Differential Equations

Comp Neuroscience

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Neural processes are dynamic phenomena, which means that they change in time. These temporal variations are extremely important; indeed, many sensory stimuli are coded according tho firing *rates* of the neurons and not their absolute membrane potentials. The most accepted models of memory and learning depend on the rates of *change* of the neurons, that is, the correllation between the activities of the post- and pre-synaptic cells. Recent evidence has pointed to the importance of 40 Hz oscillations in binding diverse properties of visual and olfactory stimuli. Dynamic phenomena play an obvious role in motor activity as well. Locomotion, whether stereotypical, such as trotting of horses and grinding of the lobster stomato-gastric system, or driven by feedback, as in navigation of an obstacle course, depends on precise temporal relations between the limbs and the various components of the locomotor event. Autonomic processes such as breathing, hormonal secretion, circadian cycles, and others also depend on temporal processes such as regular rhythms and more complex phemonena, e.g. spike bursts and irregular activity.

Many pathologies are due to temporal difficulties in neural systems; notable among these are epilepsy, Parkinsonian seizures, and various EEG abnormalities. Indeed, the EEG is nothing more than a time series of the lumped activity of many active neurons.

The language of dynamic phenomena is differential equations. A differential equation is an equation that relates the rate of change of some process to other processes that are changing in time. The simplest example and one that will play a role in neurobiology is the decay to rest of the membrane potential. A passive membrane can be modeled by a capacitor with capacitance C and a resistor with resistance R and battery with potential V_z in parallel, Fig 1

The quantity of interest is the voltage across the capacitor, V. This voltage slowly leaks out of the capacitor across the resistor. Elementary circuit theory tells us that the rate of change of the voltage is proportional to minus the

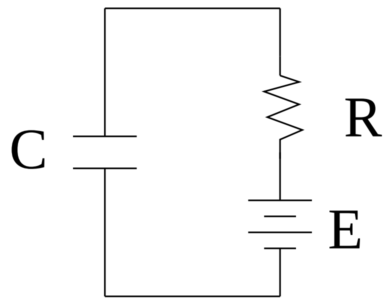

Figure 1: Passive Membrane Model

voltage difference. The rate of change of a quantity, $V(t)$ with respect to time is of course the derivative of that quantity with respect to time. Thus, our statement above can be translated into mathematics to read as follows:

$$dV/dt = -k(V - E) \tag{1}$$

where $k \geq 0$ is the constant of proportionality. For the circuit here, the constant is $1/(RC)$, where R is the resistance in ohms and C is the capacitance in farads. Note that the product of one ohm with one farad has the value of one second. The quantity, RC is called the membrane time-constant. Thus, a membrane with $1M\Omega$ resistance and $.01\mu F$ capacity would have a time constant of 10 ms. The objective of the theory of differential equations is to try to understand the behavior of systems like (1) and to use this knowledge to predict the behavior of experiments. There are at least 5 different levels at which one can study (1):

1. The most satisfactory may seem to be an explicit solution to the equation in terms of all of the parameters and time. This is usually impossible (and certainly impossible for all but the most elementary models of neural processes). Also, it is often fairly useless as anyone who has spent a few minutes with a symbolic algebra program will attest. For (1) an exact solution is easy to find.

2. Prove that a solution of the desired type exists. This is difficult for non-mathematicians to understand: a proof is true and always true. For equation (1), one might try to prove that positive solutions are always decreasing. (You mathematicians should have no problem with this)

3. Qualitative analysis of the equation. This means that rather than obtaining a precise solution to the equation, we attempt to analyse the behavior by using properties of the equation. This methodology is ideally suited to biological systems, where precise formulas for the various quantities of interest are not known. For example, in a negative resistance preparation such as various vertebrate neurons with excitatory transmitters applied, the shape of the $I - V$ relation is only experimentally known and no exact formula for the shape can be given. Qualitative methods (which we will emphasize) are very good for this purpose (see the Chapter 5 in the Koch-Segev book)

4. Numerical solutions. This is the best known way of studying models that depend on differential equations. All simulation tools such as Genesis, the Hinds simulator, and XPP, numerically solve differential equations as a means of understanding their behavior. Together with qualitative methods, this tool provides a very complete combination for studying differential equations.

5. Approximation methods. In many biological systems, there are many different temporal regimes varying from milliseconds to months. In many cases it is possible to hold some variables constant (those that slowly change) or assume that their rapid variation can be averaged (for those that are changing quickly). When this is done, one can often obtain a simpler set of equations that can be explicitly solved or analyzed. This is the technique we have used to analyze the lamprey CPG.

Equation (1) is called a first order differential equation (ODE) and in order to solve it, we must specify one more condition. To see why, suppose I tell you that someone is driving at 50 MPH down the turnpike. After one hour, how many miles down the pike is he? To answer this, you must know what milepost he started at. That is, you must be given the initial position. In general, you must specify an initial condition for each first order differential equation. Thus, we must give the initial voltage in the capacitor in order to solve (1). Equation (1) is of the following form:

$$dx/dt = f(x)g(t) \qquad x(0) = x_0 \tag{2}$$

which can be solved by integration:

$$dx/f(x) = g(t)dt$$

so, we get:

$$\int_{x_0}^{x} dx/f(x) = \int_0^t g(t)dt$$

For the above equation $f(x) = -kx$ and $g(t) = 1$, hence:

$$\ln((V - V_z)/(V_0 - V_z) = -t/(RC)$$

Inverting this equation, we obtain:

$$V(t) = V_z + (V_0 - V_z)\exp(-t/(RC))$$

The voltage decays exponentially from its initial value. The larger the resistance, the slower it decays.

HOMEWORK

1. Suppose that the membrane has a resistence of $20M\Omega$ and a capacitance of 120 picofarads. The initial potential is 100 mV and the battery is $-60mV$ (a) What is the membrane time constant. (b) What is the potential drop after 100 msec. (c) After how long has the potential dropped to 25 mV.

2. A simple model for a periodically varying calcium conductance is:

   $$CdV/dt = g_{Ca}(1 + .5\sin(\omega t))(V_{Ca} - V)$$

   (a) Assuming that $V(0) = 0$, what is the potential as a function of time. (b) What are the dimensions of all the parameters. (c) As $t \to \infty$, what does the membrane potential tend to? (d) If $V(0) = V_{Ca}$, does the voltage ever change?

There are usually many differential equations in a model system. Consider the following psychological example. Suppose that Harry is a fickle suitor and Sally is the woman who he is interested in. The rate at which her love for him changes depends on his love for her. Harry on the other hand is interested only when she is not and loses interest as soon as she finds him attractive. Let x denote the amount that Harry is attracted to Sally and let y denote the amount that Sally is attracted to Harry. Then the equations are:

$$dx/dt = -y \quad (3)$$

$$dy/dt = x \quad (4)$$

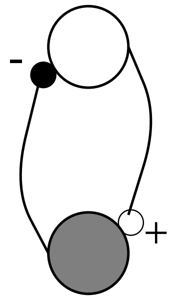

Figure 2: Typical negative feedback interaction

If $x(0) = x_0$ and $y(0) = y_0$, then it is simple to verify that the solution to (3) is:

$$x(t) = x_0 \cos(t) - y_0 \sin(t), \quad y(t) = x_0 \sin(t) + y_0 \cos(t)$$

The point is not that this equation is solvable, but rather that it typifies the interactions of "excitatory" and "inhibitory" processes. The variable y "inhibits" x and x "excites" y as in Fig 2.
This type of interaction often leads to oscillations and is a form of delayed inhibition. Another way to induce a delayed inhibition is to put it in directly:

$$dx(t)/dt = -x(t - \pi/2)$$

This is an example of a delay-differential equation. We will not study these too much since they are very difficult to solve. However, solution to *this* problem is $x(t) = A\sin(t)$ We will see later that this notion of delayed inhibitory feedback is responsible for most if not all oscillatory behavior in neurons. Now consider a general system of two linear differential equations:

$$\begin{aligned} dx/dt &= ax + by \\ dy/dt &= cx + dy \end{aligned}$$

The general solution to this equation (except for some special cases) is:

$$\begin{aligned} x(t) &= A\exp(\lambda_1 t) + B\exp(\lambda_2 t) \\ y(t) &= C\exp(\lambda_1 t) + D\exp(\lambda_2 t) \end{aligned}$$

where A, B, C, D are constants (perhaps complex) that depend on the initial conditions and the parameters a, b, c, d and $\lambda_{1,2}$ are the *eigenvalues* of the 2x2 matrix:

$$M = \begin{pmatrix} a & b \\ c & d \end{pmatrix}$$

Recall that the eigenvalues of a matrix M are the roots of the *characteristic polynomial* which is

$$p(\lambda) = \det(\lambda I - M)$$

where I is the identity matrix of all zeros except the 1's along the diagonals. For the present example,

$$p(\lambda) = \lambda^2 - (a + b)\lambda + ad - bc \tag{5}$$

This second degree polynomial has two roots. The quantity $(a + d)$ is the *trace* of the matrix M and the quantity $ad - bc$ is the determinant of the matrix. The roots of the polynomial can be either real or complex. If the real parts are positive, then it is clear that the solutions $(x(t), y(t))$ will grow exponentially fast as t increases. Thus, the solutuion will not be bounded. On the other hand, if all the real parts are less than or equal to zero, then the solutions will remain bounded as $t \to \infty$. As an example, the Harry-Sally problem has $a = 0, b = -1, c = 1, d = 0$. So that the eigenvalue equation is:

$$\lambda^2 + 1 = 0$$

The roots of this are $\pm i$, where $i = \sqrt{-1}$. Since $\exp(it) = \cos t + i \sin t$, we see that we recover the originally found solutions.

HOMEWORK

1. (a) Find the eigenvalues if $a = 1, b = -2, c = 2, d = 1$. Do solutions grow exponentially or do they stay bounded. (b) How about if $d = -3$.

2. Answer (1a) for the following cases: (i) $a = 2, b = 3, c = 4, d = 0$ (ii) $a = -1, b = 2, c = -3, d = -2$ (iii) $a = 1, b = -3, c = 2, d = -1$

A short aside in linear algebra

Linear differential equations, which are ultimately very important since many nonlinear systems are approximated by them near equilibria, are solved by using techniques from linear algebra. The most crucial ideas are the notions of eigenvalues and eigenvectors. I will assume that you know how to multiply matrices together and that you can find the transpose of a matrix and the inner product of two vectors. The *norm of a vector* is the square root of the sum of the squares of each element. The *inner product* of two vectors is the sum of the products of each of the elements. Just for notational sake, A is an $n \times m$ matrix means that A has n rows and m columns. The *matrix norm* of A is the maximum over all rows of A of the sums of the absolute values of the elements in each row. A *row vector* is a $1 \times n$ matrix and a *column vector* is a $m \times n$ matrix. Matrices are multiplied in the usual manner . To multiply an $n1 \times n2$ matrix by an $n3 \times n4$ matrix, you must have $n2 = n3$ and the result is an $n1 \times n4$ matrix. The ij entry of the product of two matrices takes the i^{th} row of the first times the j^{th} column of the second (*ie* the inner product of a row from the first with a column from the second.) This is why the number of columns in the first must equal the rows in the second. A square matrix has an *inverse* if there is a square matrix B such that $AB = BA = I$ where I is the square matrix with 1 along the diagonal and 0 everywhere else. A matrix is invertible if and only if the determinant of that matrix is nonzero.

EXAMPLES

I define 4 matrices,

$$
\begin{aligned}
A &= \begin{pmatrix} 1 & 2 & 0 \\ 2 & -1 & 3 \end{pmatrix} \\
B &= \begin{pmatrix} 1 & 2 \\ 2 & 5 \end{pmatrix} \\
C &= \begin{pmatrix} 1 & -1 \\ 2 & -1 \\ 1 & 0 \end{pmatrix} \\
D &= \begin{pmatrix} 0 & 1 & -2 \end{pmatrix}
\end{aligned}
$$

Note that D is a row vector. You can multiply BA but not AB since A has 3 columns and B has 2 rows so they are not compatible. If you multiply AC you get a 2×2 matrix,

$$
\begin{pmatrix} 5 & -1 \\ 3 & -1 \end{pmatrix}
$$

but if you multiply CA you get a 3×3 matrix

$$\begin{pmatrix} -1 & 3 & -3 \\ 0 & 5 & -3 \\ 1 & 2 & 0 \end{pmatrix}$$

Only square matrices have inverses. It is easy to show that

$$B^{-1} = \begin{pmatrix} 5 & -2 \\ -2 & 1 \end{pmatrix}$$

The norm of the row vector, D is $\sqrt{5}$. The matrix norm of A is 6. The transpose of B is itself. We say such a matrix is *symmetric.* Symmetric matrices play an important role in the theory of "neural nets." The transpose of D is a column vector.

Eigenvalues

Let A be a square matrix. Often we want to find vectors v such that multiplication by A is equivalent to scalar multiplication:

$$Av = \lambda v \tag{6}$$

where λ is a complex or real scalar. If we can find pairs (λ, v) such that equation (6) holds, then we say that λ is an eigenvalue and v is an eigenvector for A. How do we solve this problem. Subtracting, we must have:

$$(\lambda I - A)v = 0$$

This is a linear system of equations. One solution is that $v = 0$ If the matrix, $M(\lambda) \equiv \lambda I - A$ has an inverse, then this is the only solution. Thus, we must find values of λ such that A is not invertible. Recall that a matrix is noninvertible if it has a zero determinant. Thus, we take the determinant To do this, we take the determinant of $M(\lambda)$ and set it to zero. This results in a n^{th} degree polynomial, *the characteristic polynomial* that has n roots. Thus, a general $n \times n$ matrix has n eigenvalues.

Eigenvalues are either real or complex. A matrix which satisfies $A^T = A$ that is it is its own transpose (i.e. symmetric) *always* has real eigenvalues.

EXAMPLE

The matrix A from the above examples is symmetric. Since A is 2×2, it follows that the characteristic polynomial is given by (5) so the eigenvalues satisfy:

$$\lambda^2 - 6\lambda + 1 = 0$$

whose solutions are $\lambda = (6 \pm \sqrt{6^2 - 4})/2$ or $\lambda = \{5.82, .18\}$.

HOMEWORK

1. Use the matrices, A, B, C, D defined in the examples above. Compute the following quantities:

$$AA^T \qquad B^2 \qquad DC \qquad B + AC$$

2. Compute AC and find its eigenvalues