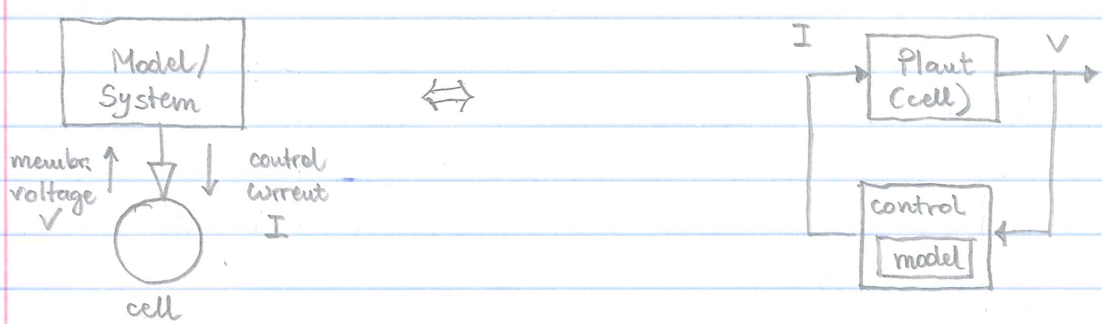
LECTURE 5

Thus far, our approach has been based on two pillars:

- We build models that relate neural measurements to non-neural variables (e.g., kinematics) by using a data-driven approach;

- We invert these models (or use them as part of filters) to estimate the non-measured variables given the neural measurements for sake of prediction

Let us now consider the case where all the variables are related to the neural activity and we want to use the measurements to steer the dynamics (i.e., behavior) of the neural system via dynamic clamp:



A preliminary step toward the regulation of the plant consists in:

1) Selecting a model that is useful but not accurate ($\Rightarrow$ We want to model the dynamics of the plant, not its actual physiological components)

2) Estimating the parameters of the model "on-the-fly", i.e., as the plant's dynamics evolve (instead of using training data offline)

With regard to point 1), let us assume that we are interested in a single cell and that such cell can be approximated as a single compartment $\Rightarrow$ The cell can be modeled as a Hodgkin-Huxley neuron:

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$$C_m \frac{dV}{dt} + I_{Na}(V) + I_K(V) + I_L(V) = I_{ext} \qquad (*)$$

where : $I_{Na}(V) \triangleq g_{Na}\, m^3 h\,(V - V_{Na})$ — g_{Na}, V_{Na} - to be chosen

$I_K(V) \triangleq g_K\, n^4 (V - V_K)$ — g_K, V_K - to be chosen

$I_L(V) \triangleq g_L (V - V_L)$ — g_L, V_L - to be chosen

and gating variables m, h, n satisfy the first order ODE:

$$\frac{dx}{dt} = \frac{x_\infty(V) - x(t)}{\tau_x(V)}$$

where $x = m, h, n$

$x_\infty(V), \tau_x(V)$ - trascendental functions

The HH neuron is a model (i.e., it is based on simplifying assumptions like independence of the ion channels one from one another, infinite supply of ions in the extracellular bath, constant temperature, etc.) but it preserves biophysical variables ⇒ It turns out a 4th dimensional model that is hard to mathematically analyze and numerically simulate (if replicated in a large-scale network) ⇒ We need a model with fewer variables

Approximation 1 (Rinzel Model, 1985)

$$\left.\begin{array}{l} \tau_m(V) \cong 0 \quad \forall V \\ h_\infty(V) \cong n_\infty(V) \\ \tau_n(V) \cong \tau_h(V) \ \forall V \end{array}\right\} \Rightarrow \begin{array}{l} m(V,t) \cong m_\infty(V) \quad \forall t \\ h(t) \cong 1 - n(t) \quad \forall t \end{array}$$

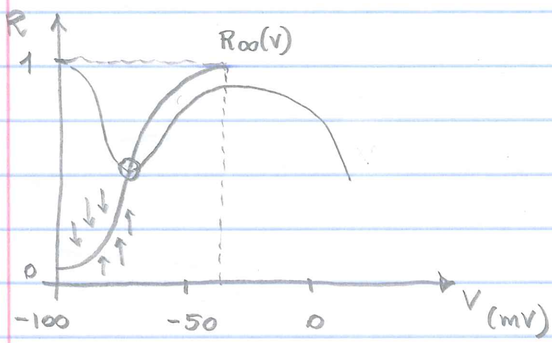
The original model $(*)$ can be approximated by:

$$C_m \frac{dV}{dt} + g_{Na}\, m_\infty^3(V)\,\big(1 - R(V,t)\big)(V - V_{Na}) + g_K R^4(V,t)(V - V_K) + g_L (V - V_L) = I_{ext} \qquad (**)$$

$$\frac{dR}{dt} = \frac{R_\infty(V) - R}{\tau_R(V)}$$

where R is the new (approximated) gating variable and $R_\infty(V)$, $\tau_R(V)$ are trascendental functions

Model (**) consists of two variables and can be studied via graphical tools (i.e, phase portraits):



$$\frac{dR}{dt} = 0 \iff R = R_\infty(V)$$

$$\frac{dV}{dt} = 0 \iff g_K R^4 (V - V_K) + g_{Na} m_\infty^3 (1-R)(V - V_{Na}) + g_L (V - V_L) - I_{ext} = 0$$

Assuming $I_{ext} = 0$, we can re-arrange the formula and obtain:

$$R^4 \left[g_K (V - V_K) \right] + R \left[-g_{Na} m_\infty^3 (V - V_{Na}) \right] + \left[g_{Na} m^3 (V - V_{Na}) + g_L (V - V_L) \right] = 0$$

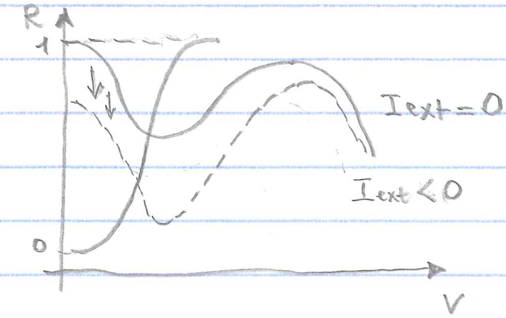
polynomial function of R with coefficients that depend on $V \Rightarrow$ It can be shown that the solution is a N-shaped curve in the phase portrait

The phase portrait is useful because it highlights a few things:

- The two curves correspond to condition $dR/dt = 0$ and $dV/dt = 0$, respectively (they are "nullclines") $\Rightarrow$ Their intersection indicates the value V^* and the state R^* for which the neuron is in equilibrium

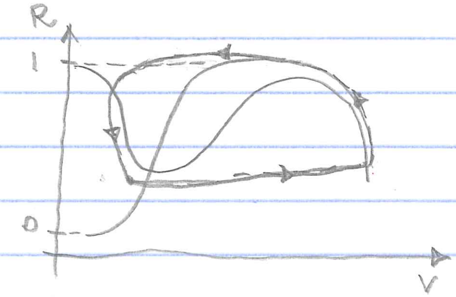
- If one moves around each nullcline, it can be determined the regions (V, R) where $dV/dt \gtrless 0$ and $dR/dt \gtrless 0 \Rightarrow$ For any set of initial conditions, one can predict the trajectory of the system in the (V, R) plan starting from the assigned initial conditions $\Rightarrow$ The phase portrait allows us to depict the vector field associated with (**)

- While the nullcline of R is fixed, the nullcline of V depends on I_{ext} $\Rightarrow$ The equilibrium may change because of a shift and/or deformation in the nullcline of V



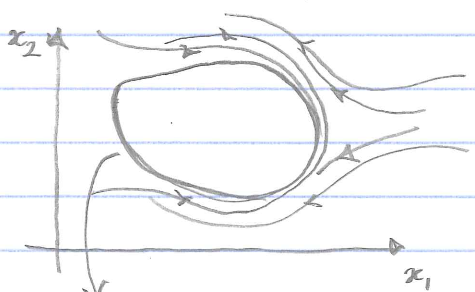
- An action potential corresponds to a circular trajectory in the (V, R) plan $\Rightarrow$ If it is a closed-loop, then an oscillation arises:

$$\exists T > 0 : \quad V(t+T) = V(t)$$
$$R(t+T) = R(t) \quad \forall t$$



Note that, while for linear systems the existence of a periodic solution implies the existence of infinitively many periodic solutions within any small neighborhood of an oscillation, nonlinear systems may have much more complicated behavior: the oscillation may be isolated and circled by trajectories that are not closed-loop and either spiral toward the oscillation or away from it $\Rightarrow$ Hence the definition:

limit cycle $\overset{\text{DEF}}{\Longleftrightarrow}$ a closed-loop trajectory surrounded by a sufficiently small neighborhood wherein all the trajectories are spirals

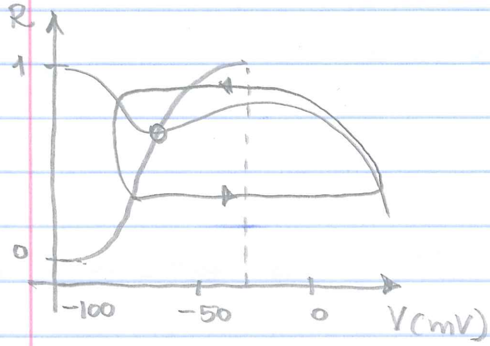


limit cycle

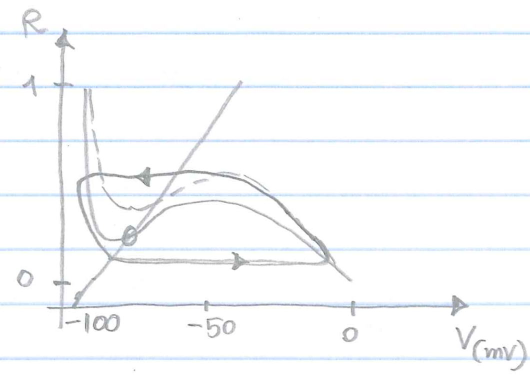
limit cycle
- asymptotically stable $\overset{\text{DEF}}{\Longleftrightarrow}$ trajectories spiral toward it as $t \to \infty$
- unstable $\overset{\text{DEF}}{\Longleftrightarrow}$ trajectories spiral away from it as $t \to \infty$

From these considerations, we derive that the dynamics of the HH neuron and model (**) are univocally determined by features of the correspondent phase portrait:

A)



B)



- Equilibrium Point
- Limit cycle (stable/unstable)

- Equilibrium Point
- Limit cycle (stable/unstable)

What about the phase portrait in B)? Although B) corresponds to a different neural system, it has the same features as the system in A) and similar changes in response to changes in I_{ext} ⇒ A) and B) capture qualitatively-similar dynamics

However, system B) is less complicated than the Rinzel model A):

$\left.\begin{array}{l}\text{R- nullcline is linear}\\ \text{V- nullcline is cubic}\end{array}\right\}$ ⇒ A model that satisfies these conditions is:

Approximation 2 (FitzHugh-Nagumo, 1961)

$$C\frac{dV}{dt} + g_{Na}(V)(V - V_{Na}) + R(V - V_K) = I_{ext}$$

$$\frac{dR}{dt} = \frac{1}{\tau_R}\big(\underbrace{\alpha V + \beta}_{R_\infty(V)} - R\big) \qquad (***)$$

with $g_{Na}(V)$ polynomial function of V (quadratic in V);

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Model (***) is a variation of the classic FitzHugh - Nagumo model derived to keep the Ohm's Law component and the dependence on the Nernst potentials V_K and V_{Na}

To verify that model (***) has a phase-portrait as in B), note:

$\frac{dR}{dt} = 0 \iff R = \alpha V + \beta$ - linear

$\frac{dV}{dt} = 0 \iff R = \frac{I_{ext} - g_{Na}(V)(V - V_{Na})}{V - V_K}$ and, for $I_{ext} = 0$, we have:

$$\left.\begin{array}{l} V \to V_{Na} \Rightarrow R \to 0 \\ V \to V_K \Rightarrow R \to \infty \end{array}\right\} \Rightarrow$$ The V-nullcline is N-shaped

Therefore, with regard to 1), a reduced-order model of the neural system can be used if it preserves the features of the phase portrait of the original system

Note that the "preservation" of phase portrait features can be mathematically defined in terms of topological equivalence:

DEF: Two models are TOPOLOGICALLY EQUIVALENT iff a continuous one-to-one transformation exists to transform one model into the other without changing the number of equilibria or their stability

Based on this argument, simplified models like (**) and (***) can be used for sake of dynamic clamp, provided that they are topologically equiv. to the original one, i.e., they show similar dynamics when I_{ext} is applied
$\Rightarrow$ See results in the slides

□

With regard to point 2), the issue is that our model is continuous in time, nonlinear, and with noisy measurements $\Rightarrow$ How can we estimate the model parameters?

- First, to cope with the discrete-time nature of the measurements and the fact that some state variables are not measured, let us integrate the model:

$$\left.\begin{array}{l} \dot{x} = f(x,\lambda) \\ y = G(x,\lambda) + \eta \quad \eta \sim N(0,R) \end{array}\right\} \Rightarrow \begin{array}{l} x(t+\Delta t) = x(t) + \int_t^{t+\Delta t} f(x(\tau),\lambda)\, d\tau \\ y(t) = G(x(t),\lambda) + \eta \end{array}$$

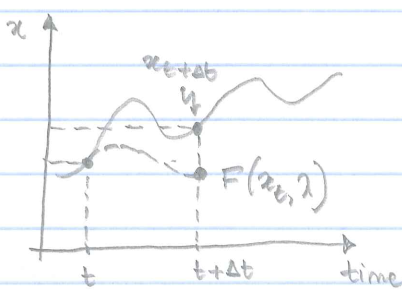
$x \triangleq$ vector of non-measureable state variables (e.g., R in the Rinzel's model)
$y \triangleq$ measurable variables (e.g., V in the models of neuron)
$\lambda \triangleq$ vector of model parameters

Let us use the notation: $x_{t+\Delta t} \triangleq x(t+\Delta t) \quad y_t \triangleq y(t)$

$$F(x_t,\lambda) \triangleq x_t + \int_t^{t+\Delta t} f(x_\tau,\lambda)\, d\tau$$

and write:

(a) $$\begin{array}{l} x_{t+\Delta t} = F(x_t,\lambda) \\ y_t = G(x_t,\lambda) + \eta_t \end{array}$$

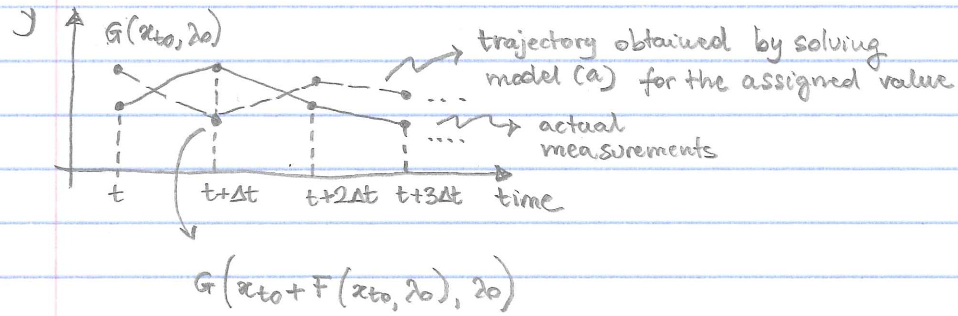


However, $F(\cdot)$ is now the integral of a model $\Rightarrow$ Because a model introduces an approximation, $F(x_t,\lambda)$ may be different from the true $x_{t+\Delta t}$ $\Rightarrow$ We must take model uncertainty into account

$\Downarrow$

Note: in the estimation problems considered thus far, we gave a precise characterization of the model uncertainty (i.e., Gaussian, additive, etc.) $\Rightarrow$ We are relaxing our assumptions now

- Second, let us choose an initial (guess) value for x_t and λ (i.e., x_{t_0}, λ_0) and let us solve model (a):



$\Rightarrow$ The mismatch between trajectories depends on model limitations and initial guess of x_t and λ

While the model structure in (a) is assigned, the values of x_t and λ can be varied $\Rightarrow$ We can formulate an optimization problem:

- Let us define: $P(y_{t_1}, y_{t_2}, \ldots, y_{t_n}) \triangleq P(G(x_{t_1}, \lambda) = y_{t_1}, \ldots,$

  $G(x_{t_n}, \lambda) = y_{t_n})$ - probability of observing the given measurements with the assigned model

- Because: $P(y_{t_1}, y_{t_2}, \ldots, y_{t_n}) = P(y_{t_1}, y_{t_2}, \ldots, y_{t_n} \mid x_t, \lambda)$, we aim to:

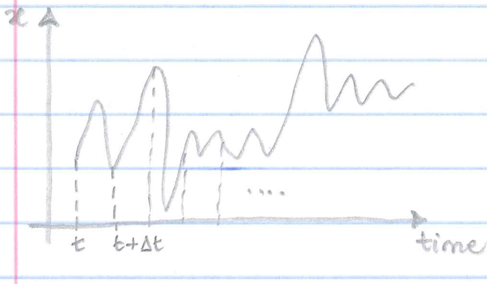
$$(\hat{x}_t, \hat{\lambda}) = \arg\max_{x_t, \lambda} P(y_{t_1}, y_{t_2}, \ldots, y_{t_n} \mid x_t, \lambda)$$

- As long as the noise η_t on the measurements is Gaussian and $\eta_t \sim N(0, R_t)$ the solution of the problem above is equivalent to:

(b) $$(\hat{x}_t, \hat{\lambda}) = \arg\min_{x_t, \lambda} \sum_{j=1}^{n} \frac{(y_{t_j} - G(x_{t_j}, \lambda))^2}{R_{t_j}}$$

where x_{t_j} is the state at time j along the state trajectory stemming from the initial state x_t

Note that the problem (a)-(b) consists in finding the initial conditions the make the most likely evolution $\Rightarrow$ In order for the solution to be acceptable (i.e., non-divergent, unique, etc.) the model $F(\cdot)$, $G(\cdot)$ must be smooth and weakly nonlinear



If the state is fast varying and irregular or the model is highly nonlinear, the solution to problem (a)-(b) diverges

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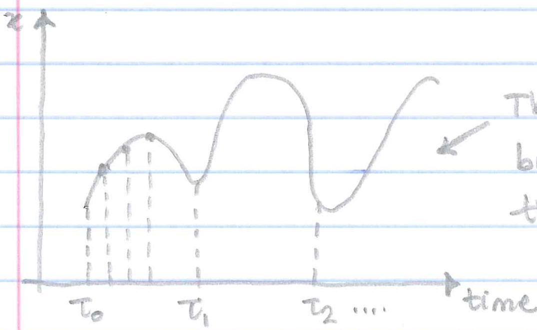
A practical alternative consists in breaking the trajectory into many, consecutive windows and solve problem (a)-(b) in each window $\Rightarrow$ the method is called "Multiple Shooting"



The sampling time Δt is the same as before but we assume that, over a window $[\tau_i, \tau_{i+1})$ that includes a few samples, the evolution is smooth enough

In this case, we have initial conditions $x_0 = x(\tau_0)$, $x_1 = x(\tau_1)$, etc. to be chosen along with parameters $\lambda \Rightarrow$ Problem (a)-(b) can be modified as:

$$(\hat{x}_0, \hat{x}_1, \dots, \hat{x}_m, \hat{\lambda}) = \underset{(x_0, \dots, x_m, \lambda)}{\arg\min} \sum_{j=1}^{n} \frac{(y_{t_j} - G(x_{t_j}, \lambda))^2}{R_{t_j}}$$

s.t.:

$$x_{t+\Delta t} = F(x_t, \lambda)$$

$$y_t = G(x_t, \lambda) + \eta_t$$

$$x_{\tau_j} = x_j \qquad j = 1, 2, \dots, m \qquad (c)$$

Note that condition (c) implies equality constraints at the boundaries, i.e., the end-point of the trajectory x_t stemming from initial condition x_j at time τ_j must coincide with the initial condition x_{j+1} of the following window ⇒ See slides

II.

Note that both problem (a)-(b) and the Multiple Shooting problem can be solved numerically by using standard minimization tools (e.g., Gauss-Newton method) but require that all the measurements are available (off-line) and assume that parameters λ are fixed

• Alternatively, one can assume that λ is slowly varying over time and treat the parameters as variables ⇒ We can expand model (a):

$$\lambda_{t+\Delta t} = \lambda_t + \varepsilon_t \qquad \varepsilon_t \sim N(0, Q_t)$$

(i) $$x_{t+\Delta t} = F(x_t, \lambda_t)$$

$$y_t = G(x_t, \lambda_t) + \eta_t \qquad \eta_t \sim N(0, R_t)$$

Model (i) has now an extended vector of state variables:

$$z_t \triangleq \begin{bmatrix} \lambda_t \\ x_t \end{bmatrix} \qquad \tilde{F}(z_t) \triangleq \begin{bmatrix} \lambda_t \\ F(x_t, \lambda_t) \end{bmatrix} \qquad \tilde{\varepsilon}_t \triangleq \begin{bmatrix} \varepsilon_t \\ 0 \end{bmatrix} \qquad \tilde{G}(z_t) \triangleq G(x_t, \lambda_t)$$

we have: $$z_{t+\Delta t} = \tilde{F}(z_t) + \tilde{\varepsilon}_t$$
$$y_t = \tilde{G}(z_t) + \eta_t$$

Note: noise ε_t is introduced to model the fluctuations of the parameters λ when - as in our case - there is no generative model for λ ⇒ Covariance Q_t becomes a tuning parameter that we may vary to minimize the distance between y_t and the actual measurements

Now: z_t - not measurable
y - measured
$\vec{F}, \tilde{G}$ - nonlinear
Q_t, R_t - known

$\Rightarrow$ We can estimate x_t and λ_t given y_t and model (i) by using the UKF

- Example: Let us now consider the F-N model:

$$C\frac{dV}{dt} + g_{Na}(V)(V - V_{Na}) + R(V - V_K) = I_{ext}$$

$$\frac{dR}{dt} = \frac{1}{\tau_R}(\alpha V + \beta - R)$$

$$g_{Na}(V) = \gamma_1 + \gamma_2 V + \gamma_3 V^2$$

It can be shown that this model is topologically equivalent to:

$$\frac{dV}{dt} = c\left(R + V - \frac{V^3}{3} + U\right)$$

$$(\Delta\nabla) \qquad \frac{dR}{dt} = -\frac{V - a + bR}{c}$$

where U is the exogenous input (related to I_{ext}) and parameters a, b, c to be chosen to preserve the equilibria

First, let us use model $(\Delta\nabla)$ and let us put it in discrete form:

$$\frac{dV}{dt} = c\left(R + V - \frac{V^3}{3} + U\right) \Rightarrow V_{t+\Delta t} = V_t + c\int_t^{t+\Delta t}\left(R_\tau + V_\tau - \frac{V_\tau^3}{3} + U_\tau\right)d\tau$$

$$\frac{dR}{dt} = -\frac{V - a + bR}{c} \Rightarrow R_{t+\Delta t} = R_t + \frac{a}{c}\Delta t - \frac{1}{c}\int_t^{t+\Delta t}(V_\tau + R_\tau)\,d\tau$$

Then let us define the augmented nonlinear model:

$$z_t \triangleq \begin{bmatrix} a_t & b_t & c_t & V_t & R_t \end{bmatrix}^T \qquad y_t \triangleq V_t \qquad \tilde{G}(z_t) = \begin{bmatrix} 0 & 0 & 0 & 1 & 0 \end{bmatrix} z_t$$

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$$\tilde{F}_t(x_t) \triangleq \begin{bmatrix} a_t \\ b_t \\ c_t \\ V_t + \int_t^{t+\Delta t} \cdots \\ R_t + \int_t^{t+\Delta t} \cdots + \frac{a}{c}\Delta t \end{bmatrix}$$

With this setup, one can then implement the UKF $\Rightarrow$ See slides $\square$