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Graded assignment 2 - Due Sunday, 11-4 at 6pm

1. Read the paper by Lisman and Idiart (1995). https://www.ncbi.nlm.nih.gov/pubmed/7878473

2. In a few short paragraphs, answer these questions:
    a. What is the goal of this model?

    To model oscillations that store short-term memories within a single neural network. The model incorporates some findings about oscillatory patterns in the hippocampus, and seeks to integrate the effects of the afterdepolarization (ADP) induced by the presence of certain neuromodulators (acetylcholine and serotonin).

    b. What are the assumptions and ingredients?

    Researchers assumed that each neuron receives three inputs; an excitatory/ suprathreshold input (will elicit an action potential) that carries information to be stored as memories and a subthreshold low-frequency alpha-theta (5 to 12 Hz) oscillatory driver (will not elicit an action potential). These neurons also exhibit feedback inhibition which make high-frequency beta-gamma ("40 Hz") subcycles nested within the low-frequency oscillation possible; these subcycles are what store memories.

    This model is reinforced by the findings of Sternberg et al (1966). They found that response time increases by 37ms for each additional item on the list, corresponding with the time range for high frequency beta-gamma oscillations.

    c. What are the results and predictions?

    The researchers successfully produced a model which nests high-frequency (at the scale of beta-gamma) oscillations in low-frequency (at the scale of alpha-theta) oscillations whose phase differences enable distinction between the oscillatory patterns of seven subnetworks, which are hypothesized to correspond to seven memories. The network produced is based on biologically feasible parameters when considering oscillatory frequencies and findings about afterdepolarization (ADP).

    The researchers predicted that there is a mechanism of oscillations and timing that allow for the processing of short-term memories. They identify a role for ADP in the network, as this is what enables cells in the network to fire at the same phase in consecutive cycles, allowing a memory to be encoded in oscillatory phase.

3. Read the equations and answer these questions (in the reference list):
    a. What types of neurons are modeled?

Researchers used pyramidal cells modeled as identical integrate-and-fire neurons. The parameters used align with observed properties of hippocampal and cortical neurons, but the purpose of this model was primarily theoretical so this storage mechanism could be used elsewhere in the brain as well.

b. What does each variable represent?

$$(1)\quad \tau_v \frac{dV_i(t)}{dt} = -V_i(t) + V^{rest} + V^{osc}(t) + V_i^{ADP}(t) + V^{inh}(t)$$

τ_v is assumed to be small compared to any other time constant so:

$$(2)\quad V_i(t) \approx V^{rest} + V^{osc}(t) + V_i^{ADP}(t) + V^{inh}(t)$$

τ_v : *time constant*
V_i : *membrane potential of neuron* i, *function of time*
V^{rest} : *membrane potential of neuron at rest* $= -60\ mV$. Equation (1) resets to this value when it exceeds the set threshold value of $V^{thresh} = -50\ mV$
$V^{osc}(t)$: *membrane potential of oscillating neuron*, *function of time*
$V_i^{ADP}(t)$: *membrane potential induced by the afterdepolarization* (ADP), *function of time*
This is due to the presence of neuromodulators, which means that firing will induce afterdepolarization, which will subsequently lead to a short burst of increased excitability
$V^{inh}(t)$: *membrane potential induced by inhibition*, *function of time*

c. How is inhibition generated?

A subnetwork is used that converges the pyramidal cell excitatory synapses onto an inhibitory interneuron. This creates feedback inhibition on the pyramidal cells, which is what makes subcycles possible.

d. What does the oscillatory input do?

Provides an input to each pyramidal cell which causes the membrane potential to oscillate at theta frequency below threshold levels. Due to this input, when the pyramidal cells receive a suprathreshold informational input, they can oscillate at theta frequency.

e. What is included in these equations that is new to you?

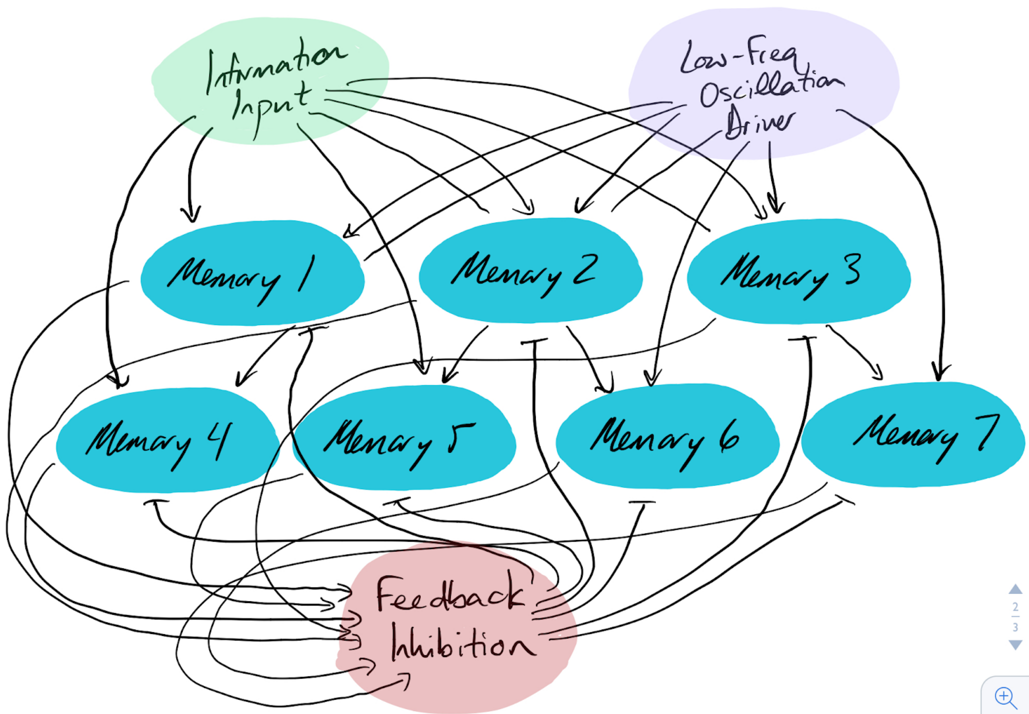
The oscillatory input for each neuron is a new feature that has not been encountered before. In addition, the concept of ADP activated by an informational input has not been modeled in this course.

4. Create a graph of the network setup

In the graph below, each memory node represents a subnetwork of cells which fire in synchrony at a certain phase in the oscillatory cycle and therefore encodes a certain memory. Note that these nodes may consist of more than one cell and, possibly, share overlapping cells (although ADP may prevent this from being possible).

The oscillatory driver is responsible for the low-frequency oscillation in which the high-frequency oscillations are nested.

The information input is what introduces the memory that each subnetwork encodes. ***Note that this node will introduce a unique input to each memory node, otherwise this network would not be able to encode multiple memories*** *(as it would only be introduced to one, and due to afterdepolarization 6 of the memory nodes would be inactive).*



5. Explain in your own words how this works, be specific

   The researchers created a neural network that has continued firing due to an increased membrane excitability that is reset after a cycle of oscillations. It is known that in the presence of neuromodulators, such as acetylcholine and serotonin, there will be an afterdepolarization (ADP) induced by firing. The ADP allows for the storage of information between oscillation cycles in the range of 5 to 12 Hz, which is within the theta-alpha range. This creates a cascade where ADP within one cycle is able to trigger the firing of the next. This would allow for one short term memory to be stored within this neural network pattern of firing. Lisman and Idart took research from Sternberg, which allowed them to hypothesize that seven cycles of high frequency oscillations could be nested within a low-frequency oscillation - essentially creating a neural network where different memories could be stored within different high-frequency cycles of a lower-frequency oscillation.

   Lisman and Idart rely on the slow rise of ADP because this would mean that the earliest cells to fire could be categorized as the most excitable, which within this model would mean the most excitable cells in the first low-frequency oscillation subcycle would also be the cells that fired in the previous iteration. This slow rise also means that multiple memories can be ordered.

   The neurons in this model receive two inputs: a continuous oscillatory input and feedback inhibition, which subdivides the cycles into subcycles.

   To begin the trial, the network was loaded with memories using a brief activation of informational inputs. A "memory" was a group of cells that would all fire at the same time during any of the subcycles. By the time the eighth pattern is generated from the informational inputs, the next subcycle of the next cycle is started. Memories are shifted so that only seven memories are stored within the neural network - the eighth memory within the last subcycle is subsequently "lost". This mechanism ultimately means that multiple memories can be stored and be separated by oscillatory subcycles. There is a limit to the number of short-term memories that can be stored, this limit is contingent on the subcycles that fit within a single low-frequency cycle.

   The researchers also introduced the concept of time compression, which means that memories that are sequential can be recreated within the network. This time compression factor allows the activation of the N-methyl-D-aspartate subtype of glutamate receptor, which would allow the formation of associations between events that occur at greater intervals.

   Cells, within this model, are not going to fire on sequential 40-Hz sub-cycles because each sub-cycle is holds different memories.

6. Name at least two ingredients or assumptions that are crucial to make this work and explain why they are

One assumption of the model is that the time constant, τ_v , is small compared to other time constants. This assumption was made because the time constant does not affect the qualitative features of the model, and allows the researchers to model the voltage of each pyramidal cell using equation 2.
A second key assumption is that each neuron receives an oscillatory and an informational input. It is because of both of these inputs that each pyramidal cell is able to have subsequent spikes for a brief period of time after it receives an informational input allowing it to store the short term memory. These inputs are assumptions of the model, and not supported by any relevant experimentation.

7. What do you think ?

   The basis behind this model is very interesting but there are still many unanswered questions about its plausibility. For one, the synchronized "bump" that pushes all encoded memories back a phase when new information is introduced seems like it would be difficult to accomplish in such a complex biological context. The authors cite an observation of such systemic phase changes in hippocampal neurons, but I would want to do further research to determine the plausibility of this.

8. Relate this in a short paragraph to what you learned about neural assemblies, oscillations and phase precession. Can this serve as a plausible model for the existence of neural assemblies? Why or why not?

   This is similar to the idea of binding by synchrony suggested by Christopher van der Malsburg in the 1970s. Problems with this theory are that when synchronous events have been observed, all neurons tend to be phased-locked at the same time and there is a practical limit to how many different "bindings" can be achieved. Likewise, this neural assembly model is limited in the number of short-term memories that can be stored within the sub-cycles due to the phase-locking of the oscillatory input.
   This may serve as a plausible model for the existence of neural assemblies but there are still limitations to consider. One such limitation that is brought up by the authors of the paper from footnote 21, is whether or not the recorded spike trains are dependent on oscillatory storage processes. The researchers suggested that through experimentation they might be able to determine this by differentiating between spike train and field potential recordings.
   In a dispatch published by Lisman in 2010, he recounts his research with Idiart and how working short-term memory is organized by theta and gamma waves (https://www.sciencedirect.com/science/article/pii/S0960982210004471). Over 20 years of research in this area suggests that studying these oscillations is the key to understanding short-term memory.