Contents

1 Introduction and Recap

- Last few weeks of semester is utilized for our projects
  (a) In the last weeks, they will help with finding project.
  (b) Two kinds of projects: dig deeper or original research (write code or algebra about neuroscience problem)
- We are touching/brushing over very important topics.
- Today's Lecture:
  (a) synaptic connectivity
  (b) synaptic plasticity
  (c) plasticity in neural nets
  (d) but first, take the quiz!

2 The Brain: a gigantic directed graph

- About 10^{11} neurons

2.1 Renyi random graph

- A well-known random graph: $G_{n,p}$ or the Erdo"s - Renyi random graph [1959]
- Structure in which there is a probability that two nodes are connected
- $Pr[edge i \to j] = p$, independent of other pairs
- $p < \frac{1}{n}$: dwarf components $\sim ln(n)$
- $\frac{1}{n} < p < \frac{ln(n)}{n}$: a giant component, still disconnected
- $p > \frac{ln(n)}{n}$: connected
- This structure has implications on how connected subgraphs are
- In particular, there are sharp thresholds that transtion the graph from having dwarf components of size ln(n), a giant disconnected component, or a connected components

2.2 Power law graph

- An undirected graph where the probability that there is a node of degree d is about $n^{-\alpha d}$
- $Pr[\text{there is a node of degree d}] \sim n^{-d\alpha}$
- The graph describes the internet, which has an alpha of 2.6-2.8
- probability goes down polynomially (not exponentially)
- Graphs with higher degrees are few but are the best connected

2.3 Small world graph

- represented as a grid, where going distance d away has a probability of d^{-2}
- e.g. six degrees of separation. Use shortest path algorithm, you will find the path.
- Which of these random graph types is the most like the brain? Can brains be random?

- How fruit flies remember smells: neurons excite more neurons, in the end there is a random projection, which is good for learning. Axel's group found a random bipartite graph (but more differences than would be expected if random). We have complete connectome of the fly. Left and right are completely different graph. Is it that the randomness exist in the DNA, or the DNA has a random-generator? The second is correct because the left and right are different.

- Step by step:
  - Step 1: Odorant receptor neurons (ORN) first get stimulated by odor and center the mean
  - Step 2: Random projection to projection neurons (PNs)
    - Olfactory responses show random bipartite graph, except that the degree distribution of the LHS is not uniform
  - Step 3: Projected to Kenyon Cells (KCs) and winner takes all

3 Generative model of the Human connectome

3.1 How long does the growth cone travel?

- Many yards

- On average: 4mm in the cortex

- Growth cone travels some micro m in local circuits

- Splits from growth cones seem to be important

  (a) Some are very long (c.f. giraffe)

  (b) Many navigational strategies. Is there a split? Can have Axon colaterals [Han, Nature, 2018]. Only 3% stay in the visual cortex.

- Connectome: Sebastian Seung. We are a connectome.

- Human Connectome Project, Blue Brain project. Imagine creating an animal where every neuron has a barcode. Look at which proteins in the brain are connected to each other. Will happen in three years.

- Protocadherin proteins and molecular self-avoidance. 7 possible genes, 7 possible options. 49 types. Bushy cell because they see that they've touched a cell already so grow the other way.

3.2 Navigational strategies

- Sometimes there are early scaffold neurons
- Other times there are signpost neurons
- There are also splits called axon collaterals
- Splits are important because more than 3/4 of neurons go to many areas of the brain

3.2.1 Blue Brain Project

- Digital reconstruction of the brain by understanding order of the proteins / amino acids and how they're connected to one another in neurons
- Will building the human connectome help us understand how the brain works? It will help, but probably a tiny step because, even if we build out the brain, its neurons, and synpatic weights, we don't know how they work and why they do.

4 What kind of graph is the connectome?

4.1 Connectome

- A comprehensive map of neural connections in the brain, and may be thought of as its "wiring diagram"
- Hypothesis: Locally Erdo"s – Renyi and Internet-like
- Hypothesis: Two-way connected neurons (10 times more more likely than Erdo"s)
- Hypothesis: Three neuron connectivity (if there is a synapse from neuron A to B and A to C, then 3 times more likely to have a synapse between B to C)
- Reasons: geometry? plasticity of brain? power-law graph-like property, in which there exists a preferential attachment process?
- Synapses in the connectome are created and destroyed along the way (number of synapses in muscular fibers are like a bell-curved graph with the peak at birth)
- Your connectome changes. New connections are formed and existing ones are destroyed throughout life. Number of synapses, muscular fibers.
- How is this deletion done? Algorithmic work on graph sparsification [Spielman and Teng, 2004] How to sparsify graph without helping the function. Use flow, conductance, eigenvalues. What's an algorithm that would select the synapses.

- Recall: Hubel and Wiesel's simple cells: How do all these ganglia know that they are on a straight line in the retina? Evolution? Development? Learning and synapse deletion (real-time)? The three different time scales. In computer science terms: Programming time, compile time, run time. Mouse V1 pathways develop before their eyes first open. But after birth there is still a critical period.
- An axon can touch the postsynaptic dendrite at many places. How do these add up to affect the postsynaptic neuron? Sum of products or product of sums?
- most importantly, existing ones become stronger or weaker at a large range of time scales (1ms to months); plasticity: the way brains learn

4.2 Potential graphs

- Two way conected neurons: 10 times mor likley than Erdo's-Renyi predicts
- Three neuron connectivity: Song et al shows that counts relative to random increase as the set of three neurons is strongly connected and undirected
- Why: geometry or plasticity
- Plasticity: your connectome changes as new connections are formed and existing connections are destroyed
- As soon as we're born, we start getting rid of synapses quicker than we create them

4.3 Hubel and Wiezel's Simple Cells

- Unaswered questions:
  - How are these synapses formed?
  - How do all these ganglia know that they are on a straight line in the retina?
  - Evolution?
  - Learning and synapse deletion?

4.4 Additional Things to Consider

- An axon can touch the postsynaptic dendrite at many places
- Many "edges of the tree"
- How do these add up to effect the postsynaptic neuron? (Sum of products?, products of sum?)

4.5 Connections btw Neurons

- New ones are formed (in embryo, baby, and adult)
- Existing ones are destroyed
- Existing ones become stronger or weaker at a large rnage of time scales (1ms to months)
- Plasticity is the way brain learns
- The fact that pre-synaptic activity affects magnitude of post-synaptic response illustrates plasticity

5 Plasticity

5.1 History

- 1890: Ramon y Cajal hypothesizes that synapses between neurons are the agents of learning
- 1949: Hebb's rule: neurons that fire together wire together
- 1966: Lomo observes long term potentiation (LPT) in the rabbit brain
- 1970s: Long term depressiong (LTD) is observed
- 1980s: The biochemical basis of plasticity discovered to be Ca^{++} and NMDA receptors
- 1986: Backpropagation, software plasticity through SGD (modelling plasticity computationally)
- 1995: Spike timing dependent plasticity (STDP)
  - If spike arrives in time, some gain
  - If spike arrives just in time, big gain
  - If spike misses it completely, some loss
  - If spike misses it closely, big loss

5.2 Models

- Black box models (we can't model it computationally)
- Spike timing models
- Biochemical models: plasticity seem to do with receptors, spine shape change, etc.

(a) synapse w, pre-synaptic cell x, post-synaptic cell y

(b) Hebb: $\Delta w \propto xy$ (wire together if fire together)

(c) Vector Hebb: $\Delta W \propto Xy$ (X is vector of presynaptic neurons)

(d) Covariance form of Hebb (assuming y is the average input times W): $\Delta W \propto cov[X]W$ ($cov[X]$ is how correlated they are).

(e) So far, nothing is negative, everything is positive.

(f) Hebb with LTD: $\Delta W \propto X(y - \theta)$ - but then LTD if $y = 0$

(g) BDM (three famous neuroscientists) came up with rule that corrects this: $\Delta W \propto y(y - \theta)$. Elaboration: oijeahrs rule.

5.3 Homeostasis

- Organism is stable, its parameters stay in check and its resources are not depleted
- The mechanism that makes sure plasticity does not cause synaptic weights to become infinite is through the sum of all presynaptic weights being gradually renormalized to one
- Begets competition between presynaptic cells

5.4 Spike timing-dependent plasticity

The closer the spike timing to 0, the absolute value of the delta of synaptic change increases