Computer Simulation in Medicine

These are some notes I took for myself when going through the material. My main motivation was to obtain some background in order to understand (and not just solve) the exercises. Reference to the slides is sometimes required.

Forward Euler Discretization: Compute $(y_0, y_1, \ldots)$ that approximate the given function. — Computation :

$$y_{n+1} \leftarrow y_n + f(y_n, t_n) \cdot h$$

where

- f is tangent at point y_n
- h is step width

for a *linear initial value problem* (given $\frac{dy}{dt} = -ay$ for $a \in \mathbb{R}_+$ and $y(0) = 1$), finding f is easy: it is exactly $-a \cdot y_n$

Amplification of error By the above construction, consider

$$y_0 - ahy_0 = y_0 \cdot (1 - ah) = \; y_1$$
$$\vdots$$

so, the difference between two steps is a multiplication by $(1 - ah)$. We have $|1 - ah| \leq 1 \Leftrightarrow ah \leq 2 \Leftrightarrow h \leq {}^2/_a$.

- For $h = {}^2/_a$, the solution "jumps" between -1 and 1.
- For $h > {}^2/_a$, the "error" amplifies, the approximation is numerically unstable.
- For $h < {}^2/_a$, we have an approximation in the proper sense. Then, the resulting y_i becomes smaller over time (we iteratively multiply with something smaller than one).

Backward Euler Method *Add tangent/slope at next point* — Given a linear initial value problem, we define

$$y_{n+1} \leftarrow y_n + f(\mathbf{y_{n+1}}, \mathbf{t_{n+1}}) \cdot h$$

We can plug in the definition of f and solve for y_{n+1}. For example:

$$y_{n+1} = y_n - ay_{n+1} \cdot h = \ldots = {}^1/_{1+ah} \cdot y_n y_{n+1} = (\frac{1}{1+ah})^{n+1} \cdot y_0$$

so, the approximation is numerically stable for all $h > 0$.

Passive Membrane Model [1] *Change in voltage is voltage, divided by resistance, plus impulse, divided by capacity of membrane.*

$$\frac{dV}{dt} = \left(\frac{V_m - V}{R_M} + I(t) \right) \cdot {}^1/_{C_M}$$

- C_M is capacity of membrane
- R_M is resistance of membrane
- V_m is some (material-specific?) constant I don't know about yet — omitted in slides

Motivation: We have a neuron, apply voltage to it and want to have a model on how it reacts.

Hudgkin-Hoxley-Model *(Single-compartment) Based on [2] (bad formatting but the text itself is very nice to read).*

Same basis as passive membrane model, only we have some I_{ion} replace the expression $\frac{V}{R}$. I_{ion} is defined based on the idea that a nerve membrane has three different kinds of ion channels (with different conductance values)

Each voltage-dependent channel can be pictured as being like a tunnel with a small number of *gates* arranged one-after-another within it. In order for the individual channel to be open and allow ions to flow through, all the gates within that channel must be open simultaneously. If even one gate is shut, then the whole channel is shut.

The individual gates open and close randomly and quite rapidly, but the probability of a gate being open (the *open probability*) is dependent on the voltage across the membrane. In molecular terms, the gates are thought to act like charge-carrying particles, and hence the position they occupy within the membrane, which determines whether they are open or shut, is affected by the electrical potential across the membrane (the voltage).

These gates can transition from *open* to *closed* with some rate constants α_k and β_k (specific per class of gates, i.e. channel). From here, we want to derive *open/close probabilities*. For some proportion $P \in [0, 1]$ *of gates that are in the open state*, we have

$$\text{fr. of gates opening} = \alpha_k(1 - P)$$
$$\text{fr. of gates closing} = \beta_k P$$

Note that α and β are dependent on the voltage!

We can now derive a differential equation describing the fraction of open channels of some channel class k, let this be P_k. Assuming that α and β change instantly with a change in voltage, the rate of change of P_k is equal to the difference in the rate of closing and the rate of opening gates:

$$\frac{dP_k}{dt} = \alpha_k(1 - P_k) - \beta_k P_k$$

We can further express the probability of a single channel of some specific class being open (all open channels make up P) as the combined probability that all its gates are open.

We can then express the conductance of all channels of a class (of the entire membrane w.r.t one channel class) as the single open probability times some maximum possible conductance, for instance, for the K channel with a gate open probability of ${}^1/_2$ and 4 gates.

$$gK = n^4 gK_{max}$$

[1] http://www.math.pitt.edu/~bard/classes/compneuro/passive3.pdf
[2] https://www.st-andrews.ac.uk/~wjh/hh_model_intro/

From there, we can calculate the actual current I. This will take into account the membrane potential V and the equilibrium potentials E_k (individual to classes of channels). *This defines I_{ion} from the slides, i.e.*.

$$I_{ion} = gK_{max} \cdot n^4 + ... + ...$$

This resembles the V from the Passive Membrane Model.

To come around, consider the dynamic behaviour for $\frac{dI_{ion}}{dt}$ (voltage, electric potential). Since α and β (and this P) are dependent on voltage, their values will be dyanmic in this respect, i.e. the regulation of gates and channels.

HH-Model (Multi-compartment) We additionally have the incoming impulse from neighbouring compartments/neurons:

$$\frac{dV}{dt} = (-I_{ion} + I_{stim} + I_{axial}) \cdot {}^1\!/_{C_M}$$

with (taking into co-axial resistances into account)

$$I_{axial} = \frac{v_{n-1} - v_n}{{}^1\!/_2(R_{n-1} + R_n)} + \frac{v_{n+1} - v_n}{{}^1\!/_2(R_{n+1} + R_n)}$$

Stimulation for a neuron can then be modelled as coming from a point source outside of the axis (*extracellular stimulation*), then based on the distance of some neuron to the stimulus point and some extracellular resistance value, we can compute the stimulus for this neuron.

Finite-Element Method Discretization of some geometric object into finite elements which are arranged into a mesh. To each of these objects, assign behaviour expressed in (partial) differential equations (in two or three dimensions, e.g. the heat equation). Additionally, set *boundary conditions* on boundaries of the geometric shapes (describing their state at the “edge”. Example: Room with a set temperature for a wall and some object in it, PDEs model heat dissipation).

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