Synaptic Transimission

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Quantal hypothesis of neurotransmitter release

Bernard Katz and colleagues, armed with the newly developed intracellular recording techniques, conducted experiments to study the mechanisms of neuromuscular synaptic transmission in the early 1950s. While studying the end-plate potential (EPP) by nerve stimulation in the frog neuromuscular junction, they observed the muscle fibers also exhibited small EPPs in the absence of any nerve stimulation, and these were termed miniature end-plate potentials or mEPPs. mEPPs has intriguing properties: they seemed to have a defined, unitary size or occasionally a multiple of defined size. The release of neurotransmitter also requires Ca^{2+}. When the extracellular solution contains very low concentrations of Ca^{2+}, most nerve stimulations would not evoke any EPPs. When the EPPs did occur, its amplitude is the same of mEPPs. Further reduction of the Ca^{2+} change the frequency of mEPPs occurrence, but not its amplitude. This led to the Quantal hypothesis of neurotransmitter release, that is, neurotransmitters are released in discrete quanta of uniform size.

How can we test this hypothesis? In low Ca^{2+}, the release probability is also very small. If different quanta are released independently, the probability of releasing k quanta can be calculated by the Poisson distribution:

$$P(k) = \frac{m^k}{k!} e^{-m}, \tag{1}$$

where m is the mean number of quanta that respond to an individual stimulus. By knowing the mean m, theoretically, we could immediate calculate the number of observations that have no quanta release, one quanta release, two quanta release, etc. The amplitude of a single quanta also has a defined variance σ^2. When k quanta are independently released, the total variance should be $k\sigma^2$. The theoretical curve has a good agreement with the experimental distribution. ,

Modeling synaptic inputs

The synaptic current I_s could be described by the following equation

$$I_s = \bar{g}_s P(V - E_s), \tag{2}$$

where P is the neurotransmitter release probability. If we consider the fact that the rising time has certain delay τ_r, one could use the following equation

$$P = \frac{P_{max} t}{\tau_r} \exp(-t/\tau_s).$$

However, when $\tau_r \ll \tau_s$, we may assume that the release probability approaches some constant value P_{max} immediately after the the action potential arrives at time t_k, and then decay with a time constant τ_s: $P = P_{max} e^{-(t-t_k)/\tau_s}$, for $t > t_k$. By multiplying both sides with $\bar{g}_s P(V - E_s)$, and by assuming the amplitude of EPSP is much less than the reversal potential of a synapse $V \ll E_s$, one could treat $\bar{g}_s P_{max}(V - E_s) = w$ as the synaptic weight, and the total synaptic current is given by summing all the spikes from the past

$$I_s = w \sum_j K(t - t_k),$$

where $K(t) = \exp(-t/\tau_s)$. In the form of a differential equation, this equation can be rewritten as

$$\tau_s \frac{dI_s}{dt} = -I_s + \tau_s w \sum_k \delta(t - t_k) \tag{3}$$

When we are summing synaptic inputs coming from many neurons, the total synaptic currents become

$$\tau_s \frac{dI_s^i}{dt} = -I_s^i + \tau_s \sum_j w_{ij} \sum_k \delta(t - t_{j,k}) \tag{4}$$

Spike-Train Statistics

Before we delve deeply into Equation 4, let's first look into the statistics of spike trains, which might help us solve this equation. As we discussed in previous lectures, such as in the integrate-and-fire model, constant external current could give rise to periodic spiking pattern with the same inter-spike interval. However, is this what we have seen in a real neuron? The answer is not. The patch-clamp recording of neuronal activity *in vivo* demonstrates that the firing pattern is highly irregular. To analyze its statistics, let's introduce a critical concept in the field of computational neuroscience, the firing rate of a neuron r. Formally, we have the following mathematical definition Given that

$$\rho(t) = \sum_k \delta(t - t_k) \tag{5}$$

The firing rate is defined as

$$r(t) = \frac{1}{\Delta t} \int_t^{t+\Delta t} d\tau \langle \rho(\tau) \rangle \tag{6}$$

where $\langle ... \rangle$ denotes an average over different trials, or even different neurons with very similar firing patterns. In practice, we may even choose a specific weighting function $\omega(\tau)$, which leads to

$$r_{approx}(t) = \int_{-\infty}^{\infty} \omega(\tau) \rho(t - \tau) d\tau$$

A useful weighting function is

$$\omega(\tau) = [\alpha^2 \tau \exp(-\alpha\tau)]_+,$$

which implies that the firing rate at time t depends only on spikes fired before t. The weight function vanishes when the argument τ is negative.

With the introduction of firing rate, we could now discuss the statistics of spike-train with some mathematical rigid. The spike-train can be viewed as a point process. In general, the probability of an event occurring at any given time could depend on the entire history of preceding events. However, if the events are themselves statistically independent, we have a Poisson process. The Poisson process provides an extremely useful approximation of irregular neuronal firing, as we will see immediately.

We denote the firing rate for a homogeneous Poisson process by $r(t) = r$, because it is independent of time. For a Poisson process, the probability of firing n spike in a time interval T is given by

$$P(n) = \frac{(rT)^n}{n!} \exp(-rT), \tag{7}$$

where rT is simply the mean number of spike in the time window T. Note that for large rT, the poisson distribution approaches a gaussian distribution. The variance of a Poisson distribution,

$$\sigma_n^2 = \langle n^2 \rangle - \langle n \rangle^2 = rT$$

Thus the variance and mean of the spike count are equal. The ratio of these two quantities, $\sigma_n^2 / \langle n \rangle$ is called the Fano factor and takes the value of 1 for homogeneous Poisson process, independent of time interval T.

Another important quantity that needs to be mentioned is the interspike interval. let's denote $\tau < t_{i+1} - t_i < \tau + \Delta\tau$, that is after the ith spike, the $i + 1$ spike will occur between $t_i + \tau$ and $t_i + \tau + \Delta\tau$. The probability of having no spike in an interval τ is $\exp(-r\tau)$, and the probability to have one spike to occur

between $t_i + \tau$ and $t_i + \tau + \Delta\tau$ is simply $r\Delta\tau$. Thus, the probability density to have an interspike interval τ is just given by

$$p(\tau) = r\exp(-r\tau)$$

. Moreover, We can calculate the mean interspike interval

$$\langle\tau\rangle = \int_0^\infty \tau r d\tau \exp(-r\tau) \tag{8}$$

Integrating by part, we found not surprisingly, $\langle\tau\rangle = 1/r$. The variance of the interspike interval is given by $\sigma^2(\tau) = \langle\tau^2\rangle - \langle\tau\rangle^2$.

$$\langle\tau^2\rangle = \int_0^\infty \tau^2 r d\tau \exp(-r\tau) = \lim_{\alpha\to1} \frac{1}{r}\frac{d^2}{d\alpha^2}\int_0^\infty d\tau \exp(-\alpha r\tau) = \frac{2}{r^2}$$

Thus, $\sigma^2(\tau) = \frac{1}{r^2}$. As mentioned in the last lecture, we can also define the coefficient of variation of the interspike interval $\mathbf{CV} = \sigma/\langle\tau\rangle$. For poisson process, we found CV=1.

When the firing rate depends on time, we could also extend the homogeneous Poisson process to inhomogeneous Poisson process. When n spikes occurs in an interval T with $0 < t_1 < t_2 < ... < t_n < T$, the probability density is given by

$$p[t_1, t_2, ..., t_n] = \exp\left(-\int_0^T r(t)dt\right)\prod_{i=1}^n r(t_i) \tag{9}$$

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