

# Biophysics I (BPHS 4080)

Instructors: Prof. Christopher Bergevin (cberge@yorku.ca)

Website: <http://www.yorku.ca/cberge/4080W2018.html>

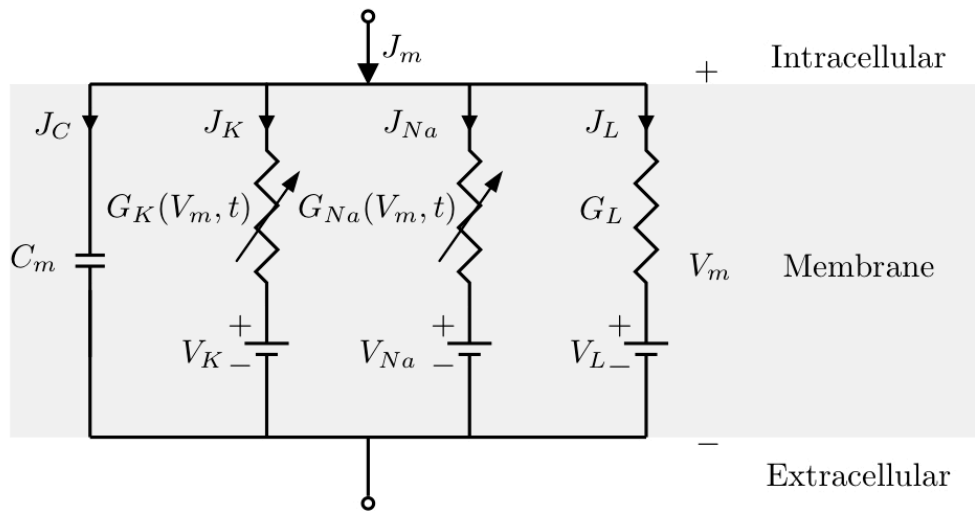


Figure 4.6

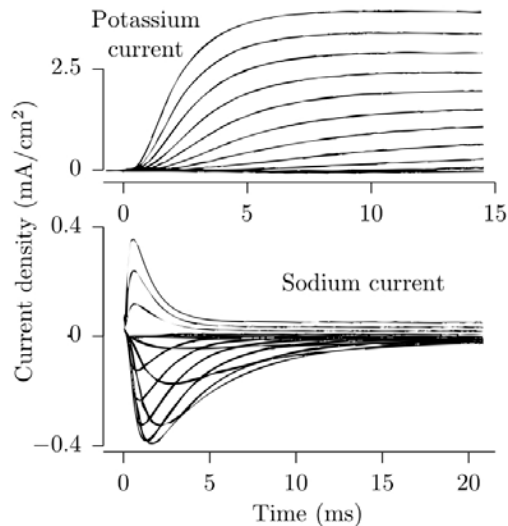
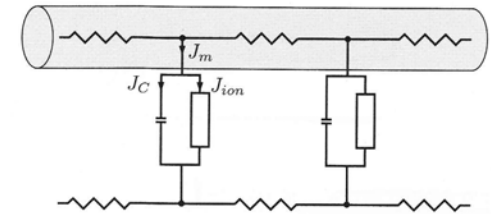


Figure 4.20

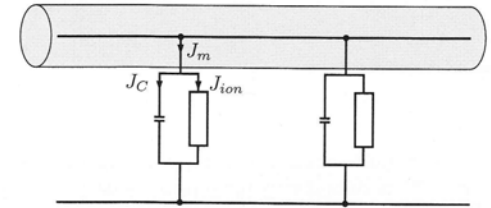
→ Physiological data suggests  $\text{Na}^+$  activates and then inactivates while  $\text{K}^+$  simply activates (based upon  $V_m$ )

What are  $G_K(V_m, t)$  and  $G_{Na}(V_m, t)$ ?



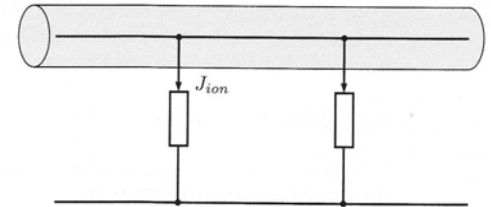
Space clamp

$$\frac{\partial V_m}{\partial z} = 0$$

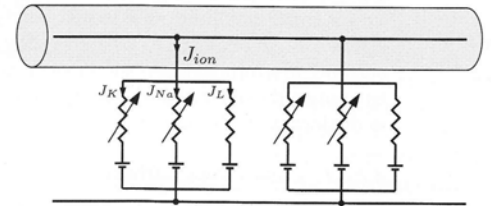


Step voltage clamp

$$\frac{\partial V_m}{\partial z} = \frac{\partial V_m}{\partial t} = 0$$



Separation of ionic currents



→ First order kinetics

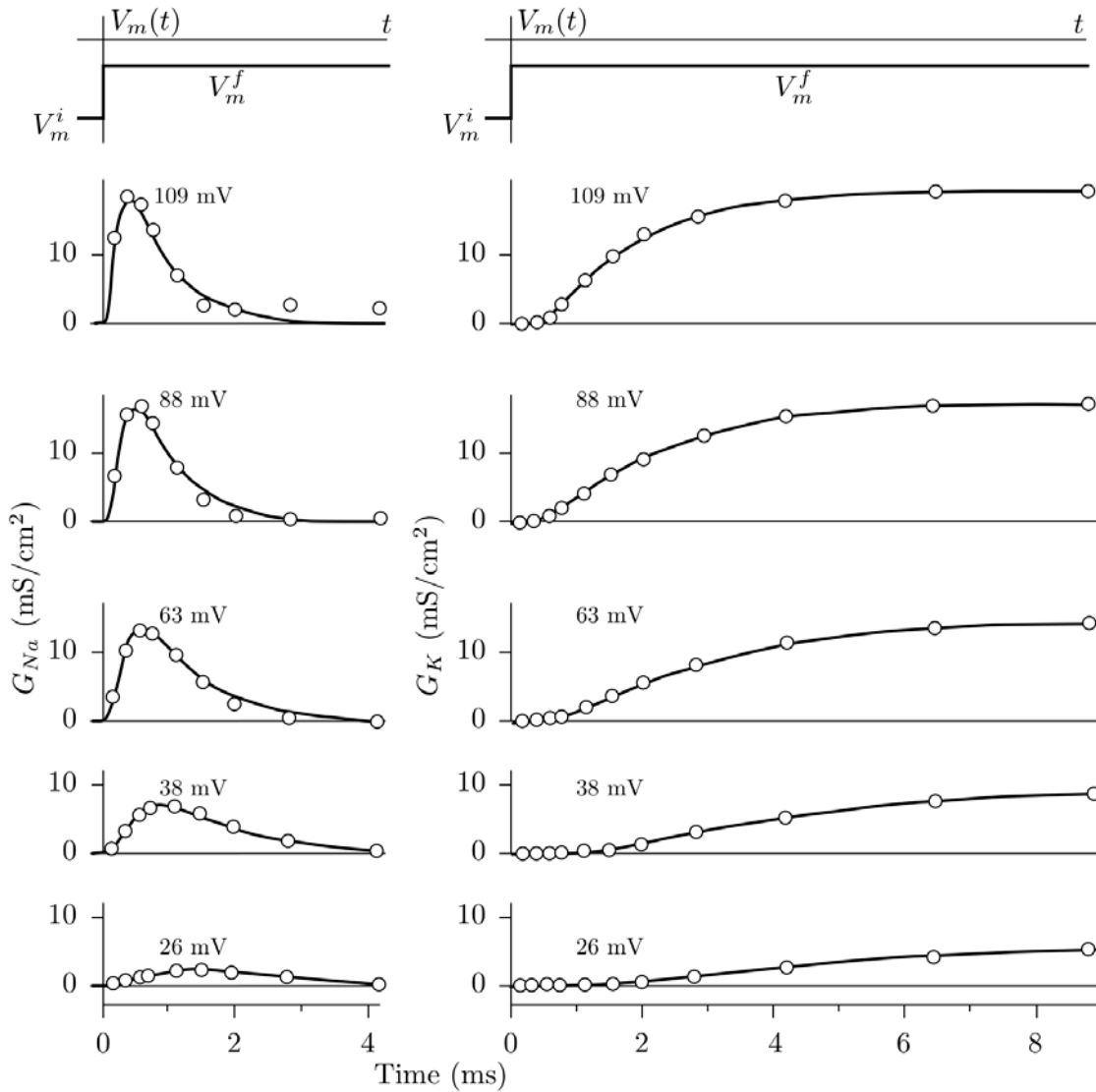


Figure 4.23

$$n(V_m, t) + \tau_n(V_m) \frac{dn(V_m, t)}{dt} = n_\infty(V_m)$$

$$m(V_m, t) + \tau_m(V_m) \frac{dm(V_m, t)}{dt} = m_\infty(V_m)$$

$$h(V_m, t) + \tau_h(V_m) \frac{dh(V_m, t)}{dt} = h_\infty(V_m)$$

$$\tau_m = \frac{1}{\alpha_m + \beta_m}, \quad \text{and} \quad m_\infty = \frac{\alpha_m}{\alpha_m + \beta_m},$$

$$\tau_h = \frac{1}{\alpha_h + \beta_h}, \quad \text{and} \quad h_\infty = \frac{\alpha_h}{\alpha_h + \beta_h},$$

$$\tau_n = \frac{1}{\alpha_n + \beta_n}, \quad \text{and} \quad n_\infty = \frac{\alpha_n}{\alpha_n + \beta_n}.$$

$m$  – sodium activation

$h$  – sodium inactivation

$n$  – potassium activation

→ First order kinetics

Hodgkin & Huxley assumed  
(serendipitously?):

$$G_K(V_m, t) = \bar{G}_K n^4(V_m, t)$$

$$G_{Na}(V_m, t) = \bar{G}_{Na} m^3(V_m, t) h(V_m, t)$$

Then this becomes a fitting exercise  
(nonlinear regression) to obtain the  
various constants:

$$\alpha_m = \frac{-0.1(V_m + 35)}{e^{-0.1(V_m + 35)} - 1},$$

$$\beta_m = 4e^{-(V_m + 60)/18},$$

$$\alpha_h = 0.07e^{-0.05(V_m + 60)},$$

$$\beta_h = \frac{1}{1 + e^{-0.1(V_m + 30)}},$$

$$\alpha_n = \frac{-0.01(V_m + 50)}{e^{-0.1(V_m + 50)} - 1},$$

$$\beta_n = 0.125e^{-0.0125(V_m + 60)},$$

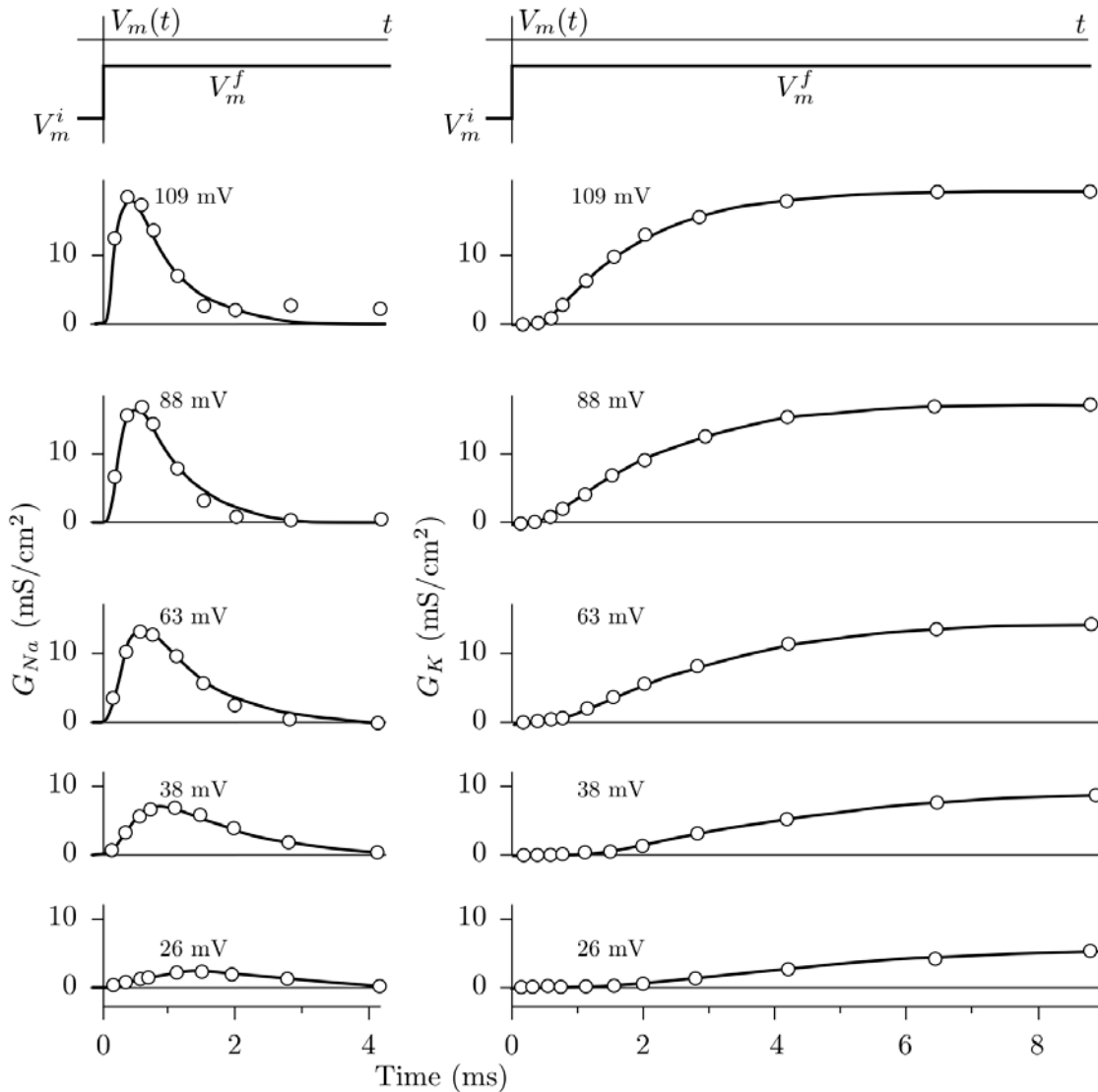
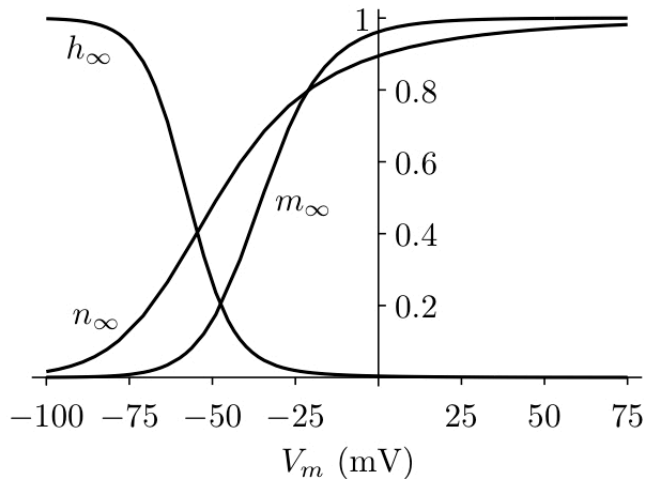
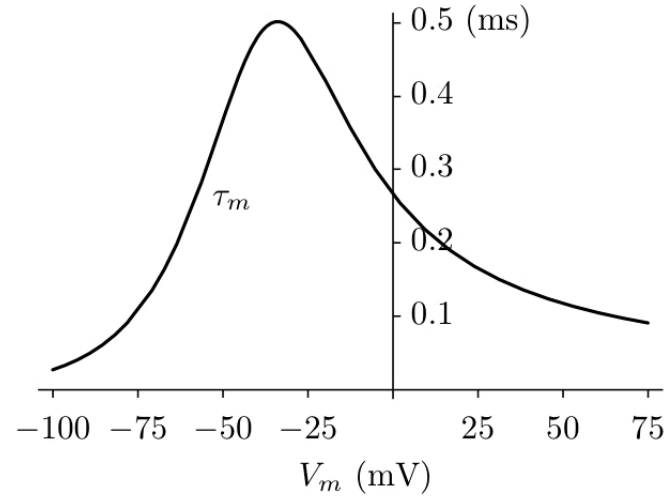
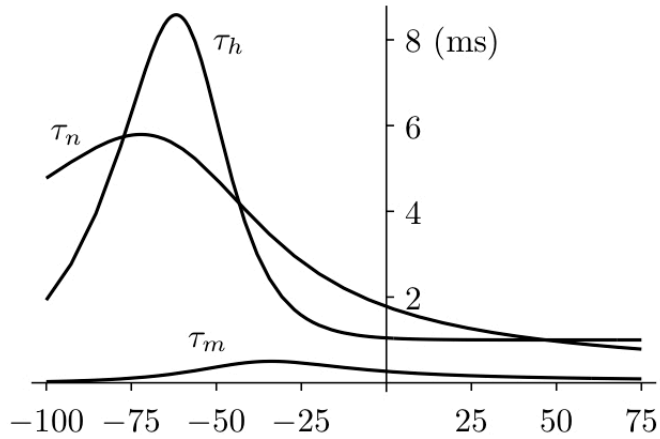


Figure 4.23



→ Fast Na<sup>+</sup> activation

→ Slower Na<sup>+</sup> deactivation and K<sup>+</sup> activation

$\bar{G}_{Na} = 120$ ,  $\bar{G}_K = 36$ , and  $G_L = 0.3$  mS/cm<sup>2</sup>;  $C_m = 1$  μF/cm<sup>2</sup>;  $c_{Na}^o = 491$ ,  $c_{Na}^i = 50$ ,  
 $c_K^o = 20.11$ ,  $c_K^i = 400$  mmol/L;  $V_L = -49$  mV; temperature is 6.3°C.

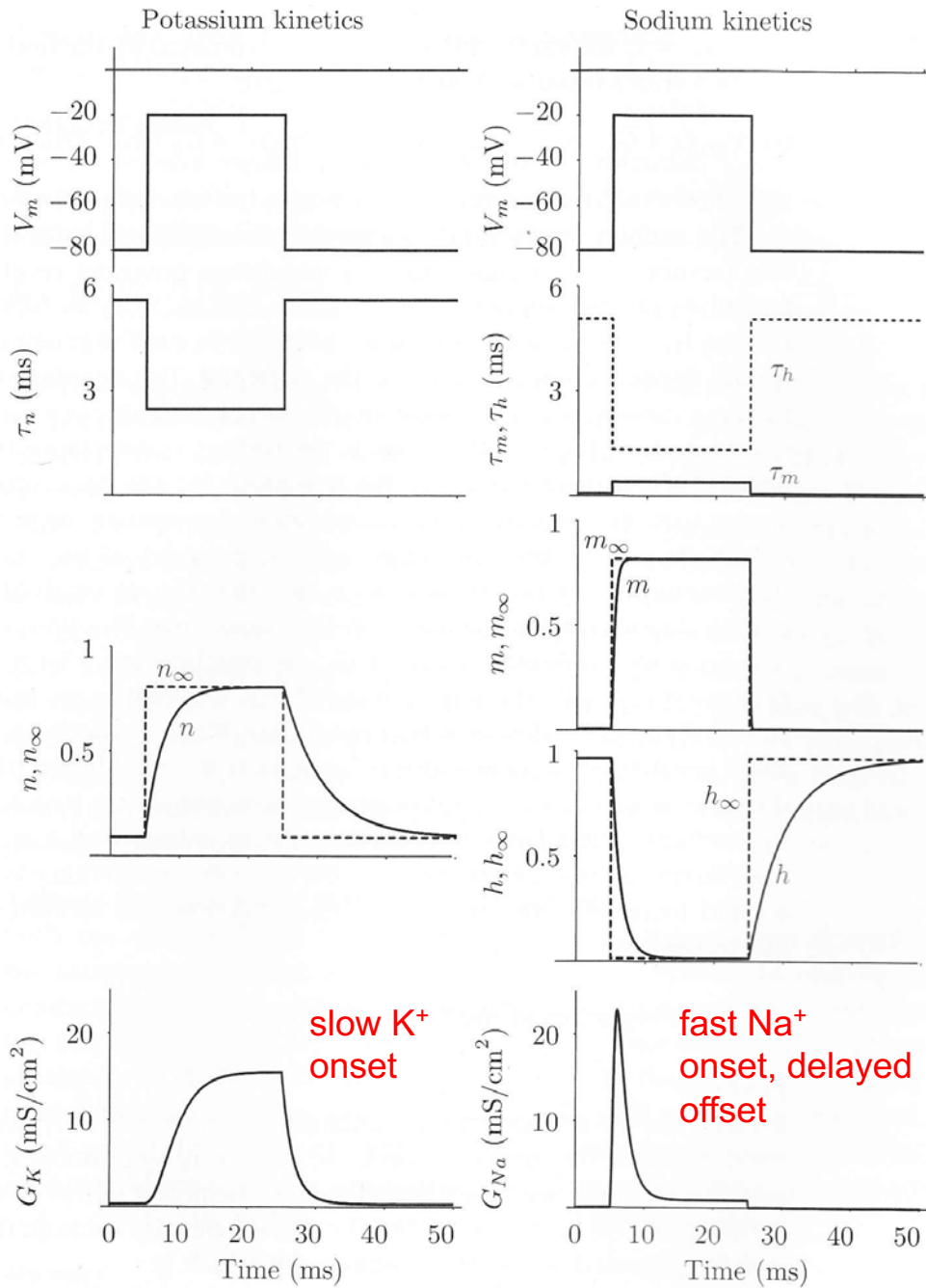


Figure 4.26

## Summary: HH Equations

$$\frac{1}{2\pi a(r_o + r_i)} \frac{\partial^2 V_m}{\partial z^2} = C_m \frac{\partial V_m}{\partial t} + G_K(V_m, t) (V_m - V_K) + G_{Na}(V_m, t) (V_m - V_{Na}) + G_L(V_m - V_L)$$

$$G_K(V_m, t) = \bar{G}_K n^4(V_m, t)$$

$$G_{Na}(V_m, t) = \bar{G}_{Na} m^3(V_m, t) h(V_m, t)$$

$$n(V_m, t) + \tau_n(V_m) \frac{dn(V_m, t)}{dt} = n_\infty(V_m)$$

$$m(V_m, t) + \tau_m(V_m) \frac{dm(V_m, t)}{dt} = m_\infty(V_m)$$

$$h(V_m, t) + \tau_h(V_m) \frac{dh(V_m, t)}{dt} = h_\infty(V_m)$$

$$\tau_x \frac{dx}{dt} + x = x_\infty \quad \frac{dx}{dt} = \alpha_x(1-x) - \beta_x x$$

$$x_\infty = \alpha_x / (\alpha_x + \beta_x) \text{ and } \tau_x = 1 / (\alpha_x + \beta_x)$$

$$\alpha_m = \frac{-0.1(V_m + 35)}{e^{-0.1(V_m + 35)} - 1},$$

$$\beta_m = 4e^{-(V_m + 60)/18},$$

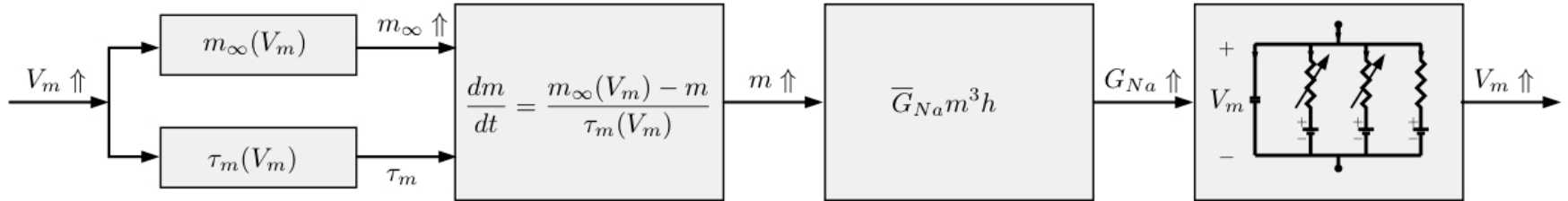
$$\alpha_h = 0.07e^{-0.05(V_m + 60)},$$

$$\beta_h = \frac{1}{1 + e^{-0.1(V_m + 30)}},$$

$$\alpha_n = \frac{-0.01(V_m + 50)}{e^{-0.1(V_m + 50)} - 1},$$

$$\beta_n = 0.125e^{-0.0125(V_m + 60)},$$

Depolarization mechanism – positive feedback



Repolarization mechanisms – negative feedback

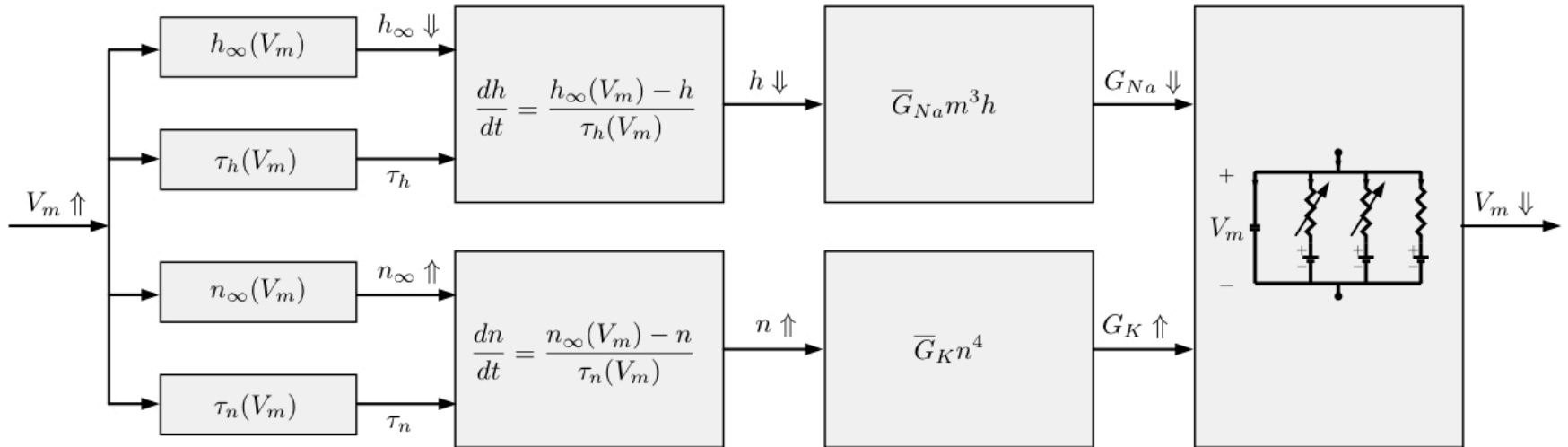


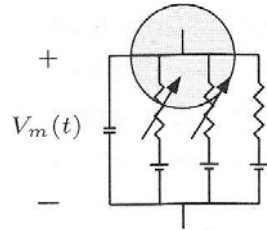
Figure 4.33



## Two (possible) Ways to Solve HH Eqns.

To reduce solving a PDE, simplifying assumptions can be made to reduce to an ODE

### 1. Membrane APs (space-clamped)



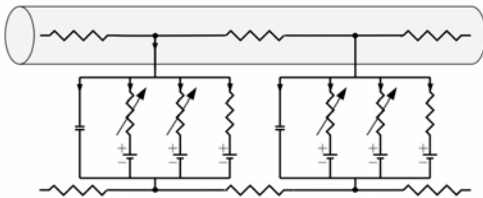
assume no spatial dependence

$$\partial^2 V_m / \partial z^2 = 0$$

$$0 = C_m \frac{dV_m}{dt} + \bar{G}_K n^4(V_m, t) (V_m - V_K) + \bar{G}_{Na} m^3(V_m, t) h(V_m, t) (V_m - V_{Na}) + G_L (V_m - V_L)$$

**1<sup>st</sup> order ODE**

### 2. Propagated APs



assume wave-like solution

$$V_m(z, t) = f(t - z/v)$$

$$\frac{\partial^2 V_m(z, t)}{\partial z^2} = \frac{1}{v^2} \frac{\partial^2 V_m(z, t)}{\partial t^2}$$

$$\frac{1}{2\pi a(r_o + r_i)v^2} \frac{d^2 V_m}{dt^2} = C_m \frac{dV_m}{dt} + \bar{G}_K n^4(V_m, t) (V_m - V_K) + \bar{G}_{Na} m^3(V_m, t) h(V_m, t) (V_m - V_{Na}) + G_L (V_m - V_L)$$

**2<sup>nd</sup> order ODE**

## (numerically) Solving HH Eqns.

### Review point

How does one numerically solve ODEs?

$$\frac{dy}{dt} = f(t, \mathbf{y}) \quad (7.1.1)$$

Idea: Since equations tell us how things change, numerically integrate to find solution(s)

$$\frac{dy}{dt} = f(t, \mathbf{y}) \quad \Rightarrow \quad \frac{\mathbf{y}_{n+1} - \mathbf{y}_n}{\Delta t} \approx f(t_n, \mathbf{y}_n). \quad (7.1.4)$$

**Approximation:**  $\mathbf{y}_{n+1} = \mathbf{y}_n + \Delta t \cdot f(t_n, \mathbf{y}_n).$  (7.1.5)

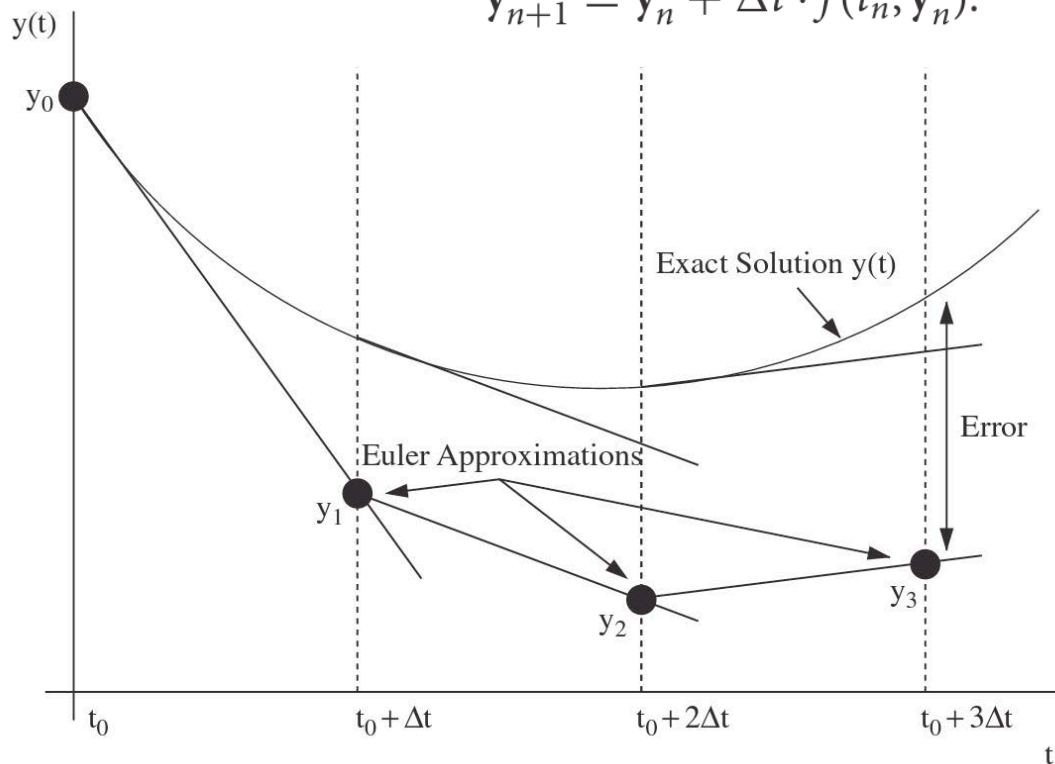
## Starting point: Euler's method

Idea: Since equations tell us how things change, numerically integrate to find solution(s)

$$\frac{dy}{dt} = f(t, y)$$

$$\frac{dy}{dt} = f(t, y) \Rightarrow \frac{y_{n+1} - y_n}{\Delta t} \approx f(t_n, y_n).$$

$$y_{n+1} = y_n + \Delta t \cdot f(t_n, y_n).$$



## Runge-Kutta (RK)

➤ 'Higher order' methods improve in a similar fashion to Riemann sums, for example:

- Euler → LEFT
- Modified Euler → MID
- Improved Euler → TRAP

➤ Most popular RK method is the 'fourth order' (RK4) and is equivalent to SIMP:

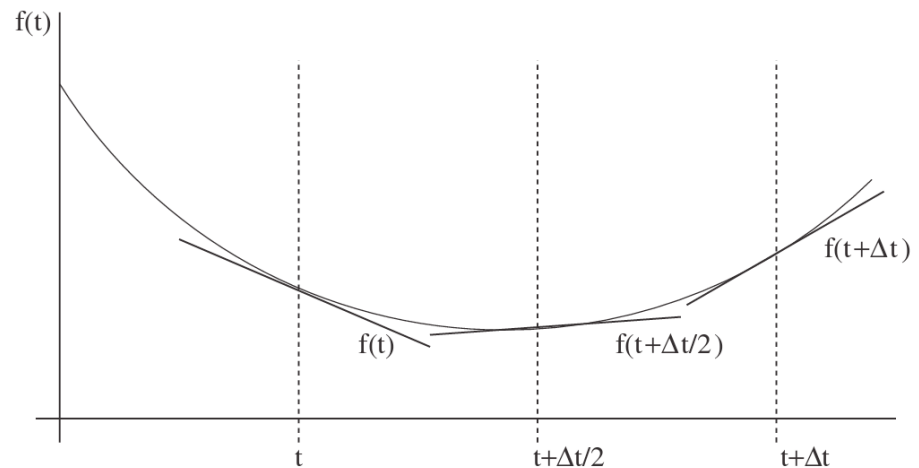
$$f_0 = f(x_0, y_0),$$

$$f_1 = f\left(x_0 + \frac{h}{2}, y_0 + \frac{h}{2}f_0\right),$$

$$f_2 = f\left(x_0 + \frac{h}{2}, y_0 + \frac{h}{2}f_1\right),$$

$$f_3 = f(x_0 + h, y_0 + hf_2).$$

$$y(x_0 + h) = y(x_0) + \frac{h}{6}(f_0 + 2f_1 + 2f_2 + f_3).$$



(numerically) Solving HH Eqns.

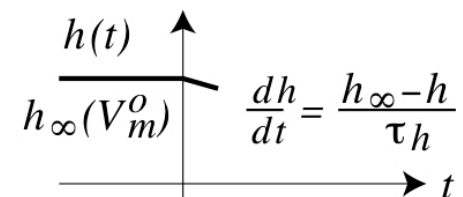
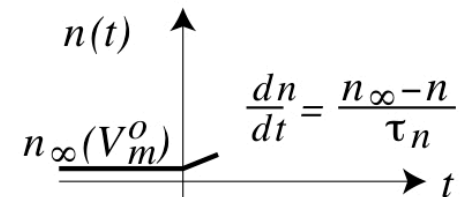
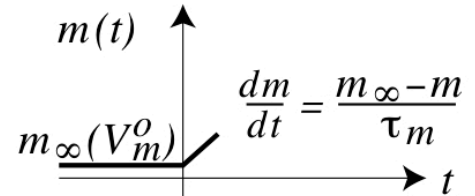
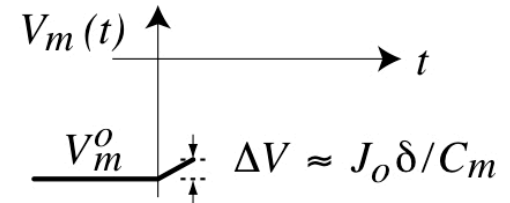
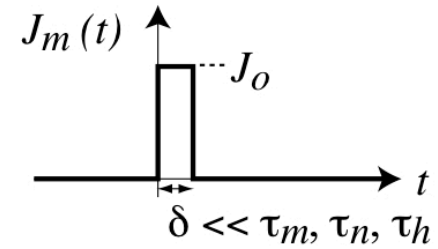
Review point

How does one numerically solve ODEs?

SoftCell numerically integrates the ODEs

(e.g., Euler method, Runge-Kutta)

How to run HH model backwards?





# Membrane APs (space-clamped)

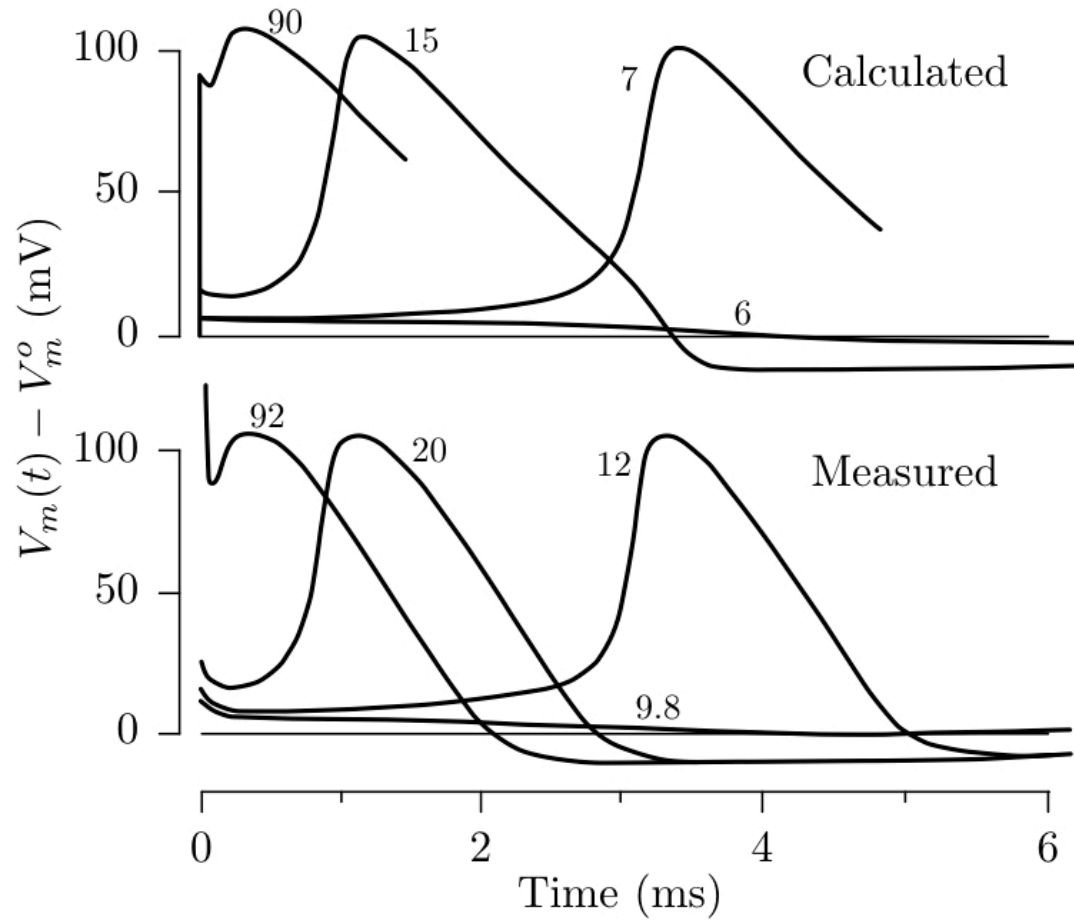


Figure 4.37

## Propagated APs

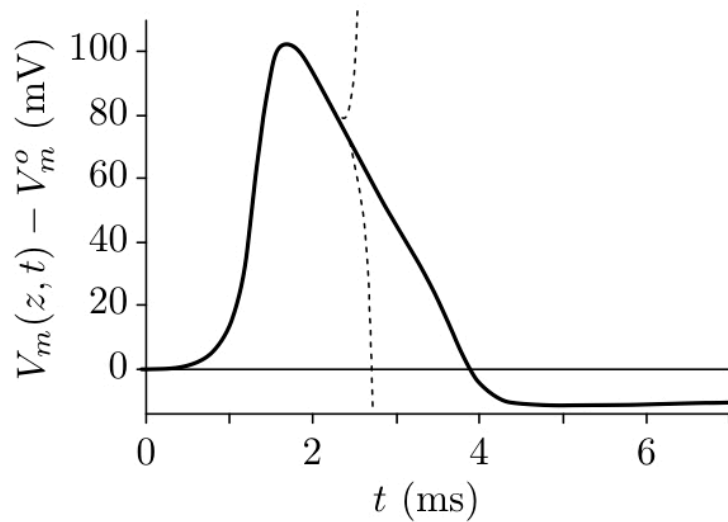


Figure 4.30

→ Solutions only stable for appropriate choice of conduction velocity

(think back to cable model;  $C_m$  matters!)

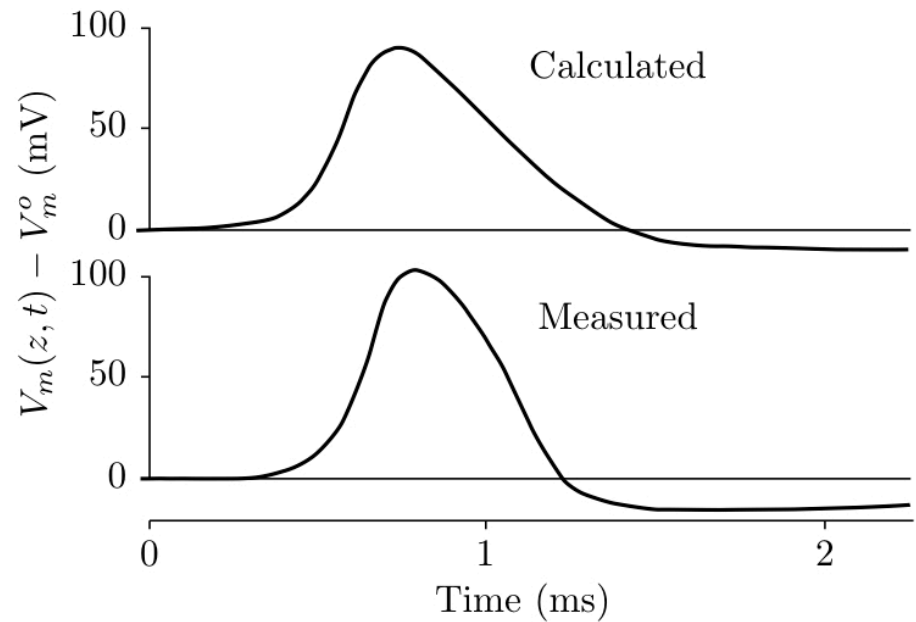


Figure 4.31



*Finally there was the difficulty of computing the action potentials from the equations which we had developed. We had settled all the equations and constants by March 1951 and hoped to get these solved on the Cambridge University computer. However, before anything could be done we learnt that the computer would be off the air for 6 months or so while it underwent a major modification. Andrew Huxley got us out of that difficulty by solving the differential equations numerically using a hand-operated Brunsviga. The propagated action potential took about three weeks to complete and must have been an enormous labour for Andrew. But it was exciting to see it come out with the right shape and velocity and we began to feel that we had not wasted the many months that we had spent in analysing records.*

—Hodgkin, 1977

# Propagated APs

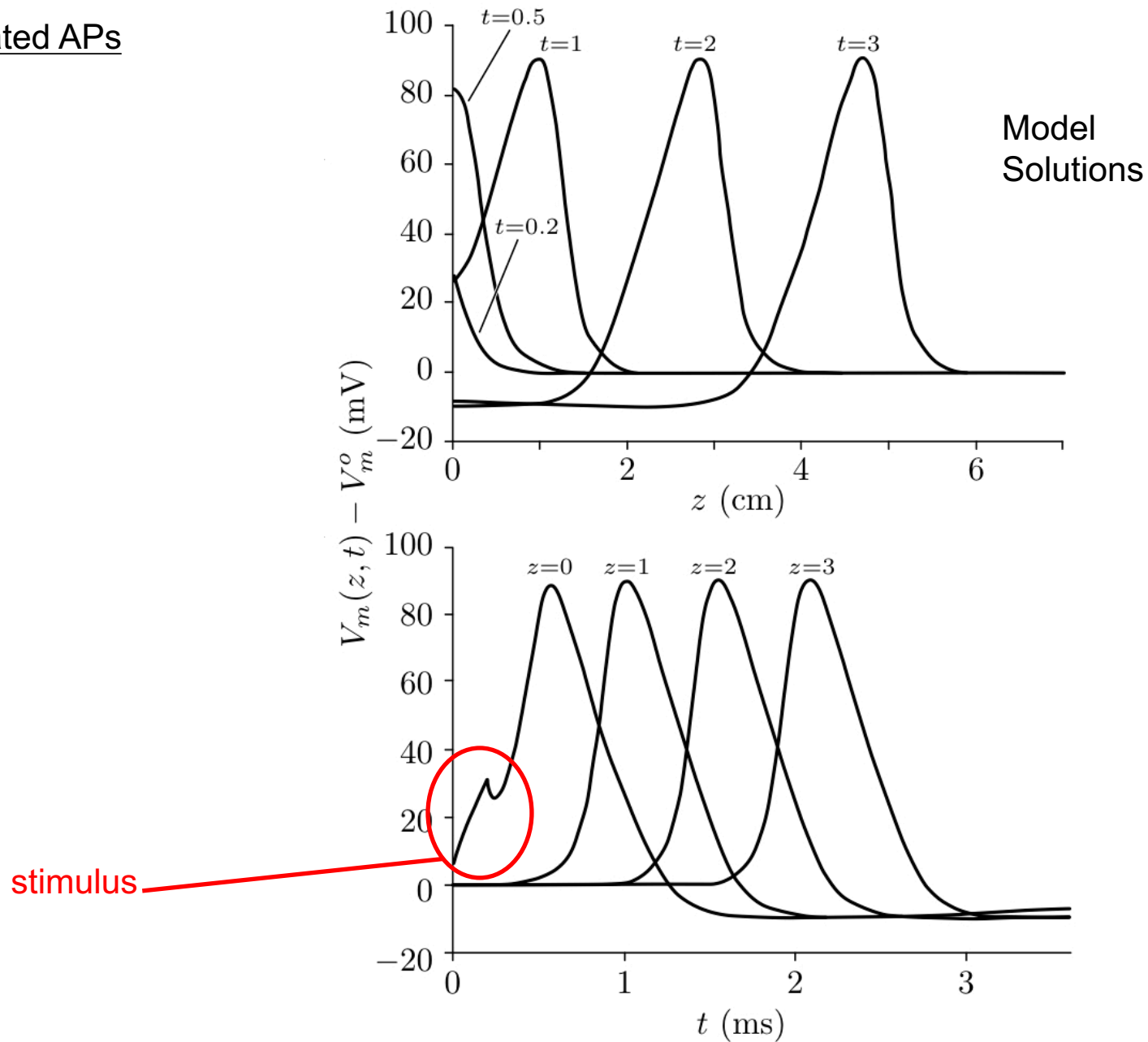
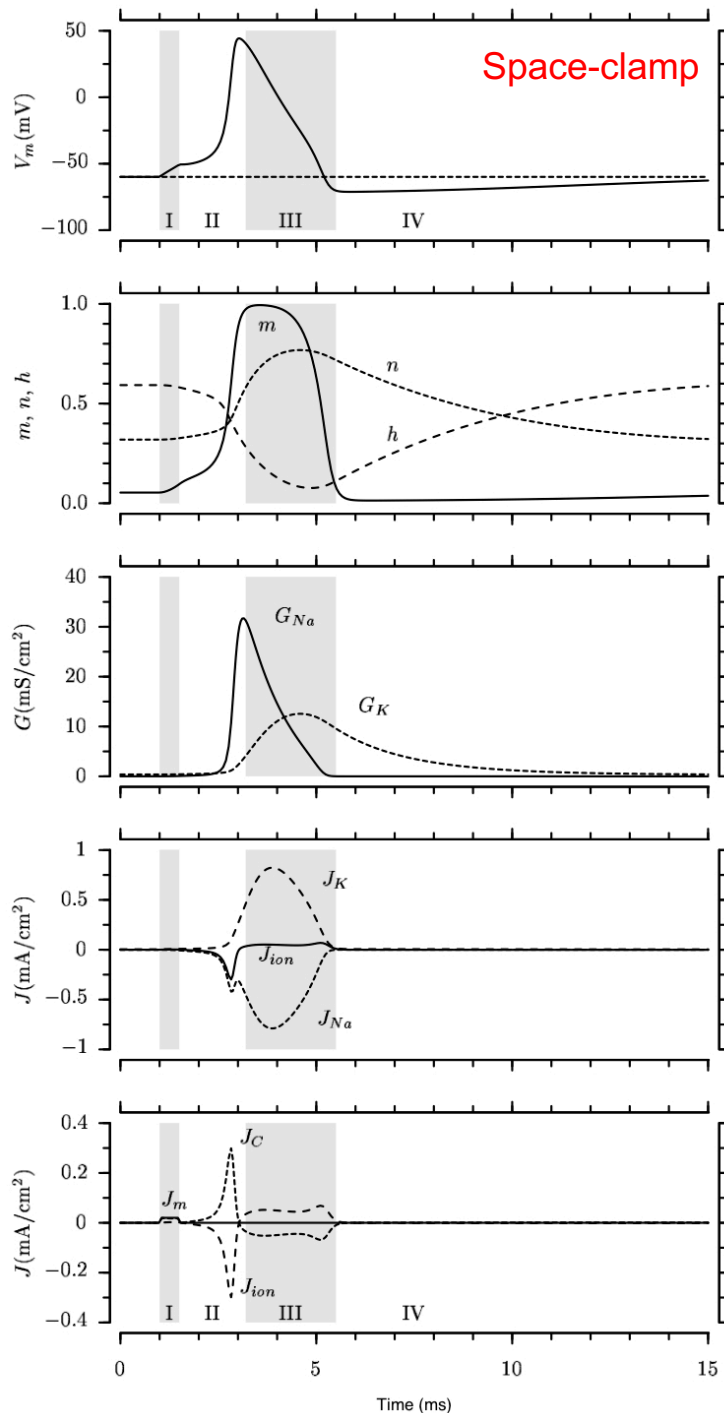


Figure 4.29



## Four phases:

1. Local disturbance due to capacitance  
(behaves like cable model)
2. Onset:  $V_m$  change triggers  $m$   
(increased  $G_{Na}$  take  $V_m$  with it)
3. Falloff:  $h$  turns off,  $n$  turns on  
(both work to lower  $V_m$  back towards  $V_k$ ,  
basis for absolute refractory period)
4. Undershoot: increased  $G_k$  pushes  $V_m$   
beyond  $V_m^0$   
(basis for relative refractory period)

Note: Membrane current ( $J_M$ ) can be parsed up into two components: a capacitive current ( $J_C$ ) and an ionic current ( $J_{ion}$ )

Ex.

State whether each of the following is true or false, and give a reason for your answer.

- a. In response to a step of membrane potential in a voltage-clamped axon, the factors  $n(t)$ ,  $m(t)$ , and  $h(t)$  are exponential functions of time.
- b. In response to a step of membrane current in a current-clamped axon, the factors  $n(t)$ ,  $m(t)$ , and  $h(t)$  are exponential functions of time.
- c. In response to an impulse of membrane current in an unclamped axon, the factors  $n(t)$ ,  $m(t)$ , and  $h(t)$  are exponential functions of time.

Ex. (ANSWERS)

State whether each of the following is true or false, and give a reason for your answer.

- a. In response to a step of membrane potential in a voltage-clamped axon, the factors  $n(t)$ ,  $m(t)$ , and  $h(t)$  are exponential functions of time.
- b. In response to a step of membrane current in a current-clamped axon, the factors  $n(t)$ ,  $m(t)$ , and  $h(t)$  are exponential functions of time.
- c. In response to an impulse of membrane current in an unclamped axon, the factors  $n(t)$ ,  $m(t)$ , and  $h(t)$  are exponential functions of time.

True

False

False

