Assignment 2
Theoretical Neuroscience

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1. **Noise in the amount of neurotransmitter per vesicle**

   A synapse has n release sites. When an action potential arrives at the synapse, neurotransmitter is released (or not) from each site *independently*. The probability of release for all sites is p. If neurotransmitter is released, the amount released, which we'll call q, is drawn from a distribution, denoted $P(q)$. This distribution has mean $\overline{q}$ and variance σ_q^2.

   (a) What is the mean amount of neurotransmitter released in terms of n, p, $\overline{q}$ and σ_q^2?

   (b) What is the variance of the amount of neurotransmitter released in terms of n, p, $\overline{q}$ and σ_q^2?

   (c) Plot the probability distribution of neurotransmitter released. Assume $P(q)$ is Gaussian with standard deviation 0.5, $\overline{q} = 1$, $n = 10$ and $p = 0.25$.

   (d) Why is the Gaussian assumption unrealistic?

   For part c, you'll need to know that the probability that neurotransmitter is released at exactly k sites, denoted $p(k)$, is

   $$p(k) = p^k (1-p)^{n-k} \frac{n!}{k!(n-k)!} \,.$$

   This is the famous binomial distribution.

2. **Maximum Likelihood estimate of a time-varying release model**

   We spend a lot of time writing down differential equations describing various processes in the brain. Those equations almost always involve parameters. How are those parameters inferred? Often direct measurements are made, but sometimes this is impossible and other times it's inefficient. The goal here is to use all the data as efficiently as possible to estimate the parameters of a neuron undergoing both short term depression and facilitation.

   Assume the probability of release, P_r, obeys the equation

   $$\frac{dP_r(t)}{dt} = \frac{P_0 - P_r(t)}{\tau} + \left[f_F(1 - P_r(t^-)) - z_i(1 - f_D)P_r(t^-) \right] \sum_i \delta(t - t_i) \,.$$

   Here the t_i are the presynaptic spike times, $P_r(t^-)$ is the release probability evaluated immediately before a spike, and z_i is a random variable that can be 0 or 1; its value is determined by

$$z_i = \begin{cases} 1 & \text{with probability } P_r(t_i^-) \\ 0 & \text{with probability } 1 - P_r(t_i^-)\,. \end{cases}$$

Both the spike times, t_i, and the values of z_i are known to you. Assume you know τ and P_0, so your only job is to estimate f_F and f_D. Conceptually, this is straightforward: the data is more likely for some settings of f_F and f_D than for others. For instance, if $P_r(t)$ is mainly much higher than P_0, then it's likely that facilitation is strong (and thus f_F is near 1) and depression is weak (and thus f_D is near 0).

But we can do better than make qualitative statements, we can make quantitative ones. The idea is to write down an expression for the probability of the data given f_F and f_D, and then find values of f_F and f_D that make this probability as large as possible. That's the maximum likelihood approach. We're going to do it in stages.

(a) Assume you know $P_r(t_i^-)$, and write down an expression for $P(\{t\}, \{z\} | \{P_r(t^-)\})$ where:
- $\{t\}$ and $\{z\}$ refer to the whole data set (all the t_i and z_i)
- $\{P_r(t^-)\}$ refers to all the probabilities right before the spike; that is all the $P_r(t_i^-)$.

(b) If this is going to help us find the maximum likelihood values of f_F and f_D, we have to express $\{P_r(t^-)\}$ in terms of f_F and f_D. How would you do that? As mentioned above, we know τ and P_0; assume also that you know that the experiment starts at $t = 0$, and $P_r(t = 0) = P_0$. The answer should be short – I'm looking for a high level, conceptual explanation.

(c) A data set, which can be found on the course website, contains a set of spike times and x's. You can load the data set into matlab using "load hwk2data". Arrays called t and x will appear in your workspace; these are a list of spike times (the t_i) and whether or not there was a release (the z_i, where 1 means release and 0 no release). Find the maximum likelihood values of f_F and f_D. Use $\tau = 100$ ms and $P_0 = 0.6$, which are the true values. How certain are you of your answer?

3. **Spike-timing dependent plasticity**

In an STDP model proposed by Graupner and Brunel (*PNAS* **109**:39913996, 2012), and simplified by me, the calcium concentration, C, in postsynaptic terminals obeys the differential equation

$$\frac{dC}{dt} = -\frac{C}{\tau} + \sum_i \delta(t - t_i^{pre} - D) + \rho \sum_j \delta(t - t_j^{post})$$

where t_i^{pre} are the times of the presynaptic spikes, t_j^{post} are the times of the postsynaptic spikes, and $\delta(\cdot)$ is the Dirac delta-function. The delay, D is positive, as is ρ. The strength of the synapse, denoted w, evolves according to

$$\tau_w \frac{dw}{dt} = \Theta(C - C_0) - \Theta(C - C_1)\Theta(C_0 - C)$$

where $\Theta(\cdot)$ is the Heaviside step function. Under this rule, the weight increases when $C > C_0$ and decreases when $C_0 > C > C_1$; it can also be written

$$\Delta w = \frac{(\text{total time for which } C > C_0) - (\text{total time for which } C_0 > C > C_1)}{\tau_w}$$

where Δw is the change in weight.

For simplicity, in what follows, assume that there is only one presynaptic spike at time $t = 0$, and one postsynaptic spike at time $t = t_0$.

(a) Assume that $1 + \rho > C_0 > C_1 > \max(1, \rho)$. List several reasons why we make this assumption.

(b) Derive an expression for $C(t)$.

(c) Derive an expression for the total change in weight (at a time long after the pair of spikes) versus t_0.

(d) Plot the expression for the total change in weight versus t_0, using $\rho = 1, C_0 = 1.2$ and $C_1 = 1.1$. How would you choose D to make this look as much as possible like classical STDP?