Beyond firing rates: some ideas about synchrony, coincidence detection and spikes

In our discussions of neural representations, tuning curves and population vectors so far, we have considered the average firing rate (or firing frequency) as the neural response parameter of interest. In many cases, this may be a valid assumption; however, one can construct a number of scenarios for which representations by average firing rates are unsatisfactory. In addition, in many experiments, changes in firing rate cannot be observed when external stimuli or tasks are manipulated. Remember the "grandmother neuron": a neuron that fires selectively when one sees, smells, hears or thinks about one's grandmother.

From photoreceptors to grandmother cells. The receptive fields of photoreceptors are simply small patches of retina, whereas those of retinal ganglion cells have center-surround structure. The ganglion cells are sensitive to variables such as contrast and the wavelength of light. In striate cortex, we encounter simple and complex receptive fields that have several new properties, including orientation selectivity and binocularity. In extra-striatal cortical areas, cells are selectively responsive to more complex shapes, object motion and even faces. It appears that the visual system consists of a hierarchy of areas in which receptive fields become increasingly more complex, moving away from V1.

Examples: Neurons in monkey visual cortex respond selectively to faces; Neurons in the hippocampus respond selectively to places …
While it is by no means settled, there are several arguments against the idea that perception is based on extremely selective receptive fields such as those of "grandmother cells". First, recordings have been made from many parts of the monkey brain, but there is no evidence that a portion of cortex has cells tuned to each of the millions of different objects that we can recognize. Then such selectivity seems to counter the principle of broad tuning that pertains throughout the nervous system.

If we do not rely on grandmother cells, how do we perceive objects? One alternative hypothesis is formed around the observation that parallel processing is used throughout the visual system (and in other brain areas). Within any given brain area, many broadly tuned cells may serve to represent features of objects. At a bigger scale, a relatively large group of cortical areas may contribute to perception.

In 1989, Charles Gray and Wolf Singer discovered that visual cortex cells in widely separated modules often fire synchronously (at the same time) when activated by the contours of a single common object. Work by these and others has shown that objects often elicit synchronous activity even across widely separated brain areas. This work suggests that the internal representation of one's grandmother may be the synchronous activity of a large population of cells distributed across the brain.

Based on the discussions we have had during the previous lectures, one can also envision something like a grandmother assembly", in which neurons many neurons respond differentially to a given stimulus; the stimulus is represented by an "across fiber pattern" of neural activity.

Representations by firing rate only cannot solve certain types of problems (sometimes referred to as "binding" and "segmentation".)
Neuron fires in response to triangle

Neuron fires in response to color gray

If we expand on this idea, we can see that when as few as two stimuli are presented at the same time, a representation by firing rate only makes it impossible to decide which stimulus characteristics are presented in the same item.

One compelling idea, first formulated in the 1970ies by the German researcher Christoph von der Malsburg is that of neural assemblies which fire simultaneously in response to overlapping stimuli, but whose action potentials are arranged in such a way that neurons responding to different features of a given stimulus fire together (in time).

One can easily see that if only "firing rates" during the time of stimulus application would be considered relevant, all neurons in this simplified example respond at the same time and at the same rate. This type of representation would not allow to assign given stimulus features (color, shape here) to the different stimuli.
If however the finer temporal resolution of firing is taken into consideration, in this example, it becomes clear which stimulus features belong together.

Response to gray
Response to black
Response to triangle
Response to star

Experimental data supporting this theory of "temporal binding" includes examples of synchronous responses to visual stimuli, places, olfactory stimuli..

**Example:** Correlations between neurons in area MT of the visual cortex of a macaque monkey carrying out a fixation task

Recordings from two cell groups with different preferred stimulus directions (1 and 2). Both groups of cells will also respond to a stimulus moving in a direction intermediate to their preferred directions.

When a stimulus with intermediate direction (3) is presented, both cell groups fire and a high number of coincident spikes can be observed. When two stimuli with preferred directions of both cell groups (4) are presented, both cell groups fire but very low number of coincident spikes can be observed.

Reminder: Neurons act as coincidence detectors!
Coincidence detection occurs at the level of individual synapses as well as at the level of dendrites and soma.

Coincidence detection at the level of the postsynaptic neuron makes "synchronous" input spikes particularly efficient at depolarizing and firing the postsynaptic neuron.
About synchrony

Reminder: Neurons function as "coincidence detectors". At the level of the synapse, as well as of the level of the membrane voltage, signals are summed in time. Action potentials from presynaptic neurons are more efficient at depolarizing a postsynaptic neuron for example, if they arrive close to each other in time (synaptic summation). One can think of coincidence detection at many different time scales. For example, a glutamatergic synapse with AMPA receptors sums up signals arriving "simultaneously" at a time scale of maybe 10-20 ms. A synapse functioning via NMDA receptors however may have an integration time as long as 300 ms. In a behavioral experiment, simultaneous may mean within hours of each other. Coincidence can thus be defined only with a specific question and scenario in mind.

Synchrony refers to the observation that in many cases, action potentials emitted from different neurons are emitted at the same time, or very close in time. Again, there is no "true" definition of synchrony; this term is dependent on the question and experimental situation.

Consider the following spike trains from two different neurons N1 and N2:

N2's action potentials always precede N1's by 5ms. In a strict sense, this means that the two spike trains (sequence of action potentials) are "phase-locked". You may also say that N1 lags N2 by 5 ms. Depending of the resolution of the analysis however, one could conclude that N1 and N2 are synchronous.
How can we measure synchrony in the brain? Obviously, in order to detect synchronous or phase-locked events, one has to be able to record from more than one neuron at a time. This can be achieved by either recording from several individual neurons (multi-unit recordings), or from a population (field potentials). Local field potential (LFP) recordings refer to extracellular recordings with relatively large electrodes with which the activity of many neurons can be recorded. Large variations in these LFP recordings usually indicate that many neurons were activated or spiking simultaneously. An LFP is a "summated" activity measure, although the contributions of individual neurons are weighted by their distance from the electrode.

Examples of odor-evoked oscillations and synchronous spiking from the antennal lobe of locust. LFP: Local field potential; PN: intracellular recording from a projection neuron.

Synchronous events can be recorded at various levels of observation:

In order to calculate how "synchronous" two spike trains are, a variety of methods can be used. One simple example consists in counting the total number of action potentials, then counting the number of synchronous action potentials, and dividing it by the latter. The results will of course depend on the definition of "synchronous". Many of the commonly employed methods (cross-correlation, coherence, next lecture) can only be used to measure reoccurring synchronous events. When counting synchronous events, one has to be careful to check if these events could be due to purely random coincidence. If one assumes that two spike trains are independent of each other, and that both of them fire randomly with a given rate, then a certain number of synchronous events would always occur (this number will increase as the rates increase). In many cases, the "expected" number of synchronous events can be calculated, and the "measured" number of synchronous events can be compared to that number. A different, often used methods is that of "spike shuffling", in which the temporal occurrence of action potentials in the spike
trains is changed, while preserving the rate and interspike interval distributions. The shuffled spike trains
are then used as the baseline against which the measured number of synchronous events can be compared.

Exercise: Consider the two spike trains below and construct a measure for “synchrony”


Exercise: With the neural models you have seen so far, construct a scenario that could create these spike
trains?

Aside:
A complete description of the relationship between a stimulus and a response would require the
probabilities corresponding to every sequence of spikes that can be evoked by a stimulus. This would
typically be expressed by "the probability" (chance, likelihood) of a spike to occur in a small time interval
\( \Delta t \). The firing rate \( r(t) \) determines the probability of firing a spike in a small interval around a time \( t \). If the
probability of generating an action potential can be considered independent (not usually true in biological
neurons) of the presence or timing of other action potentials, then the firing rate is all that is needed to
calculate the probabilities for all possible action potential sequences. An example of a process which
generates sequences of events (action potentials) which are independent of each other is the often used
Poisson Process. The Poisson process provides a very useful approximation of stochastic neuronal firing.
In a homogenous Poisson Process, the firing rate is constant. If \( r(t) \) is the firing rate, and \( \Delta t \) is the size of the
time bins under consideration, then the probability of generating an action potential in one specific bin is
\( r \Delta t \). Similarly, the probability of not having a spike in a given bin is \( (1-r \Delta t) \). For a Poisson Process, the
mean and the variance of the spike rate are both equal to \( r \Delta t \). If the spike rate (mean) varies in time, than
the process that would generate such a varying rate is called an inhomogeneous Poisson Process. Spike
sequences can be simulated by using some estimate (measure) of the firing rate, \( r(t) \), to drive a Poisson
Process.
When determining “causal” synchrony in natural spike trains, it is important to consider the amount of
synchrony that would happen by circumstance in two unrelated spike trains of the same average rate and
noise level. Often Poisson processes are used to construct the Null Hypotheses for such a scenario.

A fair method to calculate coherence, phase locking or synchrony in spike trains is the cross-correlation
function.

Exercise: Assume linear synapses (input to neuron 2 is weighted output of neuron 1). Write the equations
for this scenario. First consider a unit input (1.0) between time step 10 and 90. What is the threshold of
neuron 1? Now consider unit action potentials (x=0 or 1) and equal thresholds. What is the synaptic weight
between neuron 1 and 2?

Now consider the same two neurons, and add some noise (figure on the right)

Now consider two neurons which both have a certain input spontaneous activity as well as noise:
And have one drive the other (excitatory):

No have them both drive each other (Excitatory):

Examples:
Exercise: Look at the following spike trains and correlation functions. Explain what you see.
Exercise: Look at these pairwise cross-corelations of spike trains and discuss what they tell you about the spike trains?
Neural synchrony: how can it come about?

Consider two neurons, one of which receives external input and drives the second. If there is no noise, and neurons are integrate and fire neurons, you could see the following scenario:

**About oscillations**

In many brains areas, regular variations of the electric field potential, spiking activity or individual neurons' activities can be observed experimentally. Many of these oscillations are apparent only during certain behavioral states (for example exploration, REM sleep...). Oscillations can occur in several ranges of frequency; these include theta oscillations (2.9Hz) and gamma oscillations (40-100Hz).
If large numbers of active neurons are synchronized (i.e. emit their action potentials at the same time), and do this in a regular, repetitive fashion, a regular oscillation in the field potential can be observed.

Oscillations can be recorded with a variety of experimental techniques. In order to measure reoccurrence of patterns in a spike train, one can use a calculation called the autocorrelation function. The auto-correlation function is related to correlations (which you may know from statistics). One can also use the spike-train autocorrelation function (which should really be called auto variance because the average is subtracted from the neural response function and time is varied only between 0 and T, the time interval of interest:

\[ C_a = \frac{1}{T} \int_0^T s(t - \langle s \rangle) s(t + \tau - \langle s \rangle) dt \]  

Example and very approximate description of the autocorrelation function:
Calculating correlation coefficient of signal with itself returns scalar=1

Autocorrelation: Align signal with itself, calculate correlation coefficient. Delay signal to itself by $\Delta t$, calculate correlation coefficient again. Repeat. You get a value for each $\Delta t$. Plot these values in a histogram: autocorrelation histogram!

The autocorrelation of a white noise signal is a constant, that of a signal which repeats itself once has two peaks (one at zero), that of a sine wave is a sine wave with a peak at zero.
(Note: very commonly, you will see the autocorrelation and cross correlation function be drawn on an x-axis which goes from negative values to positive values. The negative part of the axis does not add information, it is a convention because of the definition and calculation of the function).
In order to compare two signals $s_1$ and $s_2$ (or spike trains) with each other, one would calculate a cross-correlation function, which is similar to the autocorrelation function. The cross correlation of two perfectly synchronous spike trains is a single peak at time zero, whereas the cross--correlation of two phase-locked spike trains is a single peak at the time difference between their spikes.

Of course when real spike trains are compared, the cross correlation is more difficult to interpret:

**Exercise:** Consider the following two spike trains:

*Autocorrelation (A) and cross correlation functions for neurons in the primary visual cortex of a cat. A: Autocorrelation histograms for neurons recorded in the right (upper) and left (lower) hemispheres show a periodic pattern indicating oscillations at about 40Hz. B. The cross correlation histograms for these two neurons shows that their oscillations are synchronized with little time delay.*
Now we add noise:

And connect the two neurons through inhibitory connections:

How much of the cross-correlation signal is due to the common input?
Oscillations of varying mean frequencies have been found in many brain areas. These include for example
the theta and gamma rhythms (8-10 Hz and 40-60Hz). In many brain structures, individual action potentials
are aligned with a specific phase of these oscillations (phase-locked). Often, inhibitory and excitatory
neurons are phase-locked with each other but spike at different phases of the field potential oscillation.

Aside:

\[ T \text{ (period)} = \frac{1}{f} \]

\begin{align*}
90^\circ & \quad \text{phase locked at } 180^\circ \\
\text{phase locked at } 90^\circ \\
360^\circ \\
\end{align*}

Example: Period = 40ms \rightarrow 360^\circ

\begin{align*}
90^\circ & \rightarrow 10 \text{ ms} \\
\end{align*}

Oscillations can occur in individual neurons because of their intrinsic properties as well as in networks of
neurons because of network properties. Most often, network oscillations are due to a combination of
individual properties and network properties.

Regular firing in neurons is often considered a simple form of oscillation:
Activity modes of a model thalamic neuron. With no injected current, the neuron so silent (upper panel). When a positive current is injected, the model neuron fires action potentials in a regular, periodic pattern (middle panel). When negative current is injected, the neuron fires action potentials in periodic bursts (lower panel).

When neurons that fire regularly (oscillators) are connected together via synapses, several different scenarios can arise: two synaptically coupled leaky-integrate and fire neurons which fire in a regular manner when isolated from each other continue firing in a regular manner when isolated from each other.

A: When the two neurons interact with each other via reciprocal excitatory synapses, they produce an alternating, out of phase (phase locked) firing. B. When they are coupled via reciprocal inhibitory synapses, they produce synchronous firing.

A very common oscillation mechanism that has been extensively studied consists of an excitatory and an inhibitory neuron connected together.

\[
\begin{align*}
\tau_e \frac{dv_E}{dt} &= -v_E + w_E x_E + w_I x_I + \text{Input} \\
x_E &= v_E \text{ if } v_E \geq \theta_E \\
x_E &= 0.0 \text{ if } v_E < \theta_E \\
\tau_I \frac{dv_I}{dt} &= -v_I + w_E x_E + w_I x_I \\
x_I &= v_I \text{ if } v_I \geq \theta_I \\
x_I &= 0.0 \text{ if } v_I < \theta_I
\end{align*}
\]

Reminder: The leaky integrate and fire neuron
The model of interacting excitatory and inhibitory neurons (or neuronal populations: in the equations above, E and I can represent large numbers of identical excitatory and inhibitory neurons).

This system can oscillate because the E neuron activates the I neuron, which in turn inhibits the E neuron, which makes it activate the I neuron less, which in turn inhibits the E neuron less etc.

This model is a good opportunity to have a look at some of the properties of the non-linear dynamics of neural systems. This model exhibits fixed points (\(v_E\) and \(v_I\) are constants which don't vary in time) as well as oscillatory activity, depending on the values of the parameters.

The values of \(v_E\) and \(v_I\) can be drawn as a function of time, as shown in the figure below.

In this example, the oscillatory activity of the two neurons dies out and both membrane potential values settle around a constant value (called a "fixed" point), which they will remain on unless the input value changes. In the example below, the neurons settle into an oscillatory activity which remains the same unless the input changes (called a limit cycle).

Another useful way of depicting these results is to plot pairs of values (\(v_E(t), v_I(t)\)) for a range of \(t\) values. As the firing rate changes, these points trace out a trajectory in the \(v_E-v_I\) plane, which is called the phase plane of the model.

Comments on Singer, 1999

Stimulus-induced synchronization: refers to the observation that neurons often display synchronous responses to stimuli and that there responses are synchronous beyond the synchronization that can be expected because they are responsive to the same stimulus.

Binaural sound localization: refers to the observation that animals can localize sounds using the difference in delay and intensity of arrival at the two ears. Time differences are reflected in neural circuits in the brainstem in some birds.

High temporal precision: the author argues in this paper that temporal patterning and tight synchronization at the ms level could carry information in the brain. To argue this, he reviews evidence for the occurrence and coding of temporally precise responses and stimuli.

Slow temporal integration: a counter-argument to high temporal precision is that neurons are generally believed to be slow: synaptic integration can cover several hundreds of ms and neuronal time constants are such that the effects of action potentials arriving tens of milliseconds apart are added together.

Population coding: refers to the idea that rather than being represented by a small number of highly selective neurons, features and complex stimuli are represented by large groups of widely distributed neurons. Individual neurons do not have to be highly selective to any particular feature or object, rather, the specificity of the representation arises from the particular combination of neurons that respond to a stimulus.

Synfire chains: an idea proposed by M. Abeles in which volleys of synchronous events are transmitted between layers of cortex.

Long-term potentiation: refers to experimental evidence that the synaptic efficacy (how much a synaptic event influences the membrane voltage at the postsynaptic neurons) can be enhanced by experimental manipulation. Generally, a repetitive, simultaneous activation of the pre – and postsynaptic neurons will lead to an increase in synaptic efficacy between the two neurons.

Long-term depression: refers to the experimental observation that certain manipulations can lead to a decrease in synaptic efficacy between a pair of cells. For example, low frequency stimulation of the presynaptic neuron alone can lead to a decrease in efficacy of synaptic interaction between the two cells.
Comments on Gray, 1999

The binding problem: refers to the question how the brain knows which stimuli belong together, and which do not. What all is part of an object? How do we recognize the timber of a musical instrument? Why do we smell pizza and not a number of unrelated individual odorants?

Cell assemblies: refers to the idea that stimulus features belonging to a common object may be represented by neurons spiking in synchrony with each other (binding by synchrony), and that multiple groups of neurons can represent multiple groups of features simultaneously (see example below).

Hierarchical coding: Is based on the idea that in the visual system, as we look at the stream of neural responses throughout the system, the response properties of neurons become more complex. In the retina, neurons have small receptive fields, in primary visual cortex, they have receptive fields but are also orientation selective, and in area MT for example, one can find neurons that respond to specific types of stimuli (faces are commonly mentioned example). This hierarchical representation is thought to arise from the convergence of feature representations in one layer onto cells in the next layer, which could then represent more complex features.

Population coding: refers to the idea that rather than being represented by a small number of highly selective neurons, features and complex stimuli are represented by large groups of widely distributed neurons. Individual neurons do not have to be highly selective to any particular feature or object, rather, the specificity of the representation arises from the particular combination of neurons that respond to a stimulus.

Assemblies and the temporal correlation hypothesis: this term refers to the idea that in addition to population coding, each group of neurons representing a particular feature of object at a particular time would synchronize its firing with the group. This extension of the population coding idea allows for several features or objects to be represented unambiguously at the same time.
Representations in rate and synchrony

So far, we have mostly considered tuning curves, receptive fields and neural codes which represent information as spike rates. As we saw in the last section, oscillatory dynamics and synchronization among neurons are abundant in all brain areas and thought to contribute widely to the representation, transformation and transmission of information. There are many examples in which spike rates do not systematically vary as a function of stimulus quality or behavioral relevance, whereas synchronization properties or oscillatory dynamics in a same brain area do vary. In this section we will illustrate this idea using two examples from the literature: oscillatory synchrony in the insect antennal lobes (concerned with olfactory information) and hippocampal place cells.

Do some background reading on the insect olfactory system and hippocampal place cells before class. Also read about correlations and phase plots.

Exercise

Which feature of the spike trains depicted provides information about the identity of the stimulus?

A  B  C


