

An Introduction to the Analysis of Biomathematical Models

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Typical Goals of Biological Modeling

1. Integrate and interpret the data
2. Make testable predictions
3. Design experiments
4. Find the gaps in the box/arrows diagrams

Types of equations used in dynamic models?
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Deterministic equations

With these equations, the state of the system at time $t + \Delta t$ is completely determined by the state of the system at earlier time points. For example, the equations for planetary motion are deterministic, they tell us the location of the earth tomorrow given its location today.

Stochastic equations

These equations include probabilistic events. Given the state of the system at time t , there are a range of possible states at time $t + \Delta t$, based on a probability distribution function. For example, if there are 10 ion channels in a patch of membrane and 5 are currently open, there may be 4, 5, or 6 channels open at the next instant of time, $t + \Delta t$. This would be described by stochastic equations.

Ordinary differential equations

These have a single independent variable, which is **time** in the case of dynamic models. For example,

$$\frac{du}{dt} = au^2 + bu + c .$$

The *independent variable* is time t , the single *dependent variable* is u , and a , b , and c are *parameters*. These parameters are constants that are typically adjusted over time by iterating between model prediction and experimental tests.

Partial differential equations

These have 2 or more independent variables, one of which is time for dynamic models. The others are often **spatial dimensions**. For example, the diffusion of Ca^{2+} within a cell would be described by a partial differential equation:

$$\frac{\partial u}{\partial t} = D \nabla^2 u$$

where u is the Ca^{2+} concentration at a location in the cell, D is a parameter, the *diffusion coefficient*, and ∇^2 represents partial derivatives with respect to the spatial variables.

Linear equations

These have only constant terms or terms to the first power of u in the right hand side of the differential equation. For example,

$$\frac{du}{dt} = au + b$$

where a and b are parameters. There may be several differential equations, one for each dependent variable. For example,

$$\begin{aligned}\frac{du}{dt} &= au + bv + c \\ \frac{dv}{dt} &= du + ev + f\end{aligned}$$

where u and v are the two dependent variables. This is a *system of linear ODEs*. Because of the linearity, it is possible to derive a formula for the solution. This would tell us the values of u and v in terms of time t for all points in time. Before the advent of computers, the vast majority of math models were linear!

Nonlinear equations

These have one or more terms in the right hand side of the equation involving u^2 , u^3 , e^u , etc. or with two or more dependent variables multiplied together. For example,

$$\frac{du}{dt} = au^4$$

or the system

$$\begin{aligned}\frac{du}{dt} &= auv + b \\ \frac{dv}{dt} &= cu + dv + e \ .\end{aligned}$$

It is typically not possible to write down a formula for the solution of a nonlinear ODE (or PDE). Instead, one uses a computer to solve the equations using numerical techniques, and often uses **qualitative analysis** to understand the long-term behavior of the dependent variables without actually solving the equations. **Most modern biological models are nonlinear.**

Model Dimensionality

This is typically the **number of dependent variables**, and therefore the **number of differential equations**. Models with 2 dependent variables are called **planar models**. These are the simplest models that can produce oscillations, so are often used by modelers when possible.

A special case exists for differential equations that contain a time delay. These are called **delay differential equations**. For example,

$$\frac{du}{dt} = au + bu_\tau$$

where $u_\tau = u(t - \tau)$ is the u variable delayed by τ time units. Models containing this type of equation can be useful in physiological settings, for example, when a hormone secreted from a cell has an effect on another cell, but only after it has circulated through the blood. These equations have dimension of infinity!

Analysis of a 1-Dimensional Model

Example, a one-dimensional nonlinear ODE:

$$\frac{du}{dt} = p - u(u - 0.5)(u - 1)$$

where p is a parameter. Start with $p = 0$. The RHS tells how u changes over time, i.e., the **velocity** of u .

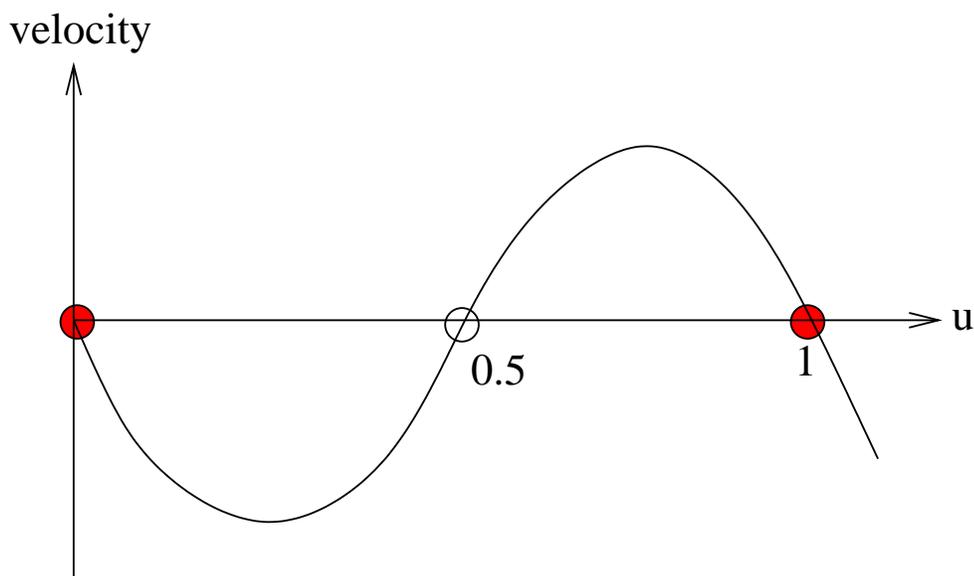


Figure 1: $p = 0$

The circles are points where the velocity is 0. That is, they are **equilibria**, also called **steady states**. Those colored in red are **stable**, while the open circle is **unstable**.

- What happens if the initial value of u (the *initial condition*) is less than 0.5?
- What happens if the initial u value is greater than 0.5?

The system is **bistable**, while the unstable steady state is the threshold between the initial conditions attracted to the leftmost stable steady state (this is the **basin of attraction** of this attractor) and the basin of attraction of the rightmost attractor.

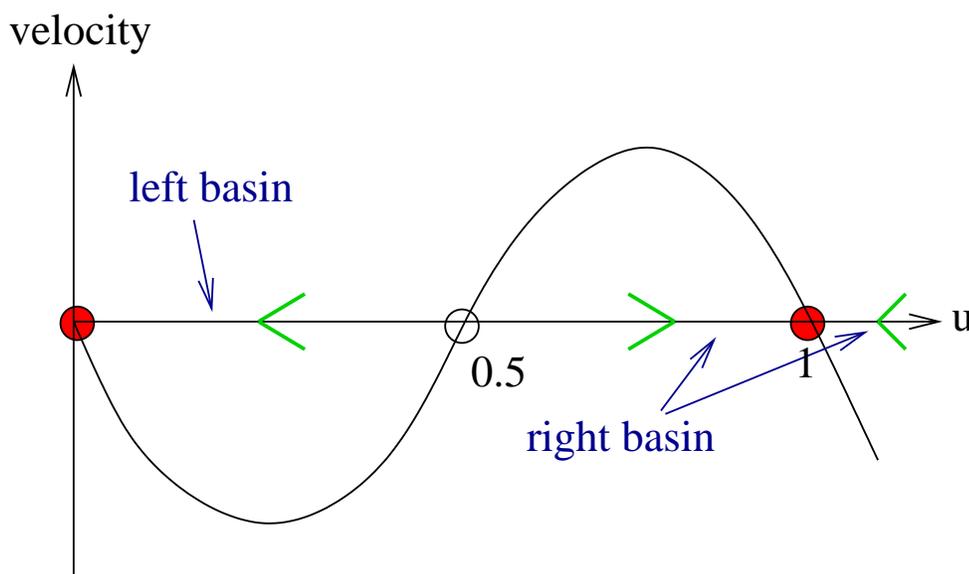


Figure 2: Phase portrait, $p = 0$

Since this system is one-dimensional, the **phase space** is just

a line, the x-axis of the figure above. The figure showing the flow on the phase space is called a **phase portrait**. The dynamics can also be viewed as u versus time for different initial values of u , as follows

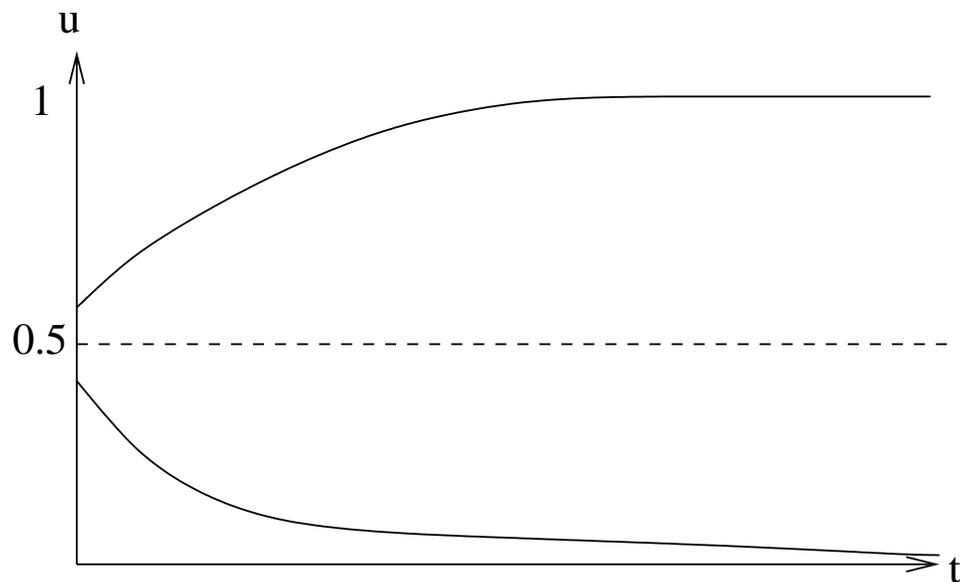


Figure 3: Time course, $p = 0$

Note: This analysis was all done without solving the differential equation. No computer is required!

Example: $p > 0$

When the parameter p is increased the velocity curve is trans-

lated upwards. This shifts the locations of the steady states. For p sufficiently large the two leftmost steady states coalesce and disappear, leaving only a single steady state (blue). This event is called a **bifurcation**, since the qualitative properties of the system change here.

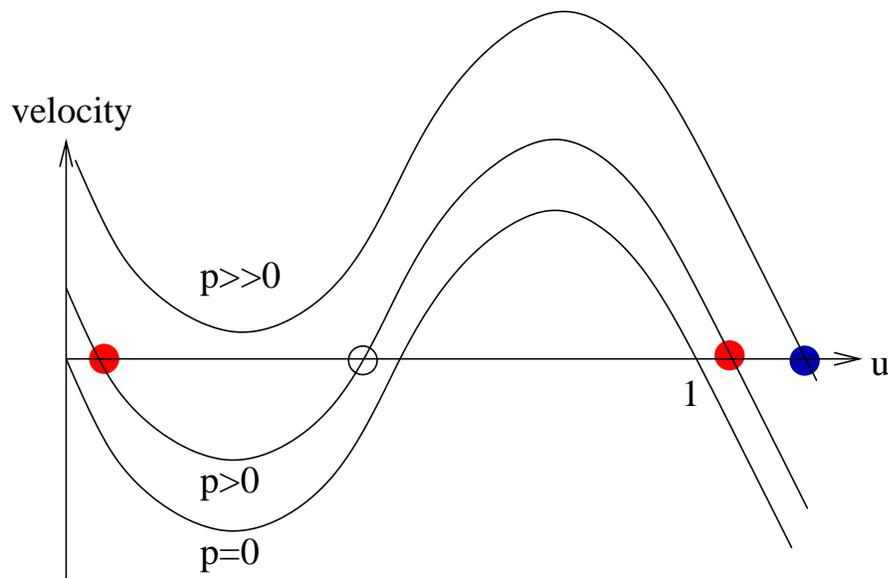


Figure 4: Various p values

The change in the long-term dynamics as p is increased can be summarized with a **bifurcation diagram**. We plot the equilibria for a range of values of the parameter p , indicating whether they are stable (solid curve) or unstable (dashed

curve).

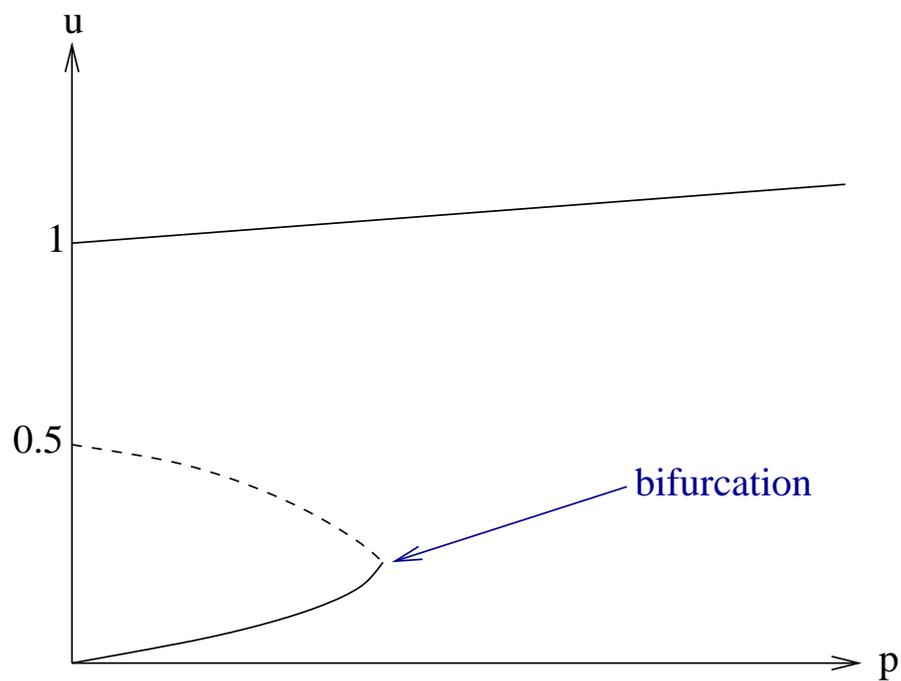


Figure 5: Bifurcation diagram for 1-D model

Analysis of a Planar Model

As an example we look at a well-known planar model for electrical activity in a barnacle muscle. This model, the Morris-Lecar model (1981), has been used as the starting point for models of many other cell types, including endocrine cells.

The Morris-Lecar Model

- One **hyperpolarizing current**: $I_K = \bar{g}_K w (V - V_K)$, where V is the membrane potential, V_K is the K^+ Nernst potential, \bar{g}_K is maximum conductance and w is an **activation variable**, the fraction of open K^+ channels. w approaches its equilibrium value, $w_\infty(V)$, with a **time constant** $\tau_w = \tau_w(V)$:

$$\frac{dw}{dt} = [w_\infty(V) - w] / \tau_w(V) .$$

- One **depolarizing current**: $I_{Ca} = \bar{g}_{Ca} m_\infty(V) (V - V_{Ca})$, which is assumed to activate instantaneously.
- One **leakage current**: $I_L = g_L (V - V_L)$, which is depolarizing and has a V -independent conductance.
- One **capacitance current**: $I_C = C \frac{dV}{dt}$, where C is the membrane capacitance.
- One **applied current**: I_{ap} , the current applied through an electrode.

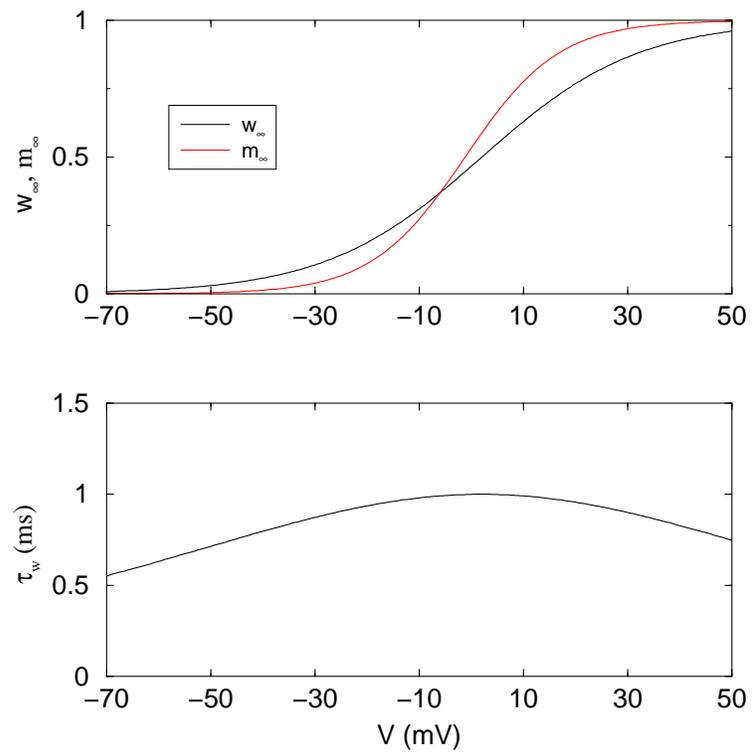


Figure 6: Calcium and potassium equilibrium and time constant functions

By Kirchoff's Current Law (conservation of charge), the sum of these current must be 0:

$$I_C + I_{Ca} + I_K + I_L - I_{ap} = 0$$

or

$$\frac{dV}{dt} = -(I_{Ca} + I_K + I_L - I_{ap})/C.$$

Summary: The ODEs for the **Morris-Lecar model** are:

$$\begin{aligned} \frac{dV}{dt} &= -(I_{Ca} + I_K + I_L - I_{ap})/C \\ \frac{dw}{dt} &= [w_\infty(V) - w] / \tau_w(V) . \end{aligned}$$

Since this model is 2-dimensional, the phase space is the 2-dimensional plane. There are a set of tools that can be used to analyze dynamics in the plane. The first tool is the **nullcline**. This is a curve in which the rate of change (velocity) of one of the variables is 0. There are two nullclines, one for each variable. **Equilibria** occur at points where the two nullclines intersect.

V -nullcline:

$$w = \frac{I_{ap} - \bar{g}_{Ca} m_{\infty}(V)(V - V_{Ca}) - \bar{g}_L(V - V_L)}{g_K(V - V_K)}$$

w -nullcline:

$$w = w_{\infty}(V) \quad .$$

We now construct the **phase portrait**, which will now be drawn in the Vw -plane.

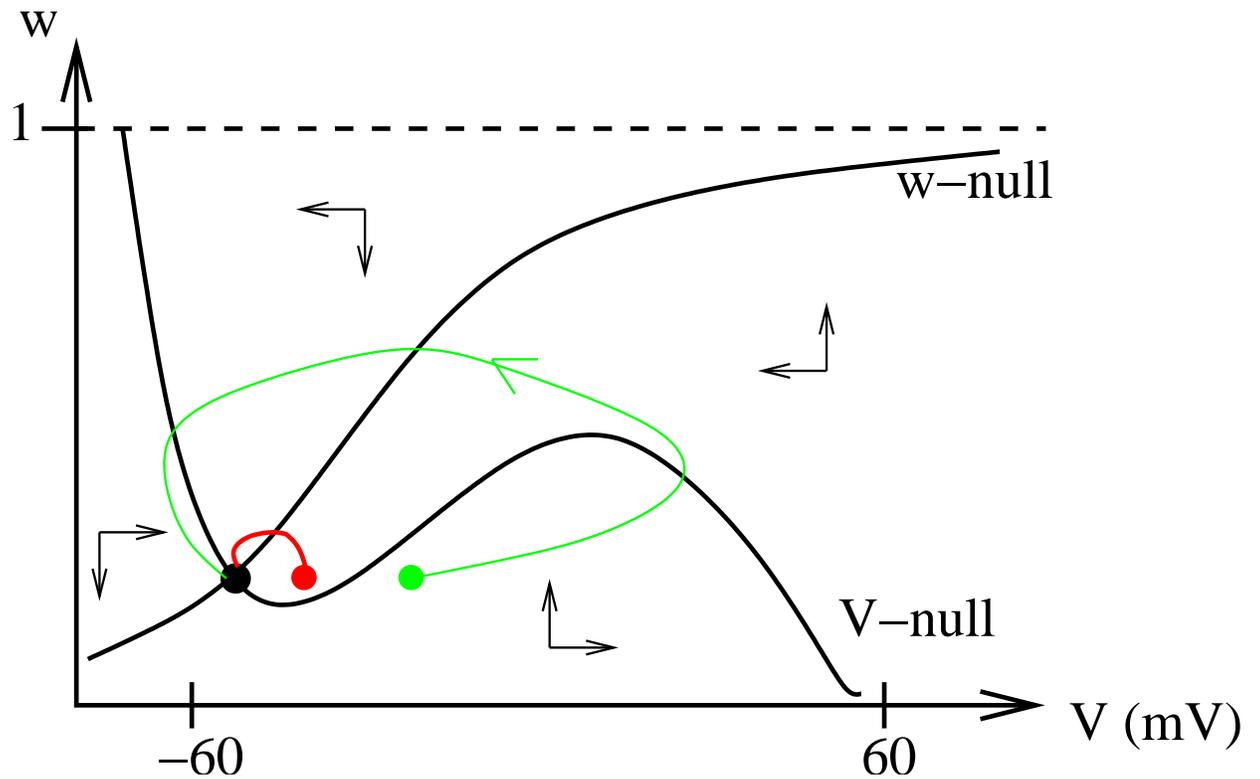


Figure 7: Black circle: equilibrium, Red: subthreshold response, Green: impulse. $I_{ap} = 0$.

The middle branch of the cubic-shaped V -nullcline is the im-

pulse **threshold**. Other planar models for impulse generation have been developed. Most have cubic-like V -nullclines.

Increasing the applied current translates the V -nullcline upward. The steady state can become **unstable** when the intersection is on the middle branch, through a **Hopf bifurcation**. The stable steady state is replaced with a stable **limit cycle**. This limit cycle represents a periodic train of action potentials.

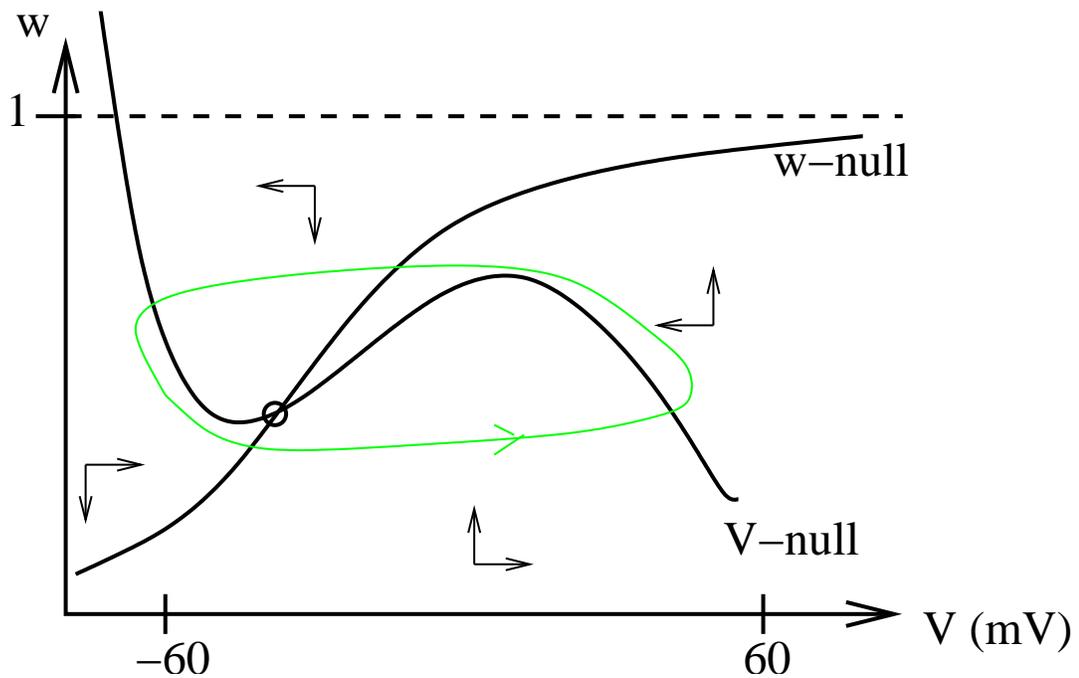


Figure 8: Green: Limit cycle. $I_{ap} = 100$ pA.

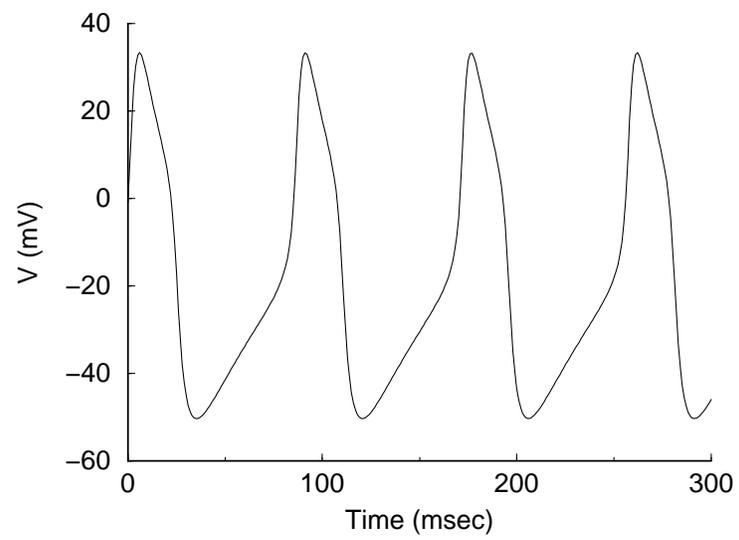


Figure 9: A periodic train of action potentials, when $I_{ap} = 100$ pA.

If the applied current is increased enough that the w -nullcline and V -nullcline intersect on the right branch, then the steady state is stabilized through a second Hopf bifurcation. This corresponds to a depolarized steady state and reflects [excitation block](#).

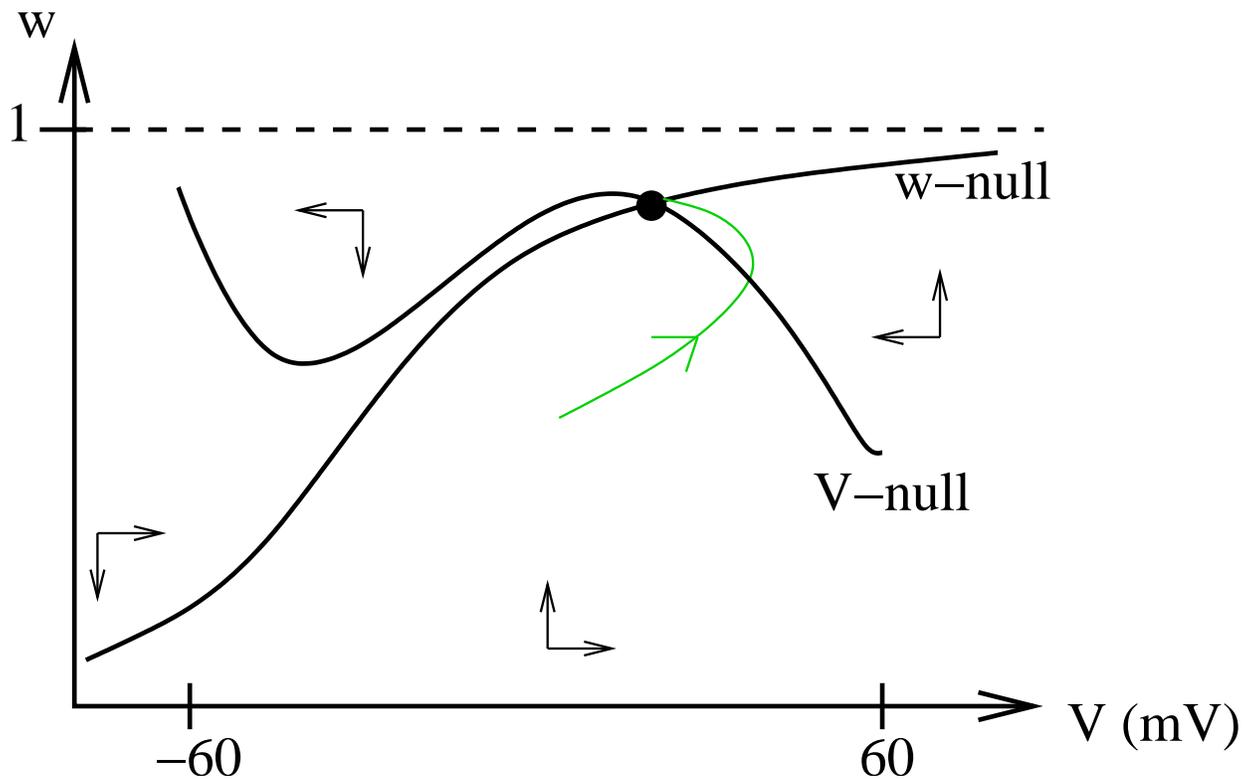


Figure 10: Depolarized resting state, when $I_{ap} = 250$ pA.

These behaviors can be summarized with a bifurcation diagram:

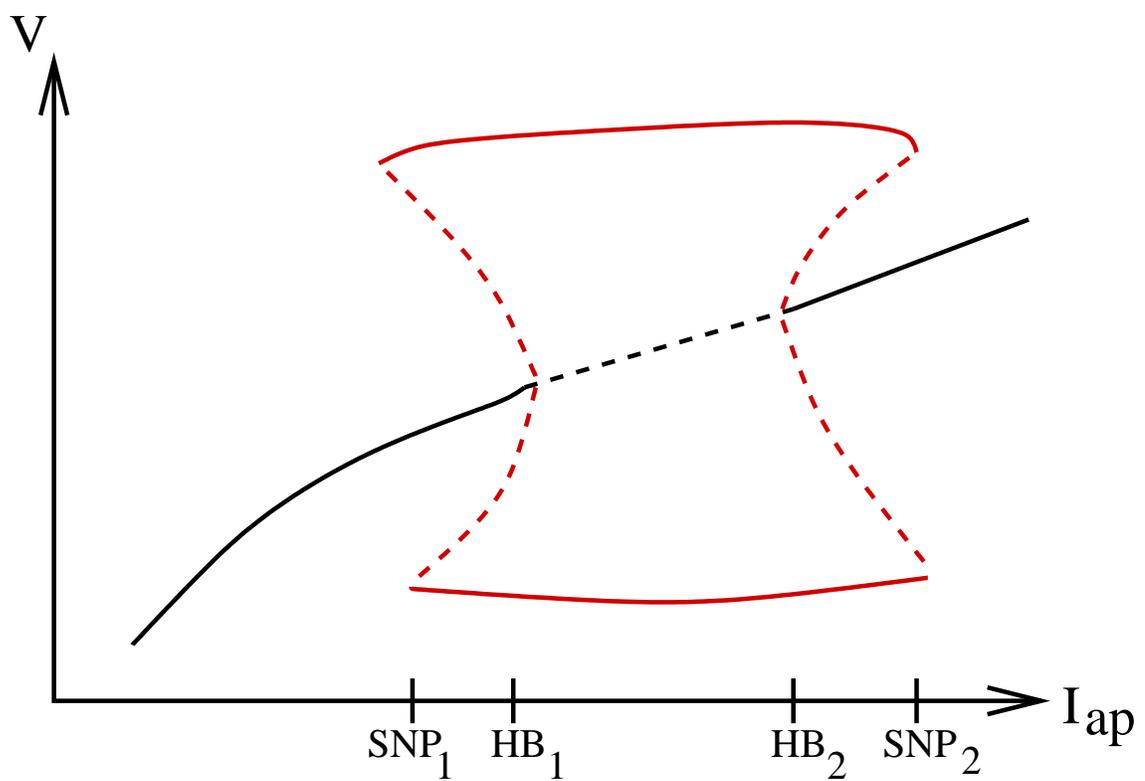


Figure 11: Morris-Lecar bifurcation diagram. Black: stationary branch, Red: periodic branch

Models with Dimension > 2

For these models the analysis is harder since nullclines are no longer applicable. More importantly, much more complicated dynamic behavior can occur. This includes **chaos**, where the time courses of the variables are unpredictable. One example is the Lorenz equations, which for a range of parameter values produce chaos:

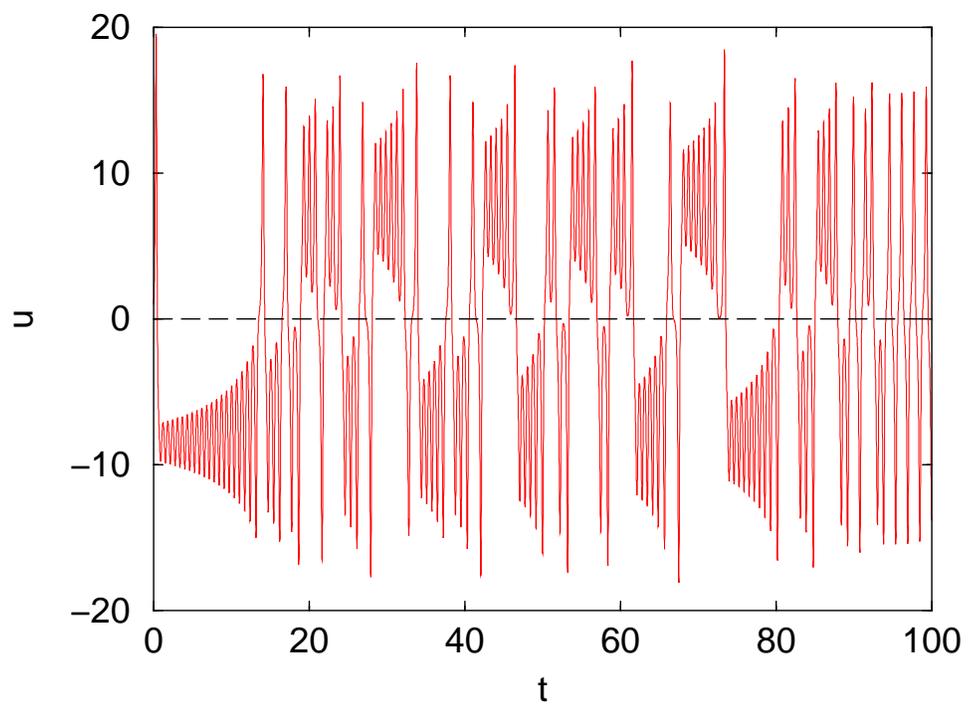


Figure 12: Chaotic time course from the Lorenz equations

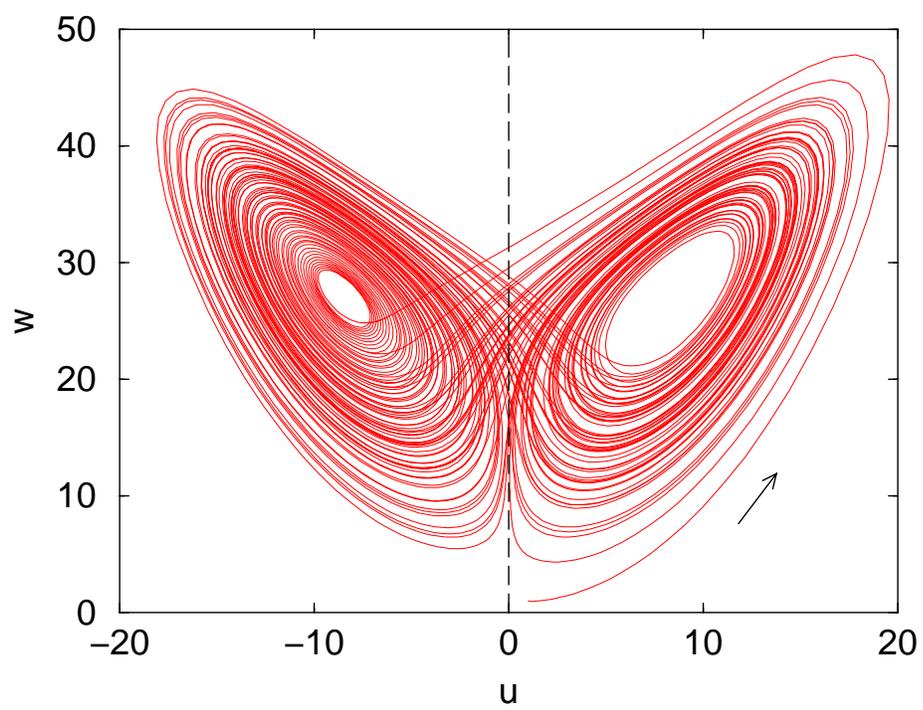


Figure 13: Chaotic trajectory in the uw -plane

Stochastic Models

In many instances the system under study has a substantial degree of randomness in it. For example, the following patch clamp recording shows the random or stochastic opening of channels in a patch that contains 4 or more ion channels.

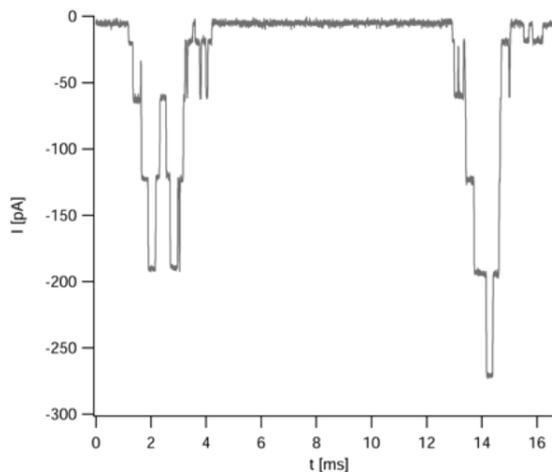
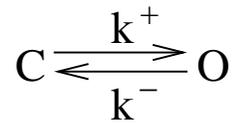


Figure 14: Cell-attached patch clamp measurement

This behavior cannot be captured by deterministic differen-

tial equations; it requires a stochastic model.

The dynamics of an ion channel can be described most simply as a 2-state [Markov process](#), with the following kinetic scheme:



where C and O represent closed and open channels states, respectively, and k^+ and k^- are forward and backward transition rates, respectively. These rates reflect probabilities, and the stochastic transitions between C and O can be simulated using a [Monte Carlo algorithm](#).

The following figure shows the result of a Monte Carlo simulation of the opening/closing of a single ion channel. 0 means the channel is closed, 1 means it is open.

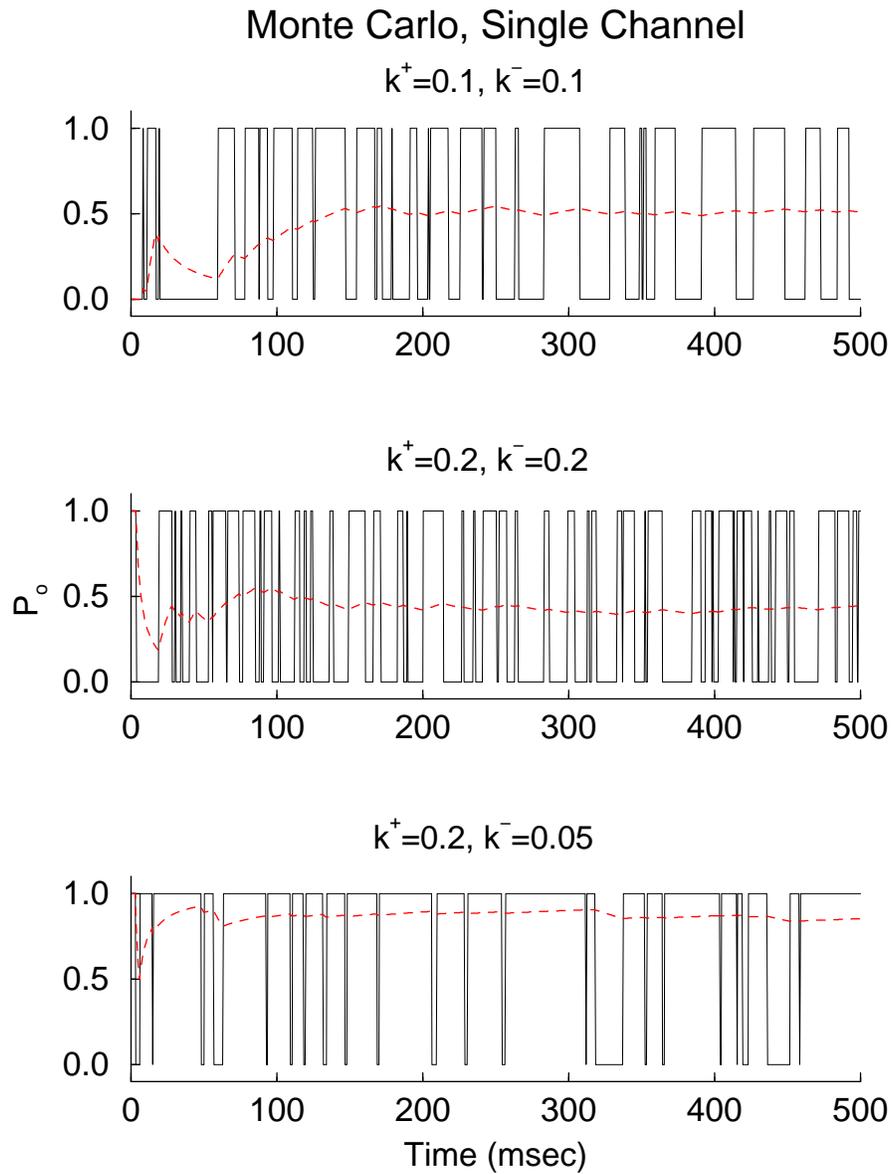


Figure 15: Monte Carlo simulation of single ion channel with various transition rates. Red curve is time average of the fraction of time the channel is open.

The Monte Carlo simulation can be applied to a population of channels, as in the case below for a population of 4 channels.

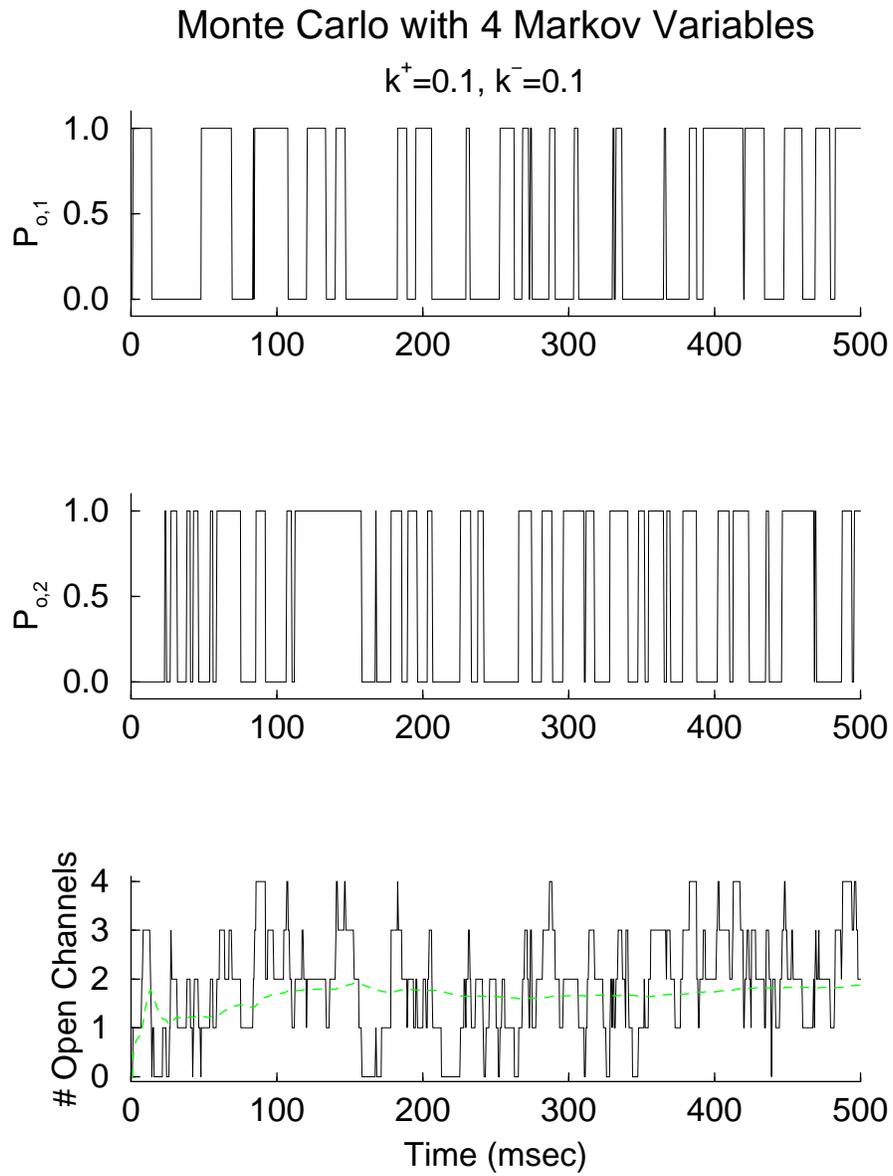


Figure 16: Monte Carlo simulation of a population of 4 ion channels. Green curve is the time-averaged number of open channels.

One can also create a **hybrid model** that combines deterministic equations with stochastic processes. For example, the voltage differential equation from Morris-Lecar can be used, but the differential equation for the fraction of open K^+ channels is replaced by a Markov process. This process consists of a population of 50 K^+ channels with opening/closing simulated with Monte Carlo. Then the fraction of open channels at each time point (w) is calculated and used in the V differential equation. This produces a noisy voltage trace.

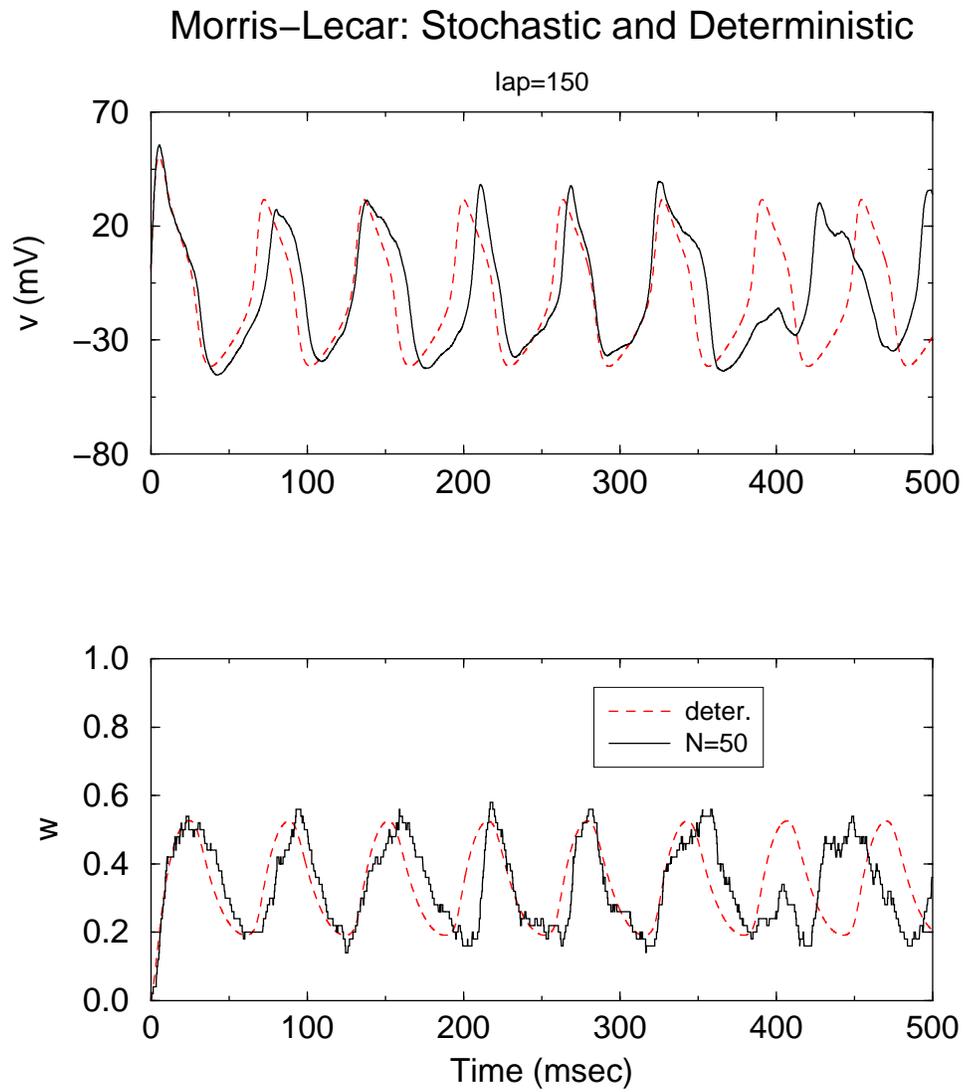


Figure 17: Simulation from a hybrid Morris-Lecar model. Red curve is the trace from the deterministic model.

That's all folks, enjoy the workshop!!