# Stochastic Systems

**Richard Bertram**

Department of Mathematics and
Programs in Neuroscience and Molecular
Biophysics
Florida State University
Tallahassee, Florida 32306

The Hodgkin-Huxley-type models of nerve activity are based on ionic currents that are produced as the result of ion flux through channels. We have thus far assumed that there are enough channels so that a deterministic approach to the fraction of open channels is appropriate. However, this assumption is not always valid. For example, patch clamp electrical recordings measure the electrical activity in a small patch of membrane, where there are only a few channels.

As another example, in some cells there are only a few (100 or less) channels of a particular type. In this case, the variance in the number of open channels can be quite large compared with the mean, so once again the deterministic approach (which is a description of the mean) is questionable. As a

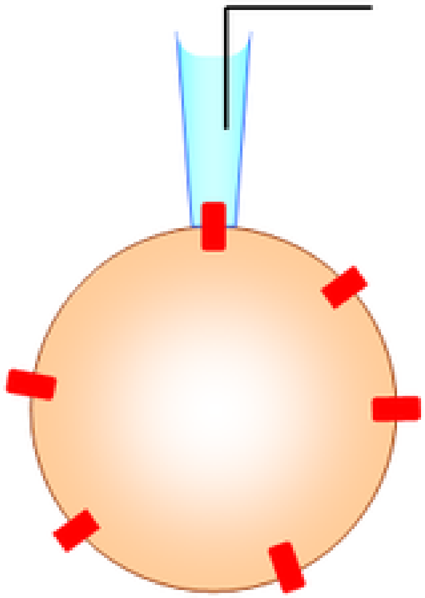


Figure 1: Cell-attached patch clamp illustration. (en.wikipedia.org/wiki/Patch_clamp)

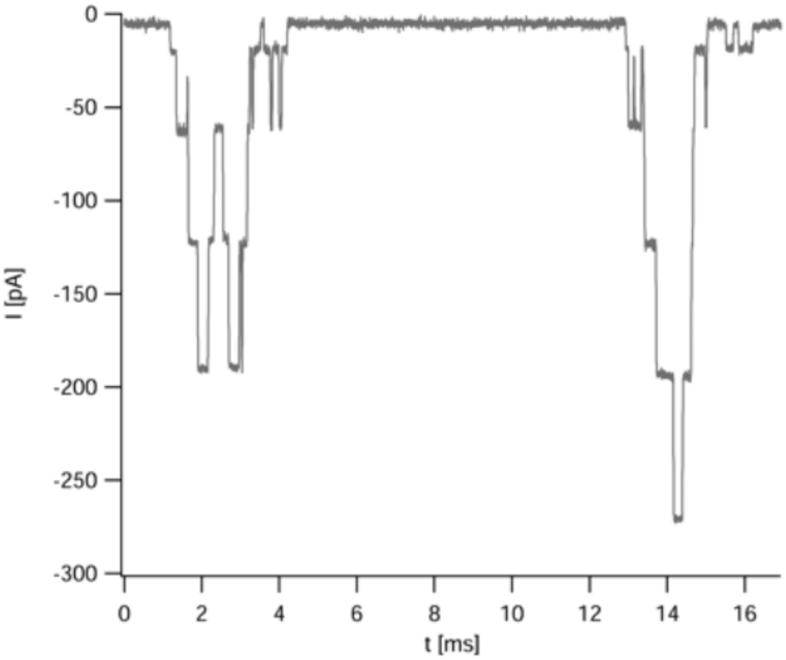


Figure 2: Current measurement using cell-attached patch clamp. (www.biophysj.org/cgi/content/full/82/6/3056)

final example, in some cases the **noise** in the system can be a key component for signal amplification and transmission. Leaving out the noise fundamentally changes the signal transduction process.

The outline for this talk is

1. Description of a stochastic ion channel using a Markov model
2. Using the Monte Carlo method to simulated the stochastic behavior of the channel and then a population of channels
3. A stochastic Morris-Lecar model
4. How noise can help, Stochastic Resonance

## Single channel as a 2-state Markov process

For an excellent reference see Chapter 11 by Greg Smith in "Computational Cell Biology" (Fall et al., 2002).

A simple ion channel has a single closed and single open state:

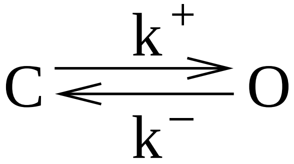


Figure 3: State diagram for a single ion channel

The state of the system is given by the **random variable** $s \in C, O$. Define

$$P_c(t) = \text{Prob}[s = C, t] \quad (1)$$

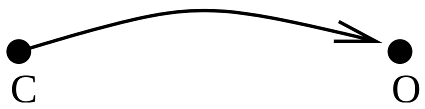
$$P_o(t) = \text{Prob}[s = O, t] \quad (2)$$

The parameter $k^+$ is the $C \rightarrow O$ rate (units of $\text{ms}^{-1}$). If the channel is closed at time $t$, the probability that it will open by time $t + \Delta t$ is

$$\text{Prob}[s = O, t + \Delta t | s = C, t] = k^{+} \Delta t \qquad (3)$$

This is a **conditional probability**. Must multiply by the probability that the channel is in state C at time $t$. Finally,

$$\begin{aligned} \text{Prob}[C \rightarrow O] &= \text{Prob}[s = O, t + \Delta t | s = C, t] \times P_c(t) \\ &= k^{+} \Delta t P_c(t) \quad . \qquad (4) \end{aligned}$$



A closed channel must either open or stay closed, so

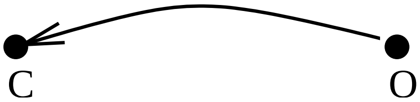
$$\text{Prob}[s = C, t + \Delta t | s = c, t] = 1 - k^{+} \Delta t \qquad (5)$$

and therefore,

$$\begin{aligned} \text{Prob}[C \rightarrow C] &= \text{Prob}[s = C, t + \Delta t | s = C, t] \times P_c(t) \\ &= (1 - k^{+} \Delta t) P_c(t) \quad . \qquad (6) \end{aligned}$$

Similarly,

$$\text{Prob}[O \rightarrow C] \;=\; k^{-}\Delta t P_o(t) \qquad (7)$$

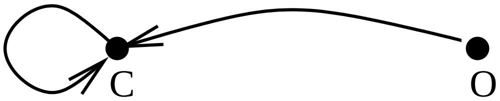


and

$$\text{Prob}[O \rightarrow O] \;=\; (1 - k^{-}\Delta t)P_o(t) \;\; . \qquad (8)$$

What is the probability that the channel is closed at time $t + \Delta t$?

$$\begin{aligned} P_c(t+\Delta t) &= \mathrm{Prob}[C \rightarrow C] + \mathrm{Prob}[O \rightarrow C] \\ &= (1-k^+\Delta t)P_c(t) + k^-\Delta t P_o(t) \quad (9) \end{aligned}$$



Similarly,

$$\begin{aligned} P_o(t+\Delta t) &= \mathrm{Prob}[O \rightarrow O] + \mathrm{Prob}[C \rightarrow O] \\ &= (1-k^-\Delta t)P_o(t) + k^+\Delta t P_c(t) \quad (10) \end{aligned}$$

These transition probabilities can be written in matrix/vector form as

$$\boxed{\vec{P}(t+\Delta t) = \mathbf{T}\vec{P}(t)} \qquad (11)$$

where

$$\vec{P} = \begin{pmatrix} P_c \\ P_o \end{pmatrix} \qquad (12)$$

and where $\mathbf{T}$ is the transition probability matrix:

$$\begin{aligned}\mathbf{T} &= \begin{pmatrix}\mathrm{Prob}[s=C,t+\Delta t|s=C,t] & \mathrm{Prob}[s=C,t+\Delta t|s=O,t]\\ \mathrm{Prob}[s=O,t+\Delta t|s=C,t] & \mathrm{Prob}[s=O,t+\Delta t|s=O,t]\end{pmatrix}\\ &= \begin{pmatrix}1-k^{+}\Delta t & k^{-}\Delta t\\ k^{+}\Delta t & 1-k^{-}\Delta t\end{pmatrix} \qquad (13)\end{aligned}$$

Notice that the elements of each column sum to 1, which must occur in any transition probability matrix.

Equation 11 is a recursion relation that tells how to move one step forward in time. Because the equation is linear it can be solved, providing a formula for moving $n$ steps forward in time:

$$\boxed{\vec{P}(t+n\Delta t) = \mathbf{T}^{n}\vec{P}(t)} \qquad (14)$$

Alternatively, one can solve Eq. 11 using eigenvalues and eigenvectors of $\mathbf{T}$. Starting from time $t=0$,

$$\vec{P}(n\Delta t) \;=\; c_1\lambda_1^{n}\vec{X}_1 + c_2\lambda_2^{n}\vec{X}_2 \qquad (15)$$

where $c_1$ and $c_2$ come from initial conditions. What do we know about the eigenvalues of $\mathbf{T}$?

- Columns of $\mathbf{T}$ add to 1, so colums of $\mathbf{T}-\mathbf{I}$ add to 0.
- Since $\text{row}_1 + \text{row}_2$ is the zero row, the two rows are linearly dependent.
- This means that $\mathbf{T}-\mathbf{I}$ is singular, so it has a 0 eigenvalue.
- This means that $\lambda_1 - 1 = 0$, so $\lambda_1 = 1$, and $\mathbf{T}$ has an eigenvalue of 1!!

The eigenvector associated with $\lambda_1 = 1$ is

$$\vec{x}_1 = C \begin{pmatrix} \frac{k^-}{k^-+k^+} \\ \frac{k^+}{k^-+k^+} \end{pmatrix} \tag{16}$$

The other eigenvalue will be less than 1 (or $\vec{P}(n\Delta t)$ would blow up as $n \to \infty$). Choosing $C = 1/c_1$, then

$$\vec{P}(\infty) \ = \ \begin{pmatrix} \frac{k^-}{k^-+k^+} \\ \frac{k^+}{k^-+k^+} \end{pmatrix} \tag{17}$$

so that the **equilibrium probability that the channel is open** $(p)$ is

$$\boxed{p = \frac{k^+}{k^+ + k^-}} \tag{18}$$

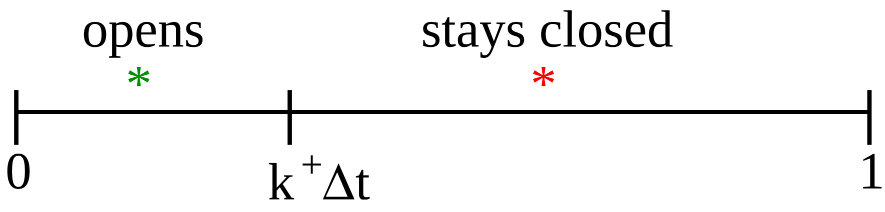
and the **equilibrium probability that the channel is closed** $(1-p)$ is

$$\boxed{1 - p = \frac{k^-}{k^+ + k^-}} \tag{19}$$

## Monte Carlo Simulation

One can simulate the stochastic gating of a single channel or population of $M$ channels using a Monte Carlo simulation. This type of simulation technique is used often in biological settings as well as other areas of application.

Consider first a single stochastic ion channel. Suppose that it is closed at time $t$. The probability that it opens by time $t + \Delta t$ is $k^+ \Delta t$. Otherwise it stays closed. To determine what happens, pick a uniformly distributed random number on the interval $[0, 1]$. Then,

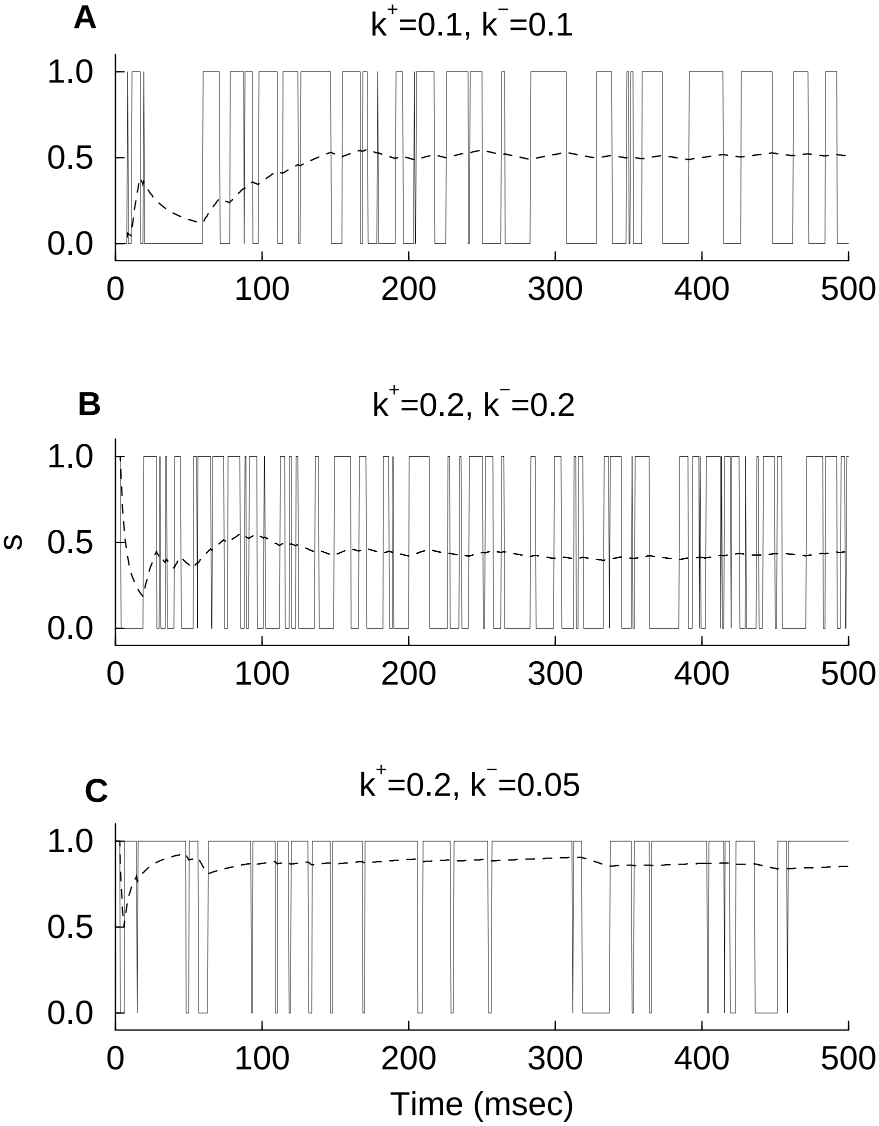


This random number ($Ran$) can be obtained from a pseudo-random number generator, available on any computer.

The value of $Ran$ determines whether the channel opens or stays closed. Once this has been determined the new state of the channel is printed out, time is incremented by $\Delta t$, and the process is repeated. The transition matrix gives the required probabilities for making either $C \rightarrow O$ or $O \rightarrow C$ transitions.

The figure below shows the results from 3 Monte Carlo simulations, each with different values of the transition rates $k^+$ and $k^-$.

Comparison of the first two panels shows that there are more transitions made with the larger $k^+$ and $k^-$, and that the dwell times in each channel state are shorter. In fact, it can be shown that the


A
k+=0.1, k−=0.1
B
k+=0.2, k−=0.2
C
k+=0.2, k−=0.05
s
1.0
0.5
0.0
0
100
200
300
400
500
Time (msec)

**mean closed** and **mean open dwell times** are:

$$
\begin{aligned}
< \tau_c > &= \frac{1}{k^+} \qquad (20)\\
< \tau_o > &= \frac{1}{k^-} \quad . \qquad (21)
\end{aligned}
$$

The dashed curve is the **running sample mean**:

$$< s > = \frac{\sum_i^n s(i)}{n} \quad . \qquad (22)$$

In the top two panels, where $k^+ = k^-$ this converges to 1/2. This is like the probability of getting "heads" with the toss of an unbiased coin. It is also equal to the eqiulibrium probability that the channel is open,

$$
\begin{aligned}
p &= \frac{k}{k + k} \qquad (23)\\
&= \frac{1}{2} \quad . \qquad (24)
\end{aligned}
$$

In the bottom panel, $k^+ > k^-$ so $<\tau_c> < <\tau_o>$, which is evident in the figure. Also,

$$
\begin{aligned}
p &= \frac{0.2}{0.2 + 0.05} \qquad (25)\\
&= 0.8 \qquad (26)
\end{aligned}
$$

which is clearly the value that the running sample mean converges to.

## Monte Carlo Simulation of a Population of Channels

Two approaches to simulating a population of $M$ stochastic ion channels:

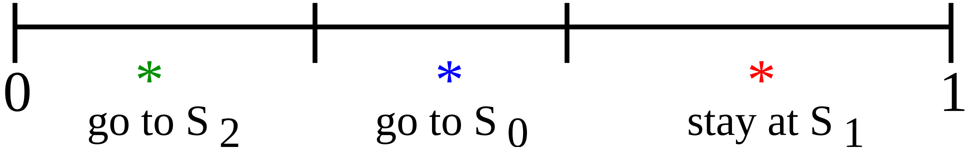
1. Use $M$ Markov variables, one for the state of each channel
2. Use a single Markov variable for the number of open channels

The first approach is a simple extension of the single-channel case. The benefit of this approach is that you know the state of each channel. The down side is that it is computationally expensive (particularly if $M$ is large), and it may produce more information than you need.

The second approach provides less information, but is computationally more efficient. Here we let $S_j$ represent an **ensemble with $j$ open channels**. Then the transition diagram is

$$\begin{tikzcd}
S_0 \arrow[r, shift left, "M\,k^+"] & S_1 \arrow[l, shift left, "k^-"] \arrow[r, shift left, "(M-1)\,k^+"] & S_2 \arrow[l, shift left, "2\,k^-"] & \cdots & S_{M-1} \arrow[r, shift left, "k^+"] & S_M \arrow[l, shift left, "M\,k^-"]
\end{tikzcd}$$

To see how to implement this using a Monte Carlo approach, suppose that there is initially 1 open channel, i.e., the system is in state $S_1$. Then the probability of moving to $S_0$ is $k^-\Delta t$ and of moving to $S_2$ is $(M-1)k^+\Delta t$. Thus,



Note: Picking the time step can be tricky. It must be small enough so that probabilities are less than 1. If it is too small than the simulation takes a long time to run. Usually trial and error is the way people set $\Delta t$. There is another method, called the Gillespie method in which the time step is determined algorithmically according to the values of the transition rates.

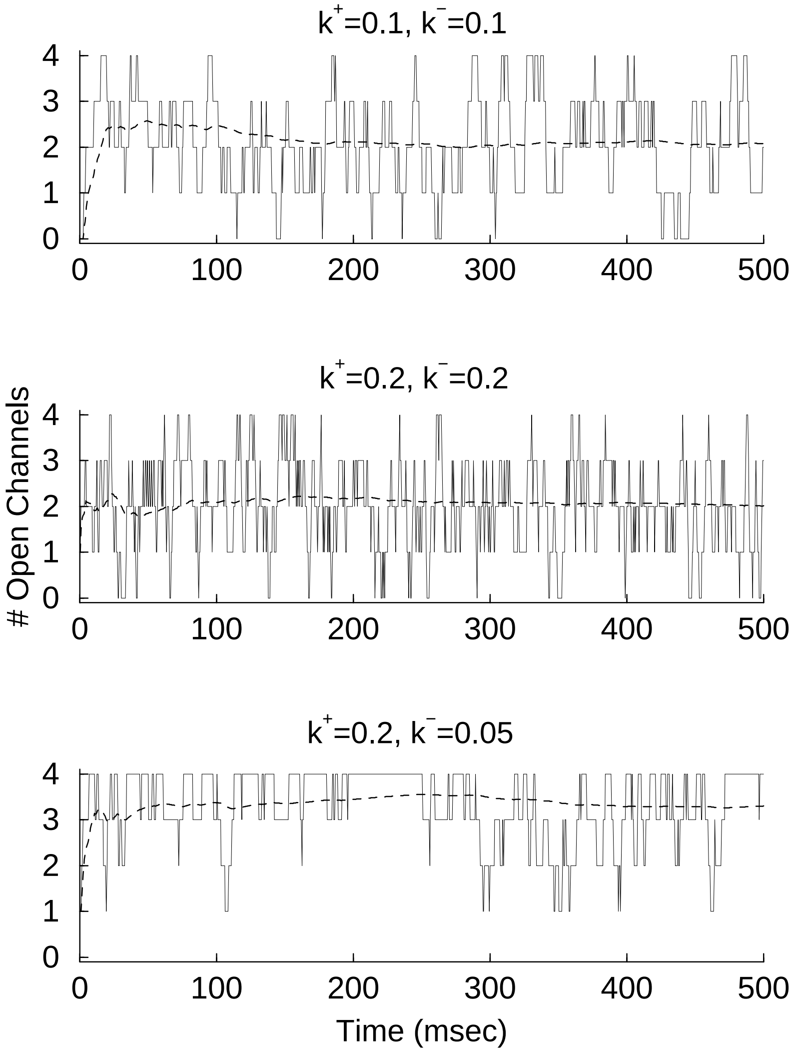


Figure 4: Monte Carlo simulation with $M = 4$ independent ion channels. Uses a single Markov variable. Running mean converges to $Mp$, where $p$ is equilibrium probability that a channel is open.

# Stochastic Morris-Lecar Model

Recall the deterministic Morris-Lecar model for neural excitability:

$$\frac{dV}{dt} = -(I_{Ca} + I_K + I_L - I_{ap})/C \qquad (27)$$

$$\frac{dw}{dt} = \left[w_\infty(V) - w\right]/\tau(V) \ . \qquad (28)$$

where an applied current is included in the $V$ equation. Also, $w$ is the fraction of open $K^+$ channels (or probability that a $K^+$ channel is open). This comes from the 2-state transition diagram

$$\mathrm{C} \underset{\mathrm{k}^-}{\overset{\mathrm{k}^+}{\rightleftharpoons}} \mathrm{O}$$

The forward and backward rates are now both **V-dependent**, and

$$w_\infty(V) = \frac{k^+}{k^+ + k^-} \qquad (29)$$

$$\tau_w(V) = \frac{1}{k^+ + k^-} \ . \qquad (30)$$

Solving for $k^+$ and $k^-$,

$$k^+ = \frac{w_\infty(V)}{\tau_w(V)} \tag{31}$$

$$k^- = \frac{1 - w_\infty(V)}{\tau_w(V)} \tag{32}$$

where the Morris-Lecar $w_\infty(V)$ and $\tau_w(V)$ functions are

$$w_\infty(V) = \frac{1}{2}\left[1 + \tanh\left(\frac{V-2}{30}\right)\right] \tag{33}$$

$$\tau_w(V) = \frac{1}{0.4\cosh\left(\frac{V-2}{60}\right)} \; . \tag{34}$$

When the number of $K^+$ channels is large one can use the **Law of Mass Action** to convert the 2-state diagram into the ODE for $w$. Then $w$ is interpreted as the **mean fraction of open channels**. The ODE describes the time-variation of the mean. However, if the number of $K^+$ channels is small, then a stochastic description is more appropriate. In this case, we have a stochastic model in which $V$ is described by the ODE and $w$ is described as a Markov process for M channels.

# The Algorithm

1. Initialize $V$ and assume that no $K^+$ channels are open (system is in state $S_0$).

2. Use the Forward Euler method to discretize the $V$-ODE:

   $$V_{j+1} = V_j - \frac{\Delta t}{C}\left[I_{Ca}(V_j) + I_K(V_j, w_j) + I_L - I_{ap}\right]$$

   where $j = 0, 1, \ldots$ is the time index. The $w_j$ is the fraction of open $K^+$ channels, determined by the Markov process (divide number of open channels by M) simulated via Monte Carlo.

3. Update the $k^+$ and $k^-$ rates using voltage $V_j$, then use these kinetic rates to update the state of the Markov variable (i.e., pick a random number and determine if another channel opens or closes).

4. Increment time and return to step 2.

## Example 1

When $I_{ap} = 80$ pA the deterministic Morris-Lecar model has a single stable steady state, at a hyperpolarized voltage. The system is excitable, so it can produce an action potential if perturbed from rest. The figures below shows simulations from both the deterministic and the stochastic M-L models, first with $M = 50$, then $M = 200$ channels, and then $M = 1000$ channels.

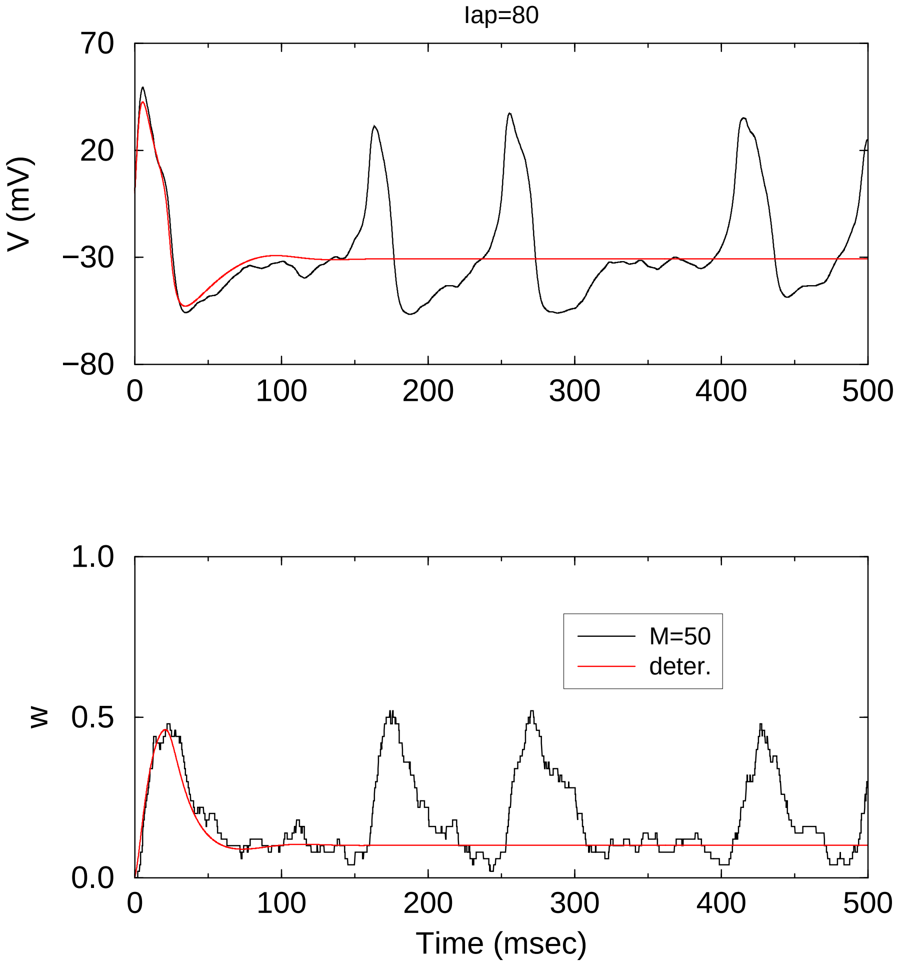


Figure 5: Deterministic (red) and stochastic (black) models with 50 $K^+$ channels. Applied current is $I_{ap} = 80$ pA.

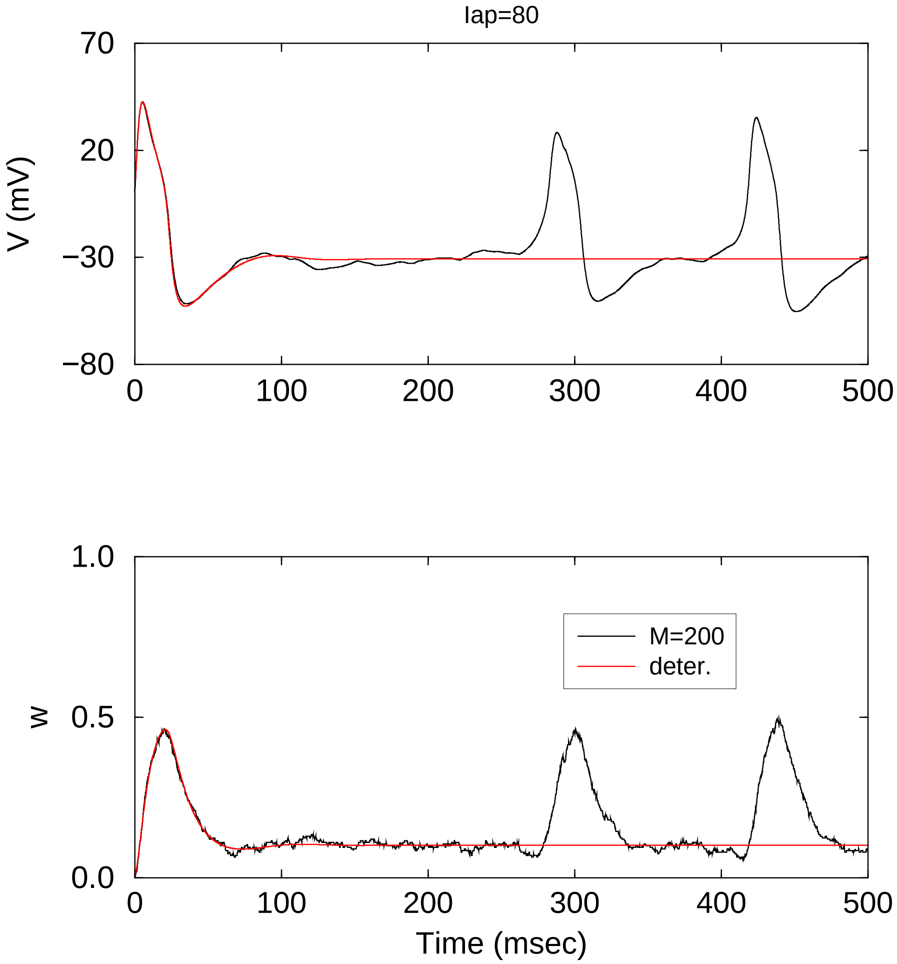


Figure 6: Deterministic (red) and stochastic (black) models with 200 $K^+$ channels. Applied current is $I_{ap} = 80$ pA.

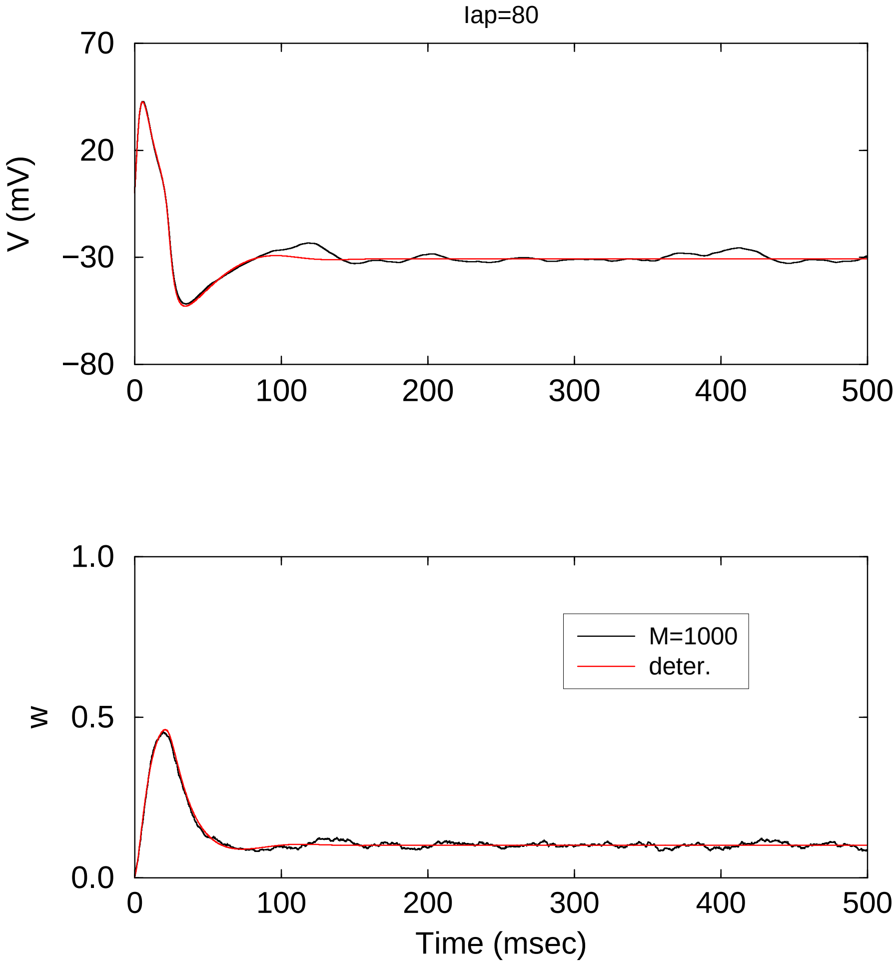


Figure 7: Deterministic (red) and stochastic (black) models with 1000 $K^+$ channels. Applied current is $I_{ap} = 80$ pA.

# Example 2

When $I_{ap} = 150$ pA the deterministic Morris-Lecar model has a stable limit cycle, resulting in periodic spiking. Even with $M = 50$ channels this behavior is mostly captured by the stochastic model. In this case the system is not sitting near a threshold, so the stochastic effects are weaker.

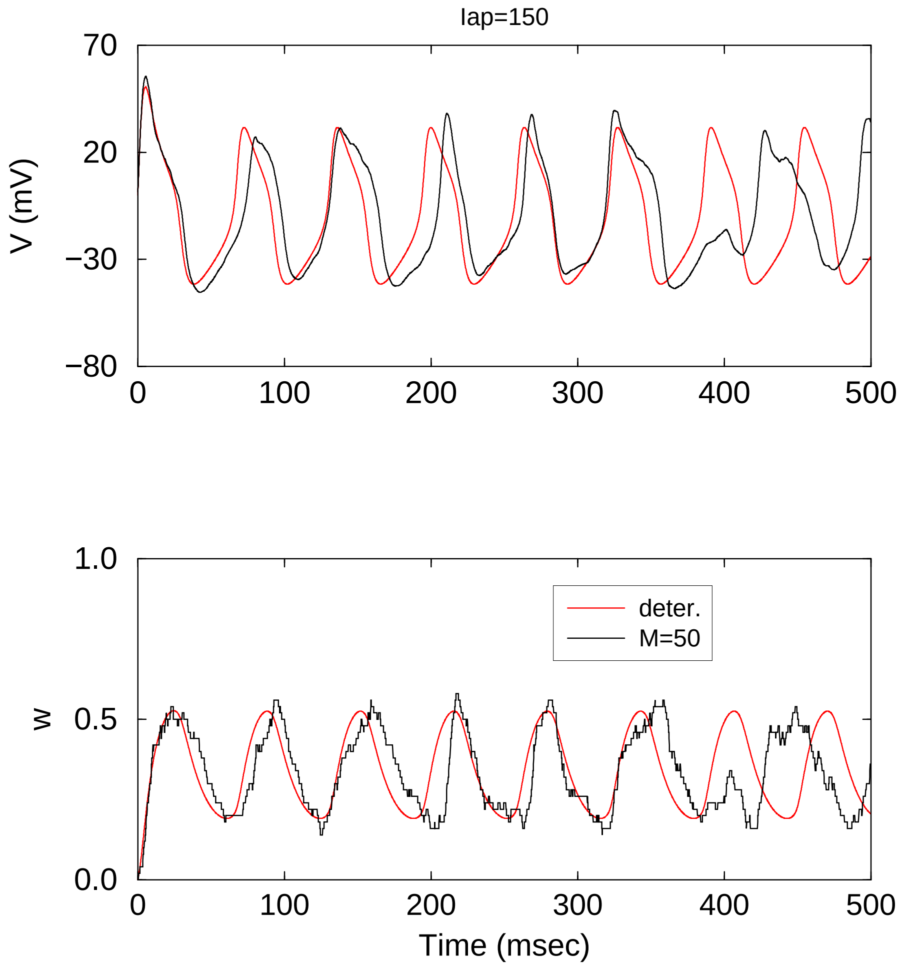


Figure 8: Deterministic (red) and stochastic (black) models with 50 $K^+$ channels. Applied current is $I_{ap} = 150$ pA.

# Example 3

In the following figure two of the M-L parameters were modified, and $I_{ap} = 80$ pA. What's happening here?

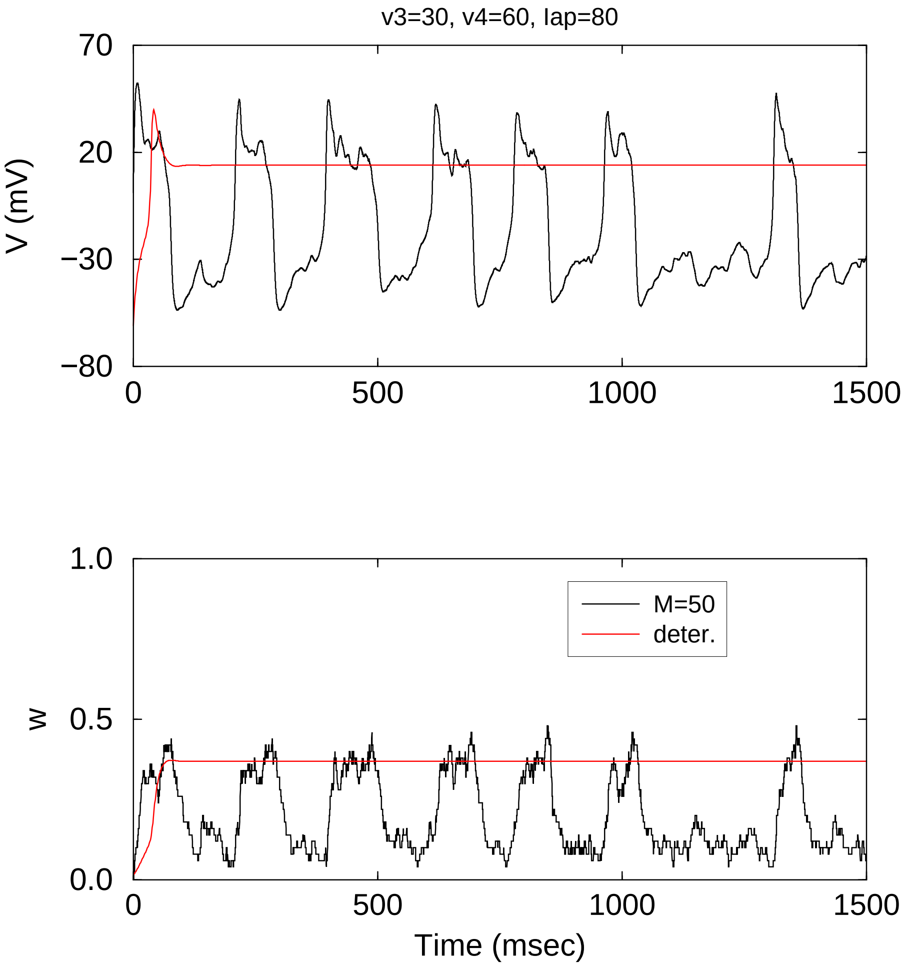


Figure 9: Deterministic (red) and stochastic (black) models with 50 $K^+$ channels. Applied current is $I_{ap} = 80$ pA, also $v_3 = 30$, $v_4 = 60$.

## Stochastic Resonance

Randomness in the system is often looked upon as a bad thing, or at least as inconvenient since simulations take longer and are harder to interpret. However, **stochasticity can be good!** In fact, it can be necessary for transmission of a signal. The concept of stochastic resonance was first described in the 1980's and has now been applied to many physical systems, including neuronal systems.

As an example, consider the stochastic Morris-Lecar model. Set the parameters so that there is a single stable steady state at a hyperpolarized voltage. The deterministic system produces a spike if perturbed past the spike threshold, but otherwise it is silent. We now add a small sinusoidal applied current with period $T = 200$ msec. This has little effect on the voltage, as shown in the figure below.

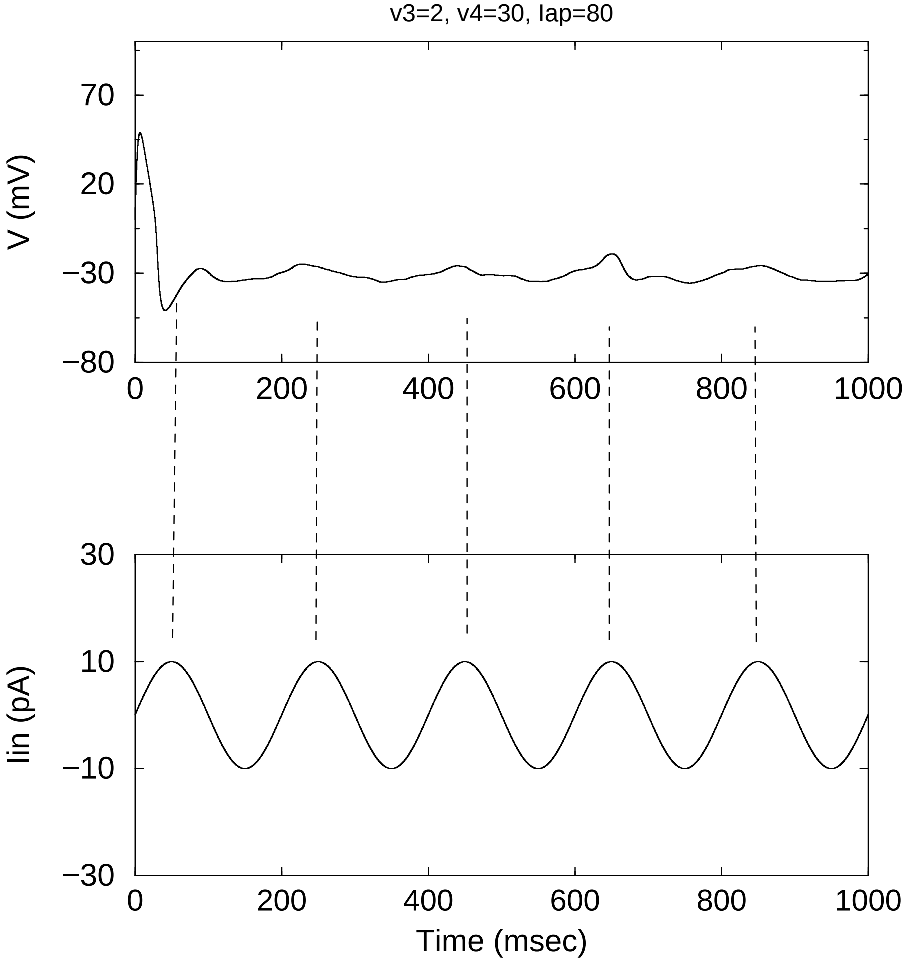


Figure 10: Deterministic Morris-Lecar model with small-amplitude sinusoidal forcing. The forcing has negligible effect on voltage.

If we apply the same sinusoidal current to the stochastic model with $M = 20$ K$^+$ channels, then we get the following:

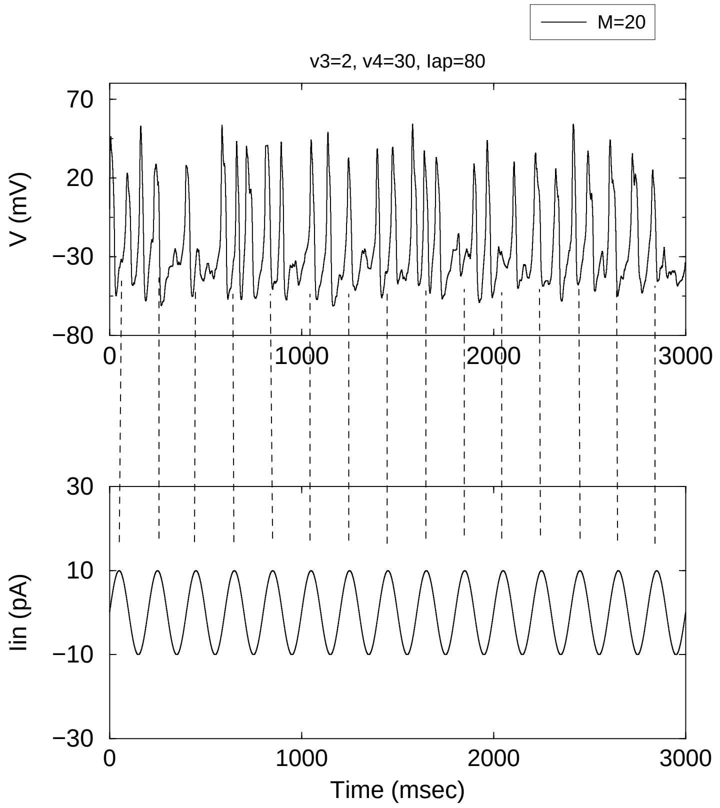


Figure 11: Stochastic Morris-Lecar model ($M = 20$) with small-amplitude sinusoidal forcing. The spiking frequency is much different than the forcing frequency.

The spiking frequency is much faster than the forcing frequency, so the weak input signal is not reflected in the cell's output.

We now increase the number of $K^+$ channels to $M = 100$:

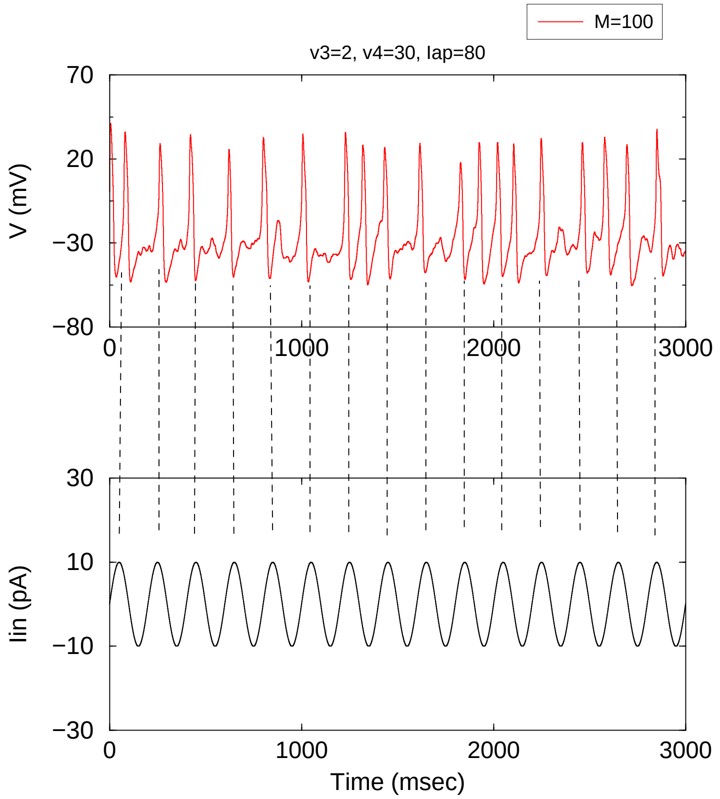


Figure 12: Stochastic Morris-Lecar model ($M = 100$) with small-amplitude sinusoidal forcing. The spiking frequency is approximately that of the forcing frequency.

Now the spiking output of the cell is approximately the same as the sinusoidal input.

That worked well, let's increase channel number further, to $M = 1000$:

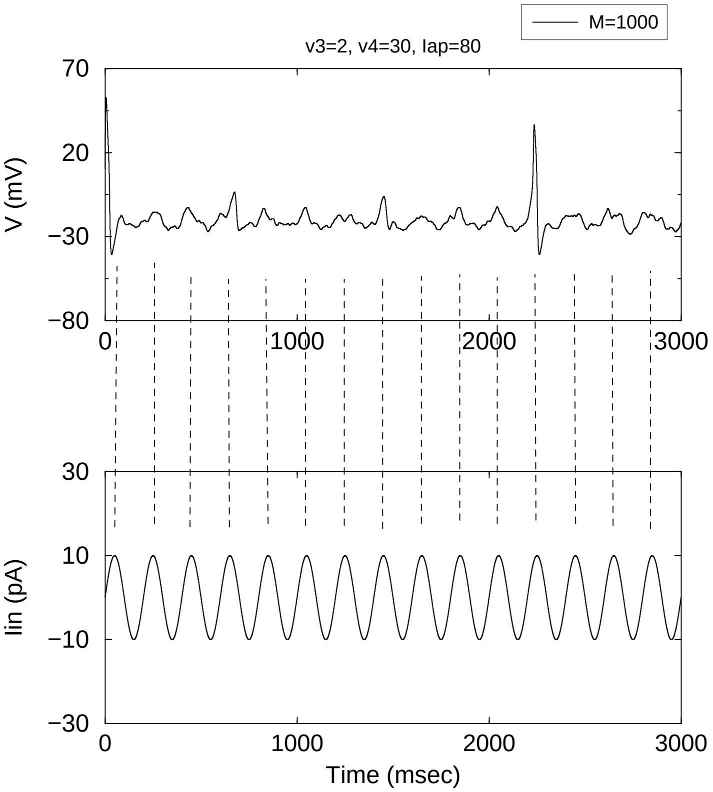


Figure 13: Stochastic Morris-Lecar model ($M = 1000$) with small-amplitude sinusoidalforcing. The cell hardly spikes.

Now the output does not reflect the input at all! With $M$ large the stochastic model is like the deterministic model.

These simulations can be summarized with a plot of the match of the output response to the input signal, where a value of 1 means a perfect match and 0 means no match.

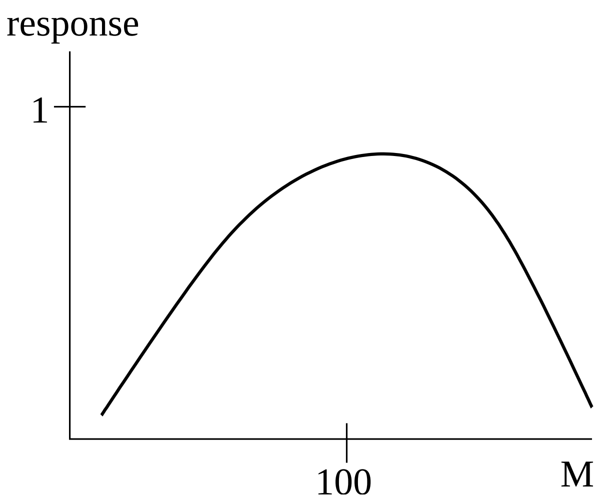


Figure 14: Match of output and input signals for different values of channel number $M$.

This is an example of stochastic resonance.

**Moral of today's story:** The stochastic model is not just a noisy version of the deterministic model. The output of the two can be dramatically different.

# References

- Computational Cell Biology, ed. by C. P. Fall, E. S. Marland, J. M. Wagner, J. J. Tyson, Springer, 2002.
- L. Glass, Synchronization and rhythmic processes in physiology, *Nature*, 410:277-285, 2001.