Computational Neuroscience

Dedicated to Synaptic Plasticity

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1 The Brain and Definitions

2 Mathematical Concepts (b)

- In-homogeneous first order ODE's are often found in Neuroscience (e.g. Integrate and Fire model for synaptic conductance, or Ion channels). Solve them using an **integrating factor**. **L2**
- **Euler Method** - $f_{n+1} = f_n + \frac{df}{dt}\delta t$
- **Runga-Kutta Method** - not examinable

3 Neuron types (c) L6

- Computational model - a mathematical model that is programmed and solved or simulated on a computer. Abstract models: simple, non biological, few parameters, fast simulation, mathematically analyse-ablem, generic; Realistic models: Detailed, measurable, lots of parameters, slow simulation, often intractable, specific.

4 McCulloch-Pitts (MP) Neurons (d) L7

- Each MP neuron performs a weighted linear sum of its inputs and then thresholds to give a binary output. $\boxed{y = \text{sign} \sum_i^n w_i x_i - \theta}$, where $w_i x_i$ are the weighted inputs, θ the threshold, and $\text{sign}(x) > 0, x > 0$, else -1. Time evolves in discrete steps.
- Synaptic plasticity can be modelled using Perceptron's (supervised) or Hopfield networks (unsupervised).
  - Perceptrons add a learning rule to adjust the weights in order to solve a classification task. The weights are simply updated as $\delta w_i = \eta(d-y)x_i$, where d is the desired output and y is actual output, and x_i is an input of a pattern. Only works if classification is linearly separable.
- **A Hopfield network is a recurrent (repeating) network of MP neurons**. Network evolves as inputs change $x_i(t+1) = g(\sum_{j\neq i}^N (w_{ij}x_j(t) - \theta)$ where $g(x)$ could be sign or some other thresholding function. The network evolves to minimise the "energy" $E = -\frac{1}{2}\sum_{ij} w_{ij}x_i x_j$. Attractor weights can be incorporated into the synaptic weights with the learning rule $w_{ij} = \frac{1}{P}\sum_a x_i^a x_j^a$, where P is the number of attractors to store, and a indexes the attractor activity.
- **Hebbian Plasticity** - "neurons that fire together wire together". Neurons that are close enough to excite one another become more efficient in firing potentials. This strengthing process is called **long-term potentiation**. If the opposite occurs and neurons get weakened synapses, its called **long-term depression**.

5 Hippocampus (e) L8

- Purpose: Long-term memory, spatial navigation
- Tasks: Pattern completion, pattern separation and path integration.
- Information flow: EC (Entorhinal Cortex) $\rightarrow$ tri-synaptic loop (DG dentate gyrus $\rightarrow$ $CA3$ $\rightarrow$ $CA1$ $\rightarrow$ Sub (Subiculum).
- **Memory**: Episodic memories (long-term past event) are encoded in the hippocampus through synaptic plasticity. They are encoded during the day, then replayed in sleep, which triggers learning in the cortex. Over time the cortex learns the memories and they become hippocampus independent.
- **Spatial Navigation**: Neurons in the hippocampus respond to aspects of the spatial environment.
  - $CA3$ and $CA1$ cells (called **place cells**) are only active when the animal is in a particular location
  - EC cells (**Grid cells**) become active when the animal is a set of location that are arranged in a hexogonal grid. It creates a sort of location grid, which place cells use to orient themselves around.
  - Sub cells and some EC cells (**Head direction cells)** become active when the animal is facing in a certain direction.
  - DG performs pattern separation (ability to differentiate between memories)
  - $CA3$ performs pattern completion (ability to complete a memory given partial or degraded partial cues)
  - Grid cells (these are also considered as neurons btw) aid path integration, i.e. using movement for spatial information. An animal can keep track of its location by integrating its direction and velocity signals.
- L9 goes into more detail about pattern separation and completion and some computational models, but don't really understand . Review!

6 Firing Rate Neurons (f) L10

- **Firing rates**: The rate at which spikes occur. A spike train indicate spikes with straight lines. The closer the lines are together the higher the rate. Bin data and count number of spikes in each bin to find rate. They are non-negative, continuous and usually latent, not directly measurable. They are typically around 0.1 to 10 spikes per second (Hz).
- **Rate coding**: These are models that describe a relationship between the intensity of a stimulus and the consequent increase in firing rate. They could be a $a \log x$ function for example (which says as stimulus (input) intensity increases the firing rate will always increase or a Gaussian which suggests if a stimulus gets too intense the frequency will decrease. I suppose the rate is encoded by the stimulus intensity.
- **Tuning curve** - is a description of firing rate as a function of some property of the stimulus. I suppose the stimulus "tunes" the firing rate
- **Receptive field** - the subset of stimulus space that a neuron responds to. The stimulus response as a function of space is usually represented by a Gaussian.
- **Rate decoding** is the opposite of rate (en)coding. Instead the aim is to decipher the stimulus given the firing rate. Proposed schemes include max likelihood and Bayesian decoding and population vectors (whatever that might be).

7 The Visual System (g) L11

- Roughly: Retina → LGN (in Thalamus, where the optic fibres end) → Primary visual cortex (V1) → V2/V4/MT etc. In reality its very complicated, there are tens of visual regions, feedback connections, and heterogeneity within regions.
- **Visual hierarchy** - the order in which humans or animals perceive visual information. Receptive fields are larger higher up the hierarchy. They are also more sensitive to the stimulus, multimodal (depend on other non-visual sensory signals), and affected by contextual information (task context, attention, behavioural state).
- **Retinotopy** - Neighbouring neurons tens to respond to neighbouring parts of the visual field, i.e. the mimic what is perceived.
- The **Dorsal visual stream** determines where something is and the **Ventral visual stream** determines what it is.
- Colour sensitivity: Cones perceive mainly the colours blue (short), green (middle), long (red). Rods are there to see at low levels of light.

7.1 V1 and sparse coding L12

- Single V1 neurons respond to basic features of the visual stimulus, like orientated edges. V1 is sometimes referred to as the 'canonical cortical region'. There are two dominant single cell types:
  - "Simple cells" which respond to oriented edges/grating stimuli in a specific part of the visual field only.
  - "Complex cells" also respond to oriented stimuli but do not seem to care where to stimuli is located in the receptive (visual) field.
- **The Cortical microcircuit**: V1 has six layers (where 1 is near the scalp and 6 is the deepest layer). Each layer has a mix of *distinct* excitatory (**pyramidal**) and inhibitory neurons (usually a $80, 20\%$ split, respectively). Inhibitory neurons have more subtypes than excitatory. Information flows; Thalamus → layer 4 → layer 2/3 → layer 5 → other brain parts.
- **Topographic maps** is the general term for when nearby neurons in the cortex perform similar tasks (functional properties). The Retinotopic map is an example of this. There are others like the tenotopic map for the auditory cortex. The visual cortex mixes (superimposes) multiple different maps found in the cortex, like orientation preference, occular dominance etc.
- Ocular dominance - when one eye is preferred to the other.
- **Kohonen map** - A computational model trying to capture topographic map formation. A neuron's output is a weighted sum of its inputs, the weights of the most active neuron plus its neighbours are updated so as to make neighbouring neurons more similar.
- **Sparse coding**: Taking sparse information and combining it to create a pattern or something (like trying to reconstruct an image from basis functions). The reason this exists because the activity in some parts of the brain are sparse (to save energy perhaps). Sparse coding has computational benefits because it creates less overlap between patterns and acts as a form of regularisation. Apparently sparse coding encourages V1-like receptive fields.

8 Leaky Integrate and Fire (LIF) Neurons and Features (h) L13, L14

- **Spike count** - number of spikes in a spike train
- **Inter-spike interval** - time between two consecutive spikes.

- **Fano factor** - a statistical measure of dispersion of a probability distribution. In neuroscience it signifies the variability of the spike trains. $\boxed{F = \frac{\sigma^2}{\mu}}$, where σ^2 and μ are the mean and variance of the spike counts (usually done by taking spike counts in windows of the total spike train data).
- **Coefficient of variation (CV)** is also a measure of variability in the spike train. $CV = \frac{\sigma_{ISI}}{\mu_{ISI}}$, where σ_{ISI} and μ_{ISI} are the standard deviation and mean of the *inter-spike intervals*.
- **Peri-stimulus time histogram**. Essentially just a histogram of spike counts given a certain small window for a bunch of repeated trials that get concatenated together. It is a good way of showing average spike response over trials.
- **Spike-triggered average** - aims to quantify what aspect of the stimulus caused the spiking. $S(\tau) = \frac{1}{N}\sum_{i=1}^{N} s(t_i - \tau)$, where $s(t)$ is the stimulus value (strength) at time t, t_i is the time of a spike from e.g. spike train data, and τ is a time interval.
- **Auto/Cross-correlograms** measure a neuron's spike timings with respect to itself (auto) or other neurons (cross). They are useful for detecting oscillations in a neuron's spiking and are used to discover a temporal relationship between neurons (i.e. if one neuron is causing another to fire).
- Decoding from a single neuron: Signal detection theory can be used to compute decoding quality for a moving dots task, apparently.
- **d'** (dee-prime) is a measure discriminability of two normal distributions (with the same variance I presume) $d' = \frac{\mu_+ - \mu_-}{\sigma}$.

8.1 The Leaky Integrate and Fire Model L14

If I have understood it correctly, essentially a neuron has a potential difference caused by a difference in sodium and potassium ions inside and outside the neuron's membrane. If it is connected to another neuron by an **excitatory synapse** the voltage inside the neuron will increase (voltage potential decreases) and then the neuron can **spike**/cause an **action potential**. The neuron has to then "recharge", taking a certain **refactory period**, to then be able to spike again. The LIF model consists of two key components:

1. An ode describing voltage dynamics in a neuron: $C_m \frac{dV}{dt} = (E_L - V)R_m + I_e$, or $\tau_m \frac{dV}{dt} = E_L - V + R_m I_e$, where:
    - E_L is the **membrane potential**, i.e. the potential difference across a neuron's membrane (given by Sodium (Na) and Potassium (K) imbalance - note, sodium is outside a potassium inside - think islands surrounded by salty sea). It the potential needed to keep the random motion (caused by temperature fluctuations) of the potassium atoms in the membrane. It is the voltage required for zero current even if there is some conductivity.
    - R_m is the membrane resistance $R_m = 1/G_m$, where G_m is the conductance.
    - I_e is the current induced by an 'e'lectron or I_s 's'ynapse.
    - C_m is the capacitance of the membrane. The amount of charge stored is thus $C_m V$.
2. A voltage-reset mechanism that mimics a spike (if statement): If $V > V_T$ then $V = V_{reset}$. V_T is usually $-55mV$.

- Neuron's are simply input-output devices (take in synaptic inputs (spikes) and output a series of spikes). One way of characterising this input-output behaviour is with a **frequency - current curve** (f-I curve), which plots *firing rate (Hz)* against $R_m I_e$ *current*.
- The LIF acts as a **low-pass filter** because the membrane capacitance takes time to recharge. Quick changing inputs get averaged out.
- **Impedance** summarises input/output transformation frequency of the signal by the neuron. $|Z|$ is equal to the ratio of the voltage amplitude to the current amplitude. $|Z| = \frac{R_m}{\sqrt{1+(2\pi f \tau_m)^2}}$. As frequency increases impedance decreases.

- Possible extensions to the LIF model: Add a refactory period, more realistic spiking mechanism, dynamic spike threshold value etc...
- The general solution to LIF equation is: $V(t) = E_L + R_m I_e + [V(0) - E_L - R_m I_e]e^{-t/\tau}$. The $f - I$ curve can be found by using the fact that at $t = T$, $V = V_R$ and then rearranging to find T in terms of I and then using the fact that frequency $f = 1/T$.

9 Synaptic Plasticity

- Synapses are connections/ends of dendrites on a neuron, they about $1\mu m$ in size. There are around 100 billion neurons in the brain and around 1000 trillion synapses.
- Synapses are absolutely crucial for brain function - working memory, episodic memory, motor memory, sensory processing and LEARNING.
- The action potential goes through the presynaptic neuron into the axon and then to the synapse where it is transferred to the postsynaptic neuron.

9.1 Computational Models of Synapses

9.1.1 Phenomenological (no molecular details, abstract)

- Static Model
  - Considers a network where the output v is a non-linear function of weights $\mathbf{w}$ and inputs $\mathbf{u}$, i.e. $v = f(\mathbf{wu}), \mathbf{w} \in R$.
  - For excitatory synapses $\mathbf{w} > 0$ and for inhibitory synapses $\mathbf{w} < 0$
  - $\mathbf{w}_i = P_{rel}q$, where P_{rel} is the release probability of neurotransmitters by vesicles in the synapse and q is the number of neurotransmitters released. The output (post synaptic response) is proportional to the weights.
- Stochastic Model
  - Response $W \sim Prob(N, P_rel, q)$ where N is the number of release sites. E.g. a Binomial release model for response $W \sim Bin(N, P_rel)$
  - Then $P(W = k) =^N C_k P_{rel}^k (1 - P_{rel})^{N-K}$, where k represents possible responses.
- Time dependent models: Leaky Integrate and Fire Model $\frac{dV}{dt} = V_{rest} - V + I_{syn}$
  - Current-based model: $I_{syn}(t) = \bar{g}_{syn} s(t)$ where g is the maximum synaptic strength.
  - Conductance-based model: $I_{syn} = \bar{g}_{syn} s(t)(E_{syn} - V)$ where E_{syn} is the reversal potential, which determines the 'sign' of a synapse. For excitatory synapses $E_{syn} \geq 0$ and for inhibitory synapses its less than zero.
  - $s(t) = e^{-\frac{t-t_{spike}}{\tau_{decay}}}$ (single) or $s(t) = e^{-\frac{t-t_{spike}}{\tau_{decay}}} - e^{-\frac{t-t_{spike}}{\tau_{rise}}}$ (double)

9.1.2 Molecular

- Can use Markov Chains

9.2 Synaptic Plasticity

- Refers to changes to the synaptic properties (usually the synaptic weight, W). Such changes allow for learning and memory apparently. Essentially changes to the output action potential signal.
- An increase in synaptic weight implies a strengthened connection between two neurons.
- Synaptic plasticity can thus be expressed as a change in weights ΔW which is function of pre-synaptic (x) and post-synaptic (y) activity. $\Delta w = f(x, y)$ - a simple Hebbian Rule or correlation-based rule.

- Synapses can change post-synaptically and pre-synaptically (from a few seconds/minutes (short-term) to hours or few days (long-term))

9.3 Short term Synaptic Plasticity (STP)

- Short term plasticity lasts for up to tens of seconds.

9.3.1 Types

- Short-term depression (STD) - Pyramidal cell sends action potential to another pyramidal cell and the output voltage spikes get reduced. Around 0.4mV. Helps prevent seizure-like dynamics - firing rate would otherwise just continue growing rapidly.
  - STD is important to control network activity, helping to prevent pathological states.
- Short-term facilitation (STF) - Pyramidal cell sends action potential to Martinotti Cell and output voltage spikes grow. Around 4mV. Used a model for working memory, where the dynamics of P_{rel} are a memory trace of previous input activity. A recurrent network of integrate and fire neurons was used to demonstrate the idea. It suggests that all 1000 trillion synapses has some form of working memory.
  - **Working memory** is our ability to keep 5-10 items in our memory for a short period of time. Key for reasoning, as it allows us link different sets of information together.
  - STF is newly proposed theory of working memory.

9.3.2 Models

- Phenomenological- Tsodyks-Markram model
  - 1) Average release from presynapse = $R \times P_{rel}$ = number of vesicles released with probability P_{rel}
  - 2) Neurotransmitters bind to postsynaptic receptors with amplitude q
  - 3) Final synaptic response or weight is then $w = qRP_{rel}$
  - 4) Some vesicles are recycled with time constant τ_D which leads to short-term depression (STD) until the number of vesicles is fully recovered again. (output spike decreases before it spikes again)
  - Results in an ODE for the number of release vesicles (STD - notice P_{rel}): $\frac{dR}{dt} = \frac{1-R}{\tau_D} - RP_{rel}\delta_s pike$
  - 5) If calcium builds up on the presynaptic side this leads to an increased release probability p (so STF occurs).
  - Then we get a system of two ODES: The number of release vesicles: $\frac{dR}{dt} = \frac{1-R}{\tau_D} - R\boldsymbol{p}\delta_s pike$ *dynamic release probability*: $\frac{dp}{dt} = \frac{P_{rel}-p}{\tau_F} + (1-p)\delta_{spike}$
    - Use $\boldsymbol{\tau_F >> \tau_D}$ (slow decay) in dynamic release probability p to remember previous items.
- This model ignores the stochastic nature of synapses and different release sites N.

9.3.3 Functions

- Network dynamics: STD helps preventing seizures, controls network dynamics
- Working memory: STF as a model for it - Not entirely sure how though... I guess that P_{rel} acts as memory trace, i.e. the vesicles act as storage and their release as transferring information.

10 Hodgkin-Huxley Neurons (j) L19,L15Hodgkin

- Ion channels are *ion-penetrable* pores in the lipid membrane of cells. A single neuron usually has between thousands and millions of ion-channels. The open and close in response to stimuli (e.g. temperature, voltage, pH, etc...), letting ions like K^+, Na^+, Ca^{2+} and Cl^-. They mediate electrical signals in the brain. The flux can be millions of ions through the channels per second.
- **Voltage gated channels** have four similar subunit channels arranged in a ring. Between these subunits is the "pore" (the ion channel) and is controlled by voltage sensitive proteins that control the subunits which in turn control the pore. They are found along the axon and in synapses.
- Other channels include Sodium-ion channels (responsible for upswing in action potential, Potassium channels (mediates the 'leak' current), Calcium channels (Responsible for some forms of dendritic spikes),
- **State-based Ion Channel modelling:** Assume each channel can be in one of a few discrete states. Depending on the cell voltage channels can transition to different states. A two state ion channel with transition rates α and β can be modelled as follows:
  - Transition rates given by: $\mathrm{s}_0 \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} \mathrm{s}_1$ (Note this implies $s_0 = 1 - s_1$). The ode that describes this is $\frac{ds_1}{dt} = \alpha s_0(t) - \beta s_1(t) = \frac{s_\infty - s_1(t)}{\tau}$, where $s_\infty = \frac{\alpha}{\alpha+\beta}$ and $\tau = \frac{1}{\alpha+\beta}$.
  - The steady state value s_∞ is found by solving $\frac{ds_1}{dt} = 0$ and setting $s_0 = 1 - s_1$ and $s_1 = s_\infty$. The second form of the ode is found by subbing in $s_0 = 1 - s_1$ and $\alpha = S_\infty(\alpha + \beta)$. Should then get $\frac{ds_1}{dt} = s_\infty(\alpha + \beta) - s_1(\alpha + \beta)$.
  - Non-linear synaptic integration. (Issues with LIF model include not having spatial layout of synaptic inputs, voltage dependent ion channels). Voltage is affected by where in the neuron the current is received from a another neuron. Dentritic spikes can also occur whereby a dendrite spikes on its own. Can think of a single neuron as a two-layer neuronal network.
  - Stochasticity - Ion channels are discrete and stochastic
  - Ion channel noise. Current through a single ion channel is $i = \gamma(E_{rev} - V)$, where γ is the conductance, E_{rev} is the reverse potential (can be calculated using the Nernst equation, apparently) and V is the voltage inside the membrane (Ohms law). Mean current for N channels is $\bar{I} = Nip$, where p is the probability of the channel being open. Noise is given by standard deviation of binomial distribution $\sigma_I = i\sqrt{Np(1-p)}$. Thus C.V. $= \frac{\sigma_I}{\bar{I}} = \frac{i\sqrt{Np(1-p)}}{Nip} = \sqrt{\frac{1-p}{Np}}$.

10.1 Hodgkin-Huxley models for the following channels

- Key idea is that probabilities of gates being open depend on voltage.
- **Potassium channels** are considered to be **persistent** gates, meaning they have one open and one closed state. The potassium gate has four subgates, its overall conductance is considered to be $g_K = \bar{g}_K n^4$, where $\bar{g}_K$ is the conductance if all the channels are open and n is the probability that an individual channel is open, so n^4 is the probability that all four are open. If we now consider n to be the proportion of gates that are open, it can be modelled as:

$$\frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n,$$

where α_n is the *rate/probility at which closed gates open* and β_n is the *rate at which open gates close.* Which can be re-written in the standard form:

$$\tau_n(V)\frac{dn}{dt} = n_\infty(V) - n(t), \tau_n = \frac{1}{\alpha_n + \beta_n}, n_\infty = \frac{\alpha_n}{\alpha_b + \beta_n}.$$

Note, here $I_K = g_K(E_K - V), E_K = -70mV$.

- **Sodium Channels** are considered to be **transient** channels because it has two closed states and one open state. Generally it goes $Closed1 \rightarrow Open \rightarrow Closed2$. Closed 1, is determined by three subgates being open with probability m (so m^3 for all). Closed state 2, does not have any subgates, is determined by probability h, note these probabilities can all be modelled like above and $h_\infty(V)$ tends to 1 for low voltage V and 0 for large voltage. $g_{Na} = \bar{g}_{Na} m^3 h$ here and $I_{Na} = g_{Na}(E_{Na} - V)$, where E_{Na} is around $55mV$.

- **Hodgkin-Huxley equation:**

$$C_m \frac{dV}{dt} = currents,$$

$$C_m \frac{dV}{dt} = g_l(E_l - V) + \bar{g}_K n^4 (E_K - V) + \bar{g}_{Na} m^3 h (E_{Na} + V) + I_e,$$

  where the first term is the leak current and I_e is an external current. So the Hodgkin-Huxley equations are a linear set of four separate odes, one for voltage, shown just above, and then for h, m and n which are governed by equations of the form

$$\frac{dx}{dt} = \alpha_x(V)(1 - x) - \beta_x(V)x$$

  , I suppose there are 6 equations if you include those for α and β.

11 Patterns (k) 16PhaseAnalysis

- Essentially Conor just looks at simplified versions of the hodgkin-huxley model, namely the **Morris-Lacer model** and the **Fitzhugh-Nagumo model**. Both form limit cycles. One application of their research is pattern generation, which are cells that send out regular bursts of neurons (?).

11.1 Phase Analysis

- Essentially just plot nullclines.