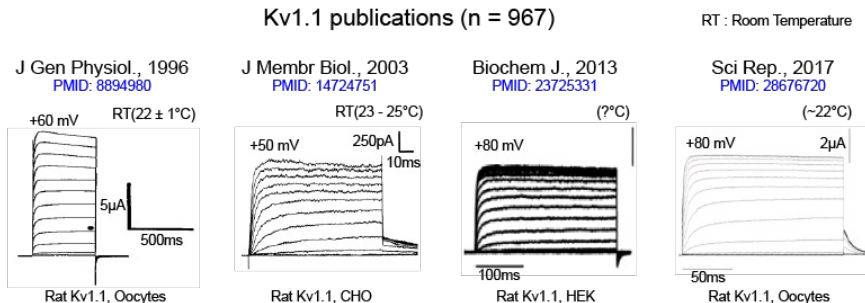
A1

Common knowledge

A2

Physiological Temperature

Literature

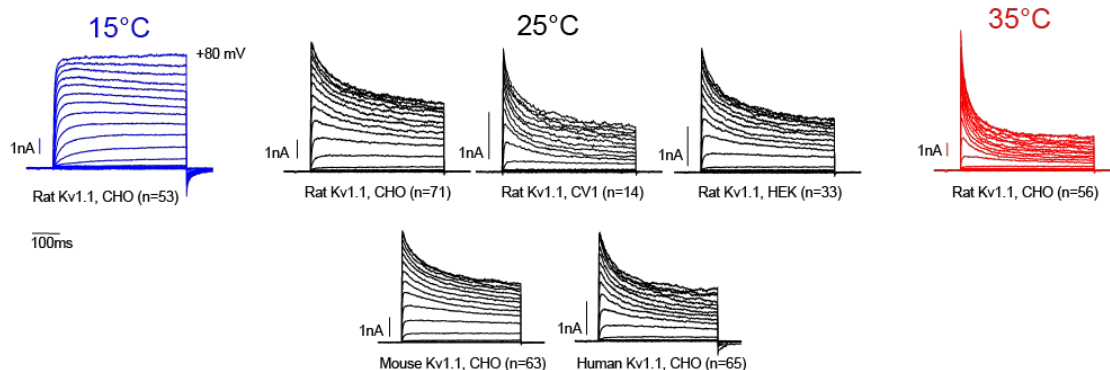


No Data

A3

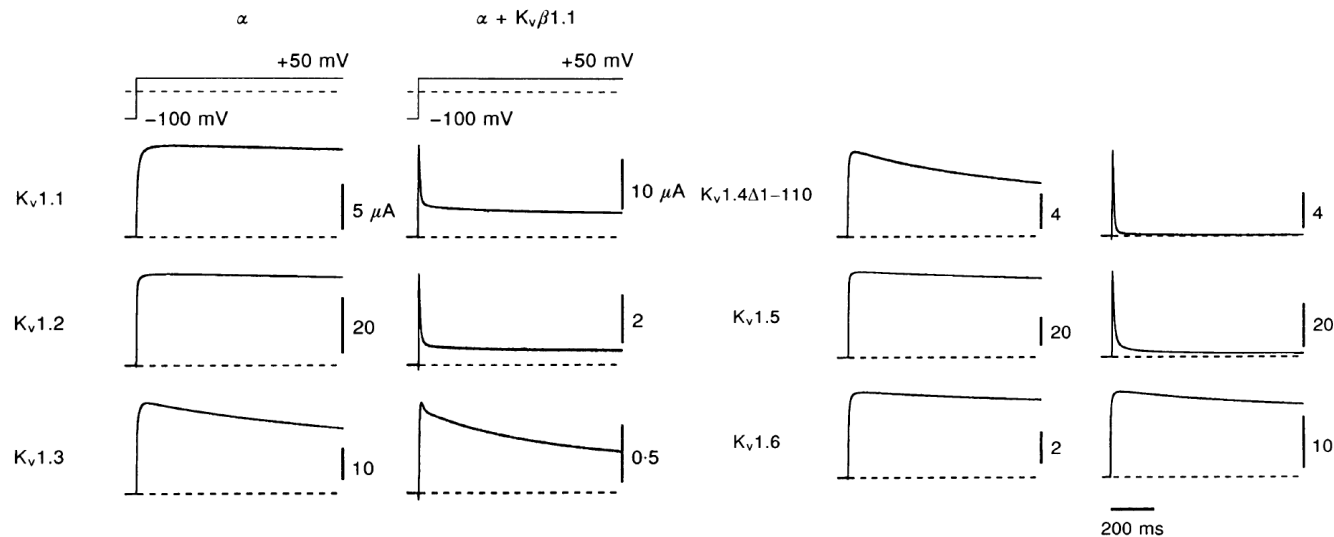
<https://channelpedia.epfl.ch/>

Ranjan et.al, 2019

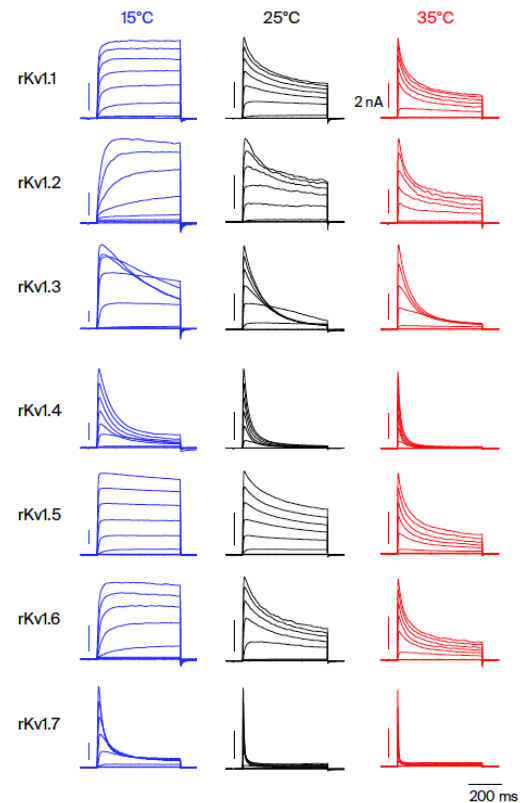


Kinetic modulation

Kinetic modulation by β -subunit

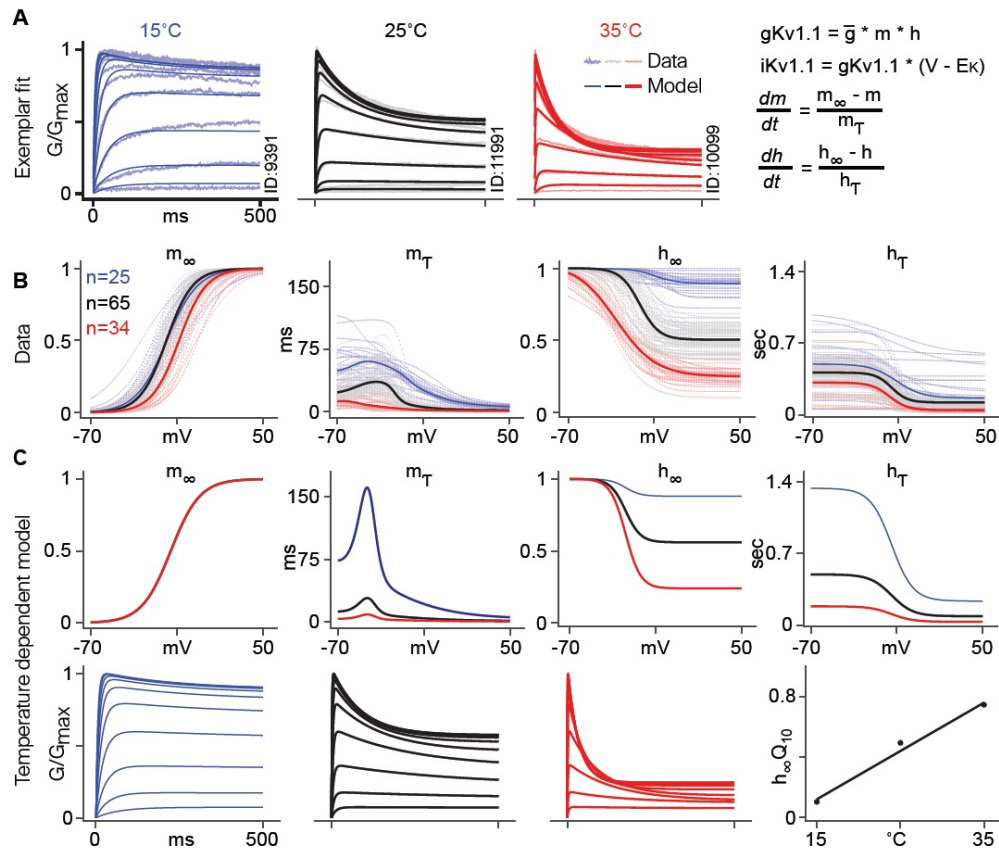
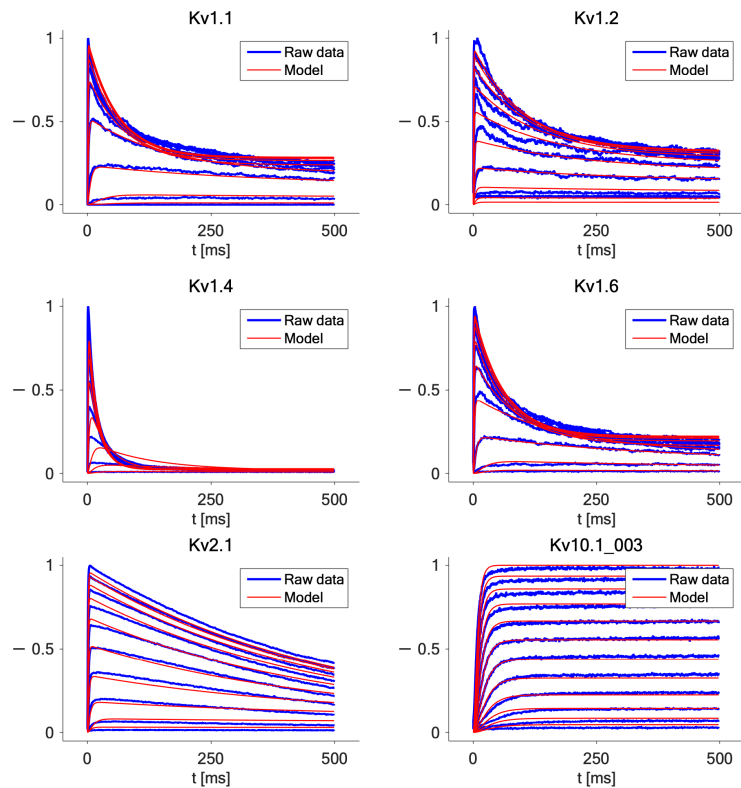


Heinemann SH, Rettig J, Graack HR, Pongs O. Functional characterization of Kv channel beta-subunits from rat brain. J Physiol. 1996;493 (Pt 3)(Pt 3):625–633.



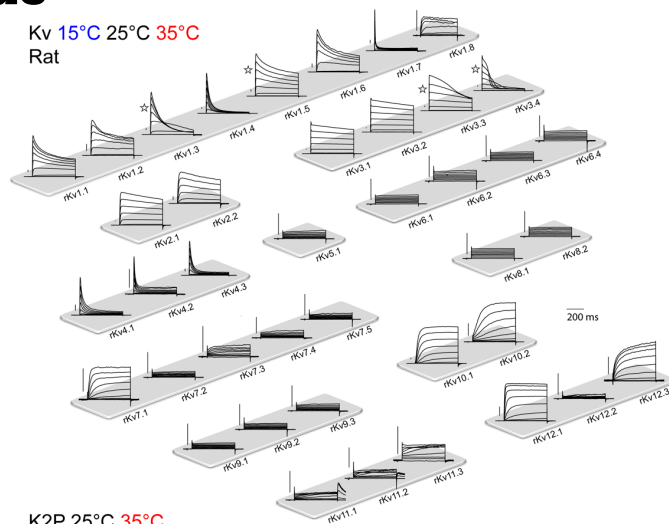
Ranjan et. al, 2019

Temperature dependent model

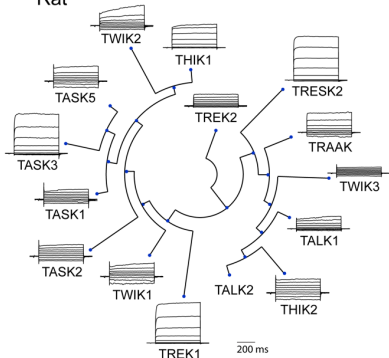


Current status

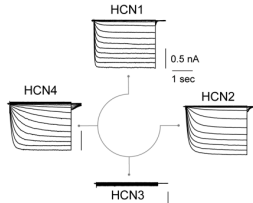
Kv 15°C 25°C 35°C
Rat



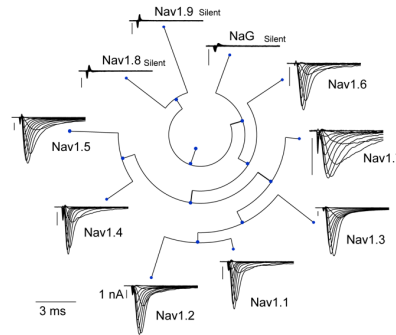
K2P 25°C 35°C
Rat



HCN 15°C 25°C 35°C
Rat, Mouse, Human

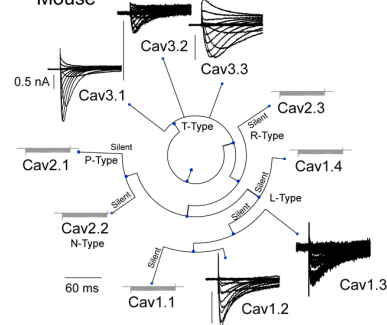


Nav 15°C 25°C 37°C
Mouse

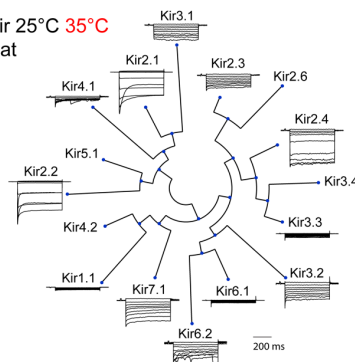


In progress

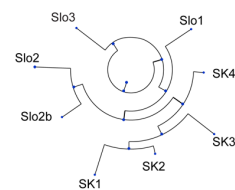
Cav 15°C 25°C 37°C
Mouse



Kir 25°C 35°C
Rat

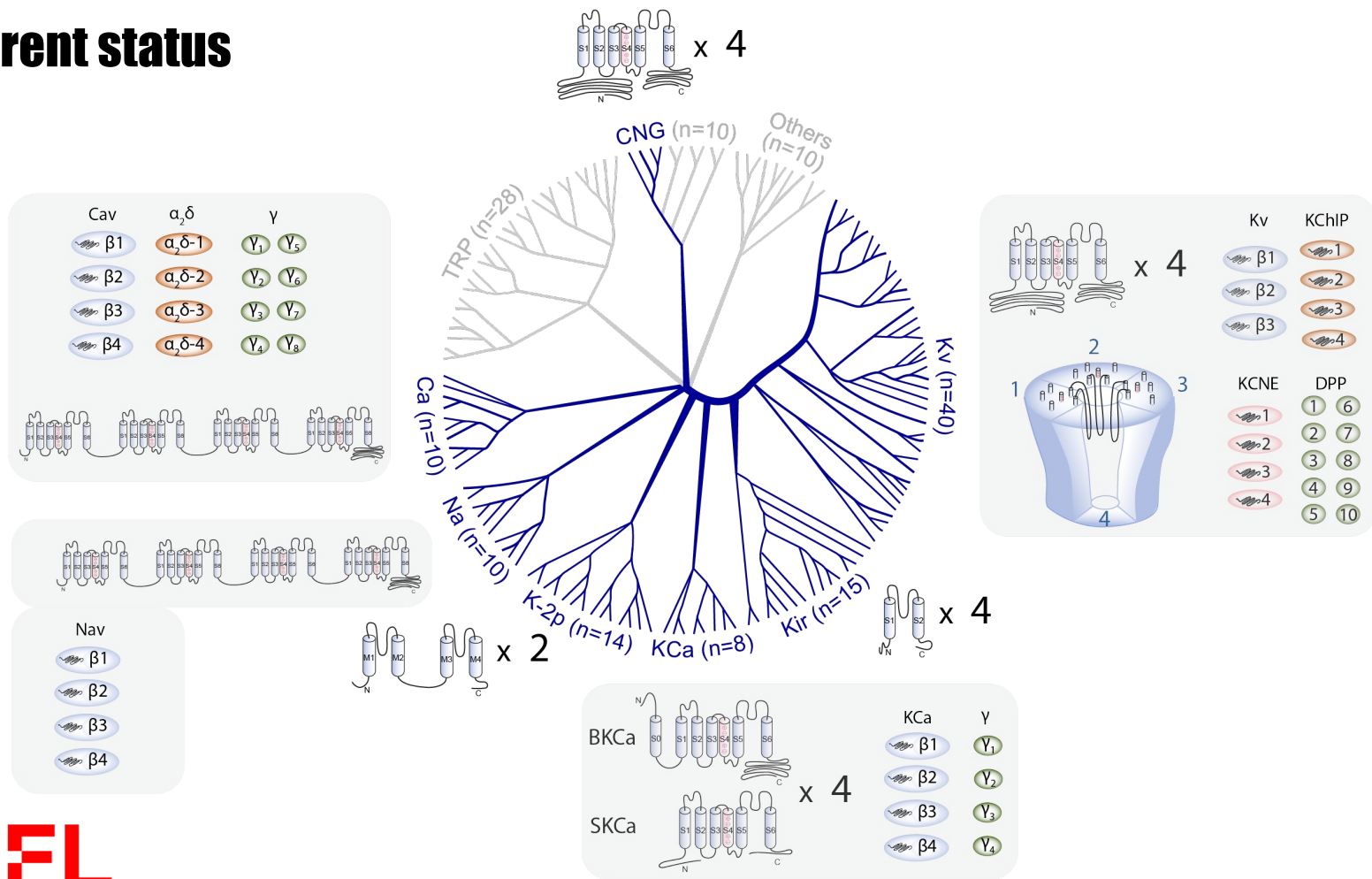


KCa
Mouse



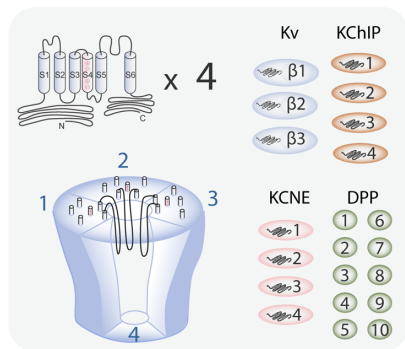
Data available at local Channelpedia <https://ic.bbp.epfl.ch> (accessible only in EPFL network)

Current status



Current status

Kv1.1

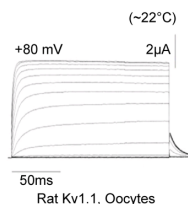
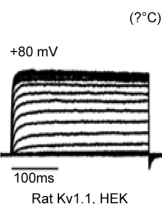
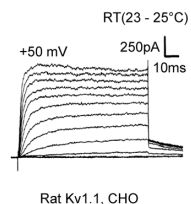


Kv1.1 publications (n = 967)

J Membr Biol., 2003
PMID: 14724751

Biochem J., 2013
PMID: 23725331

RT : Room Temperature
Sci Rep., 2017
PMID: 28676720

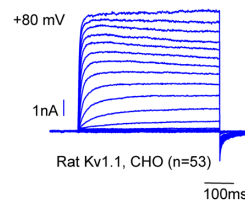


Physiological temperature

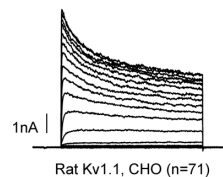
No Data

Ranjan et.al, 2019

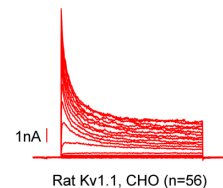
15°C



25°C

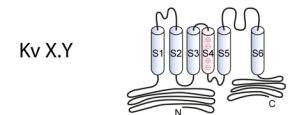


35°C

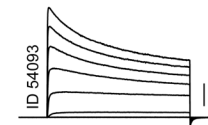


<https://channelpedia.epfl.ch/>

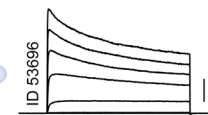
Kinetic modulation



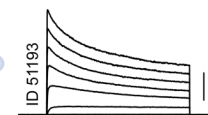
Control



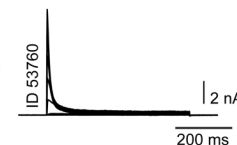
+ β1



+ β2

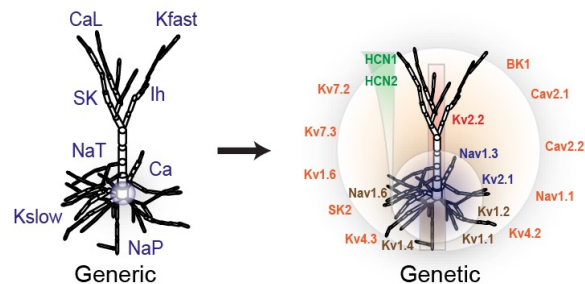


+ β3



Current status

Neuron models



A

SCIENTIFIC REPORTS
nature research
2017
PMID: 28331203

To assess the contribution of axonal Kv1 channels on intrinsic neuronal excitability, we monitored the excitability of CA3 pyramidal cells before and after puffing the specific Kv1.1 channel blocker, DTx-K or the broader spectrum Kv1 channel blocker, DTx-I.

specific Kv1.1 channel blocker, DTx-K

Cell Reports
Volume 22, Issue 12, 20 March 2018, Pages 1315-1327
2018
PMID: 29562186

To provide further clues about the channel subunit composition, we used toxins specific for one Kv1 subunit. Application of dendrotoxin-K (DTx-K; 1 μ M), a potent blocker for Kv1.1 (Robertson et al., 1996), had no effect ($p > 0.05$; Figure 4N;

DTx-K a potent blocker for Kv1.1

SCIENTIFIC REPORTS
nature research
2020
PMID: 32332769

cerebellar slices from mature GAD67-GFP mice to identify putative GABAergic-DCNs (GAD+ DCN) we show that specific Kv1 channel blockers (dendrotoxin- α /IK, DTxs) hyperpolarized the threshold of somatic action potentials, increased the spontaneous firing rate and hampered evoked high frequency

specific Kv1 channel blockers (DTxs)

PNAS
2021
PMID: 34799447

initial segment. Bath application of dendrotoxin-K (DTx-K), a selective blocker of Kv1.1 channels, leads to a larger excitability increase in control cultures than in deprived cultures. Focal puffing

DTx-K a selective blocker of Kv1.1

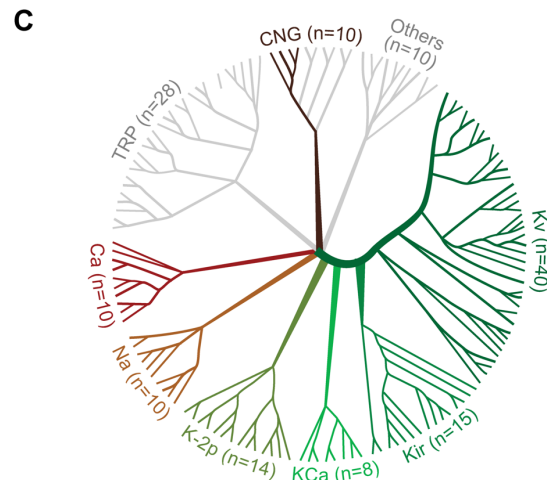
B

1996
PMID: 8612784

> FEBS Lett. 1996 Mar 25;383(1-2):26-30. doi: 10.1016/0014-5793(96)00211-6.

Novel effects of dendrotoxin homologues on subtypes of mammalian Kv1 potassium channels expressed in *Xenopus* oocytes

study. Firstly, while all three clones Kv1.1, 1.2 and 1.6 were blocked by toxin I, the closely related homologue toxin K was selective for Kv1.1. Thus toxin K will be useful in separating out the contributions from Kv1.1 subunits from other mammalian *Shaker*-family subunits in native cells, such as central neurones. Recent work [7] has shown that only one of the



Drug Screening

- Drug screenings are currently performed on cell lines only at room temperature
- Only selected ion channels are used for drug screening

Escitalopram : - Antidepressant, Anxiety disorder
- Sold under brand names Cipralex and Lexapro

Escitalopram also does not bind to or has low affinity for various ion channels including Na^+ , K^+ , Cl^- and Ca^{++} channels.

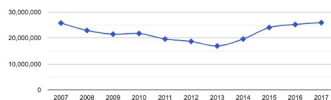
US FDA (fda.gov)

Escitalopram Oxalate

Drug Usage Statistics, United States, 2007 - 2017

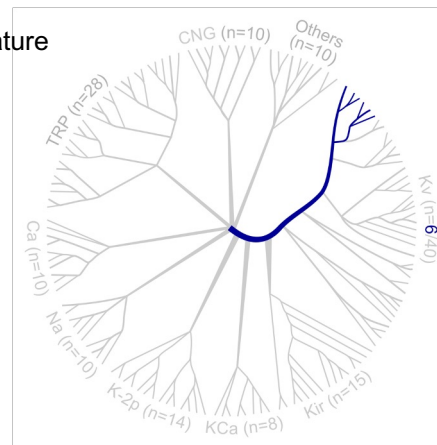
▲ ClinCalc.com • Pharmacy • ClinCalc DrugStats • Escitalopram Oxalate

Number of Prescriptions Over Time (2007 - 2017)

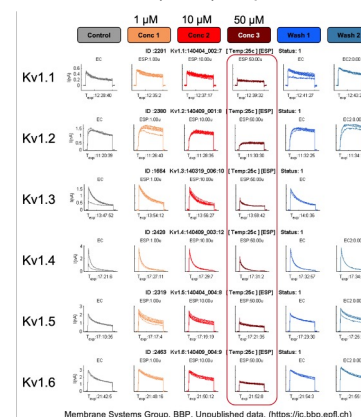


20th most commonly prescribed medication in the United States with more than **25 million** prescriptions

Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder*			
Body System / Adverse Event	(Percentage of Patients Reporting Event)		Placebo (N=427)
	LEXAPRO (N=429)	Placebo (N=427)	
Autonomic Nervous System Disorders			
Dry Mouth	9%	5%	
Sweating Increased	4%	1%	
Central & Peripheral Nervous System Disorders			
Headache	24%	17%	
Paresthesia	2%	1%	
Gastrointestinal Disorders			
Nausea	18%	8%	
Diarrhea	8%	6%	
Constipation	5%	4%	
Indigestion	3%	2%	
Vomiting	3%	1%	
Abdominal Pain	2%	1%	
Flatulence	2%	1%	
Toothache	2%	0%	
General			
Fatigue	8%	2%	
Influenza-like Symptoms	5%	4%	
Musculoskeletal			
Neck/Shoulder Pain	3%	1%	
Psychiatric Disorders			
Somnolence	13%	7%	
Insomnia	12%	6%	
Libido Decreased	7%	2%	
Dreaming Abnormal	3%	2%	
Appetite Decreased	3%	1%	
Lethargy	3%	1%	
Yawning	2%	1%	
Urogenital			
Ejaculation Disorder ^{1,2}	14%	2%	
Anorgasmia ¹	6%	<1%	
Menstrual Disorder	2%	1%	



BBP data (2014), unpublished



50 μM Escitalopram blocks all six (Kv1) ion channels by 60%

2017

> Korean J Physiol Pharmacol. 2017 Jul;21(4):415-421. doi: 10.4196/kjpp.2017.21.4.415. Epub 2017 Jun 26.

Escitalopram, a selective serotonin reuptake inhibitor, inhibits voltage-dependent K^+ channels in coronary arterial smooth muscle cells

2014

> Naunyn-Schmiedeberg's Arch Pharmacol. 2014 Jan;387(1):23-32. doi: 10.1007/s00210-013-0911-y. Epub 2013 Sep 18.

Escitalopram block of hERG potassium channels

2010

> Acta Pharmacol Sin. 2010 Apr;31(4):429-35. doi: 10.1038/aps.2010.14. Epub 2010 Mar 15.

Open channel block of Kv1.5 currents by citalopram

Drug Screening on Literature Data

Home

ChannelAID

Drug screening

Ion channels

Subunits

Host cells

Experimental data

PubMed search

Kv paper

Share your data

FAQ

Team and contacts

Admin

tetraethylammonium	tetrodotoxin	tti-a2	tityustoxin-k alpha	lidocaine	bicuculline	escitalopram	retigabine	valproate	mibefradil	clozapine							
topiramate	verapamil	nifedipine	lamotrigine	pemoline	lithium	tamoxifen	nbqx	apv	4-aminopyridine	zd7288	lacosamide	dendrotoxin-k	+				
Ion Channel																	
Kv								K2P				Kir					
Kv1.1	Kv1.6	Kv3.1	Kv4.2	Kv4.3	Kv5.1	Kv6.1	Kv6.2	TWIK1	TASK2	TWIK2	TWIK3	Kir1.1	Kir2.4	Kir3.1	Kir3.2		
Kv1.2	Kv1.7	Kv3.2	Kv6.3	Kv7.3	Kv7.4	Kv7.5	Kv8.1	TREK1	TASK3	THIK1	TASK5	Kir2.1	Kir3.3	Kir4.2	Kir5.1		
Kv1.3	Kv1.8	Kv3.3	Kv6.4	Kv8.2	Kv9.3	Kv10.1	Kv10.2	TASK1	TREK2	TALK1		Kir2.2	Kir3.4	Kir6.1	Kir7.1		
Kv1.4	Kv2.1	Kv3.4	Kv7.1	Kv9.1	Kv11.1	Kv11.3	Kv12.1	TRAAK	THIK2	TALK2	TRESK2	Kir2.3	Kir4.1	Kir6.2			
Kv1.5	Kv2.2	Kv4.1	Kv7.2	Kv9.2	Kv11.2	Kv12.2	Kv12.3	CI				Cav					
								CIC1	CIC4	CIC7	CICK1	CICK2	Cav2.1	Cav1.2	Cav2.3	Cav1.1	Cav3.1
								CIC2	CIC5	CIC11	CIC3	CIC14	Cav2.2	Cav1.3	Cav1.4	Cav3.2	Cav3.3
								CIC3	CIC6	CIC12	CIC5	KCa		HCN			
TRPC1	TRPC5	TRPM2	TRPM6	TRPV2	TRPV3	TRPV4		Nav					SK1	SK2	SK3	HCN1	
TRPC2	TRPC6	TRPM3	TRPM7	TRPV5	TRPP1	TRPP2		Nav1.1	Nav1.3	Nav1.5	Nav1.7	Nav1.8					HCN2
TRPC3	TRPC7	TRPM4	TRPM8	TRPV6	TRPP3	TRPML2							Slo1	Slo2b	Slo3		HCN3
TRPC4	TRPM1	TRPM5	TRPV1	TRPA1	TRPML1	TRPML3		Nav1.2	Nav1.4	Nav1.6	Nav1.9	NaG	Slo2		SK4		HCN4

tetrodotoxin effect on Nav1.1

Pubmed Id	format	Nb citation	Effect	Dose Response	Study type	Subject
34634134	Abstract	0	NA	NA	HUMAN	Human donor tissue
29470418	Full text	NA	CLOSE	NA	HUMAN ANIMAL	DRG neurons Wistar rats
34523364	Abstract	1	CLOSE	NA	ANIMAL	mouse esophageal mechanoreceptors
28450535	Full text	NA	CLOSE	500 nM -> significant reduction in A-CAP amplitude	ANIMAL	mice and pigtail monkeys (Macaca nemestrina)
28832970	Full text	NA	CLOSE	10 nM TTX -> 72 ± 2% inhibition of Nav1.1 IC50 values not explicitly provided for Nav1.1	CELL	HEK293T cells
22005676	Abstract	74	NA	NA	UNKNOWN	UNKNOWN
25406007	Full text	40	CLOSE	NA	UNKNOWN	UNKNOWN

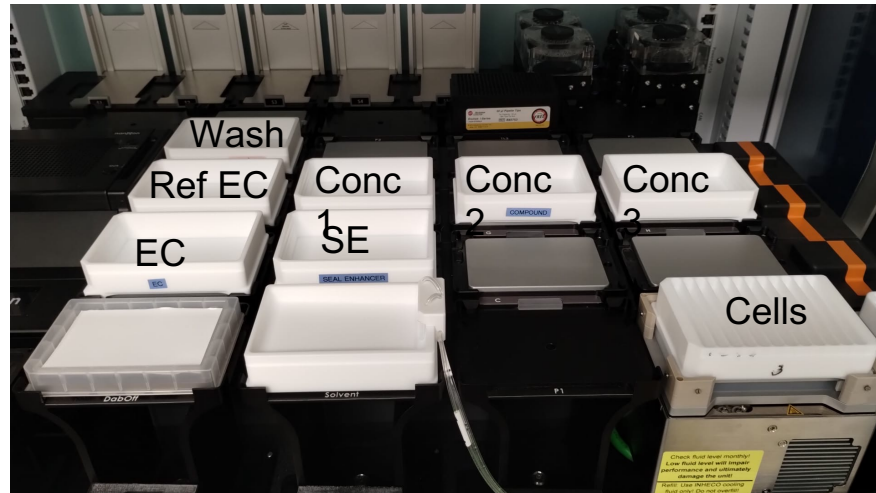
AnyChart Trial Ver

EPFL



DrugName	Reason	Info from Drugbank related to IC
1 TEA	Potassium channel blocker	
2 TTX	Sodium channel blocker	
3 TTA-A2	T type CaV3 channel blocker	
4 TitusToxin-K alpha	Kv1.2 specific blocker	
5 Lidocaine	Common anesthetic	NaV inhibitor
6 Bicuculline	Synaptic blocker (GABA A)	
7 Escitalopram	Antidepressant	no
8 Retigabine	Anti convulsant Withdrawn from market	KCNQ
9 Valproate	Anti epileptic	NaV inhibitor
10 Mibefradil (Posicor)	Anti hypertensive Withdrawn from market	Calcium channel inhibitor
11 Clozapine	Antipsychotic medication, also effective in treatment resistant schizophrenia	Kv11.1 blocker
12 Topiramate	To treat Epilepsy and migraine	
13 Verapamil	To treat high blood pressure Calcium channel blocker	CaV blocker + some kir and kv
14 Nifedipine	To treat high blood pressure & chest pain	CaV blocker
15 Lamotrigine	To treat Epilepsy, bipolar disorder	CaV blocker
16 Pemoline (Cylert)	To treat attention-deficit hyperactivity Withdrawn from market	ND
17 Lithium	Antidepressant	Glutamate R 3
18 Tamoxifen	Common Cancer drug	kv11.1 blocker
19 NBQX	Synaptic blocker (AMPA)	
20 APV	Synaptic blocker	
21 4-Aminopyridine	Kv1 blocker	
22 ZD7288	HCN blocker	

Drug Screening (Experiment setup)



24-well



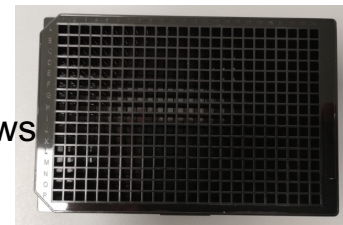
12-well



6-well



24 columns

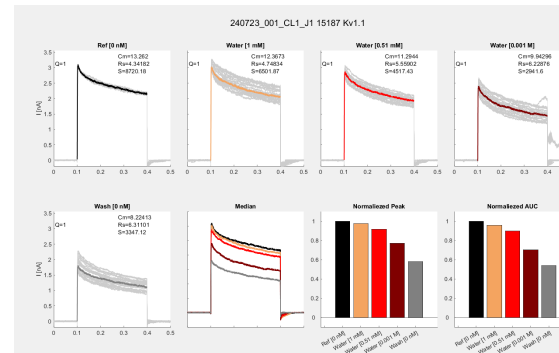
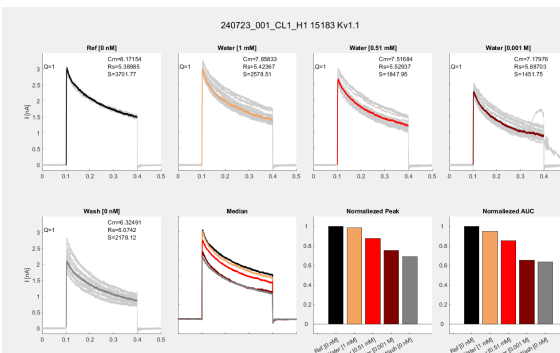
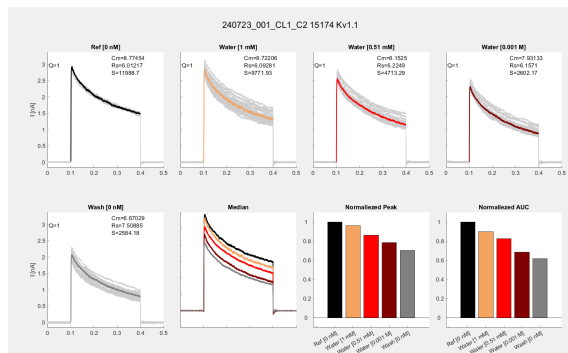
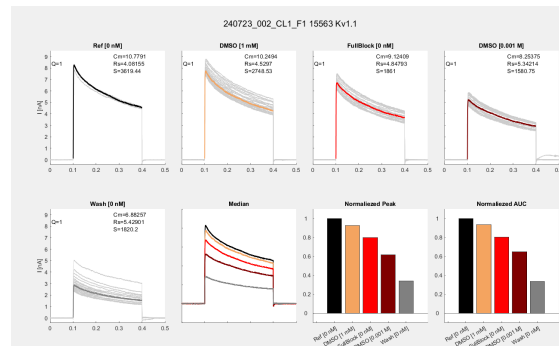
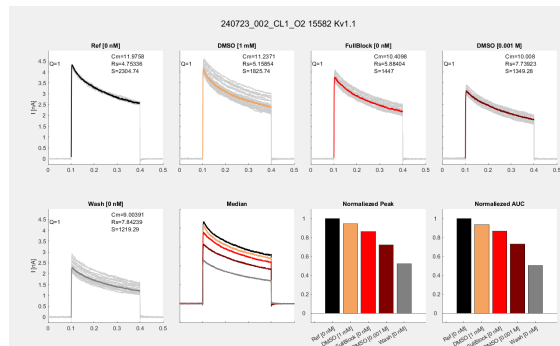
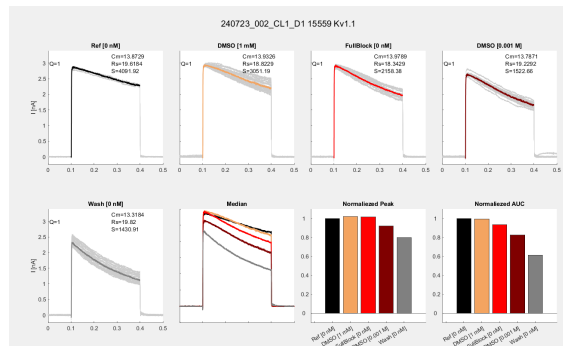


16
Rows

Compound / Cells plate

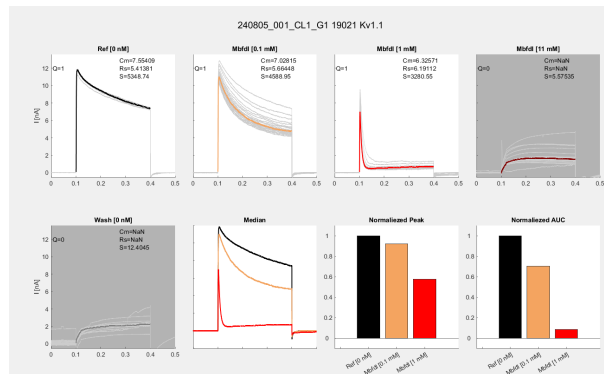
Recording chip

Drug Screening Data (Kv1.1 control)

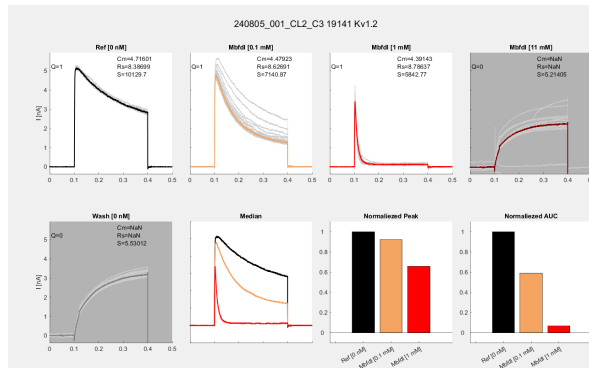


Drug Screening Data (Mibefradil)

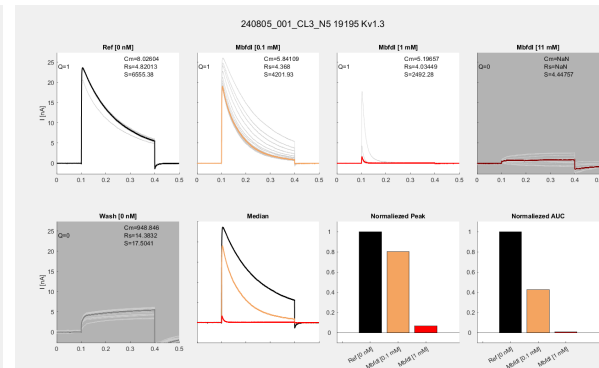
Kv1.1



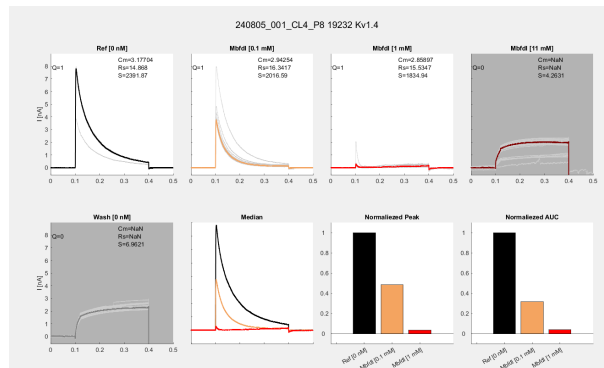
Kv1.2



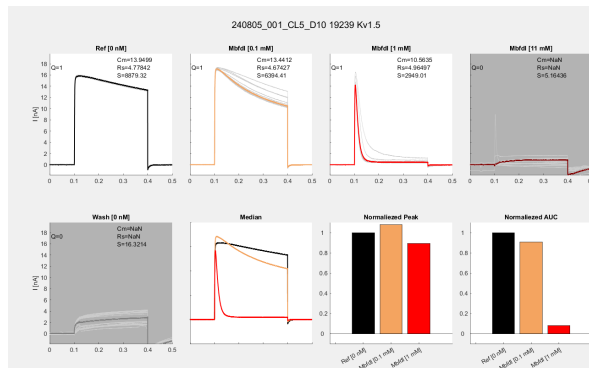
Kv1.3



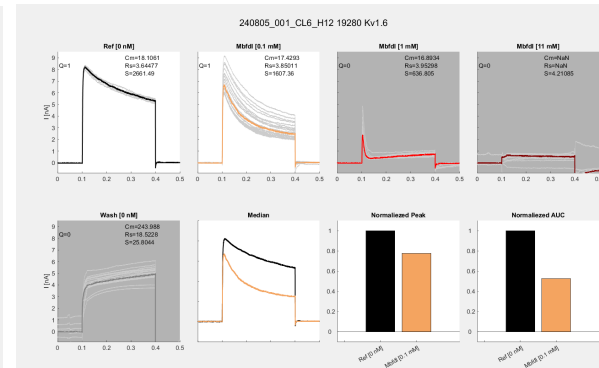
Kv1.4



Kv1.5

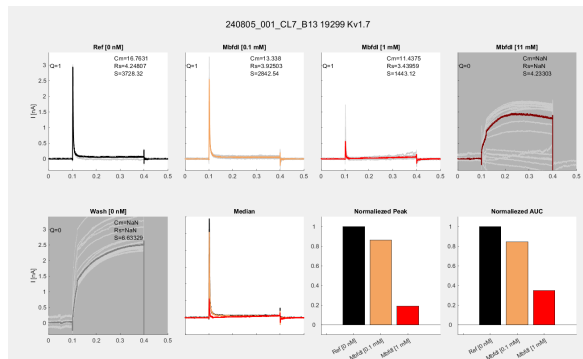


Kv1.6

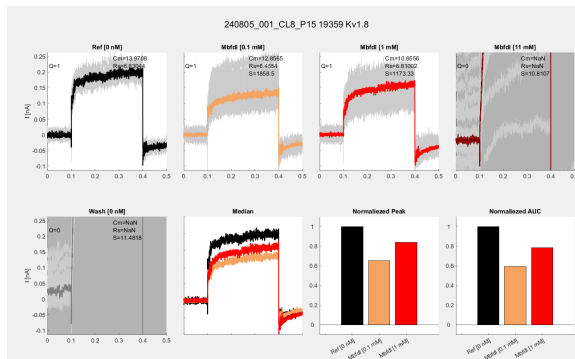


Drug Screening Data (Mibefradil)

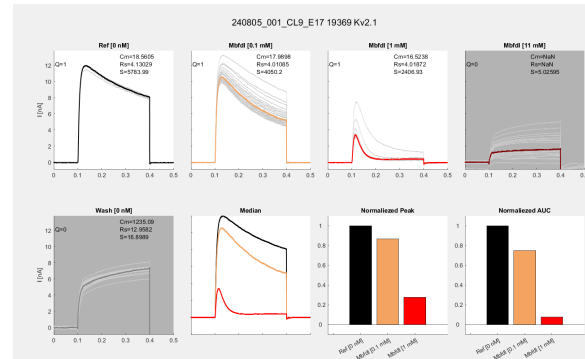
Kv1.7



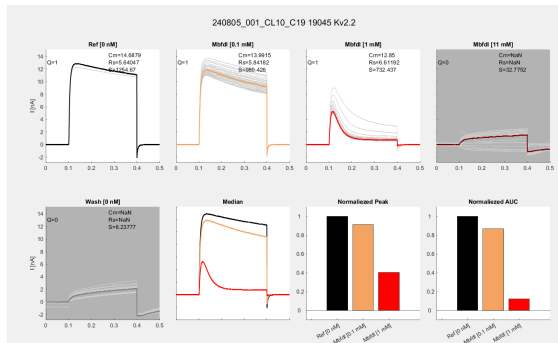
Kv1.8



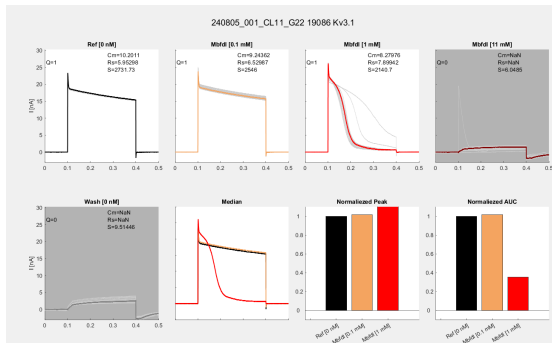
Kv2.1



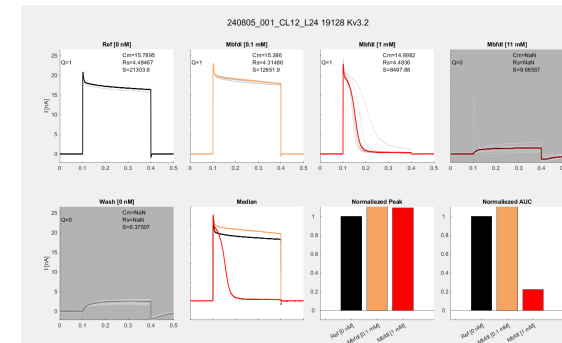
Kv2.2



Kv3.1

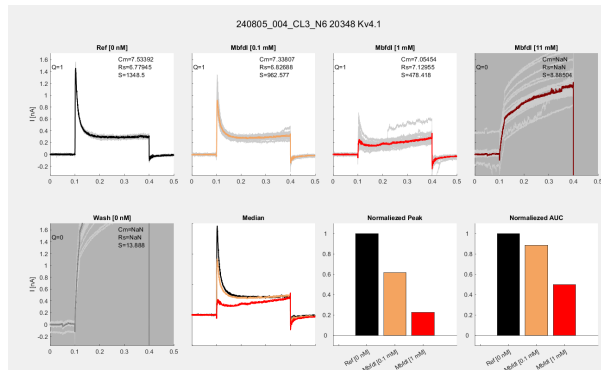


Kv3.2

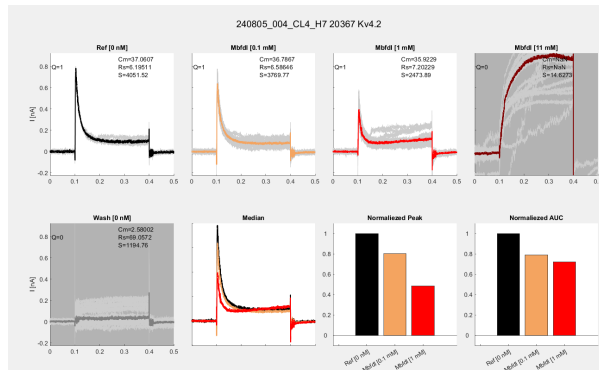


Drug Screening Data (Mibefradil)

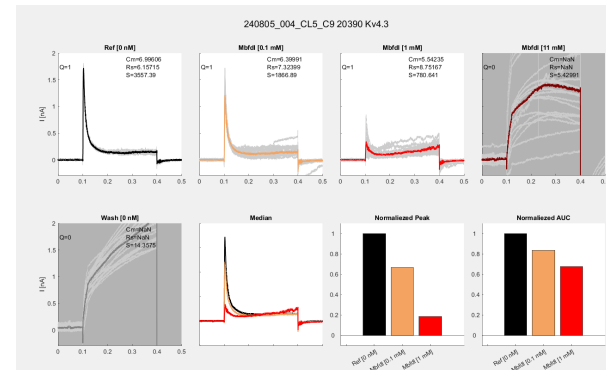
Kv4.1



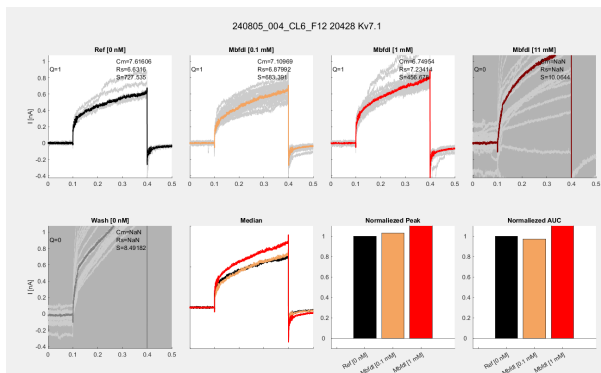
Kv4.2



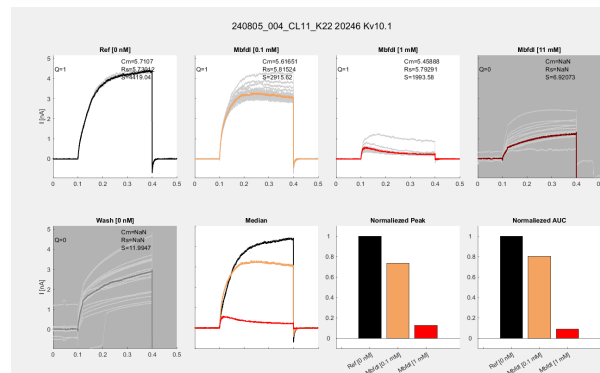
Kv4.3



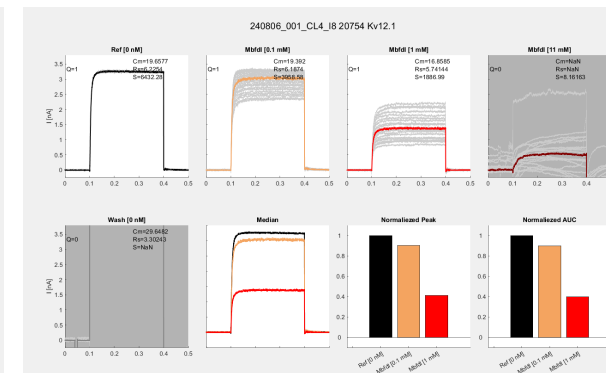
Kv7.1



Kv10.1



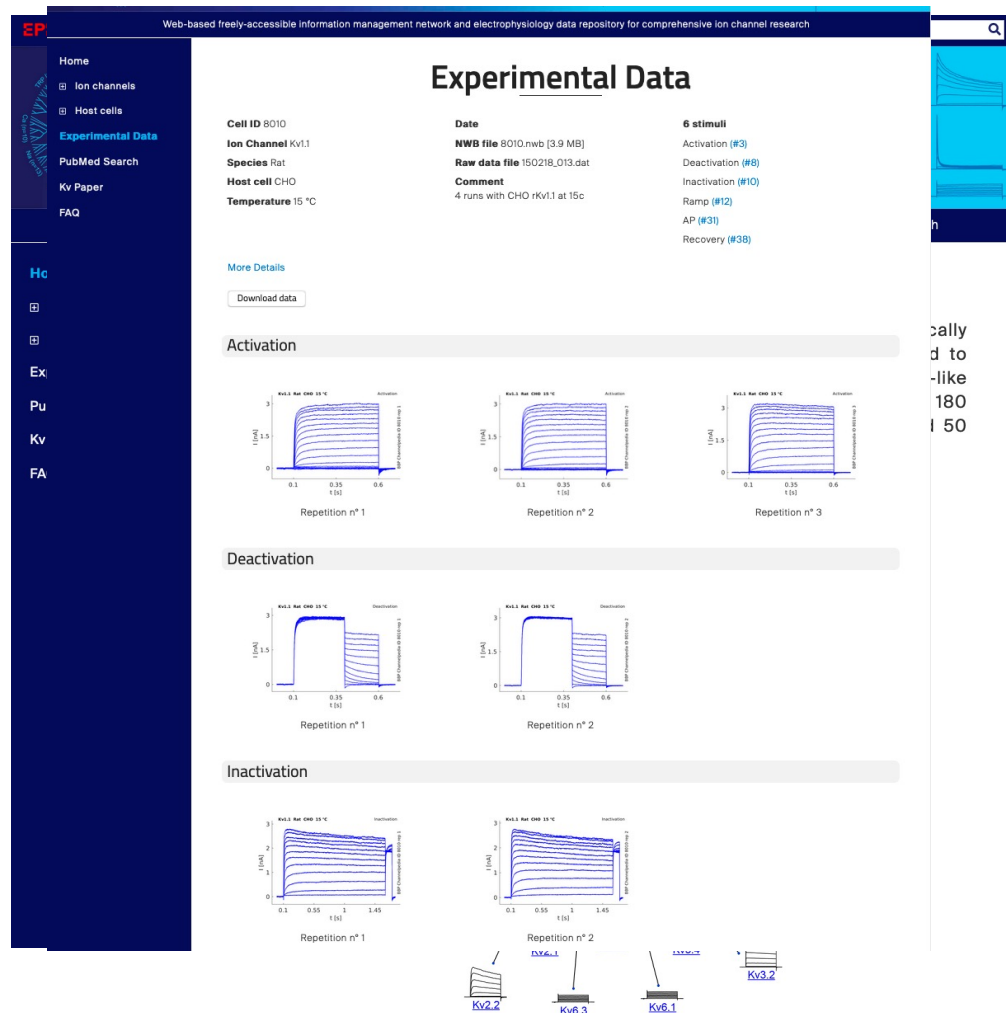
Kv12.1



Web resources

Channelpedia
ModelDB
Icogenealogy
IUPHAR

<https://channelpedia.epfl.ch>



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ModelDB is tightly coupled with [NeuronDB](#), a database of neuronal properties that are used to constrain models based on experimental observations.

Browse or search through over **1520 models** using the navigation on the left bar or in the menu button on a mobile device. To search papers instead of models, go [here](#); this may be used to identify models whose paper cites or is cited by a given paper.

Tweets by @SenseLabProject



SenseLab

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New in [#ModelDB](#): ROOTS: An Algorithm to Generate Biologically Realistic Cortical Axons (Bingham et al 2020) modeldb.yale.edu/262138



Feb 26, 2020



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New in [#ModelDB](#): Energy-efficient information transfer at thalamocortical synapses (Harris et al 2019) modeldb.yale.edu/262114



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<https://senselab.med.yale.edu/modeldb/>

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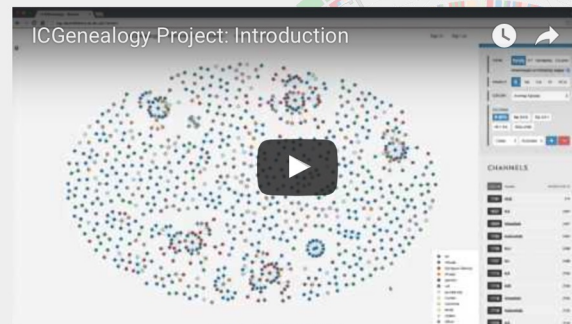
ModelDB
Channelpedia
Icgenealogy
IUPHAR

IonChannelGenealogy

Our database provides a comprehensive and quantitative assay of ion channel models currently available in the neuroscientific modeling community, all browsable in interactive visualizations.

Currently, the database contains **2378 ion channels** written for the **NEURON** simulator.

[Learn more »](#)



The ICG Project is an initiative of the **CNCB @ University of Oxford** in collaboration with the **LCN @ EPFL**.

Channel Browser

A graphical user interface to all channels currently available in our database. We offer several interactive data views to best help you choose ion channel models.

[Browse channels »](#)

Contribute

Together we can improve ICG! Upload your own channel models or submit tickets to correct existing ones should you find errors in our database.

[Submit a channel »](#)

[Create a ticket »](#)

API

All our data is accessible via an API. This enables you to run automated evaluations against current traces, or simply evaluate the metadata.

[View API description»](#)

<http://icg.neurotheory.ox.ac.uk>

Podlaski WF, Seeholzer A, Groschner LN, Miesenböck G, Ranjan R, Vogels TP. Mapping the function of neuronal ion channels in model and experiment. *Elife*. 2017;6:e22152. Published 2017 Mar 6. doi:10.7554/eLife.22152

Web resources

ModelDB
Channelpedia
Icogenealogy
IUPHAR

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Home Targets Ion channels Voltage-gated ion channels Potassium channels Voltage-gated potassium channels

Voltage-gated potassium channels

Unless otherwise stated all data on this page refer to the human proteins. Gene information is provided for human (Hs), mouse (Mm) and rat (Rn).

GlommuPdb View OFF Expand all sections Collapse all sections

Overview

More detailed introduction

The ETM family of K channels comprises the voltage-gated K_v subfamilies, the EAG subfamily (which includes hERG channels), the Ca^{2+} -activated Slo subfamily (actually with TTM, termed BK) and the Ca^{2+} -activated Slo subfamily. These channels possess a pore-forming α subunit that comprises tetramers of identical subunits (homomeric) or of different subunits (heteromeric). Heteromeric channels can only be formed within subfamilies (e.g. $K_v1.1$ with $K_v1.2$; $K_v7.2$ with $K_v7.3$). The pharmacology largely reflects the subunit composition of the functional channel.

Channels and Subunits

$K_v1.1$ - Hide summary More detailed page

Target Id	538
Nomenclature	$K_v1.1$
Previous and unofficial names	HBK1 Kon1 MBK1 RCK1 AEMK HUK1 Kona Kcpv1 potassium voltage-gated channel subfamily A member 1 RBK1 Koa1-1 mceph Shak MK1 potassium voltage-gated channel, shaker-related subfamily, member 1 (episodic ataxia with myokymia) potassium channel, voltage gated shaker related subfamily A, member 1 potassium voltage-gated channel
Genes	<i>KCNA1</i> (Hs), <i>Kcna1</i> (Mm), <i>Kcna1</i> (Rn)
Ensembl ID	ENSG00000111262 (Hs), ENSMUSG00000047976 (Mm), ENSRNOG00000019750 (Rn)
UniProtKB AC	Q09470 (Hs), P16388 (Mm), P10499 (Rn)
Associated subunits	$K_v1.2$, $K_v1.4$, $K_v\beta1$ and $K_v\beta2$ [3]
Channel blockers	tetraethylammonium pK_d 3.5 [10] - Mouse α -dendrotoxin pEC_{50} 7.7 - 9.0 [10,14] - Rat margatoxin pIC_{50} 8.4 [2]
Functional characteristics	K_v

$K_v1.2$ - Hide summary More detailed page

Target Id	539
Nomenclature	$K_v1.2$
Previous and unofficial names	BK2 BGK5 HBK51 MK2 NGK1 RAK RCK5 HK4 Potassium (K_v) channel protein alpha 2 voltage dependent potassium voltage-gated channel subfamily A member 2 RBK2 XShn2 potassium channel, voltage gated shaker related subfamily A, member 2 potassium voltage-gated channel
Genes	<i>KCNA2</i> (Hs), <i>Kcna2</i> (Mm), <i>Kcna2</i> (Rn)
Ensembl ID	ENSG00000177301 (Hs), ENSMUSG00000040724 (Mm), ENSRNOG00000018285 (Rn)
UniProtKB AC	P16389 (Hs), P63141 (Mm), P63142 (Rn)
Associated subunits	$K_v1.1$, $K_v1.4$, $K_v\beta1$ and $K_v\beta2$ [3]
Channel blockers	noxiustoxin pK_d 8.7 [10] - Rat margatoxin pIC_{50} 11.2 [2] α -dendrotoxin pIC_{50} 7.8 - 9.4 [10,14] - Rat
Functional characteristics	K_v

ACOLOGY

al Malaria Portal

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0.05 substitutions/site

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Summary 3

- Ion channels are implicated in many different diseases
- Ion channel kinetics are very sensitive to temperature
- Automated patch clamp and high throughput screening provides access to missing experimental data
- Ion channels are implicated/linked to majority of experimental neuroscience research

The team



Cloning and Cell line generation : Emmanuelle Logette, Mirjia Herzog, Magali Joffraud, Valerie Buchillier, Michela Marani, Valerie Tache

Patch clamp experiments, Analysis and H-H models : Rajnish Ranjan, Stijn Van Dorp, Hervé Arulkandrajah, Valerie Tache, Mirjia Herzog, Magali Joffraud, Balazs Kovacs, Charlotte Lorin, Maurizio Pezzoli

Data management : Rajnish Ranjan, Enrico Scantamburlo, Liviu Soltuzu, Luca Gambazzi, Georges Khazen, Dejan Jovandic, Anthony Njoku

Single cell modelling : Darshan Mandge, Cells team, Yann Roussel Molecular systems

External support : Nadine Becker, Nanion support team

BBP team, LNMC team , EPFL

Funding

The EPFL Blue Brain Project Fund and the ETH Board funding to the Blue Brain Project.

Thank you