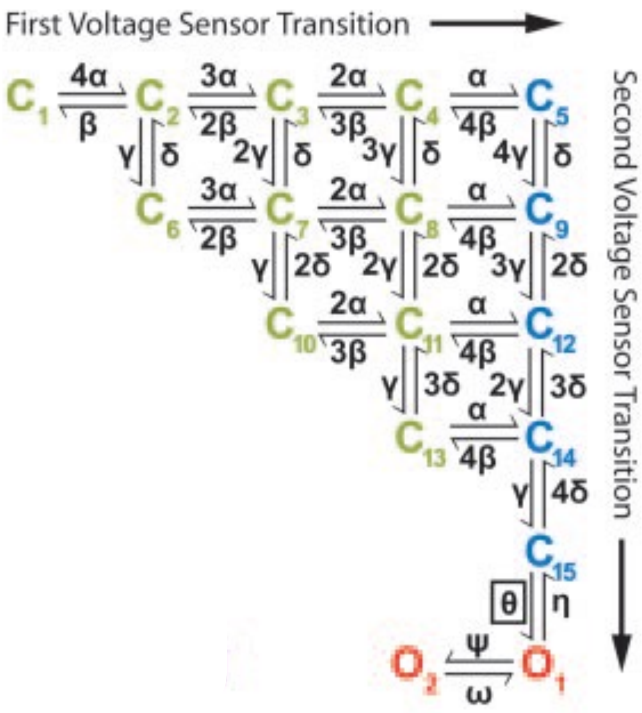
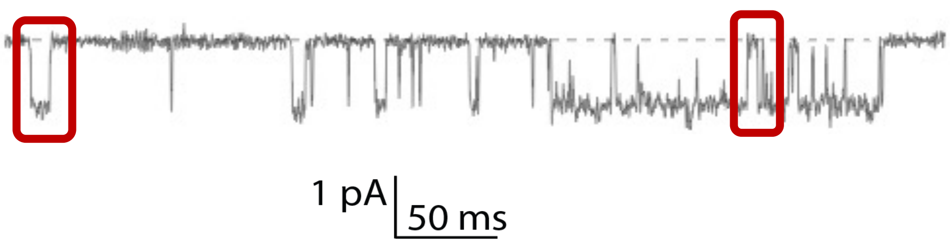
# L5: Practical aspects of building channel and cell models

## *Reconstructing excitability*

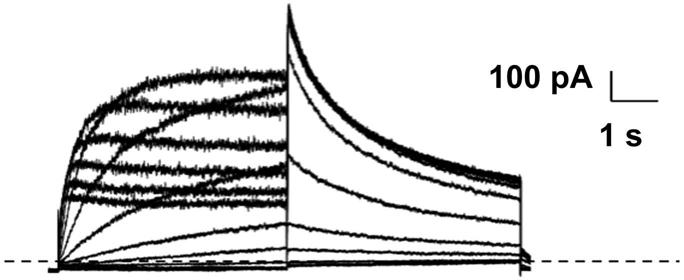
- ***Experimental data sources***
  - *Single-channel recordings*
  - *Single-channel analysis*
  - *Whole-cell recordings*
- ***Major cardiac ion current models***
  - *Hodgkin-Huxley type models*
  - *Generalised Markov models*



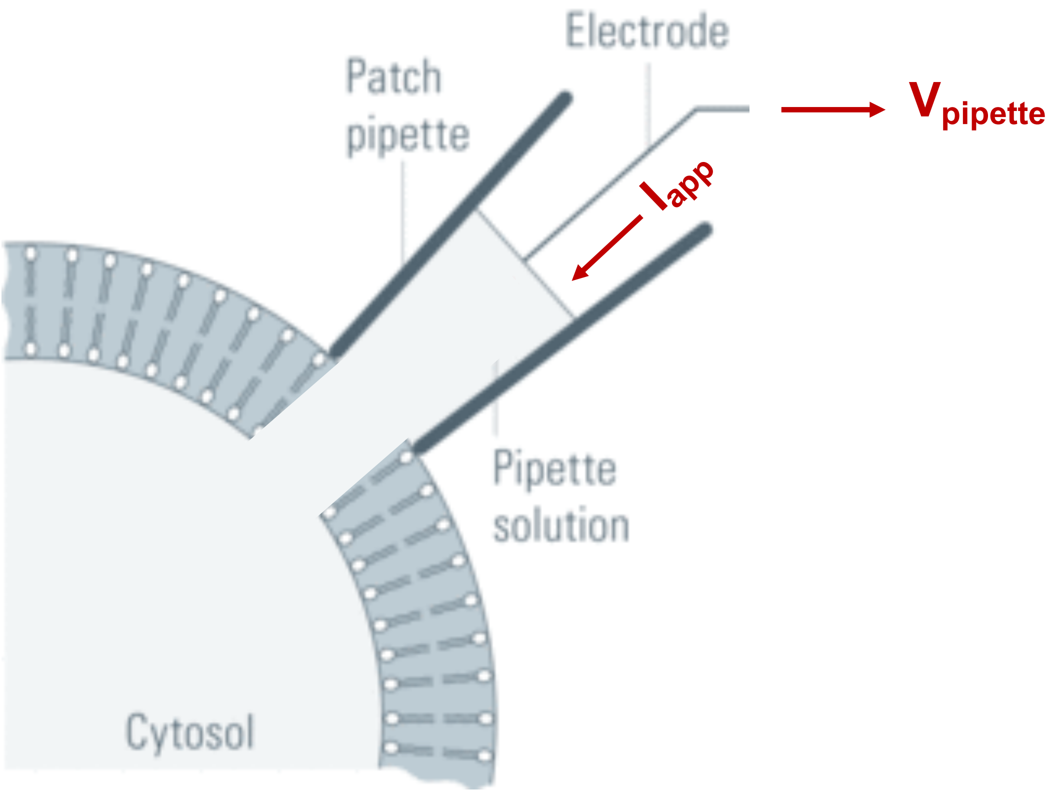

*Single-channel*




*Whole-cell*



# Microelectrode recording preparations

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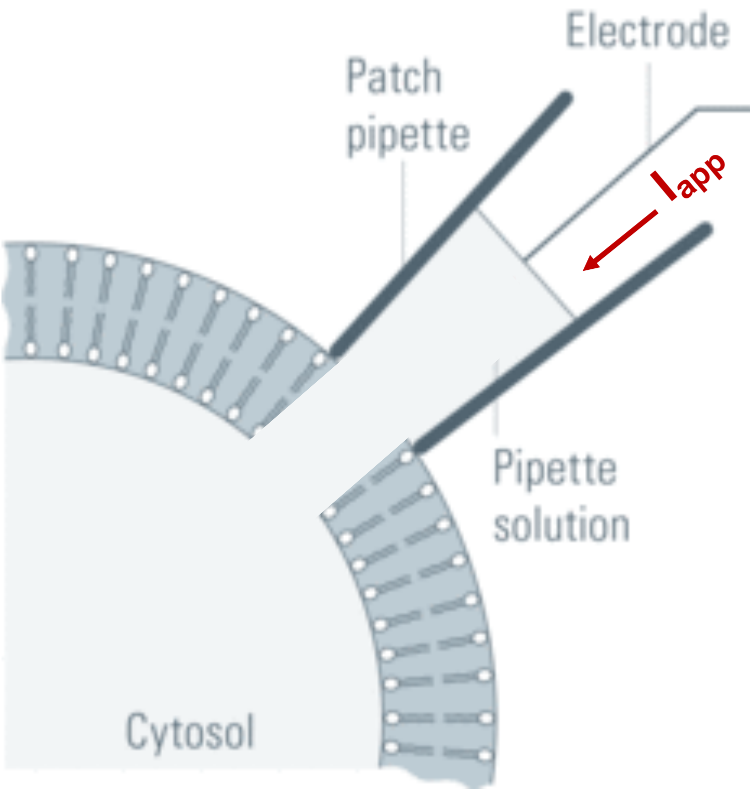
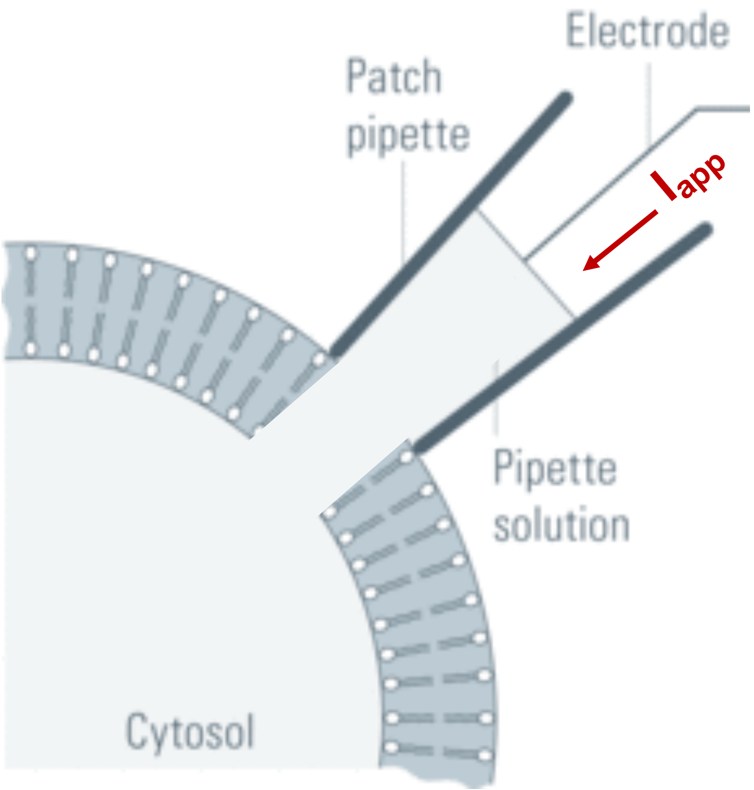




## Voltage clamp

- Membrane potential is prescribed (controlled), injected current is measured

# Microelectrode recording preparations




$V_{pipette}$

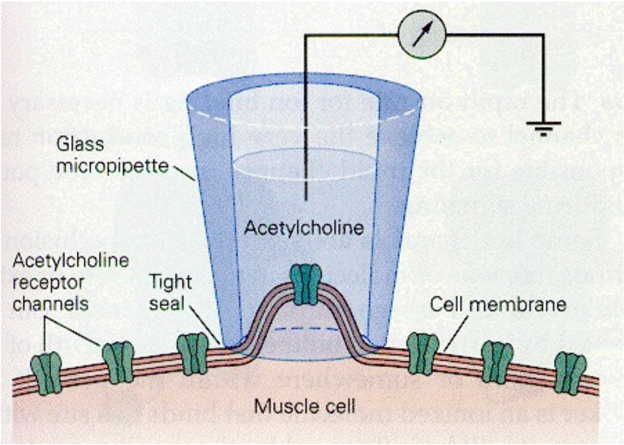
## Current clamp

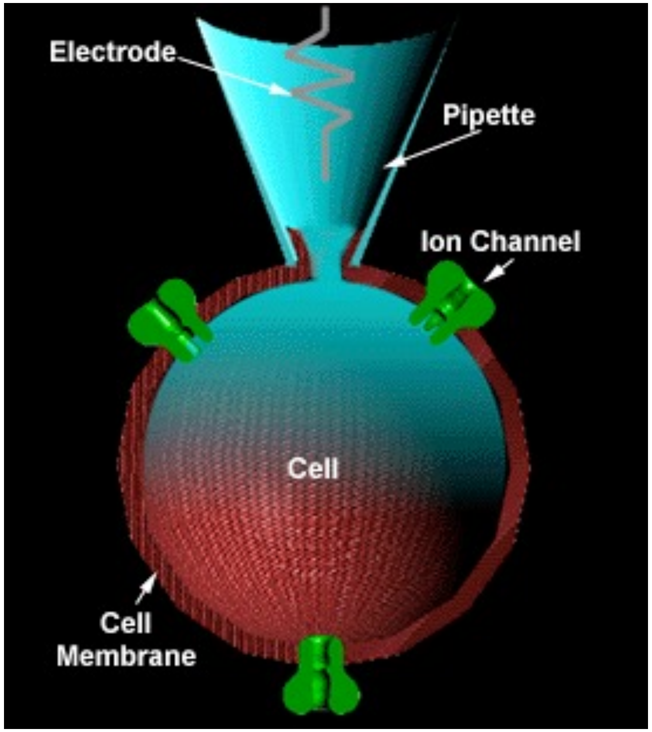
- Current injection is prescribed, membrane potential is measured

# Patch-clamp recording configurations

## Whole-cell

## Single-channel



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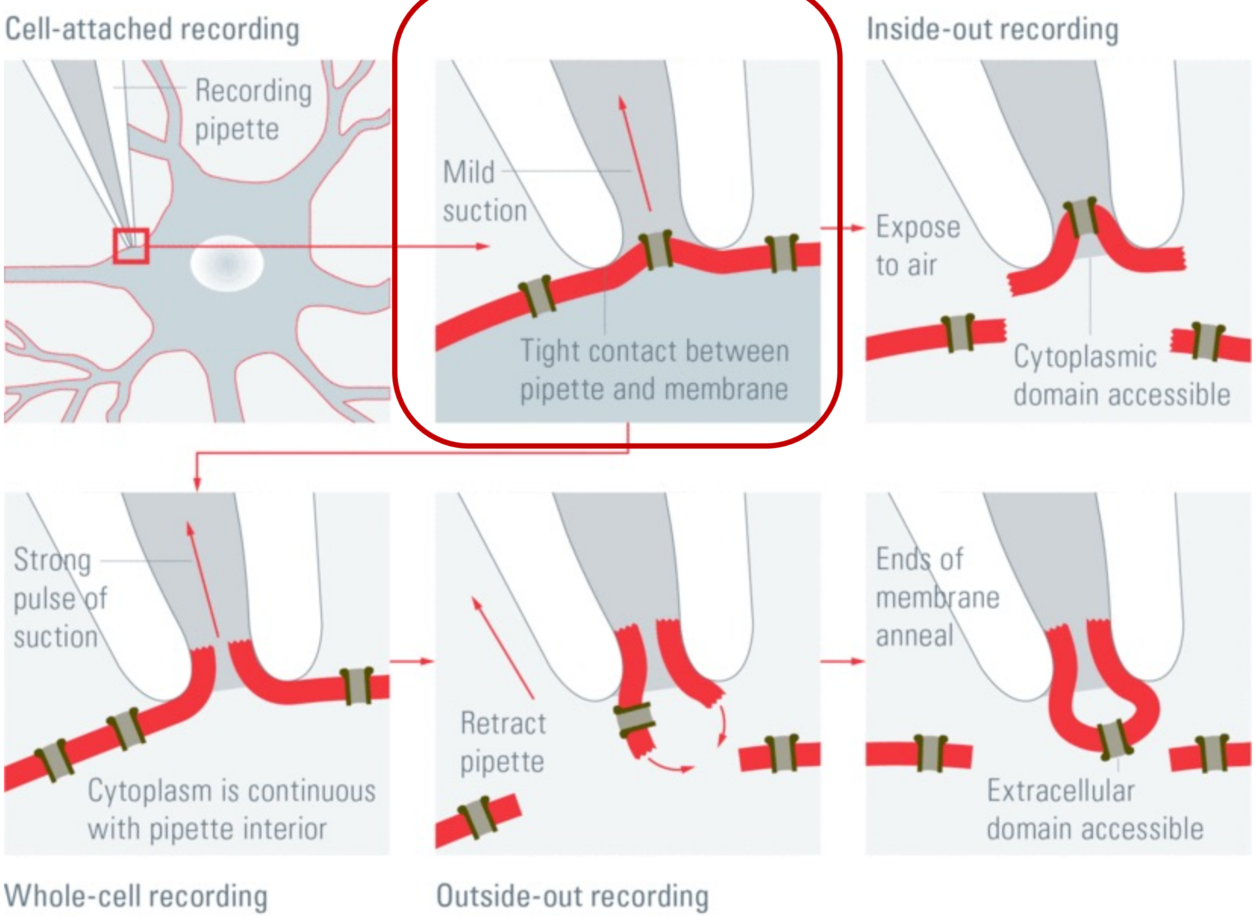
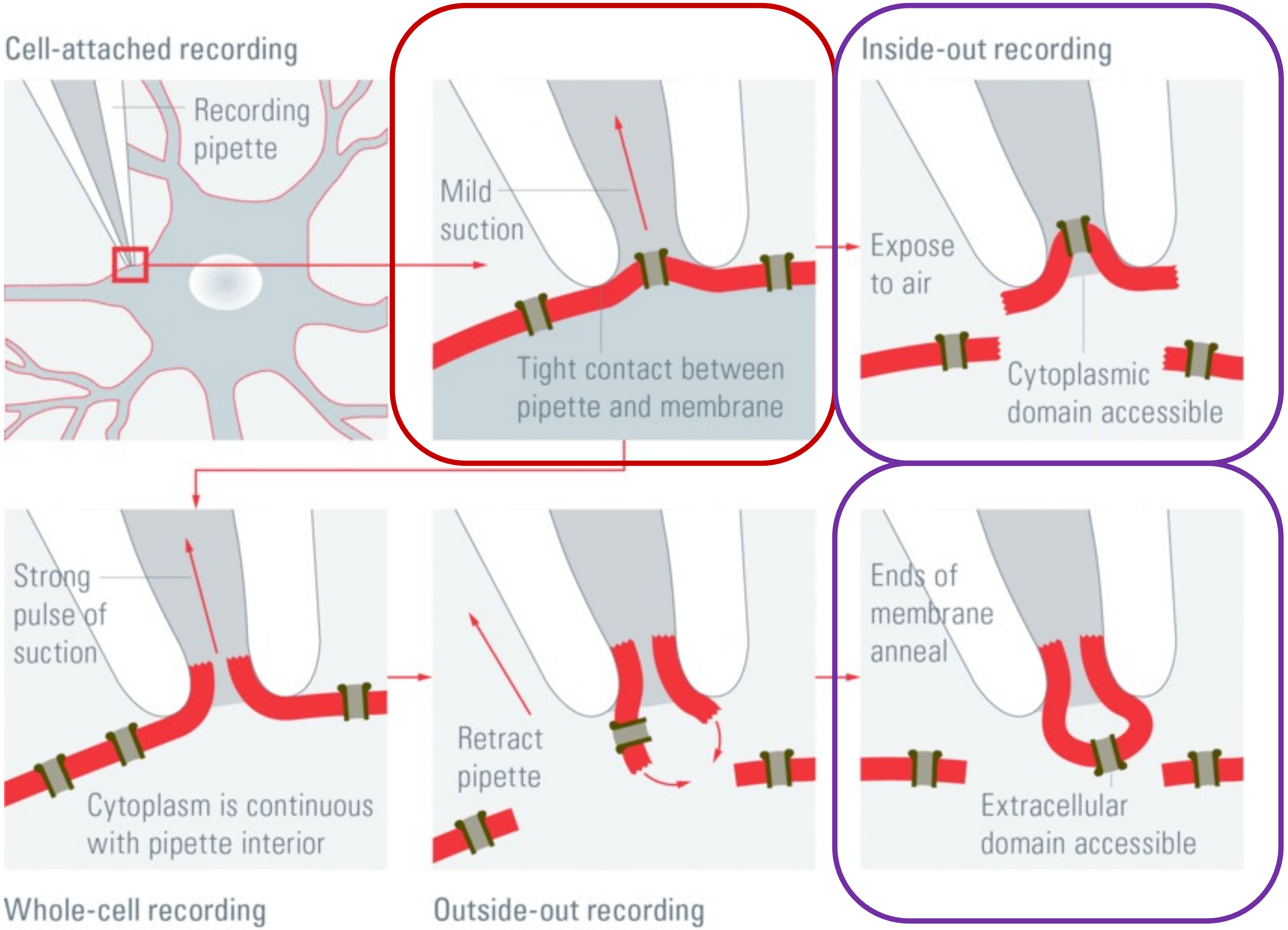



## Single channel:

- Cell attached

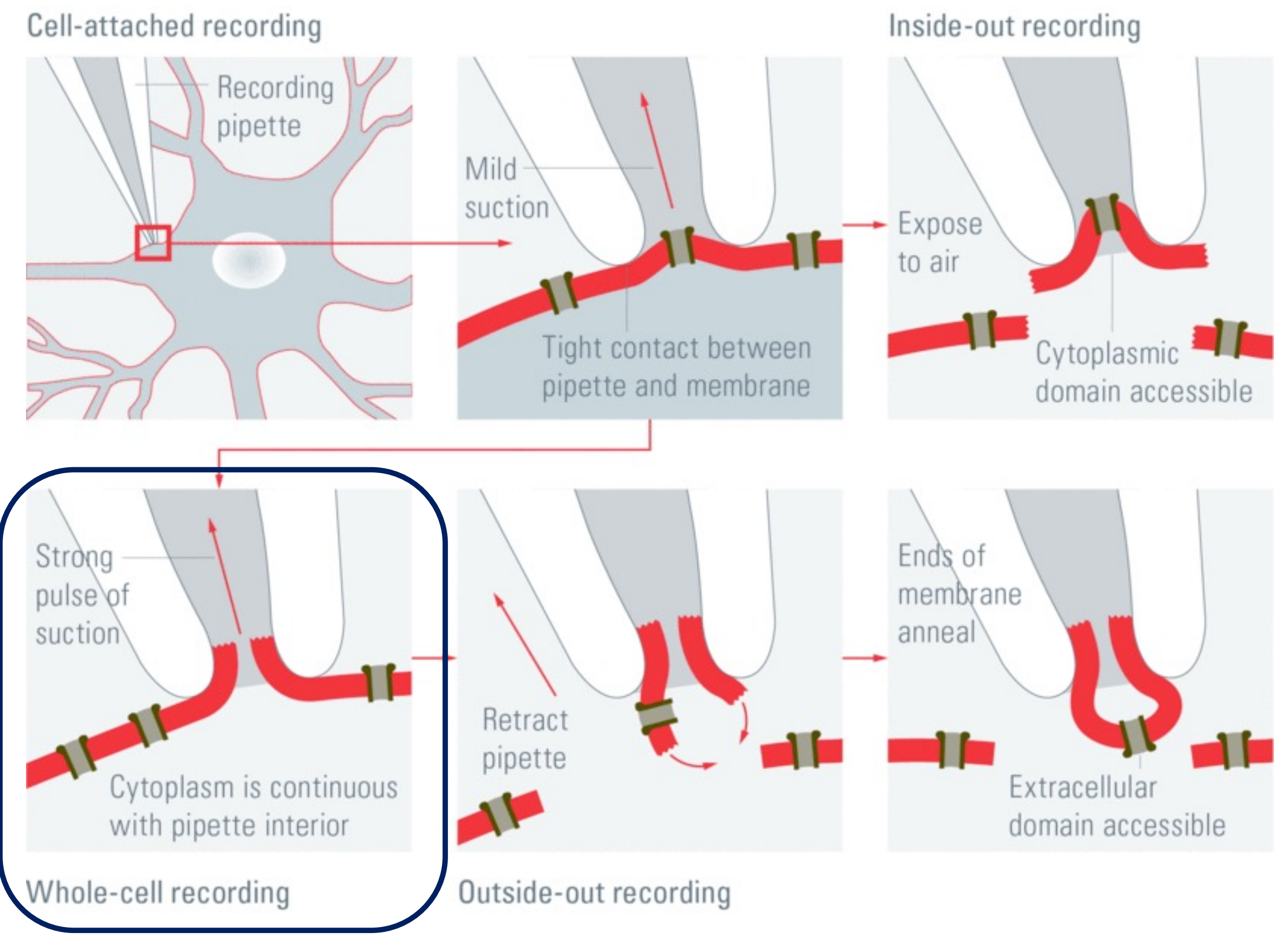
# Patch-clamp recording configurations




## Single channel:

- Cell attached
- Excised patch
  - Inside-out
  - Outside-out

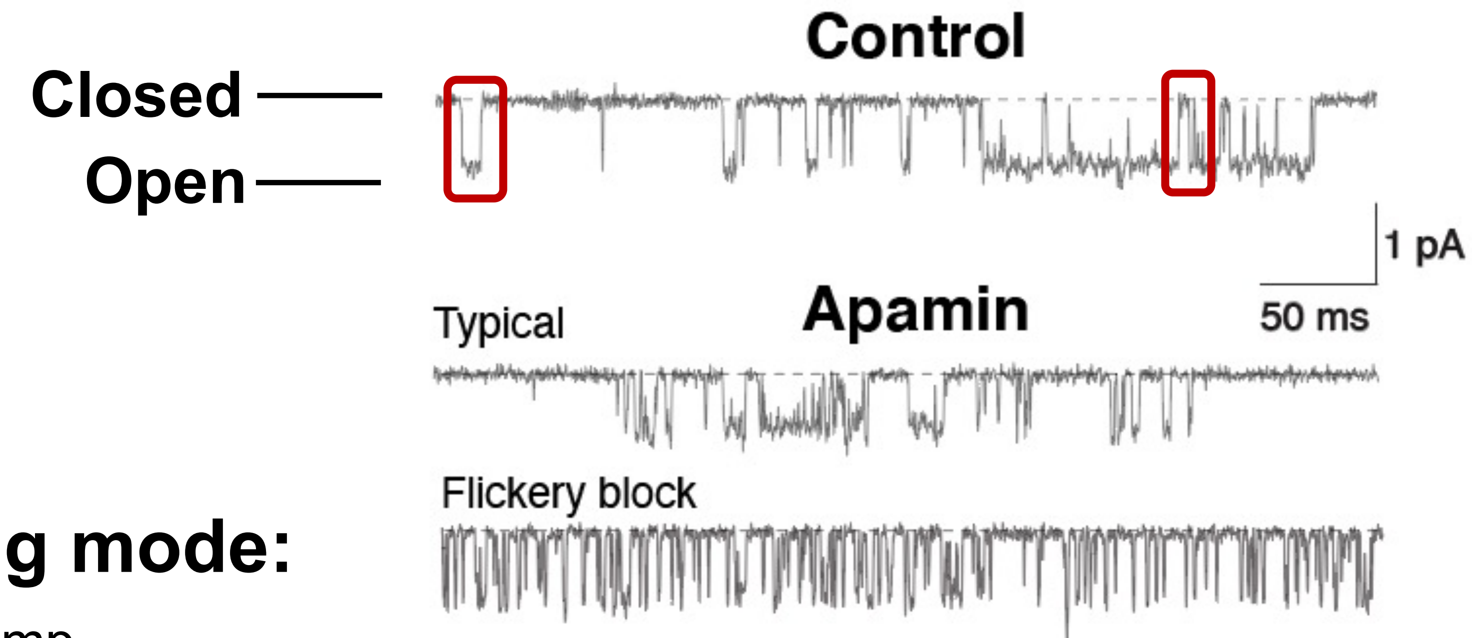
# Patch-clamp recording configurations




**Whole-cell:**

- Ruptured (suction)
- Perforated (ionophore)

# Single-channel recordings



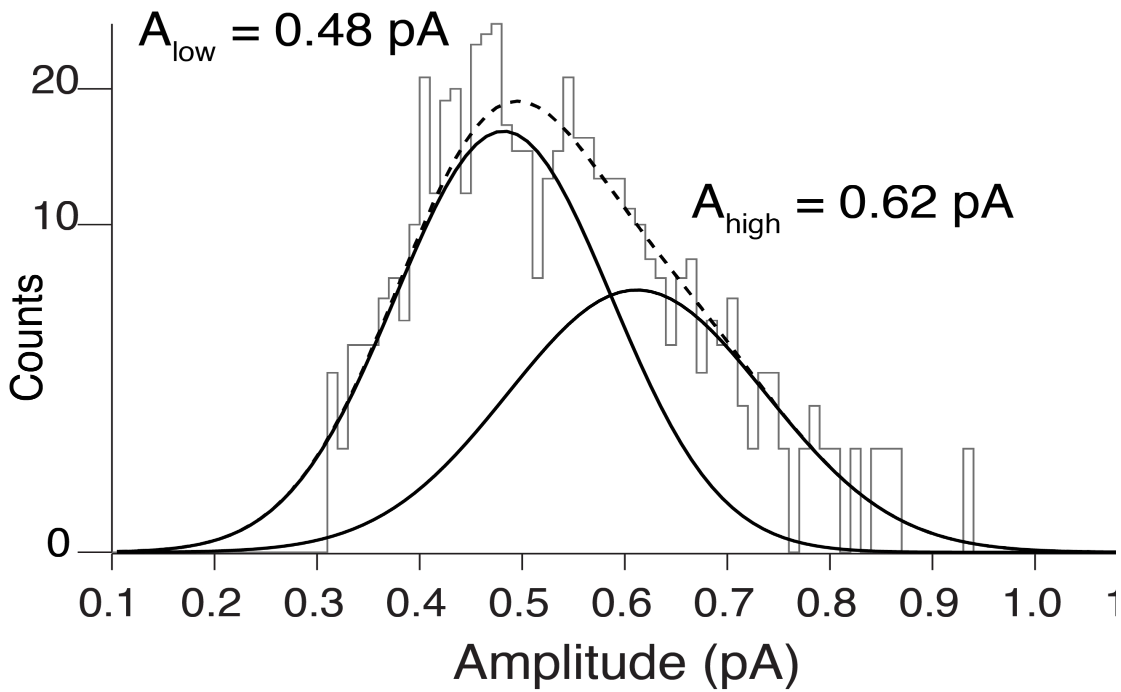

## Recording mode:

- Voltage clamp

## Event characteristics:

- Amplitude
- Open dwell time
- Closed dwell time

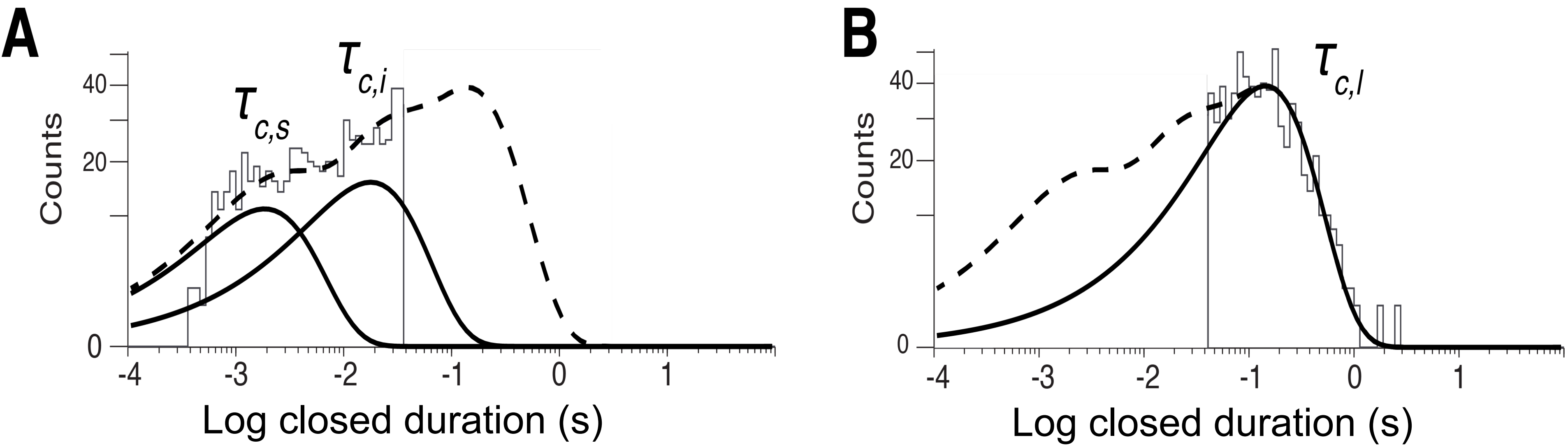
# Single-channel recordings




## Event characteristics:

- Amplitude (Gaussian)

# Single-channel recordings



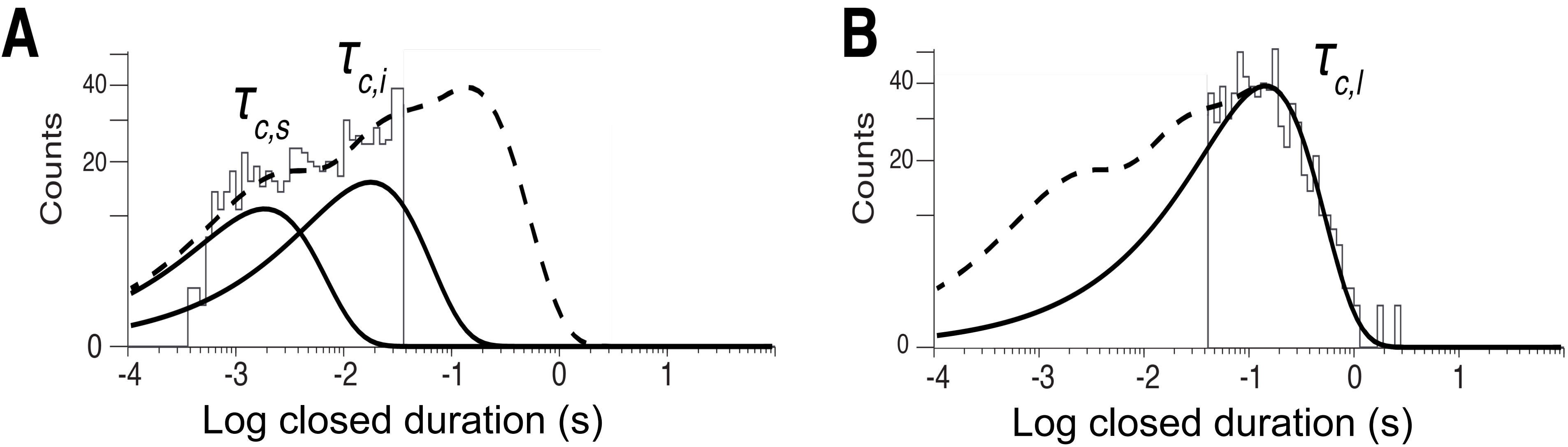

## Event characteristics:

- Open dwell time
- Closed dwell time

Mass action transition process, exponential in time:

$$p_i(t) = \frac{dP_i(t)}{dt} = K_i e^{-K_i t}$$

# Single-channel recordings




## Event characteristics:

- How many components are there?
- What do those components mean for model-building?

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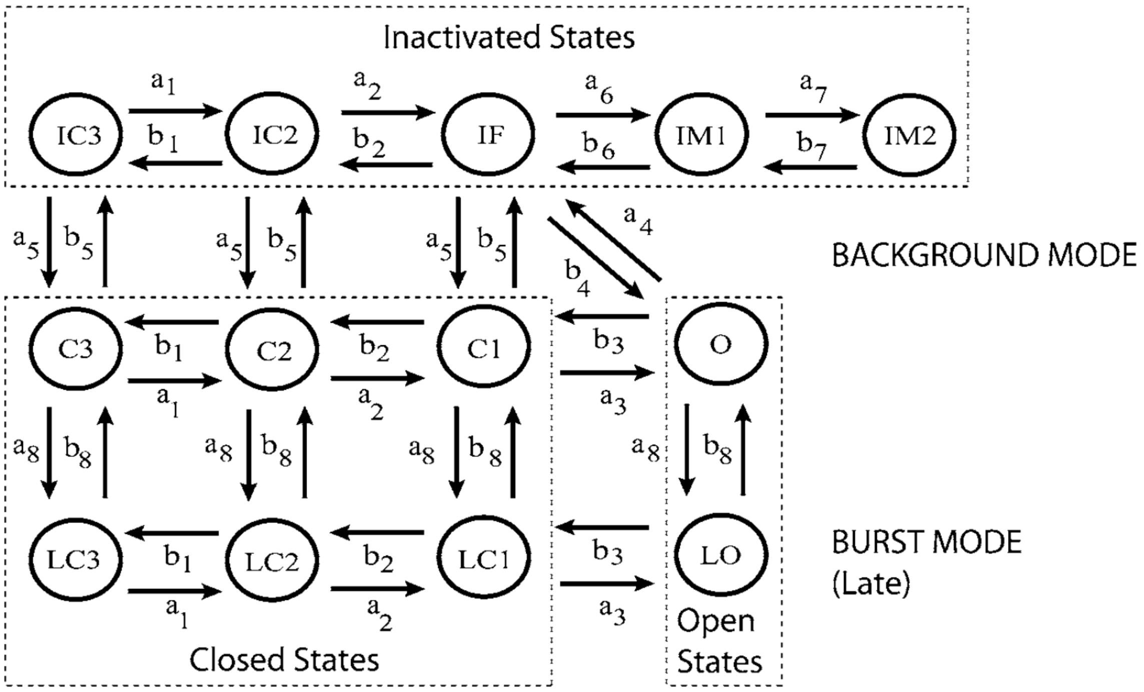
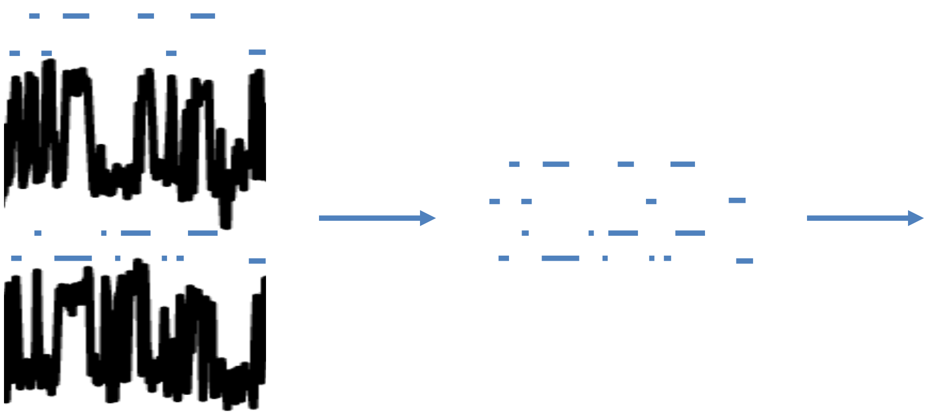


# Single-channel recordings

## Event characteristics:

- **How many components are there?**
  - We assume an exponential distribution for each single step process



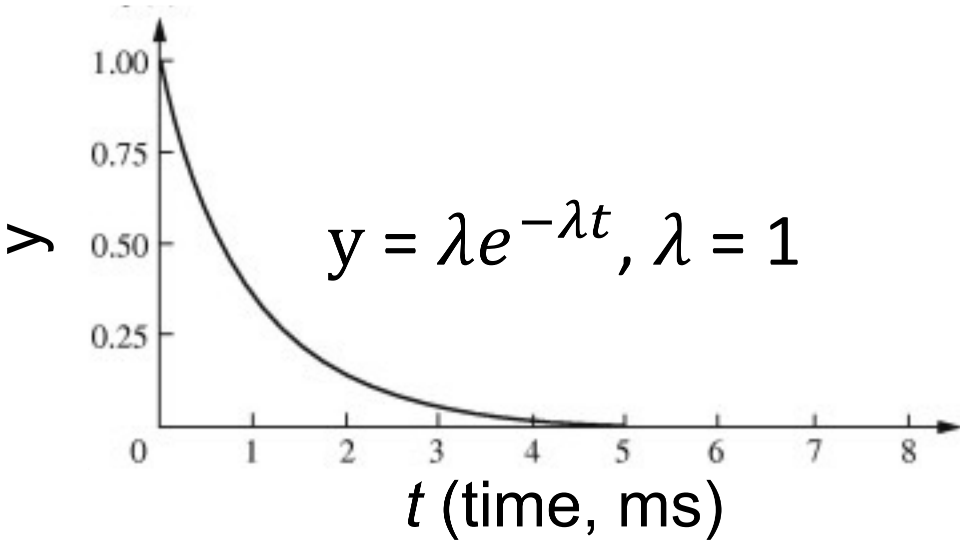
$[t_1, t_2, t_3, \ldots, t_n]$

# Single-channel recordings

## Event characteristics:

- **How many components are there**?
  - Example: closed dwell times in a simple single step gating process

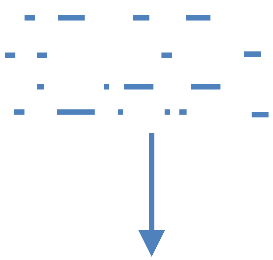
$$C \underset{\lambda}{\overset{\delta}{\leftrightarrows}} O$$



# Single-channel recordings

## Event characteristics:

- How many components are there?
  - Looking at a simple single exponential gating process



$[t_1, t_2, t_3, \ldots, t_n]$

$$y = \lambda e^{-\lambda t}$$

# Single-channel recordings

## Event characteristics:

- How many components are there?
  - Looking at a simple single exponential gating process

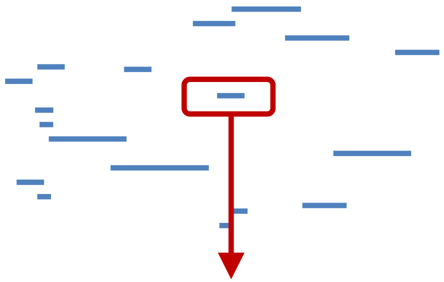
$[t_1, t_2, t_3, \ldots, t_n]$

$$y = \boxed{\lambda} e^{-\boxed{\lambda} t} \longrightarrow \underset{\lambda}{\arg\max}\, L(\lambda | t_1,\ t_2, t_3, \ldots, t_n)$$

# Single-channel recordings

## Event characteristics:

- How many components are there?
  - Likelihood of $t_1$ = 1.9 ms is simply the PDF value at *1.9 ms*



$t_1 = 1.9ms$

$$L(t_1|\lambda) = y = \lambda e^{-\lambda t}$$

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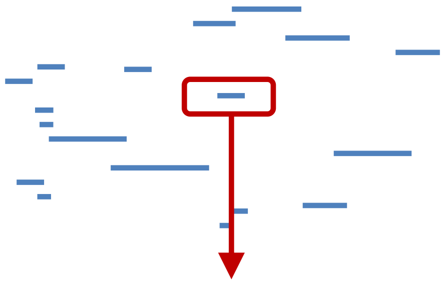
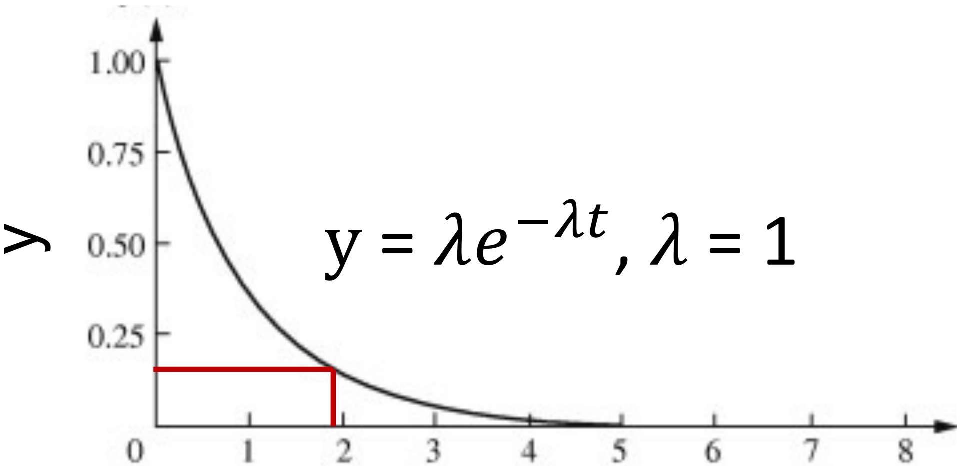


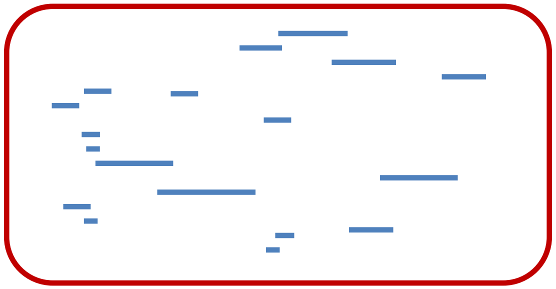
$t_1 = 1.9ms$




$$L(\lambda = 1 | t_1 = 1.9) = y = 1e^{-1 \cdot 1.9}$$

# Single-channel recordings

Now for all *t*

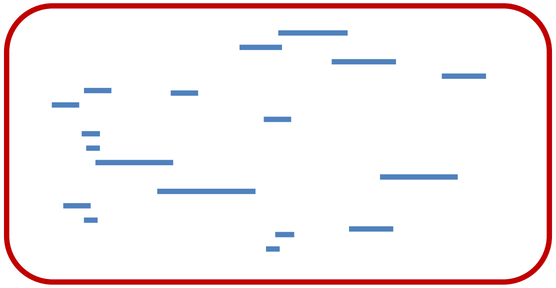


$$L(\lambda|t_1, t_2, t_3, \ldots, t_n) = \prod_{t=1}^{n} \lambda e^{-\lambda t}$$

$$= \lambda^n \left[ e^{-\lambda(t_1+t_2+t_3+\ldots+n)} \right]$$

# Single-channel recordings

Now for all *t*



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Gradient-based method (assumes convexity):

$$0 = \frac{d}{d\lambda} L(\lambda|t_1,\ t_2, t_3, \ldots, t_n) = \frac{d}{d\lambda} \lambda^n \left[ e^{-\lambda(t_1+t_2+t_3+\ \ldots+n)} \right]$$

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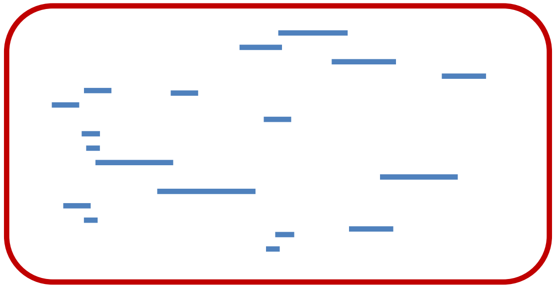

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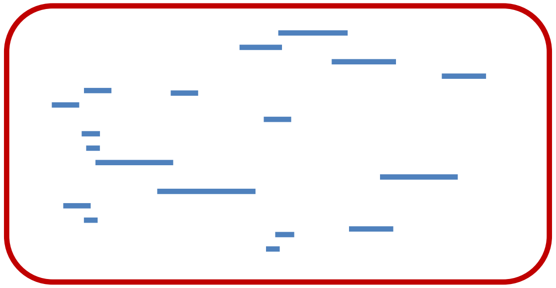

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$$= n\frac{1}{\lambda} - (t_1 + t_2 + t_3 +\ \dots + t_n)$$

$$MLE\ estimate\ of\ \lambda = \frac{n}{(t_1 + t_2 + t_3 +\ \dots + t_n)}$$

# Single-channel recordings

Multiple kinetic components:

$$L(\lambda_1, \lambda_2, \dots, \lambda_m; a_1, a_2, \dots, am | t_1, t_2, t_3, \dots, t_n) = \prod_{t=1}^{n} [a_1\lambda_1 e^{-\lambda_1 t} + a_2\lambda_2 e^{-\lambda_2 t} + \dots + a_m\lambda_m e^{-\lambda_m t}]$$

$$MLE\ (m) > MLE\ (m-1)?$$

# Single-channel recordings

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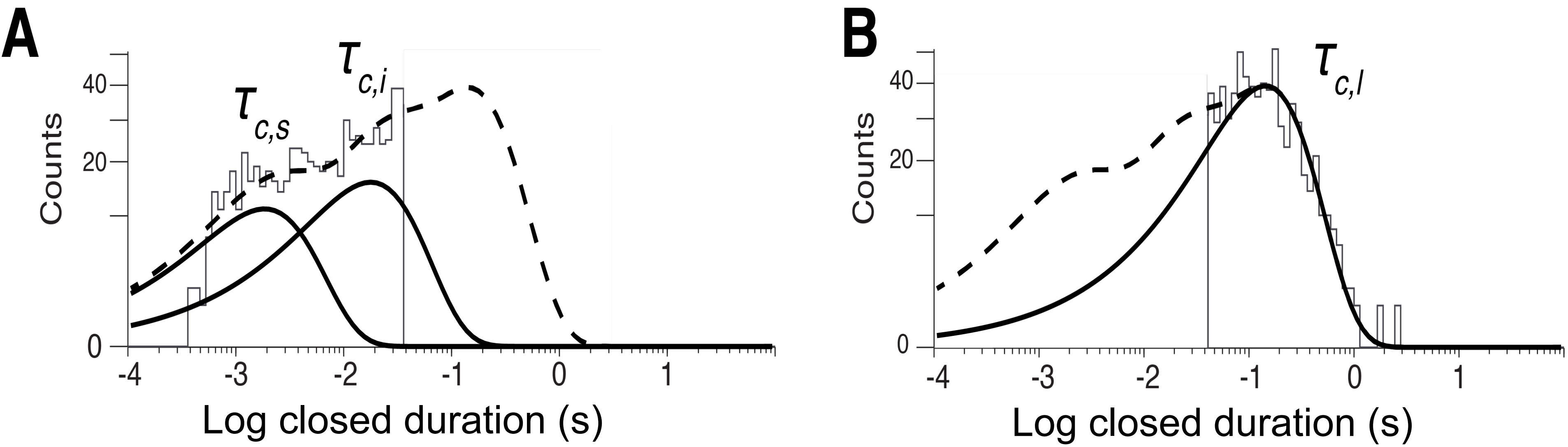
$$likelihood\ ratio\ test: \vec{t} \stackrel{\text{def}}{=} [t_1, t_2, t_3, \dots, t_n]$$

*(log transformed data)*

$$\Lambda(\vec{t}) = -2\ln\left[\frac{MLE(m-1)}{MLE(m)}\right], \quad \text{or} \quad \Lambda(\vec{t}) = -2[\ell(m-1) - \ell(m)]$$

# Single-channel recordings

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*From L4:*

$$E(T_i) = \int_0^\infty t p_i(t) dt = \frac{1}{K_i}$$

# Single-channel recordings

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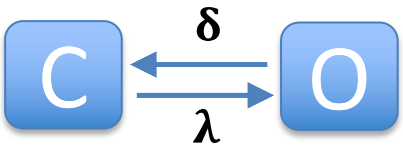
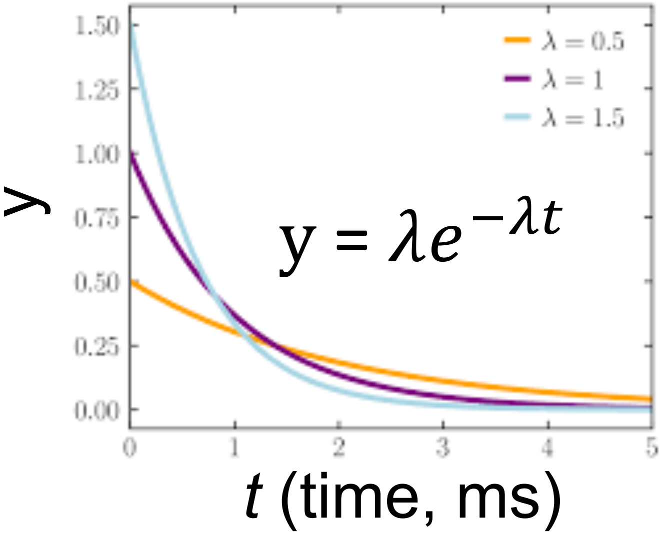
- **What do these components mean?**

*From L4:*

$$E(T_i) = \int_0^\infty t p_i(t) dt = \frac{1}{K_i}$$

$$E(t_i) = \int_0^\infty t\lambda_i e^{-\lambda_i t}\, dt,\ \ (i = 1, \dots,\ m)$$
$$= \frac{1}{\lambda_i}$$
$$= \tau_i$$
$$= \mathit{mean\ dwell\ time\ of\ ith\ component}$$



# Single-channel recordings

## Event characteristics:

- What do these components mean?

## Some conceptual exercises:

- You have data exhibiting 2 distinct closed dwell times and 1 open dwell time. Try to draw a model of this channel.

# Single-channel recordings

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- You have data exhibiting 2 distinct closed dwell times and 1 open dwell time. Try to draw a model of this channel.
- How many open states does it have?
- How many closed states does it have?
- Does it include an inactive state?

# Single-channel recordings

## Event characteristics:

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## Some conceptual exercises:

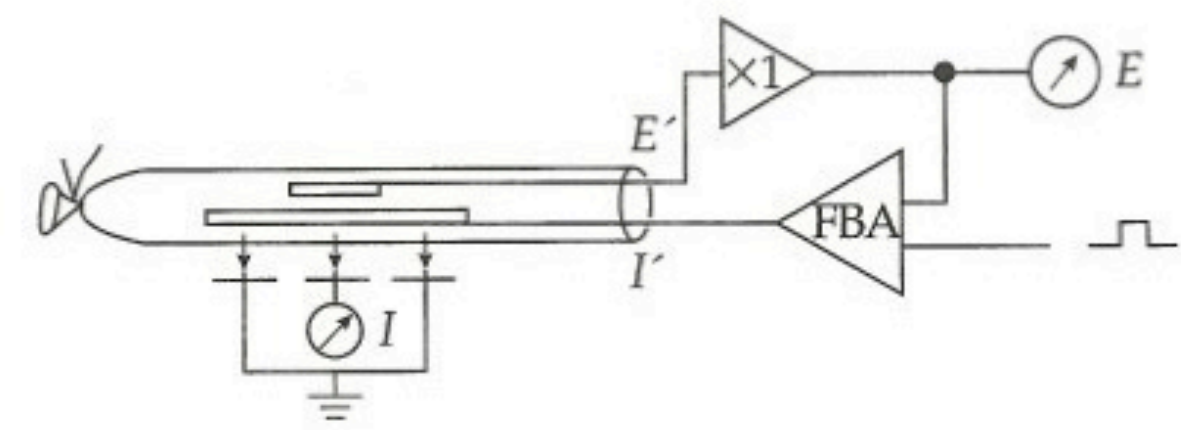
- You have data exhibiting 2 distinct closed dwell times and 1 open dwell time. Try to draw a model of this channel.
- How many open states does it have?
- How many closed states does it have?
- Does it include an inactive state?
- Try to repeat these questions for a channel with 3 closed dwell times and 2 open dwell times

# Take a break

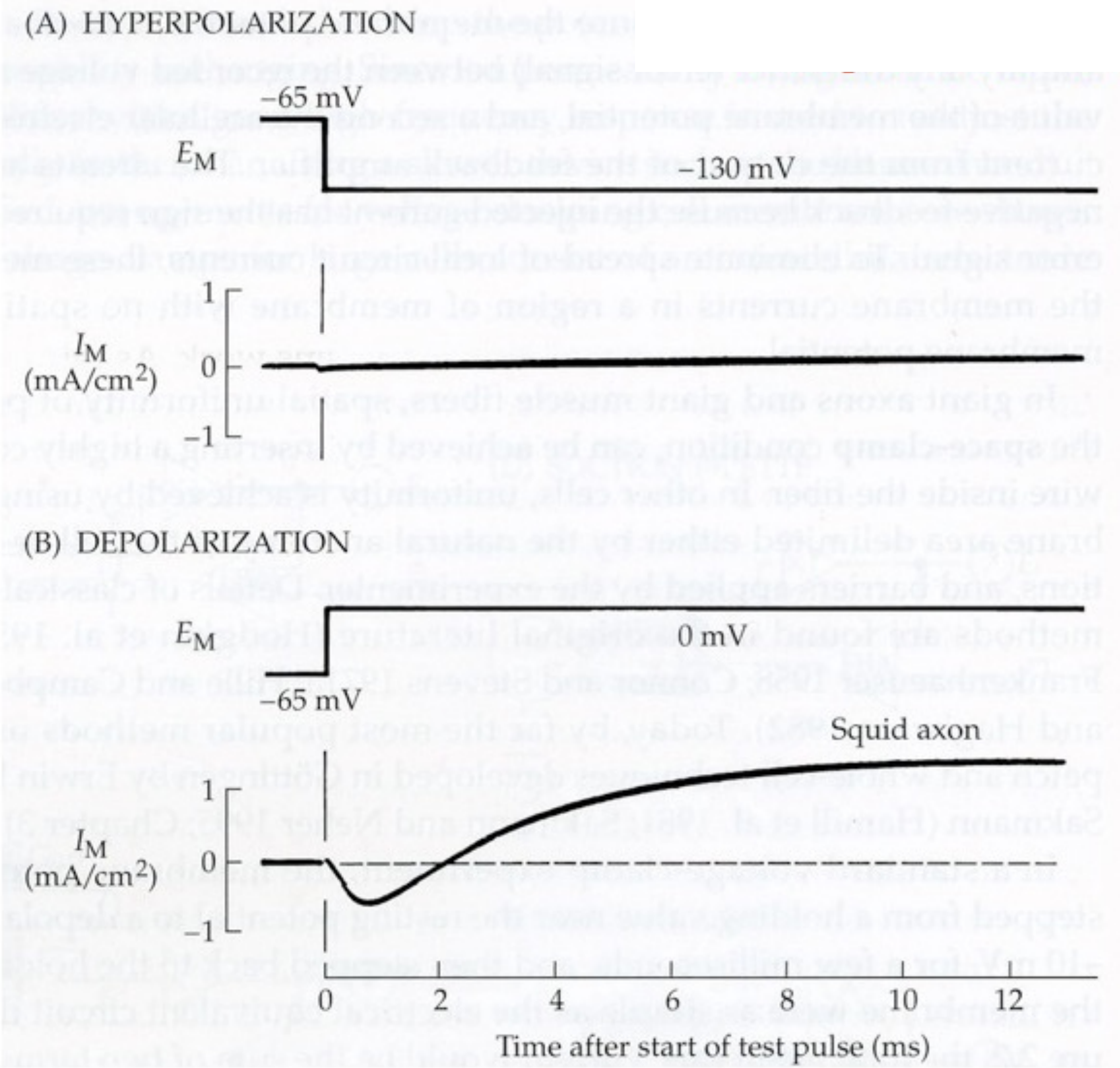
# Whole-cell recordings

- Hodgkin and Huxley voltage clamp

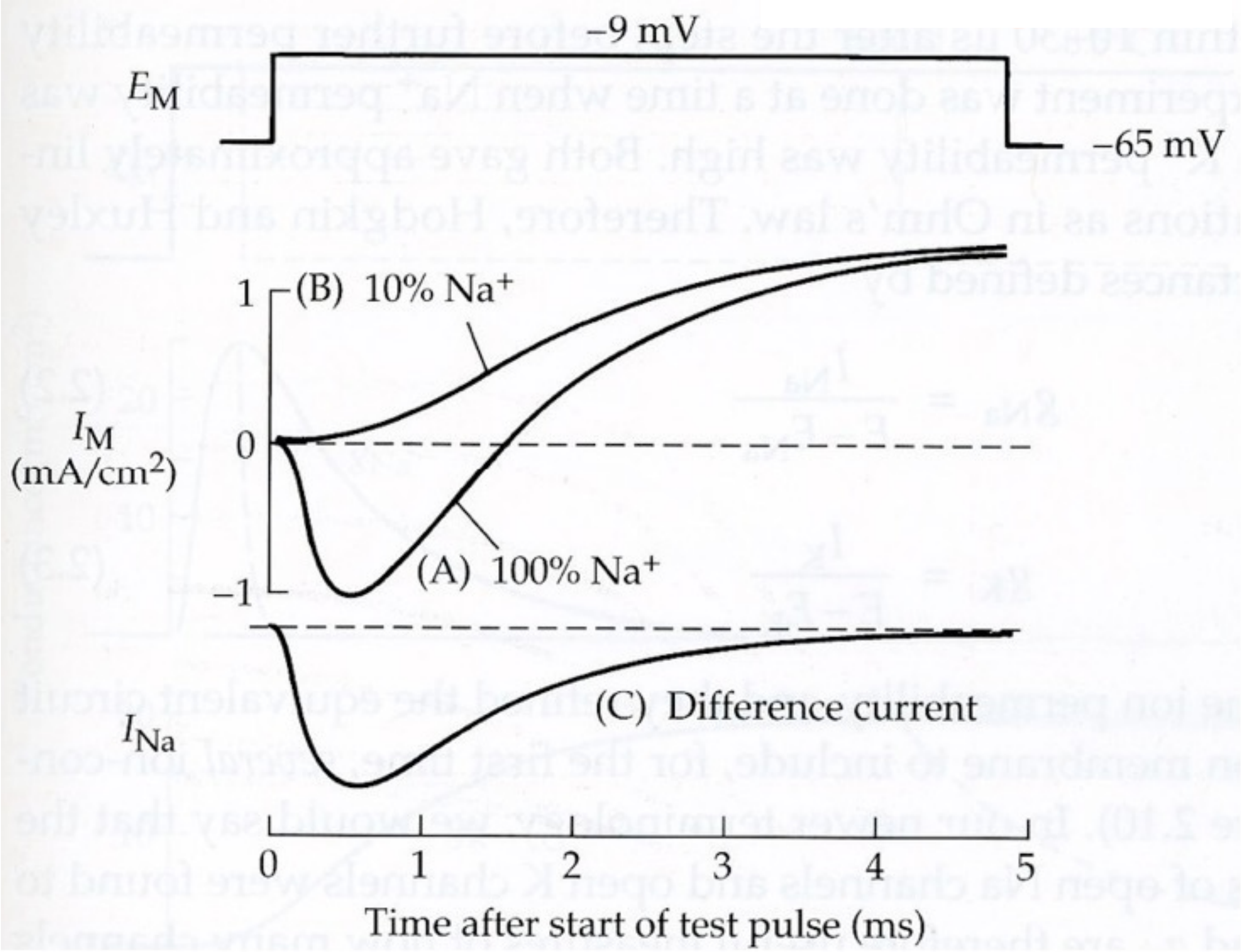
(A) AXIAL WIRE



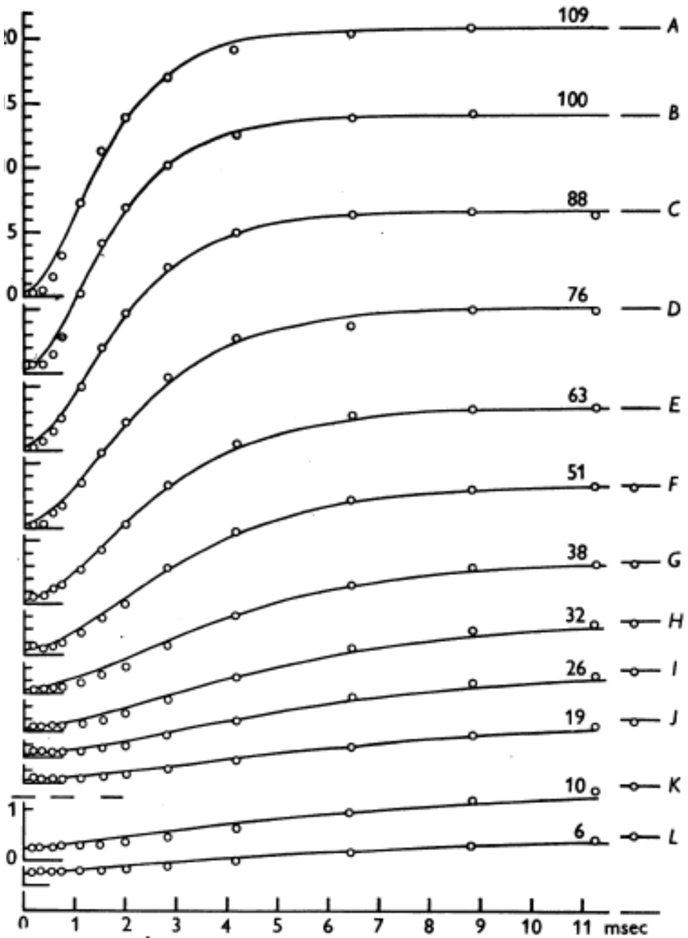
# Whole-cell recordings: Hodgkin and Huxley



# Whole-cell recordings: Hodgkin and Huxley



# Whole-cell recordings: $K^+$ current ($I_K$)




*$I_K$ measured at increasingly positive holding potentials*

- *What information can you retrieve from these traces?*

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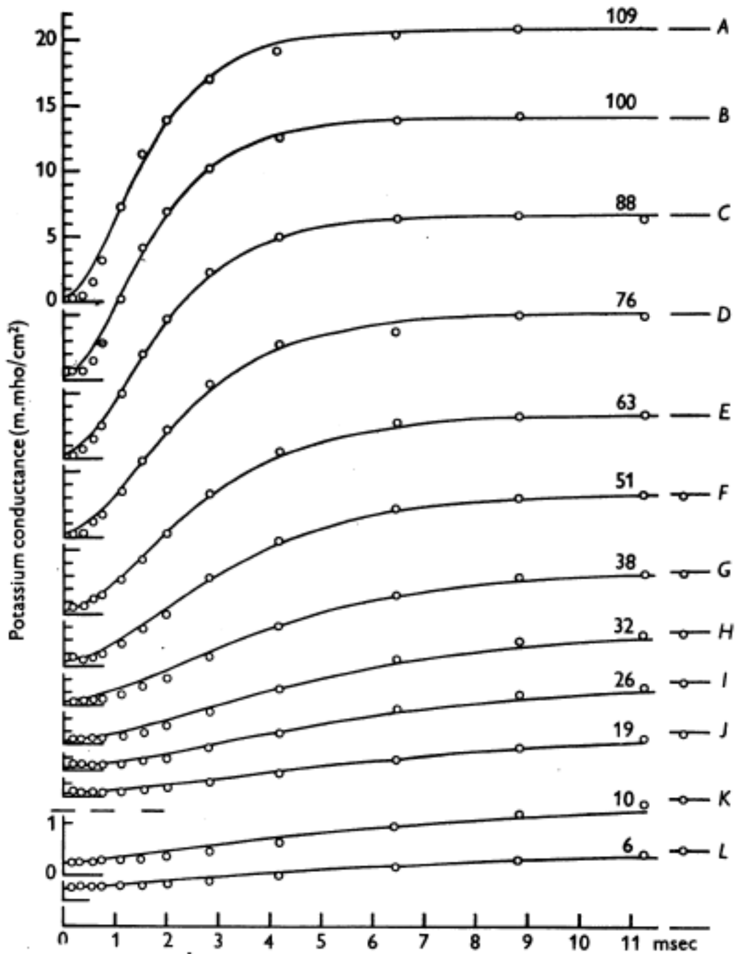


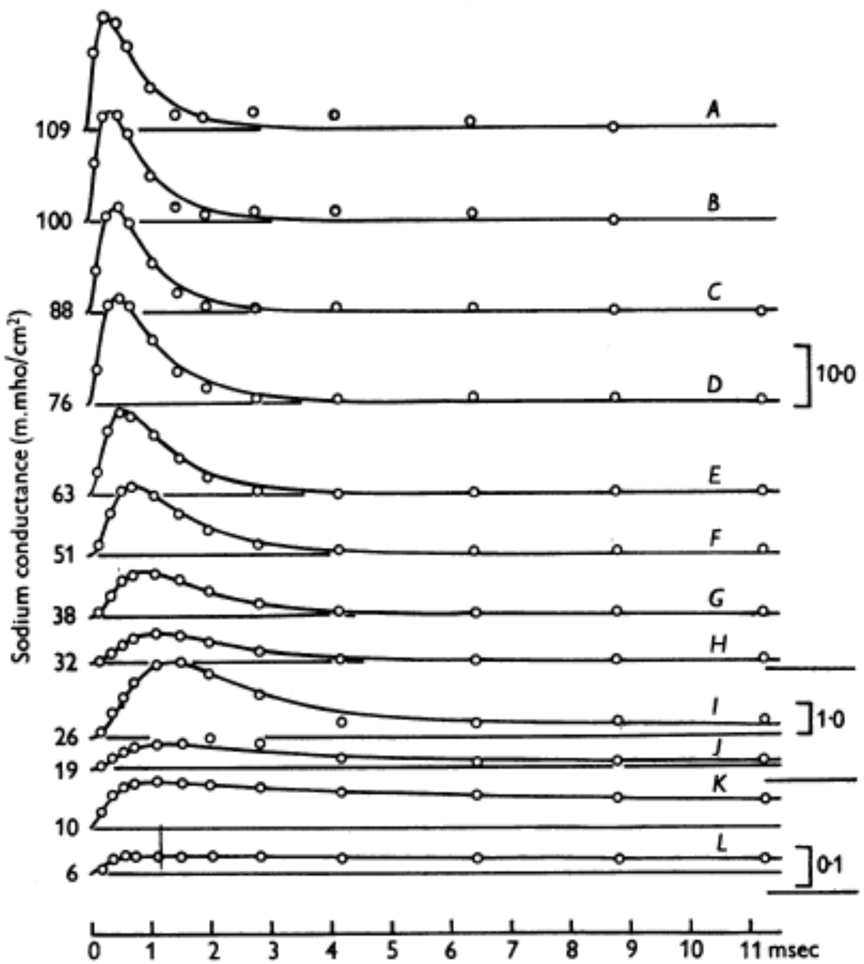

*$I_K$ measured at increasingly positive holding potentials*

- *What information can you retrieve from these traces?*

1. *Peak (equilibrium) current*
2. *Kinetics of current activation*
3. *Voltage dependence*
4. *Inactivation?*
5. *Deactivation?*

$$g_K = \bar{g}_K n^4, \text{ with } \frac{dn}{dt} = \alpha(v)(1-n) - \beta(v)n$$

# Whole-cell recordings: $Na^+$ current ($I_{Na}$)

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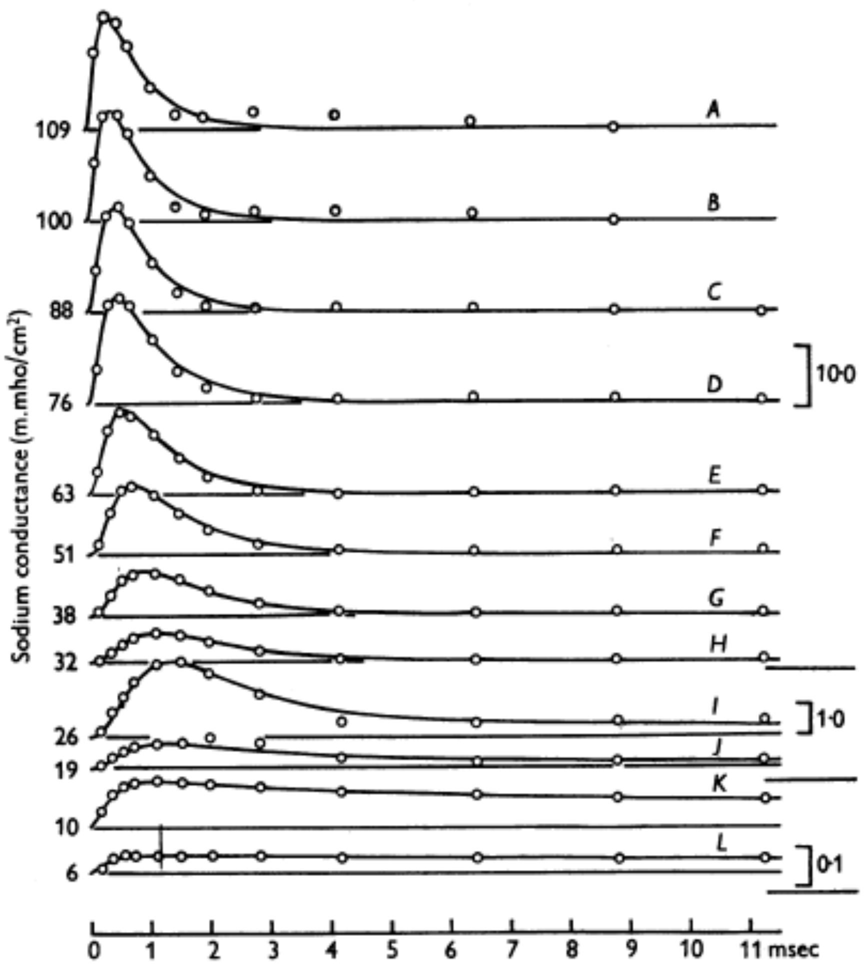
- *What information can you retrieve from these traces?*

# Whole-cell recordings: Na$^+$ current ($I_{Na}$)

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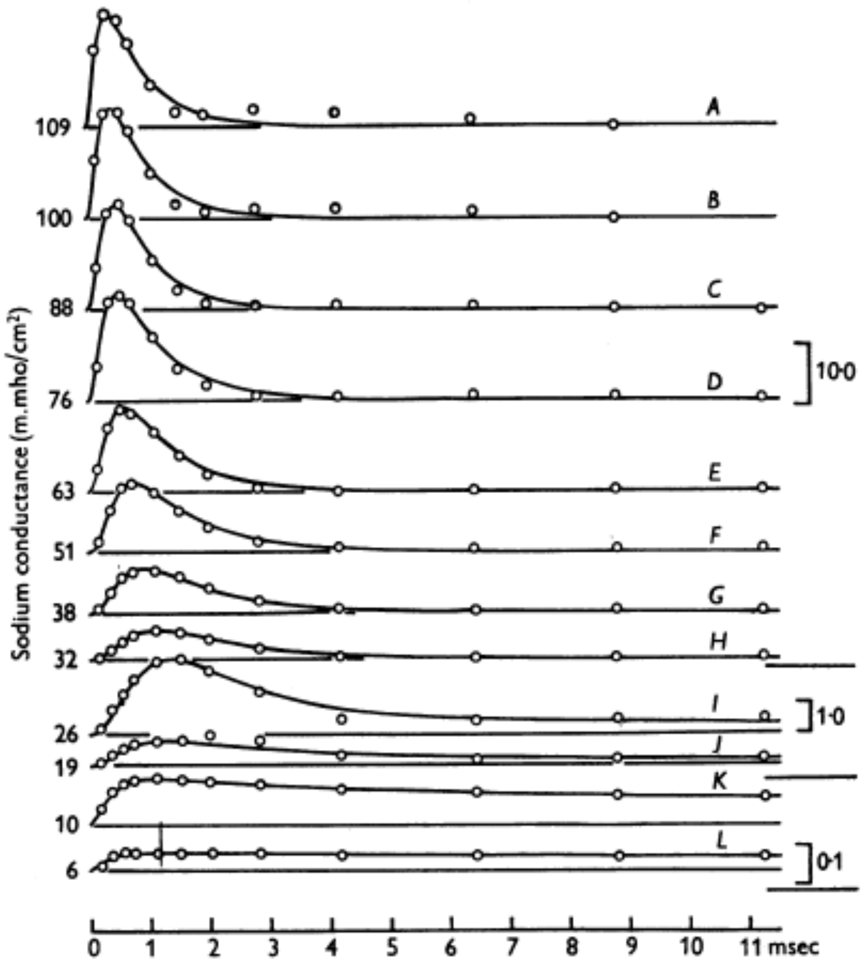


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- *What information can you retrieve from these traces?*

1. *Peak current*
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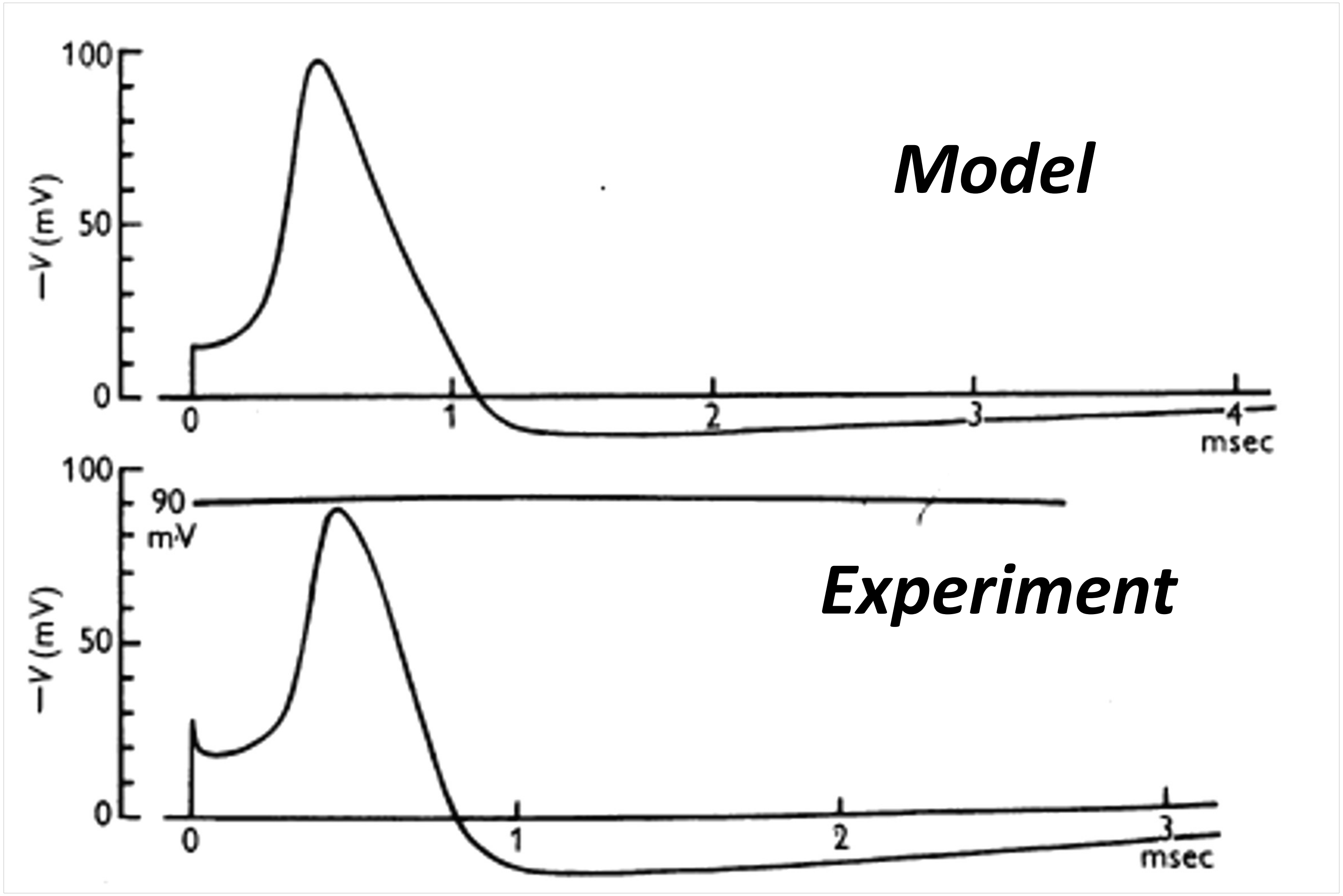
$$\frac{dg_{Na}}{dt} = \overline{g}_{Na} m^3 h$$

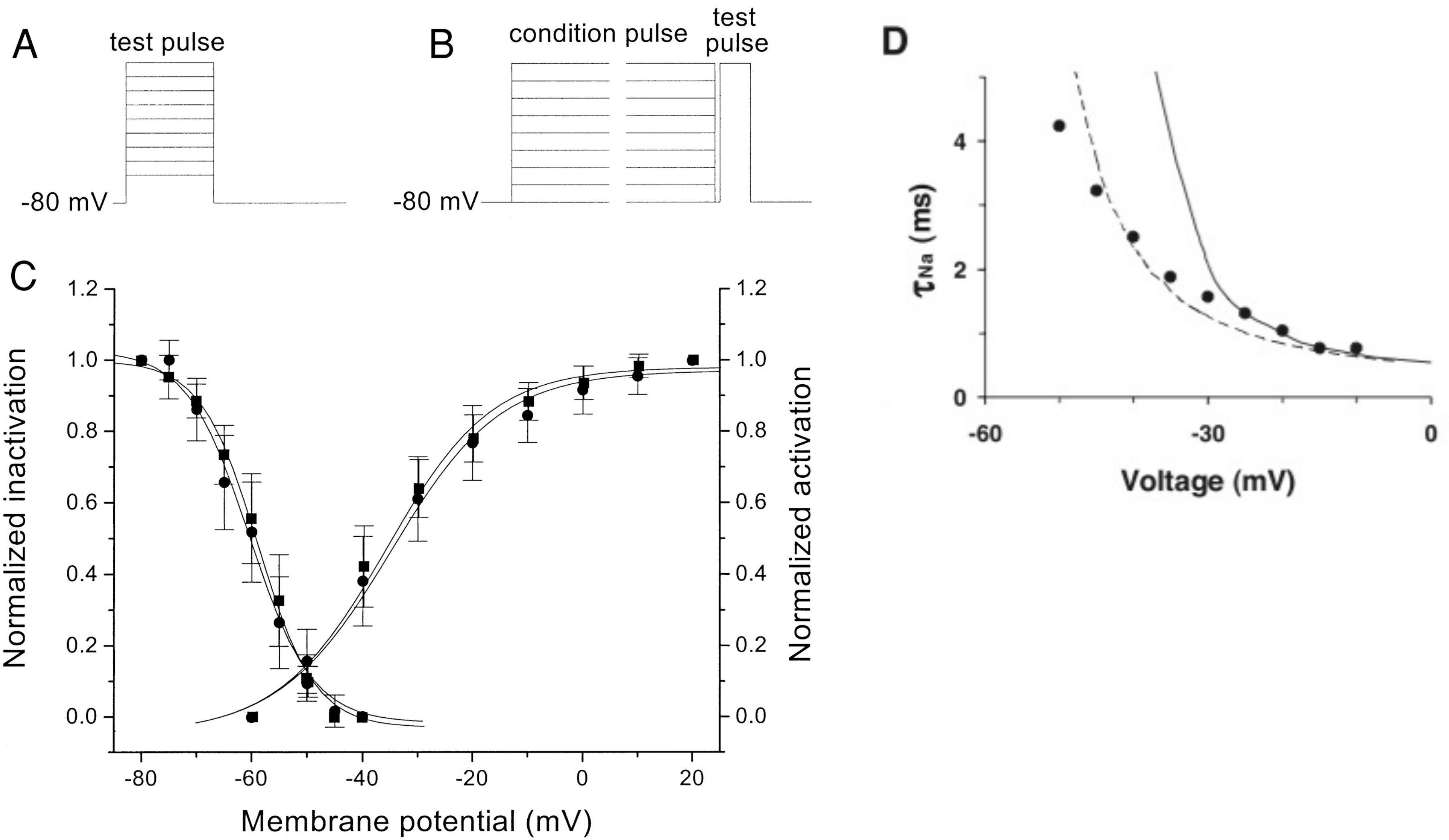
$$\frac{dm}{dt} = \alpha(1-m) - \beta m,$$

$$\frac{dh}{dt} = \gamma(1-h) - \delta h,$$

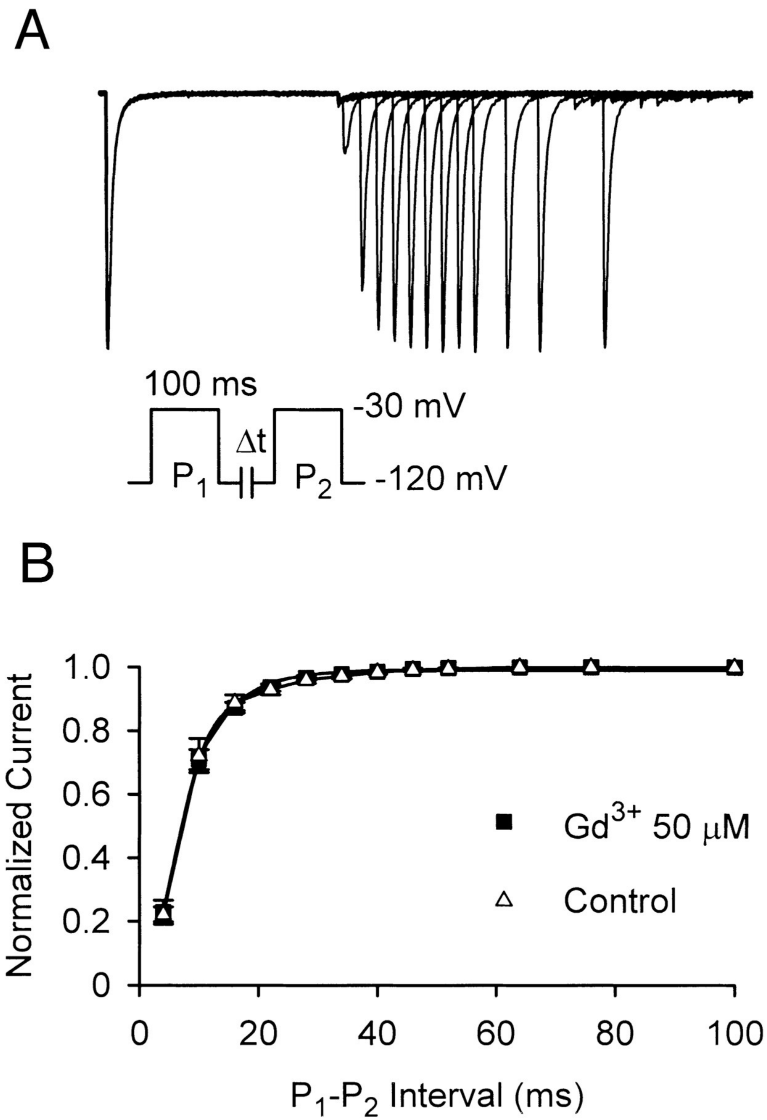
# Whole-cell recordings: Reconstructed AP



# Conventional protocols: activation and inactivation

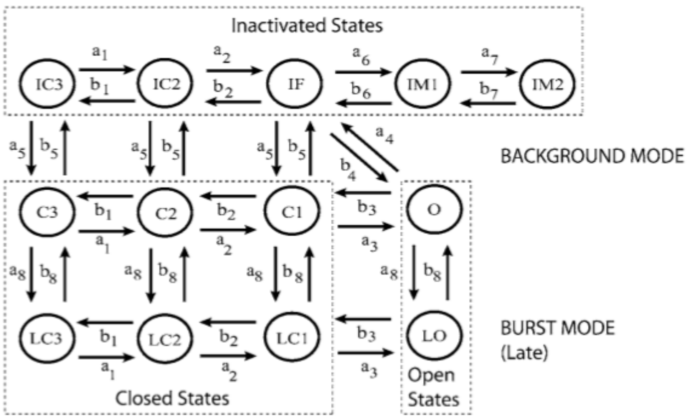


# Conventional protocols: recovery from inactivation



# Conventional protocols: combinatorial optimization

*A priori constraints*



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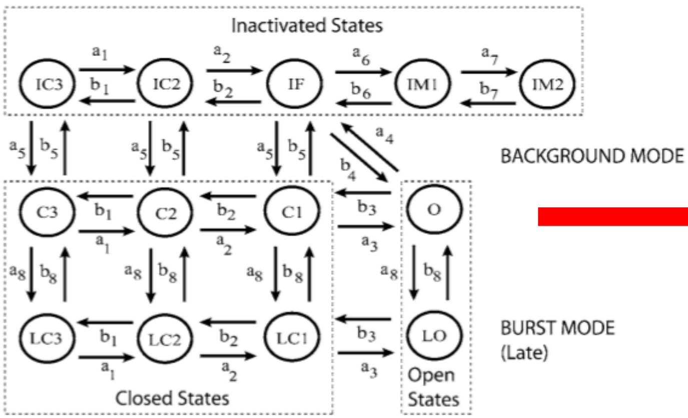
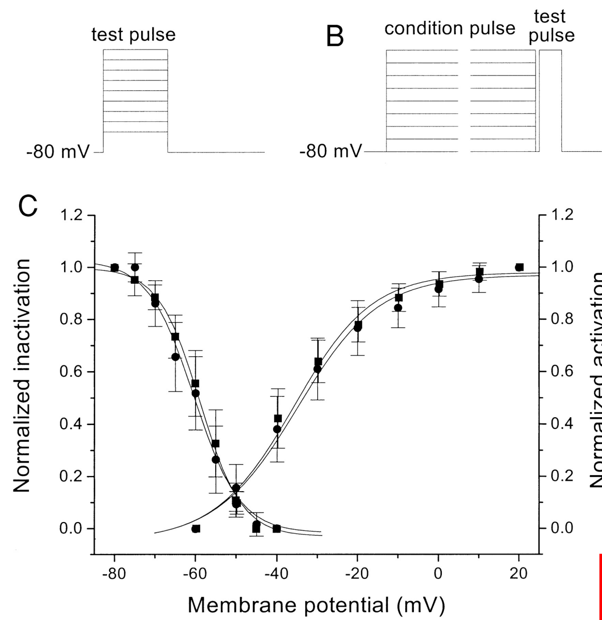
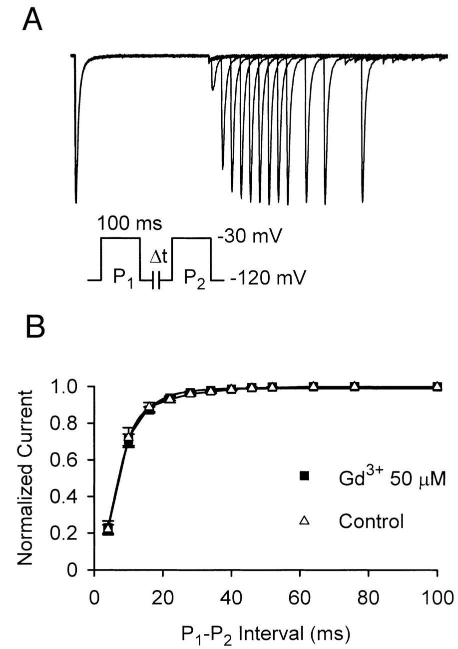


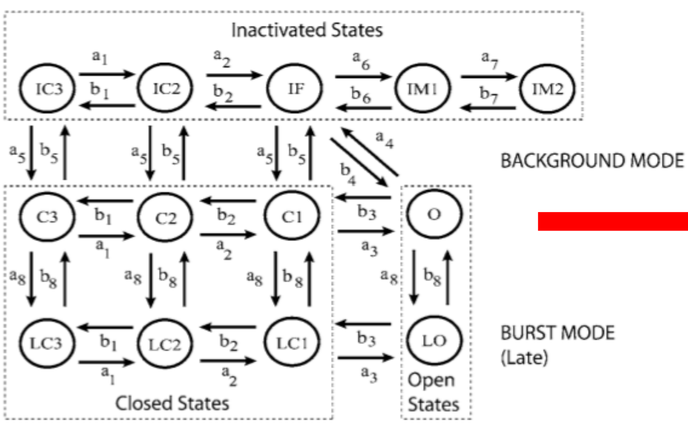



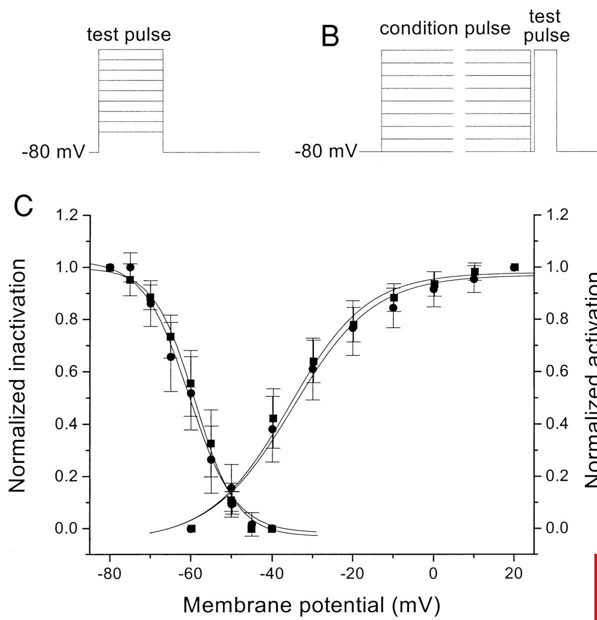

*Cost function*

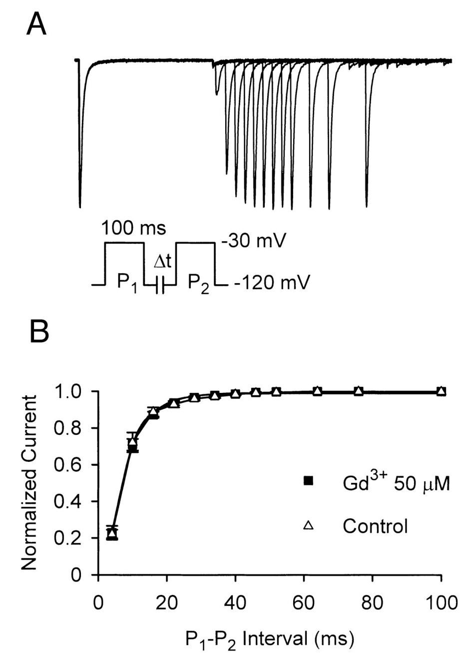
*- Error estimate*

# Conventional protocols: combinatorial optimization

*A priori constraints*



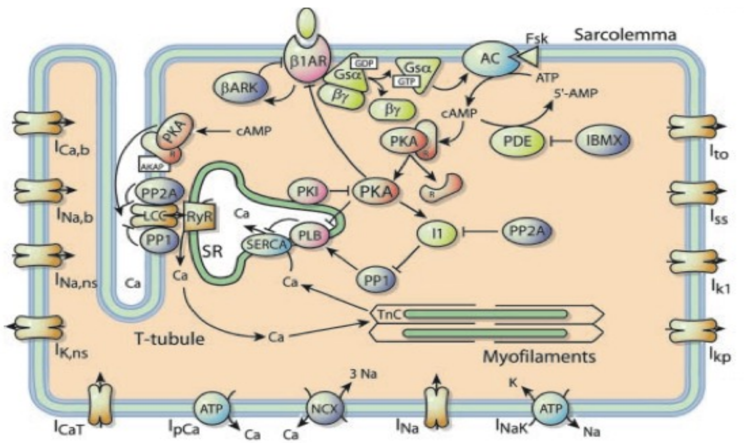

*Cost function*

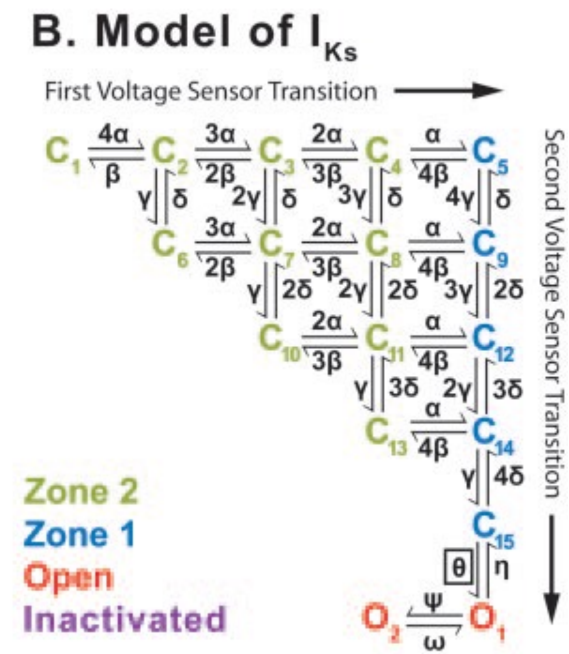
*- Error estimate*

*Optimization algorithm*

*- Parameter reconfiguration*

# L5: Practical aspects of building channel and cell models

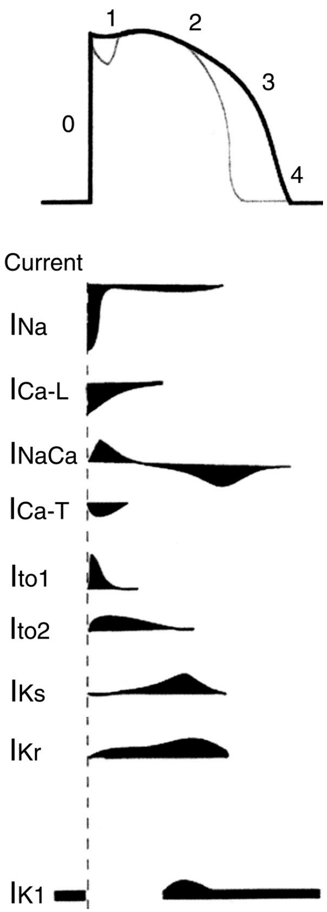


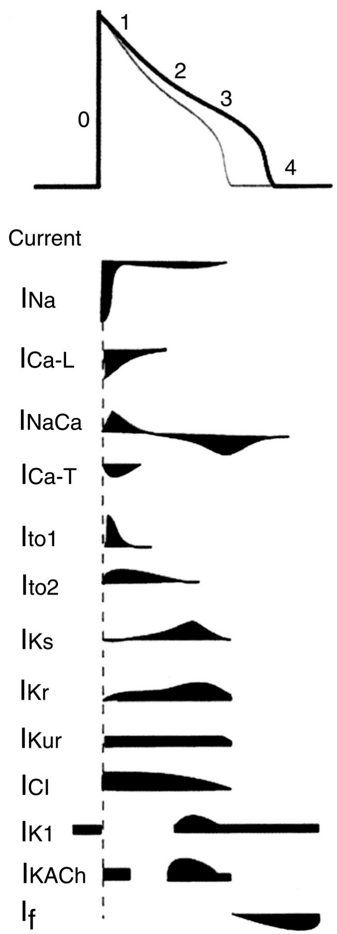

- *Reconstructing excitability*
  - ***Experimental data source***
    - *Single-channel recordings*
    - *Single-channel analysis*
    - *Whole-cell recordings*
  - ***Major cardiac ion current models***
    - *Hodgkin-Huxley type models*
    - *Generalised Markov models*

# Major cardiac ion currents

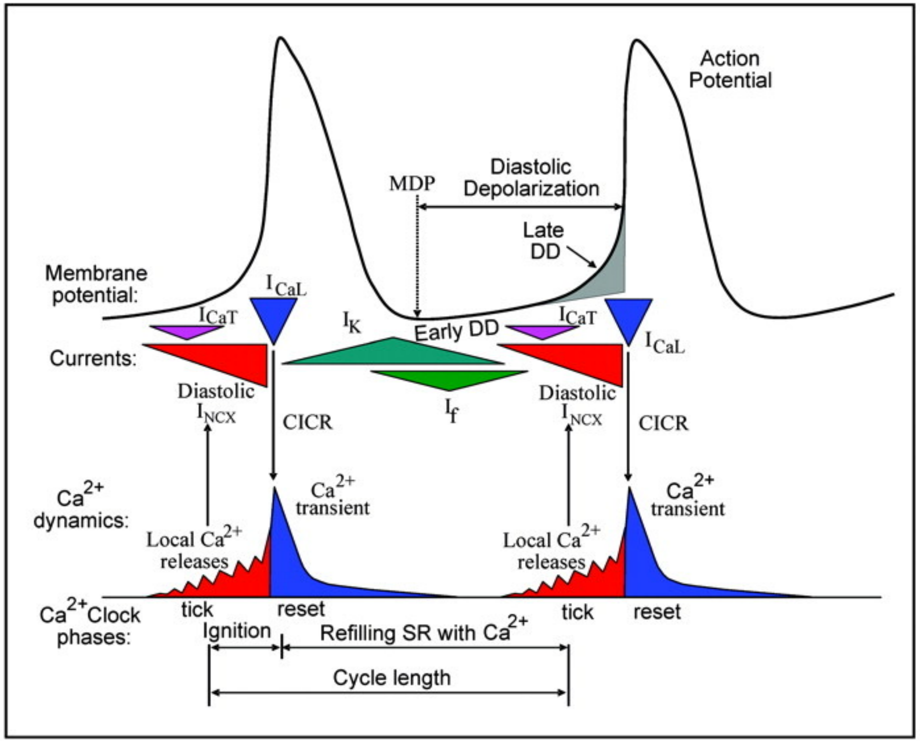
Ventricle




Atrium




*Sinus Node*



# Sodium current ($I_{Na}$) models

**Hodgkin and Huxley (1952)**

$$\frac{dg_{\mathrm{Na}}}{dt} = \overline{g}_{\mathrm{Na}} m^3 h$$

$$\frac{dm}{dt} = \alpha(1-m) - \beta m,$$

$$\frac{dh}{dt} = \gamma(1-h) - \delta h,$$

***Alpha subunit***

*GENE: SCN5a*

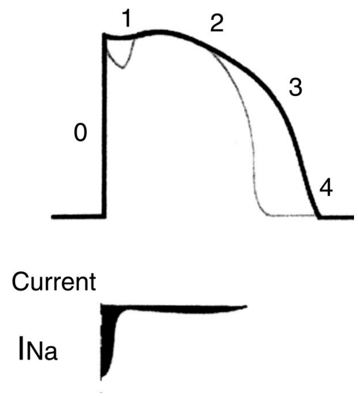
*PROTEIN: NaV1.5*

***Beta subunit***

*GENE: SCN1B*

*PROTEIN: β1B*

Ventricle



# Sodium current ($I_{Na}$) models

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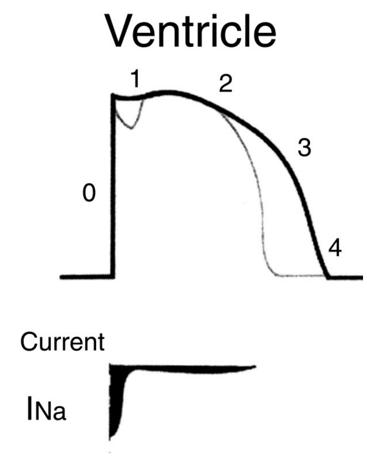
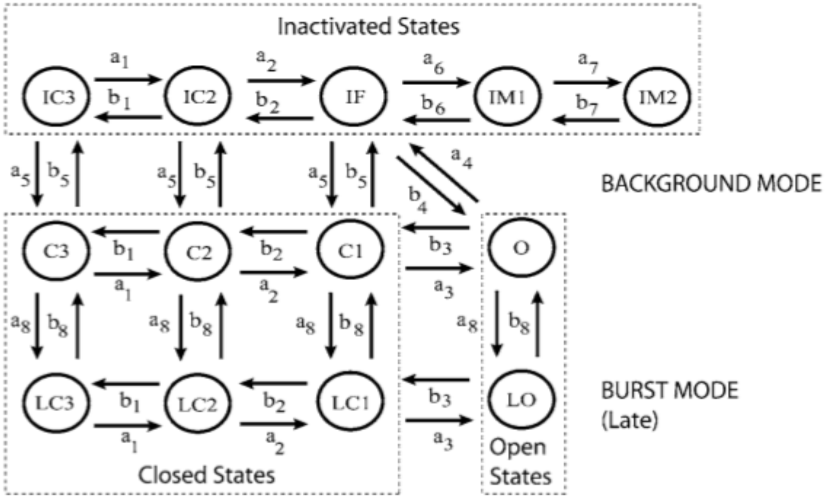
*PROTEIN: $\beta$1B*




## Clancy and Rudy (1999)

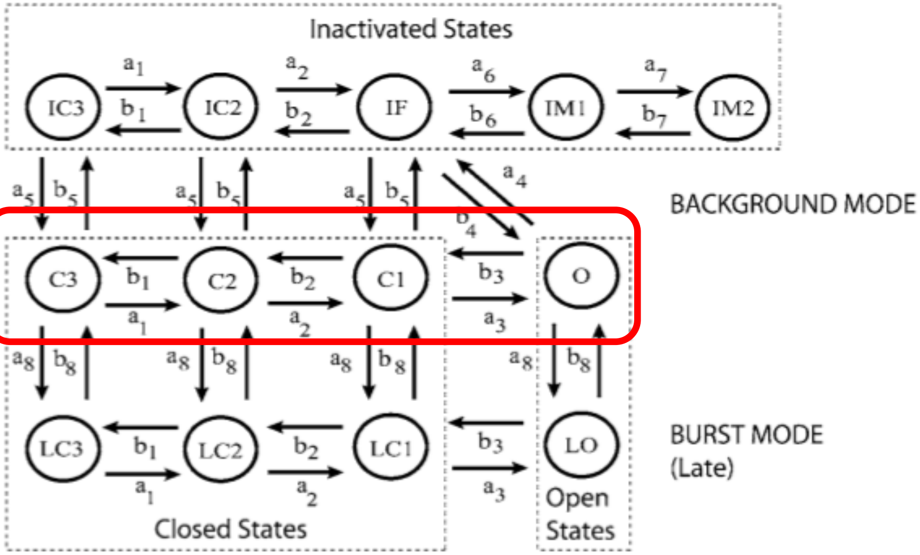


# Sodium current ($I_{Na}$) models

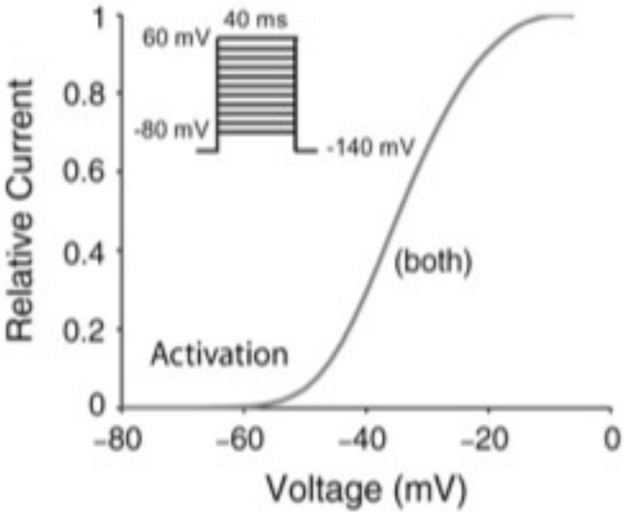
$$\frac{dg_{Na}}{dt} = \bar{g}_{Na} m^3 h$$

$$\boxed{\frac{dm}{dt} = \alpha(1-m) - \beta m,}$$

$$\frac{dh}{dt} = \gamma(1-h) - \delta h,$$




**Steady-state activation**



# Sodium current ($I_{Na}$) models

$$\frac{dg_{Na}}{dt} = \bar{g}_{Na} m^3 h$$

$$\frac{dm}{dt} = \alpha(1-m) - \beta m,$$

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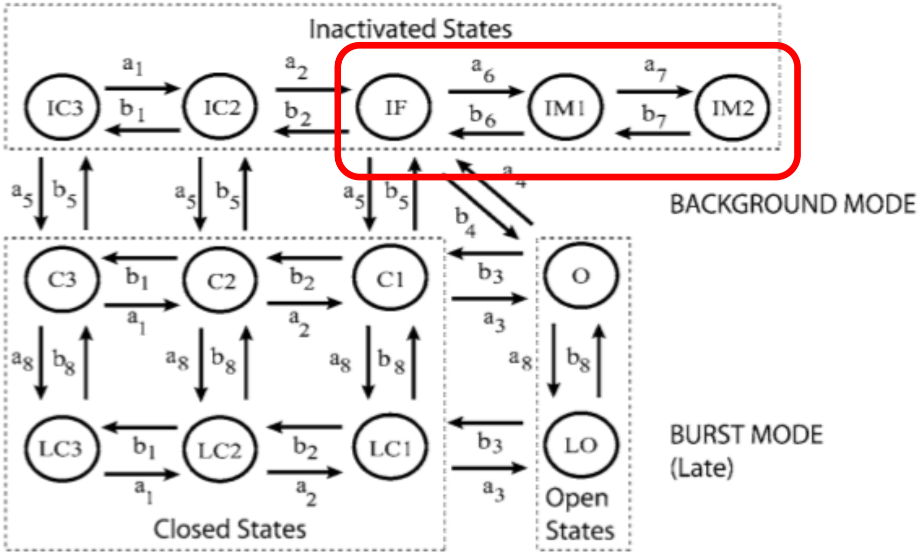
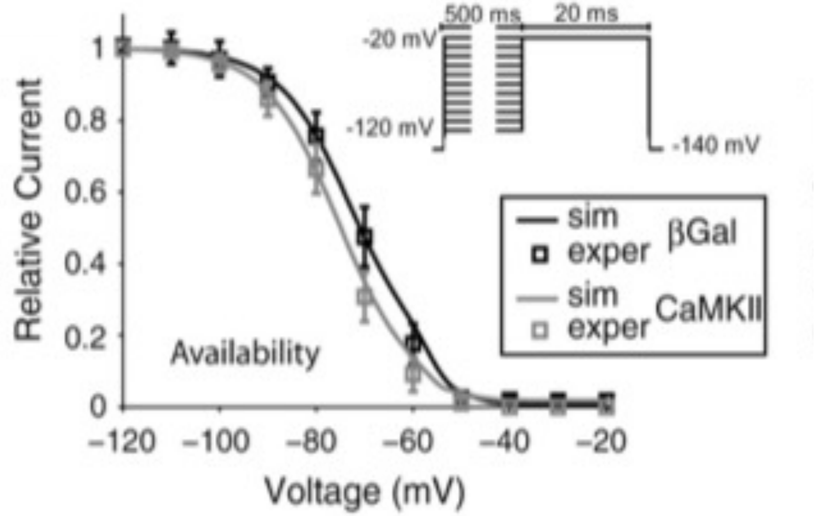



**Steady-state inactivation**

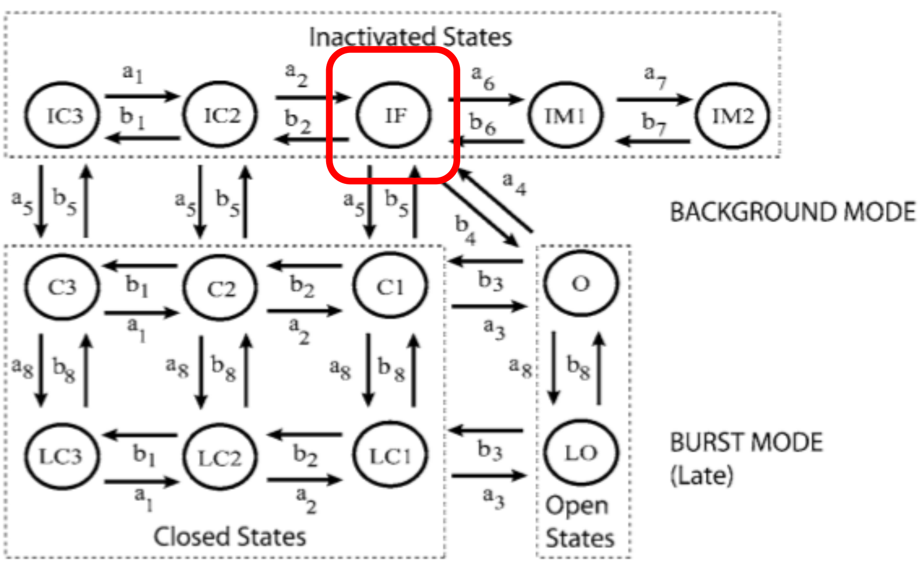


# Sodium current ($I_{Na}$) models

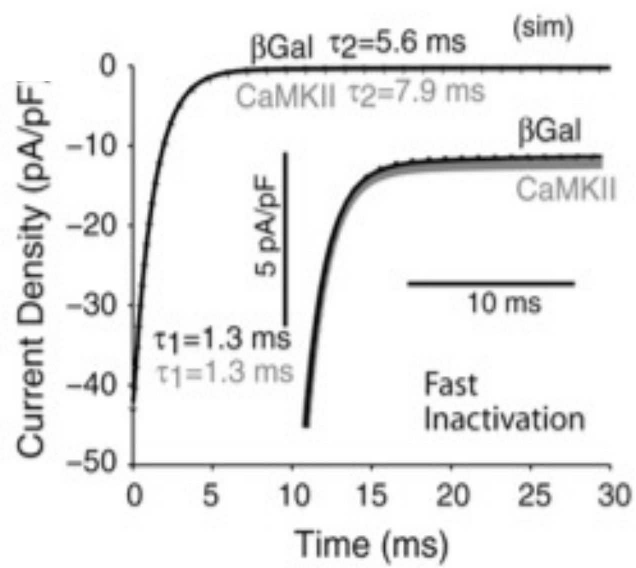
$$\frac{dg_{Na}}{dt} = \bar{g}_{Na} m^3 h$$

$$\frac{dm}{dt} = \alpha(1 - m) - \beta m,$$

$$\boxed{\frac{dh}{dt} = \gamma(1 - h) - \delta h,}$$




## Fast inactivation

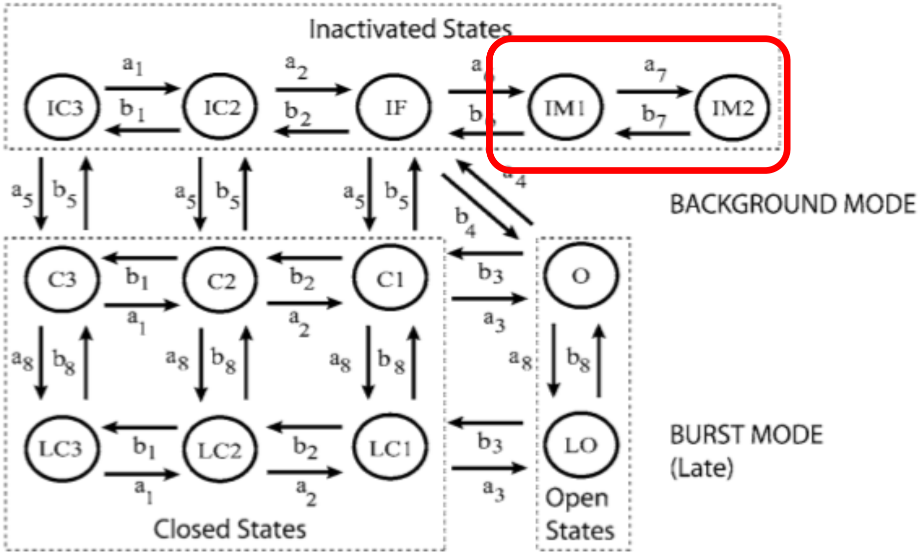


# Sodium current ($I_{Na}$) models

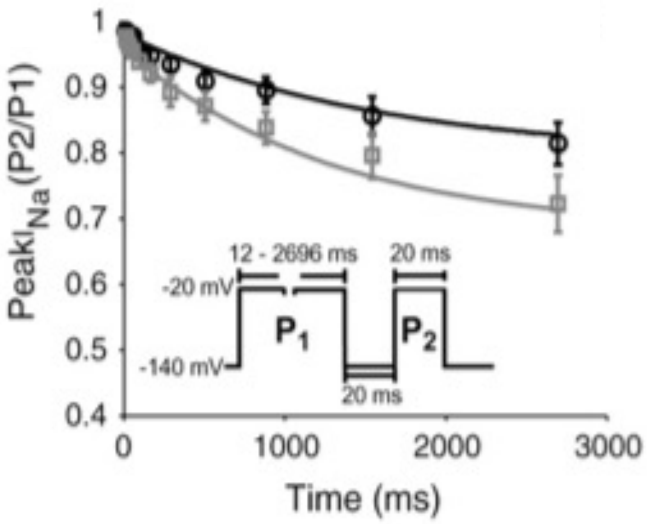
$$\frac{dg_{Na}}{dt} = \bar{g}_{Na} m^3 h$$

$$\frac{dm}{dt} = \alpha(1-m) - \beta m,$$

$$\boxed{\frac{dh}{dt} = \gamma(1-h) - \delta h,}$$




## Intermediate inactivation

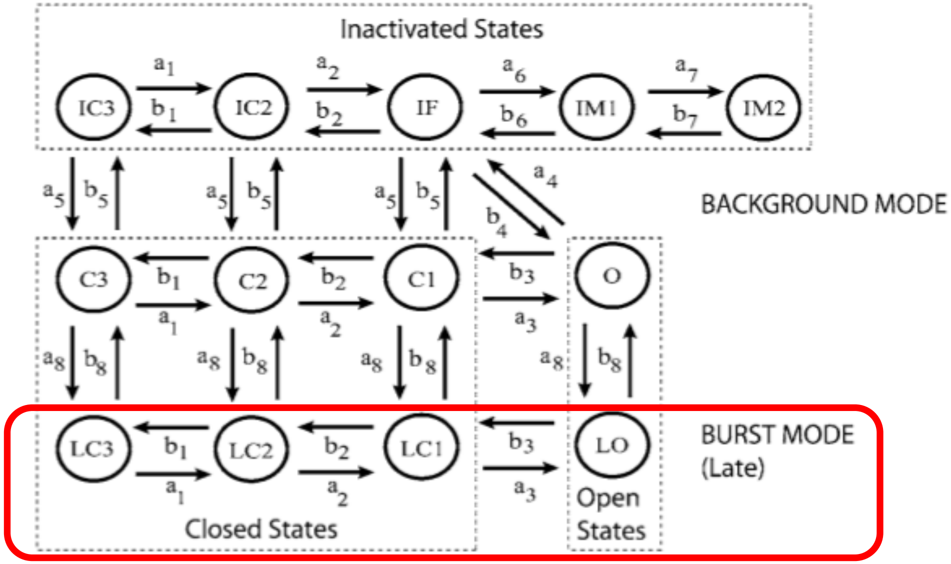


# Sodium current ($I_{Na}$) models

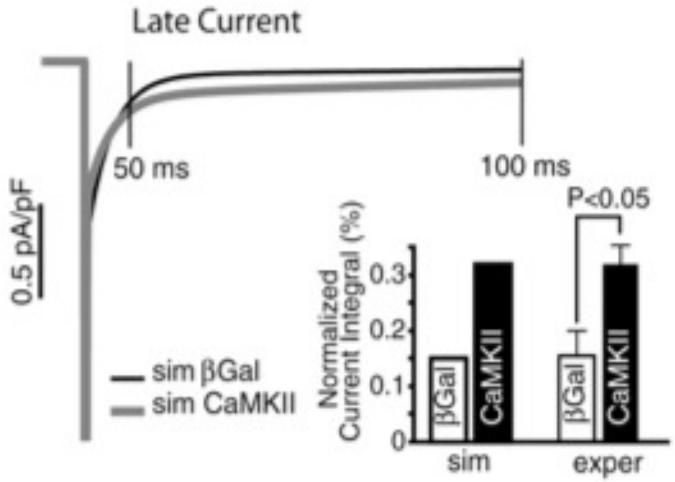
$$\frac{dg_{Na}}{dt} = \bar{g}_{Na} m^3 h$$

$$\frac{dm}{dt} = \alpha(1-m) - \beta m,$$

$$\frac{dh}{dt} = \gamma(1-h) - \delta h,$$



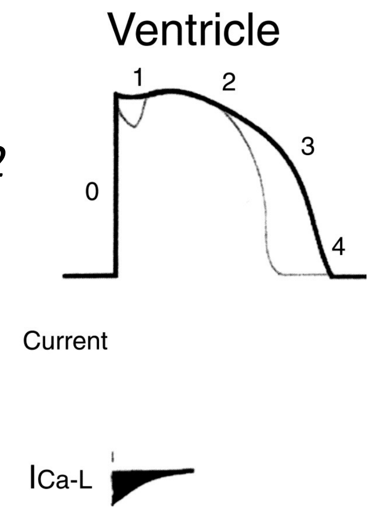

## Late $I_{Na}$



# L-type calcium current ($I_{CaL}$) models

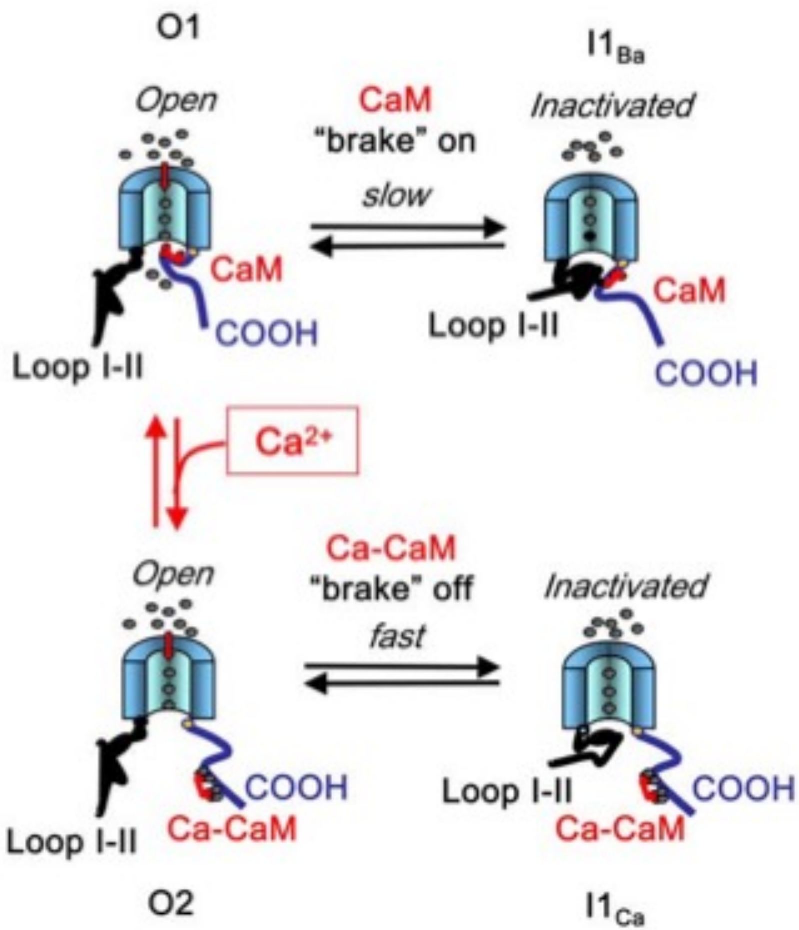
***Alpha subunit***
*GENE: CACNA1C*
*PROTEIN: CaV1.2*

***Beta subunit***
*GENE: CACN2B*
*PROTEIN: β2A*



# L-type calcium current ($I_{CaL}$) models

***Mahajan (2008)***




***Alpha subunit***

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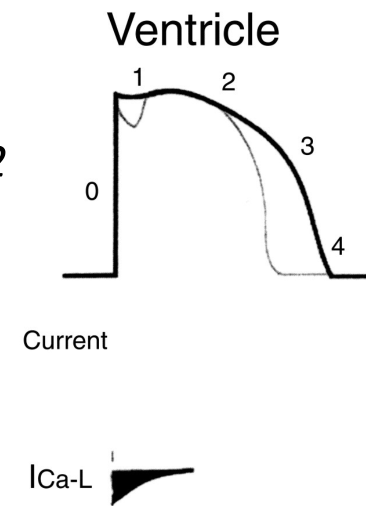
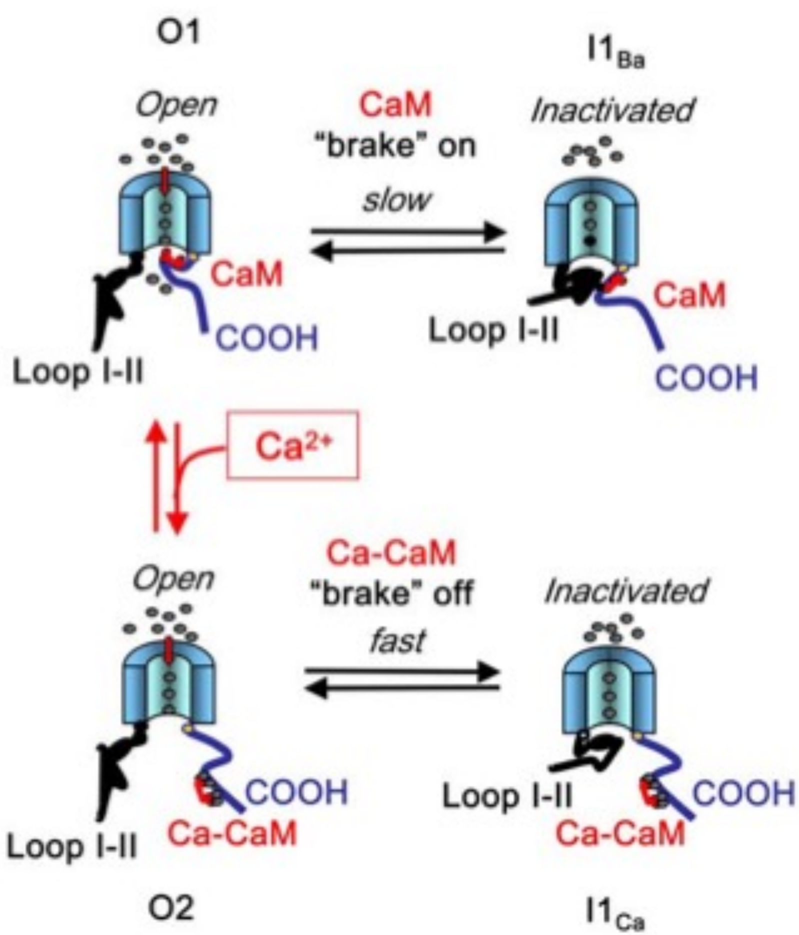


# L-type calcium current ($I_{CaL}$) models

### *Mahajan (2008)*

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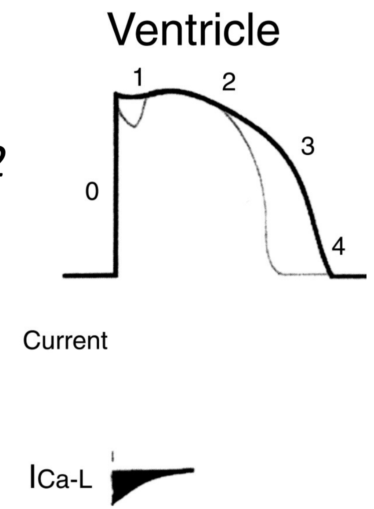
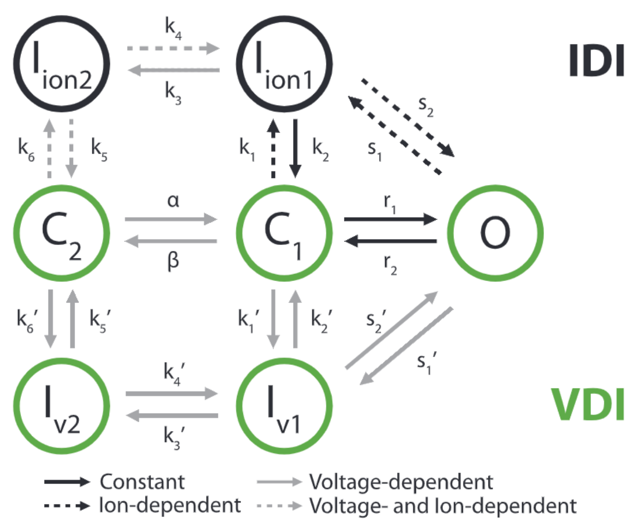


# L-type calcium current ($I_{CaL}$) models

### *Hodgkin Huxley (Shannon 2004)*

$$\bar{I}_S = P_S z_s^2 V \frac{F^2}{RT} \frac{\gamma_{Si}[S]_{SL} \exp\left(\frac{z_s VF}{RT}\right) - \gamma_{So}[S]_o}{\exp\left(\frac{z_S VF}{RT}\right) - 1}$$

$$\boxed{IP_S = d(f) f_{Ca} Q_{CaL} \bar{I}_S}$$

***Alpha subunit***

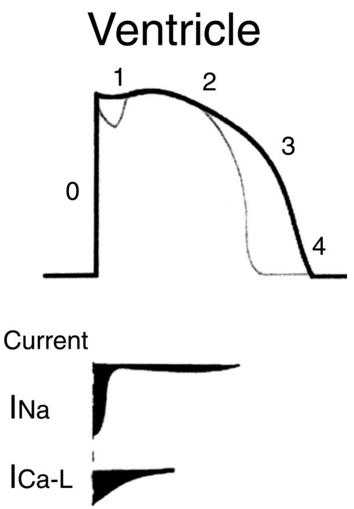
*GENE: CACNA1C*

*PROTEIN: CaV1.2*

***Beta subunit***

*GENE: CACN2B*

*PROTEIN: β2A*



# L-type calcium current ($I_{CaL}$) models

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$$\boxed{IP_S = d(f) f_{Ca} Q_{CaL} \bar{I}_S}$$

$$d_\infty = 1/(1 + \exp(-(V + 14.5)/6.0))$$

$$f_\infty = \frac{1}{1 + \exp\left(\frac{(V + 35.06)}{3.6}\right)} + \frac{0.6}{1 + \exp\left(\frac{(50 - V)}{20}\right)}$$

$$f_{Ca} = 1 - f_{CaB}$$

$$\frac{df_{CaB}}{dt} = 1.7[Ca]_C(1 - f_{CaB}) - 11.9 f_{CaB}$$

***Alpha subunit***

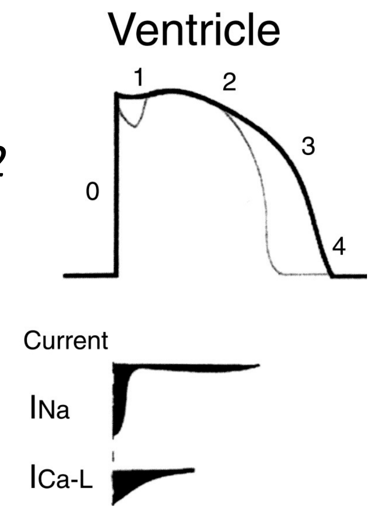
*GENE: CACNA1C*

*PROTEIN: CaV1.2*

***Beta subunit***

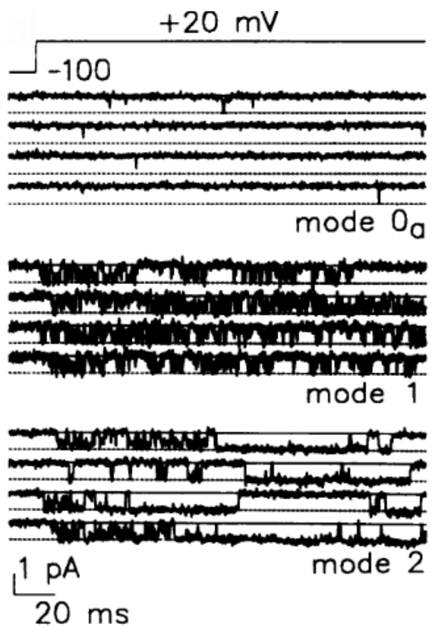
*GENE: CACN2B*

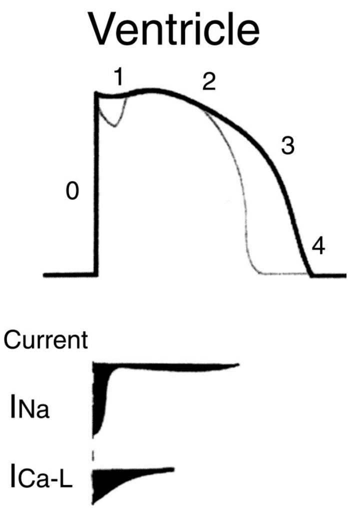
*PROTEIN: β2A*



# L-type calcium current ($I_{CaL}$) models

***Modal gating is key property for $I_{CaL}$ regulation***



# L-type calcium current ($I_{CaL}$) models

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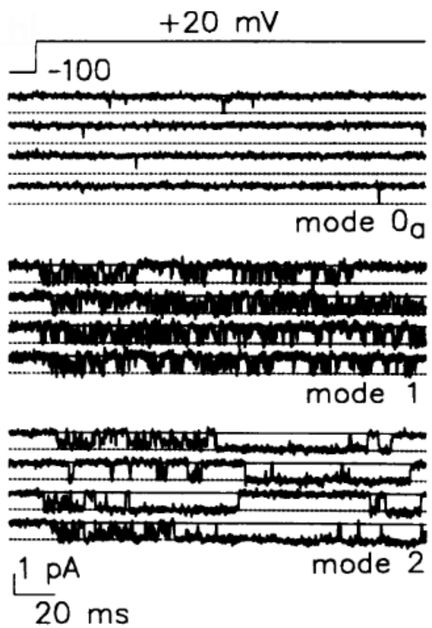
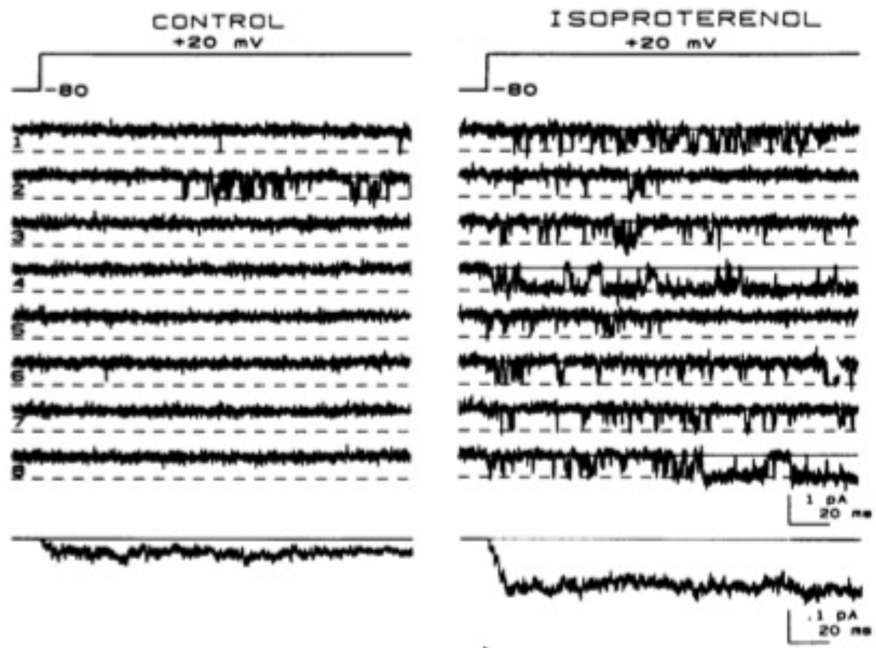
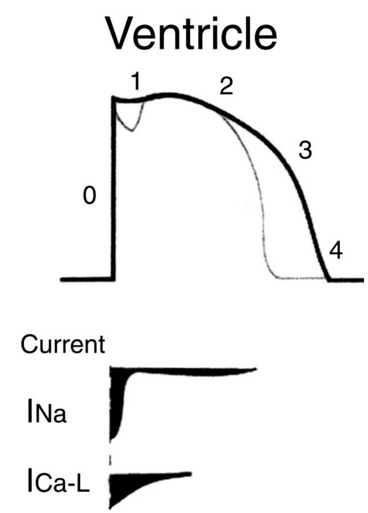


# Rapidly activating delayed rectifier ($I_{Kr}$) models

***Shannon et al. (2004)***

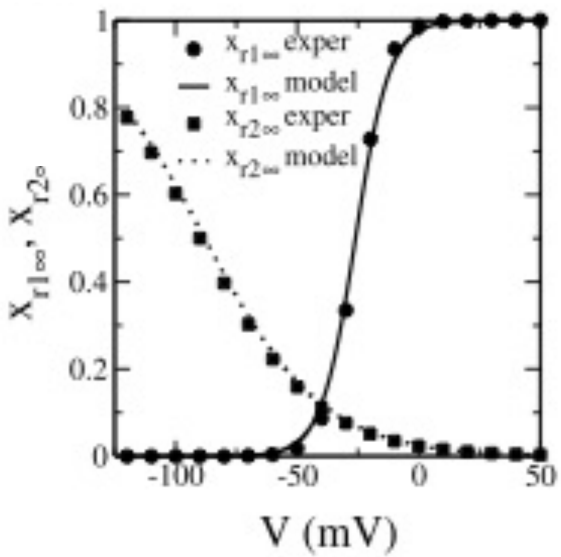
$$I_{Kr} = \bar{G}_{IKr} X_r R_r (V - E_K)$$

$$\bar{G}_{IKr} = 0.03 \left( \frac{[K]_o}{5.4} \right)^{0.5}$$

***Romero et al. (2015)***

$$C_3 \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} C_2 \underset{\beta_{in}}{\overset{\alpha_{in}}{\rightleftharpoons}} C_1 \underset{\beta\beta}{\overset{\alpha\alpha}{\rightleftharpoons}} O \underset{\beta_i}{\overset{\alpha_i}{\rightleftharpoons}} I$$

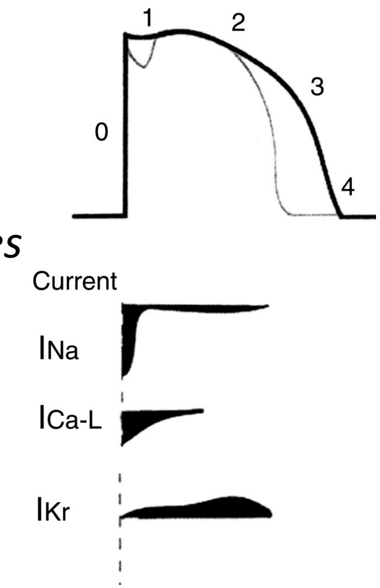
**Steady-state**




***Alpha subunit***
*GENE: KCNH2*
*PROTEIN: HERG*

***Beta subunit***
*Multiple candidates*

Ventricle



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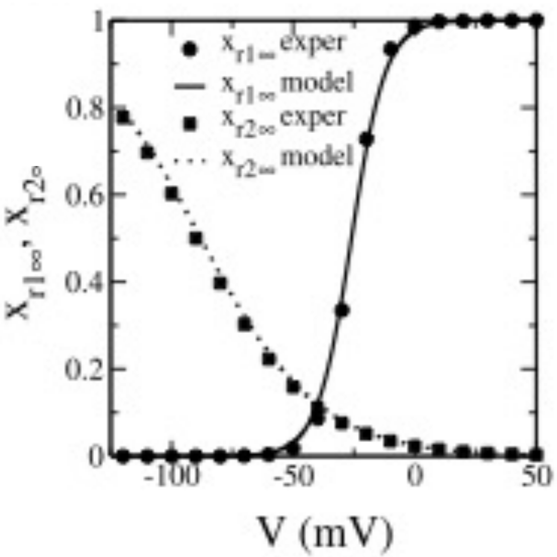
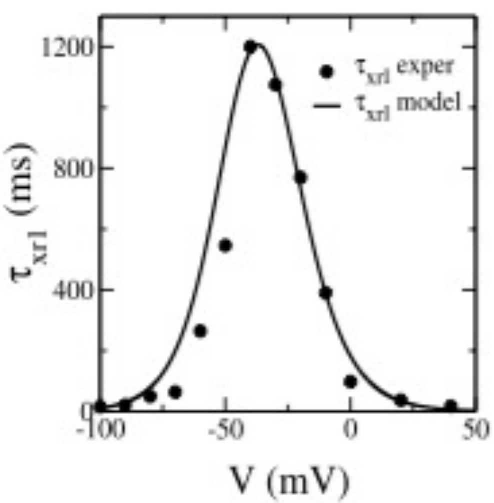
**Steady-state**




**Slow activation**




***Alpha subunit***

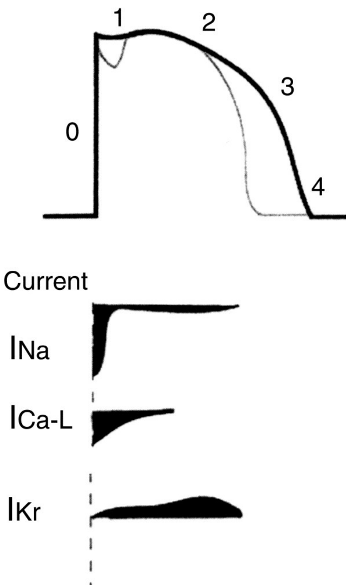
*GENE: KCNH2*

*PROTEIN: HERG*

***Beta subunit***

*Multiple candidates*

Ventricle



[ simula . research laboratory ]

# Rapidly activating delayed rectifier ($I_{Kr}$) models

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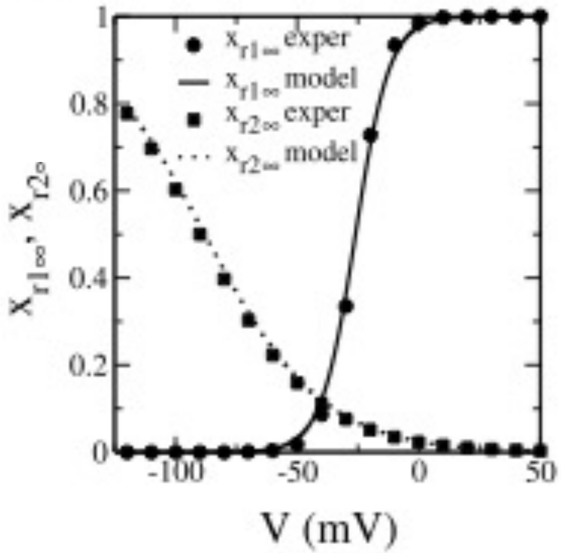
$$C_3 \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} C_2 \underset{\beta_{in}}{\overset{\alpha_{in}}{\rightleftharpoons}} C_1 \underset{\beta\beta}{\overset{\alpha\alpha}{\rightleftharpoons}} O \underset{\beta_i}{\overset{\alpha_i}{\rightleftharpoons}} I$$

**Steady-state**




***Alpha subunit***

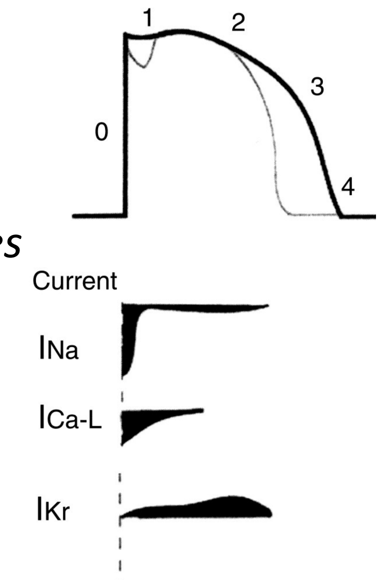
*GENE: KCNH2*

*PROTEIN: HERG*

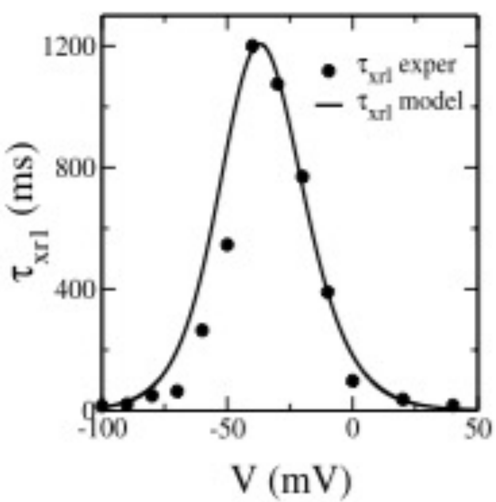
***Beta subunit***

*Multiple candidates*

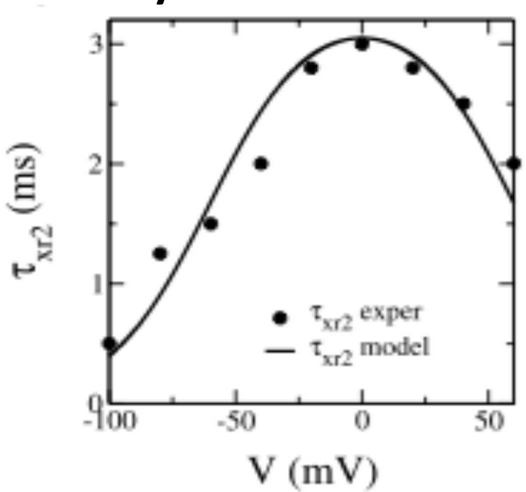
Ventricle



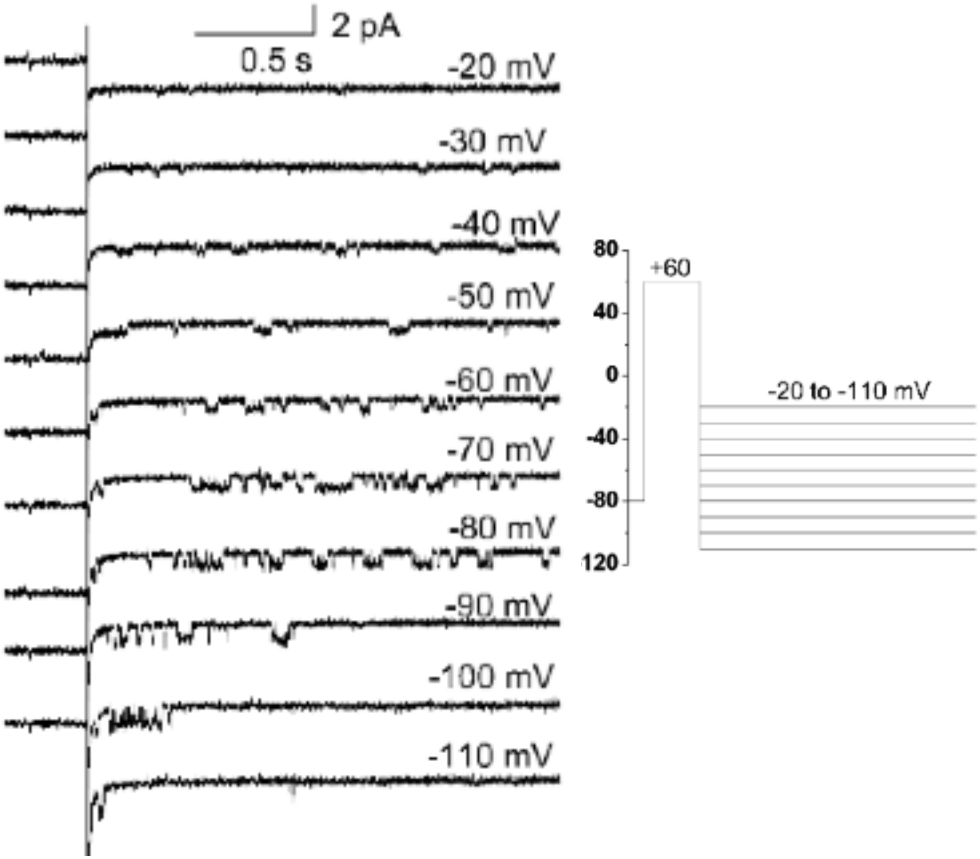

**Slow activation**




**Very fast inactivation**



# Rapidly activating delayed rectifier ($I_{Kr}$) models




***Alpha subunit***

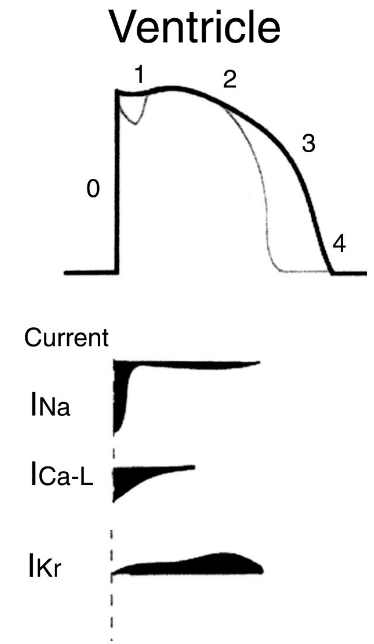
*GENE: KCNH2*

*PROTEIN: HERG*

***Beta subunit***

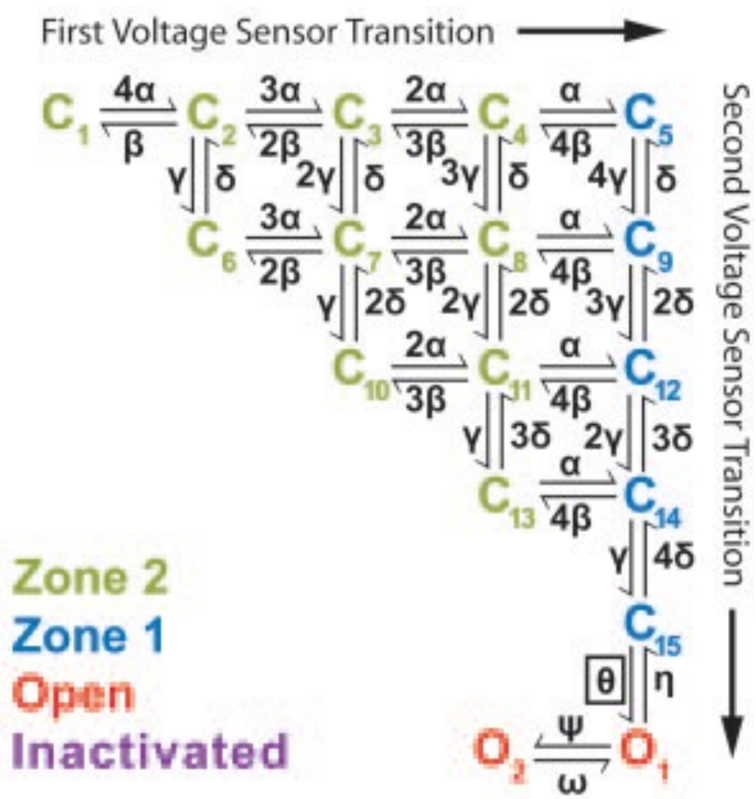
*Unestablished*

*Multiple candidates*



# Slowly activating delayed rectifier ($I_{Ks}$) models

### *Silva et al. (2005)*




***Alpha subunit***

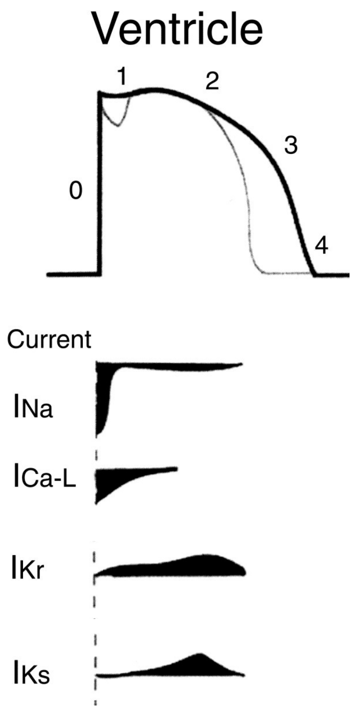
*GENE: KCNQ1*

*PROTEIN: Kv7.1*

***Beta subunit***

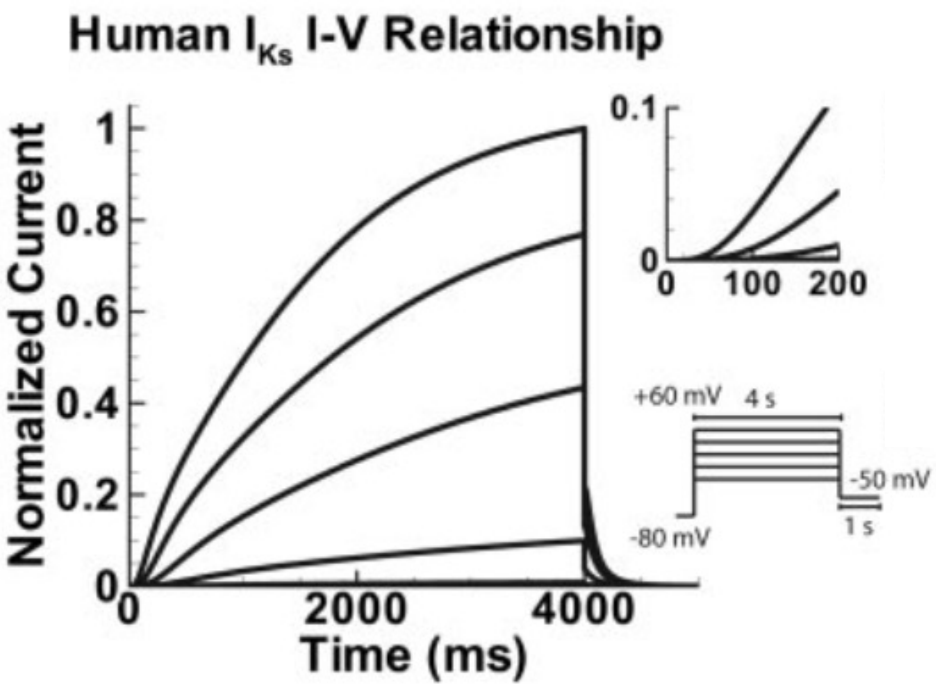
*GENE: KCNE1*

*PROTEIN: minK*



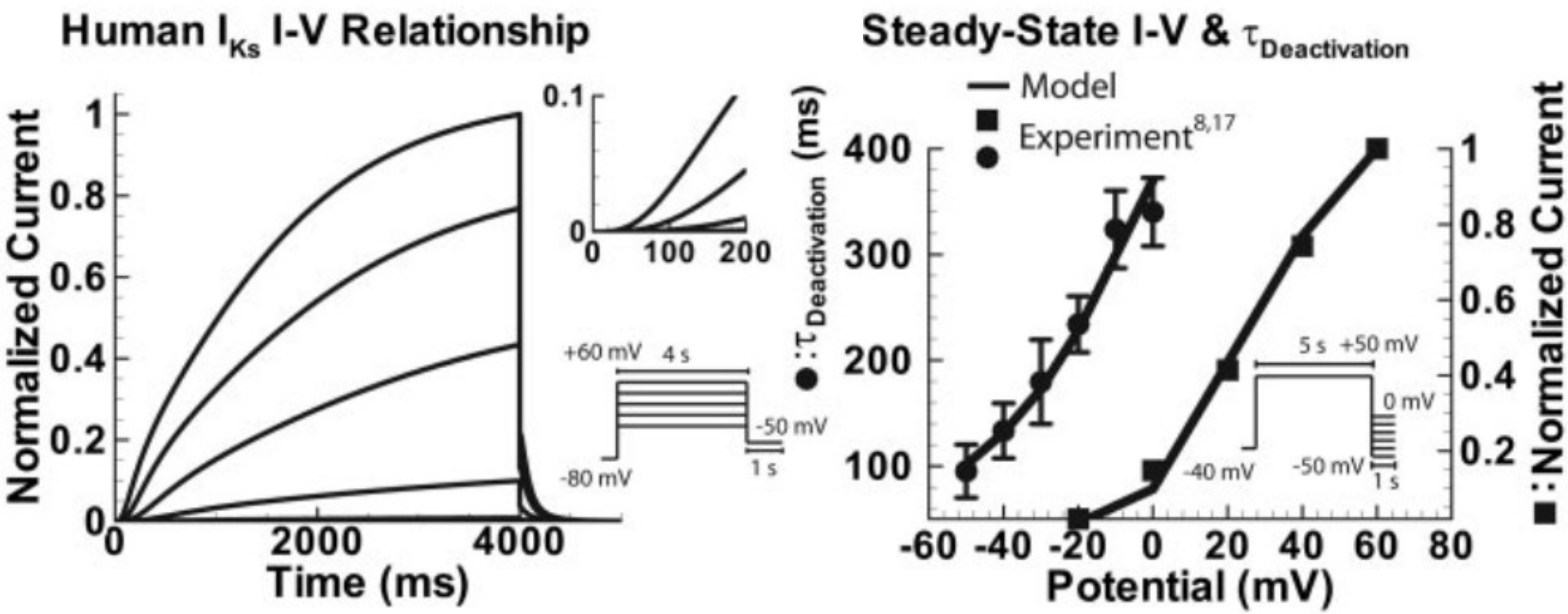
# Slowly activating delayed rectifier ($I_{Ks}$) models

***Silva et al. (2005)***



# Slowly activating delayed rectifier ($I_{Ks}$) models

***Silva et al. (2005)***



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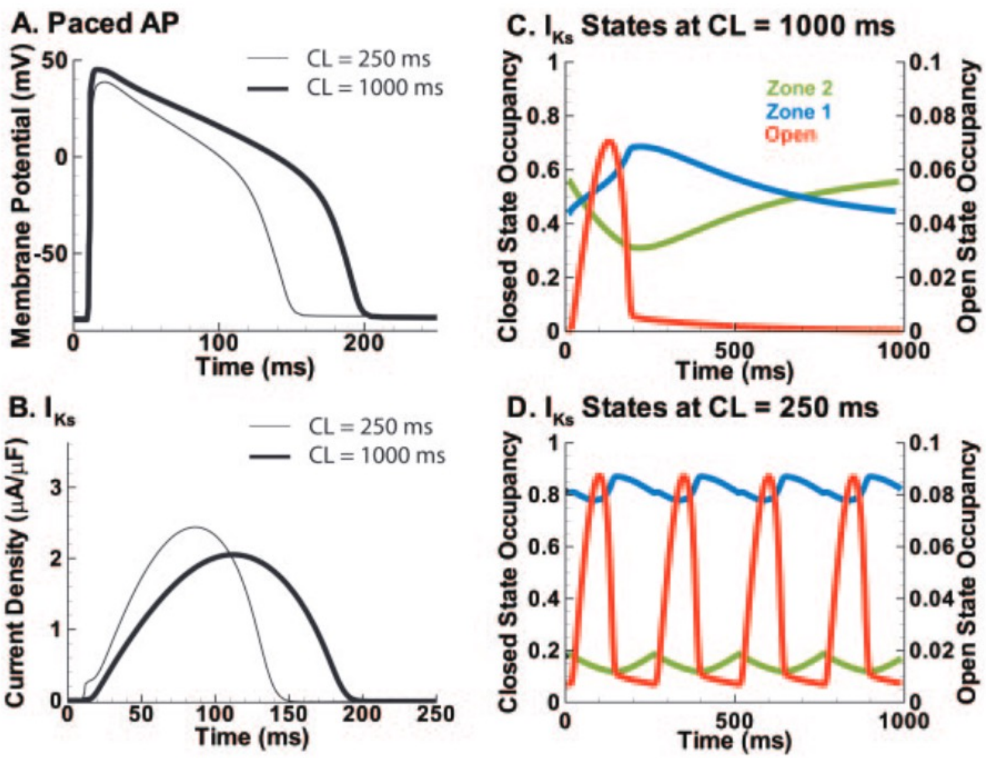


***Alpha subunit***

*GENE: KCNQ1*

*PROTEIN: Kv7.1*

***Beta subunit***

*GENE: KCNE1*

*PROTEIN: minK*