Dynamic Behavior of Neuronal Networks (193810100) Wednesday June 24, 2020 8:45-11:45

Remarks

- **All answers have to be motivated. Always!**
- This exam is open book, that is, you may use any teaching material, matlab for computations or the internet for looking up information, but no communication. Needless to say we expect you to work on this yourself.
- During the exam, we expect you to log into the Canvas Conference. We will use this channel to communicate about questions or issues, if any. Not being logged in there, means you may miss essential information.
- Handing in the test is done by uploading your work as a pdf or as a photocopy (png,jpg). Make sure it is clear which question you answer on a particular page.
- We allow for 10 minutes additional time in order to upload your answers. Uploading later than 11.55 may have consequences.
- In case you are entitled to additional time, you should hand in the test at 12:25 the latest.
- Grading is as follows

1a	2	2b	4	2g	2	4c	2	5d	2
1b	1	2c	1	3a	2	4d	2	5e	2
1c	2	2d	2	3b	2	5a	2	5f	2
1d	2	2e	3	4a	3	5b	2		
2a	1	2f	1	4b	1	5c	2		

Grade = 1+points/5 (45 points total)

Question 1

Consider the quadratic integrate-and-fire model $V' = aV^2 + bI$ with the firing threshold $V = +4$ mV, and reset value $V = -4$ mV. For convenience, we set $a = 1s^{-1}mV^{-}1$ and $b = 1mVs^{-1}mA^{-1}$.

(a) Verify that $V(t) = \sqrt{I}\tan\left(\sqrt{I}t + \gamma\right)$ is a solution for this model for $I > 0$.

(b) Determine γ to fulfill the initial condition $V(0) = V_0$.

(c) Sketch the phase line for $I = -1$.

(d) Suppose we start at steady state $V = -1$ as a current $I = -1$ is applied. Next we apply a short current block pulse, i.e., we set the current to some different value $I = I_0$ for some duration T, and then apply the normal current $I = -1$ again. Determine the minimal time to stimulate T required to elicit a spike as a function of the input I_0.

Question 2
In this exercise, we consider a reduced Hodgkin-Huxley model. It has a leak current, an instantaneous, persistent sodium current and an inward rectifying potassium current. The model is given by

$$\begin{cases} V' &= \frac{-1}{C}\left(g_L(V-E_L)+g_{Na}m_\infty(V)(V-E_{Na})+g_K n(V-E_K)\right), \\ n' &= n_\infty(V)-n, \end{cases}$$

with

$$m_\infty(V) = 1/(1+\exp((-20-V)/15)) \quad \text{and} \quad n_\infty(V) = 1/(1+\exp((-22-V)/3)),$$

and $C = 1\mu\text{F/cm}^2$, $g_L = 8$ S/cm^2, $g_{Na} = 20$ S/cm^2, $g_K = 10$ S/cm^2, $E_L = -80$ mV, $E_{Na} = 60$ mV. The parameter E_K will vary in this exercise. You may use the following pplane input:

```
V'=-8*(V-(-80))-20*minf*(V-(60))-10*n*(V-(EK))
n'=ninf-n
minf=1/(1+exp((-20-V)/15))
ninf=1/(1+exp((-22-V)/3))
and parameter EK
Display setting V=[-90,40] and n=[0,1]
```

(a) Suppose this is an experimental setup with patch-clamp in a slice to observe the neuron's membrane potential. How would you experimentally control E_K?

(b) Set $E_K = -70$ mV and sketch the phase plane (no screenshot); make sure you add nullclines, some orbits with arrows to indicate the direction of time, and determine the type of all equilibria.

(c) Summarize the attractors of the system for both $E_k = -70$ mV and $E_K = -50$ mV.

(d) There is a parameter range for E_K for which the model shows periodic orbits. Determine the lowest value of E_K for which you find periodic orbits which one decimal accuracy. Do not forget to motivate your answer, e.g., add a sketch of the phase plane explaining what happens.

(e) The upper boundary is related to a Hopf bifurcation. Determine the critical value for E_K with 1 decimal accuracy. You may show/verify that the eigenvalues of the linearization of a suitable equilibrium "behave" as for a Hopf bifurcation.

(f) Is the Hopf bifurcation sub- or supercritical?

(g) Now set $E_K = -68$ mV. Suppose that, through neurostimulation, you are able to shift the potential V to $V + 10$ instantaneously. Explain that there is a time window during the oscillation in which the stimulation can stop the oscillation.
Hint: use the option in pplane to plot the (un)stable manifolds of a saddle.

Question 3
We consider two pulse coupled neurons with almost the same frequency. With ϕ_n we denote the phase of neuron 2, when neuron 1 just spiked. Suppose the phase time map is given by $\phi_{n+1} = \phi_n^2(3-2\phi_n)$.

(a) Sketch the graph of $f(x) = x^2(3-2x)$, and use this graph to show how a solution starting at $\phi_0 = 0.4$ evolves, by showing at least three iterates, i.e., ϕ_1, ϕ_2, ϕ_3.

(b) Determine whether synchrony is stable or not.

Question 4
We consider a (model) neuron in an infinite solution. The extracellular solution contains sodium, potassium and chloride ions; the intracellular solution contains sodium, potassium, chloride and negatively charged macromolecules (A^-). All ions, except for the macromolecules, can pass the neuronal cell membrane. You learned that if all energy-dependent processes are halted, the cell will reach the Gibbs-Donnan (GD) equilibrium. Assume that $[\mathrm{Na}]_e = 150$ mmol/l, $[\mathrm{K}]_e = 3$ mmol/l (both constant) and $[\mathrm{Na}]_i = 10$ mmol/l, $[\mathrm{K}]_i = 120$ mmol/l and $[A^-] = 150$ mmol/l.

(a) Show that the intracellular sodium concentration $[\mathrm{Na}^+]_i$ at GD equilibrium is given by

$$[\mathrm{Na}^+]_i = [\mathrm{Na}^+]_e \times \frac{[A^-]_i + \sqrt{[A^-]_i^2 + 4\beta^2}}{2\beta} \tag{1}$$

with $[\mathrm{Na}]_e$ the external sodium concentration, $\beta = [\mathrm{Na}^+]_e + [\mathrm{K}^+]_e$ and $[A^-]$ the equivalent concentration of negatively charged impermeable macromolecules with valence -1.

(b) Calculate the intracellular sodium concentration at GD equilibrium.

(c) Calculate the Gibbs-Donnan equilibrium potential at 37 degrees C.

(d) Assume that the sodium flux is constant and approximately 0.2 µmol/minute/cm^2. Consider the neuron as a spherical cell with radius 10 µm. How long will it take to reach equilibrium?

Question 5
Some voltage-gated potassium channels are also activated by low ATP concentrations.

(a) Argue why such potassium channels may have a protective effect during low energy conditions.

(b) If you could design a potassium channel yourself, and the role of this channel would be protection of neurons in low energy conditions, what would be a reasonable activating variable to open this channel?

Anti-epileptic drugs have different working mechanisms, and also act on different receptors.

(c) Mention two binding sites for anti-epileptic drugs, and shortly discuss why this may limit the generation of seizures.

(d) in some conditions, activation of the GABA receptor results in excitation of a neuron. Argue how this is possible.

Brain activity of patients with epilepsy can be modeled as a dynamical system. Some types are modeled as a system where a change in a parameter results in a bifurcation. Other types of epilepsy are better modeled as a bistable system.

(e) If a seizure can be induced with periodic light flashes, which model is more more suitable? Explain your answer.

(f) Provide an example of a clinical seizure type where seizures can be induced with light flashes.