+Virtual book club

The brain from inside out by György Buzsáki

Curated by Anne Urai, @AnneEU

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Rules

1. When you start participating, please list your name, Twitter handle/email and if you'd like to discuss over video-chat.
   a. If you don't want to contribute but just read, feel free to lurk!
2. When you add a question, answer or summary, please add your name at the end (e.g. [Anne Urai]); feel free to contact others, set up video-chat meeting to talk about specific sections, and add your notes to this document.
3. Each chapter has its own section. Please stay in the sections, or put general remarks in the cross-chapter section at the end.
4. Try to see if your question or remark is already there, and add to it or answer it rather than duplicating.
5. When adding citations or resources, please write them out and add a hyperlink to the article/source. Do not simply copy/paste more reading materials, but explain briefly what can be found there and why it's of interest.
6. Do not delete other people's text, and try to keep the document readable.
7. Have fun!

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**I'd be curious to see people list their disciplines here if willing! -hb

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Chapter 1: The Problem

Summary

- Neuroscience traces its philosophical roots to concepts from empiricist philosophy (e.g. Hume) which stated that the mind must deduce the structure of the world from =observations. This is the core of the ‘outside-in’ approach to neuroscience, and can be followed through cognitivism, and current information-theoretical and signal-processing approaches in neuroscience.
    - Many approaches to neuroscience aim to find the neural correlates of some cognitive phenomenon, e.g. attention or working memory. However, there is no good reason why these terms (many of which date back to William James) should be the primary operating principles of the brain.
- In behaviorism, stimuli, signals and reinforcers are seen as distinct entities that affect the organism differently. However, it’s not clear how the brain can distinguish these different types of inputs.
- The outside-in approach likens the brain to a computer, whose goal it is to represent features of the world (e.g. Hubel and Wiesel). This then leads to the problem of binding, i.e. how are these features combined to represent meaningful entities.
- Buszaki argues that action (in the form of sensorimotor loops) is the only meaningful way to bind inputs together in a way that is meaningful to the organism. Closed-loop connections with the real world are the only way in which representations can be *grounded*.
    - This leads to a reader-centric view of neuroscience. Instead of seeing what information/representations the experimenter can find in neural signals, the question becomes: what does the next neuron/assembly do?
- Finding and breaking the neural ‘code’ is only a meaningful exercise if the syntax of the message is known.
- The brain is not a tabula rasa that receives inputs, but rather has a diversity of cell types, timescales and activity patterns that are self-generated and crucial for adaptive behavior.

Questions

- Does contemporary neuroscience fall mostly in the outside-in approach Buszaki describes? What are some examples of successful approaches that have grown out of different philosophical traditions? [AnneU]
    - I'm curious whether optogenetics or older methods like experiments using interventions of TMS or tDCS are examples of an alternative approach, or if despite the inversion of directionality (we stimulate/intervene on the brain [inside] and look for effects in behavior/perception [outside]), Buzsaki would still call this part of outside-in since we're still looking for associations between things in the world, and activity in the brain. [Jeremy]

    - Buzsaki's suggestion that brain activity should be the independent variable made me think of machine-learning techniques (i.e.MVPA) for fMRI data that use voxel-specific BOLD signals as predictors of some external event, like a presented stimulus or a button-press (as opposed to traditional fMRI methods where the task events are predictors of brain activity). It seems to me that the latter MVPA model of brain activity -> button press does fit Buzsaki's inside-out perspective. But perhaps the more common brain activity -> stimulus MVPA model does not, since of course the brain activity doesn't produce the external stimulus. This might fit more loosely into the idea that the brain creates (rather than processes) information about the outside world. [Hannah]
        - Similar to Jeremy's point above about neuromod, the inside-out perspective seems to fit best when the 'variable to be explained' is behavior [Hannah]
    - Also, the action-based models of decision-making described in Wispinski et al., 2018 seem to fit squarely in the outside-in approach [Hannah]

Further reading

- György Buzsáki: Current Biology
- Thirst regulates motivated behavior through modulation of brainwide neural population dynamics
- Wispinski et al., 2018, Models, movements, and minds: bridging the gap between decision making and action

Chapter 2: Causation and Logic in Neuroscience

Summary

- Neuroscience mostly uses correlational statistical techniques, where the outside world is the x-axis (explanans) and the brain is on the y-axis (the explanandum).
- Our goal is to deduce causal, law-like relationships between the two. This is a strong focus of Western science, in which cause and effect are considered the core of logical arguments and scientific thinking. This is not the case in many other philosophical traditions, but instead of a network of connected, coincidences of events.
- Cause and effect are really tricky in neuroscience (especially from observational data, where techniques such as Granger causality are often misused and can give the wrong answers about complex but biologically plausible neural circuits).
- Deterministic causations are not very useful in neuroscience; everything is probabilistic and depends on many co-occurring factors. In complex systems, this has led to concepts such as autogenous, endogenous and self-assembled to instead describe the functioning of the brain. In a system like the brain, feedback loops and spontaneous activity make it impossible/useless to draw cause-and-effect diagrams.
- Can intervention studies (lesion, TMS, optogenetics) help us with deriving the causal laws of the brain? Probably not - redundancies, adaptation, feedback loops make it really hard to isolate the causal role of one functional part of the brain. Instead, we should be thinking about the interaction between parts.

Questions

- If we discard the approach of isolating parts, and then studying their relationships, what's left? Dynamical systems / complexity theory?

Further reading

- [Chaos: Making a New Science]()
- [Judea Pearl's The Book of Why]() discusses the problems with drawing causal inferences from observational data using traditional statistics (i.e. regression-based methods) and instead outlines the program of why-calculus, which can be used to draw causal conclusions using Bayesian Directed Graphs. Does not really teach you the nitty gritty of the methods, but outlines very well what the general approaches are for drawing solid conclusions about causality from data. [Anne Urai]
- https://michielstock.github.io/causality/
- [Causality detection in cortical seizure dynamics using cross-dynamical delay differential analysis]()

Chapter 3: Perception from Action

Summary

- There is no perception without action (e.g. Troxler fading; without eye-movements, peripheral vision fades). Eye movements are critical for obtaining a 'second-opinion' and grounding perceptual interpretations in the real world.
- The speed of actions is the relevant timescale for an organism; no point having a better/faster perceptual system than that. Sensation by itself is of no evolutionary benefit to an organism; action by itself can have a huge advantage (e.g. blindly swimming around in search of resources).
- A thought is an action.
- The corollary discharge (or efference copy) is of crucial importance for teaching the brain which sensory signals came about as a result of its own actions, vs. those that came about through changes in the outside world.
    - Adaptive filtering can make organisms exquisitely sensitive to signals in the outside world, without being bothered by self-generated signals (e.g. chirping crickets).
    - Time-division can remove effects of optic flow, saccades etc. We only have the illusion of continuous vision; in fact, it is intermittent (or sampling-based) since saccades gives us a refractory period.
- Active sensing comes in many forms: (micro-)saccades, head motion, whisking, echolocation, sniffing.
- Actions that modulate sensors may influence the afferent signal in multiple ways, including e.g. amplification (sniffing enhances olfactory perception independently from the mechanical effect). Saccades as visual sniffs, etc.
- In development, action (e.g. baby kicks) teaches the brain about the physics of the body it controls.
    - Sleep spindles (and sleep spasms) are a remnant of motor babbling that adults still do.

Questions

- What can we infer about the potential adaptive value of micro-saccades based on the evidence that increased spiking post-micro-saccade is such a prevalent dynamic across the visual system (p. 119)? [Jeremy]

Further reading

- A Critique of Pure Vision
- Spontaneous behaviors drive multidimensional, brainwide activity
- 'Noise' in the Brain's Vision Areas Encodes Body Movements

Chapter 4: Neuronal Assembly: The Fundamental Unit of Communication

Summary

- From single neurons to the cell assembly as the unit of neural computation.
    - Hebb’s original definition is so general that it’s not really testable.
- Look at assemblies from the reader neuron’s perspective; what input assemblies activate a downstream unit? This should be the way an assembly is defined - for this, assemblies do not need to be anatomically connected or reside in the same part of the brain. The only criterion is that they are effective in driving a downstream ‘reader’ neuron.
- This driving of a downstream neuron by an assembly of cells has to happen in a time-window of 10-30ms. This is one single cycle of a gamma oscillation, which may ‘packet’ cell assembly communication (or a ‘neuronal letter’).

Questions

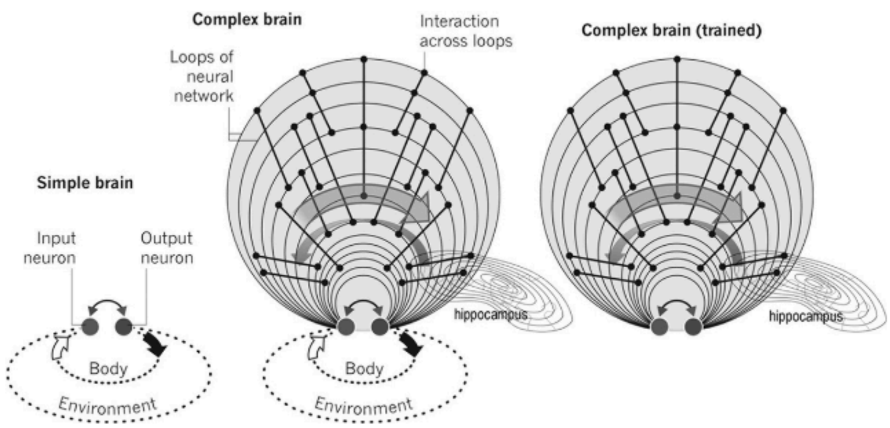
- Are spikes the only relevant output of an area? Does the LFP *influence* any local computations, but not really carry outputs along?
- What’s the relationship between a neural assembly and a cortical column?
- Does Buszaki’s definition of an assembly make it super hard to study (because there are fewer localization and cell type constraints on how we can find an assembly)?

Further reading

- Organization of cell assemblies in the hippocampus
- Packet-based communication in the cortex

Chapter 5: Internalization of Experience: Cognition from Action

Summary

- The brain learns the world through engagement and action. Once the needed relationships are learned, they can be navigated mentally through a type of simulation. The inputs to this simulation are essentially motor/action commands which have become ‘internalized’, or detached from their typical motor consequences. This allows adequately complex brains to choose actions based on predictions about their consequences, which can integrate past experiences as well as immediate environmental signals.
- 

- Navigation in physical space is done initially by 'dead reckoning', keeping track of how far and in which direction you've traveled, to determine the return journey. After exploring an environment this way, this egocentric spatial representation can be used to build an allocentric map of space in which the agent can place itself.
    - The hippocampus and entorhinal cortex may have evolved for spatial navigation in these two days, and later expanded to also represent navigation through semantic space and time: memory. Dead-reckoning systems give us episodic (egocentric) memory, and map-like representations give us semantic (allocentric memory). While not strictly necessary, episodic memory helps acquisition of semantic memory - just as exploration and dead reckoning are needed to create an internal spatial map of the environment.
- In a similar manner of disengaging neural circuits from direct action, emotions may originate evolutionarily from responses of the autonomic nervous system - but have evolved to also occur without them, organisms with higher cognitive capacity.

Further reading

- [Hippocampal “Time Cells”: Time versus Path Integration: Neuron]
- [https://doi.org/10.1146/annurev-neuro-071013-014030]

Chapter 6: Brain Rhythms Provide a Framework for Neural Syntax

Summary

- Brain activity is synchronized by oscillations at varying frequency bands, which are spaced by Euler's constant e which avoids that they interfere with each other (since they are not harmonics)
- Oscillations criticality depend on interneurons which gate and coordinate the activity of pyramidal cells, so that spikes are economically used to transmit information most effectively.
- Frequency bands of brain rhythms are highly conserved across mammalian species (since they rely on the same cell types and circuit patterns). It's a bit surprising that these same frequencies work so well in small and bigger brains, where the speed of communication across far-away brain regions is considerably slower. Small-world architecture (with highly connected hubs) can help keep the average synaptic path length down. More myelination also increases conduction velocity in bigger brains.
- Rhythms of speech and other vocal communications match the natural delta rhythms in the auditory cortex.
    - Clip from Book
    - > oscillations. The requirement for tracking the temporal dynamic of speech by brain rhythms is illustrated by experiments in which test sentences are time-warped. When speech is compressed, but comprehension is maintained, both phase-locking and amplitude-matching between the temporal envelopes of speech and the recorded brain signal are maintained. However, when speech compression is large, brain oscillations no longer effectively track speech, and comprehension is degraded.[28]

Question

- Isn’t it very energy-inefficient to have all this inhibitory spiking continually, just to keep the excitatory cells from going crazy? Are inhibitory spikes somehow ‘cheaper’ to fire?

Further reading

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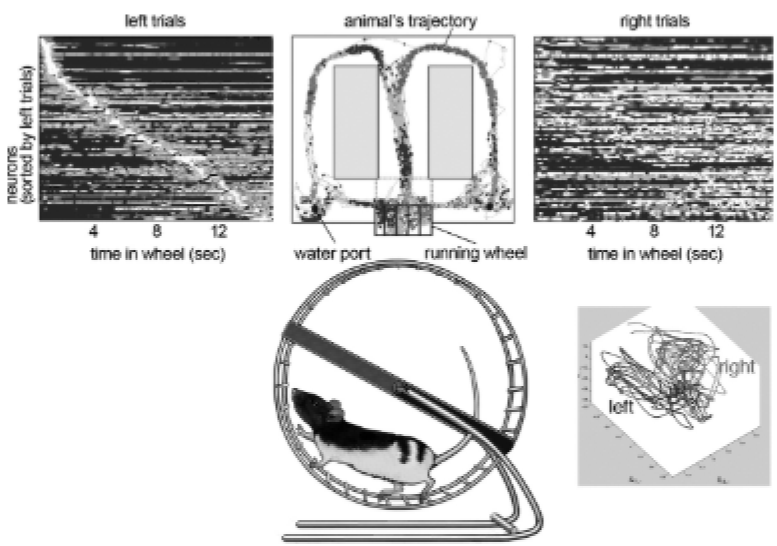
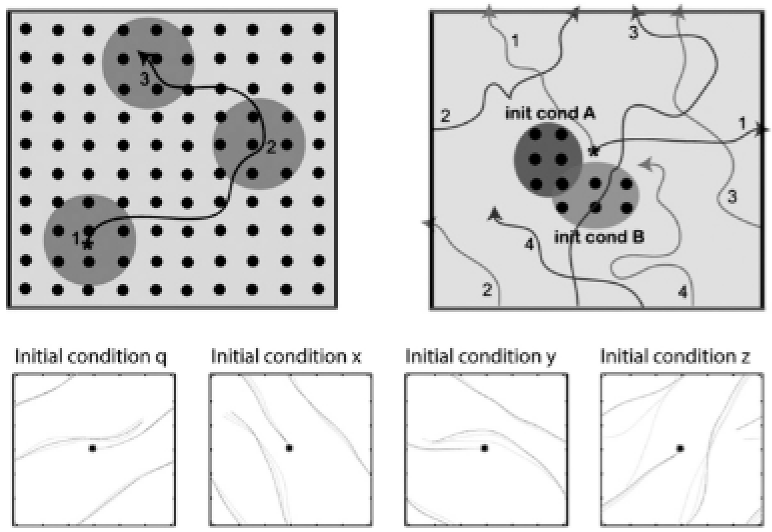
Chapter 7: Internally Organized Cell-Assembly Trajectories

Summary

- System change can be described as a motion vector in high-dimensional space. Sequential points in this space form a trajectory.
- A neural syntax is formed from trajectories across active ensembles (e.g. 200 simultaneously firing neurons at a single point in a bird song) that form syllables, words, sentences (fixed action patterns).
- Sequences can be driven from sequentially changing stimuli from the world or proprioceptive inputs (outside-in), or "internally driven self-organized patterning".
- Reader neurons use oscillations to chunk their downstream input, and create time windows in which to listen. This is analogous to active sensing, where motor rhythms determine when sensory signals are optimally processed.
- Animals without cortex can still make grooming movements, but not in the right sequence.
- Hippocampal Sequences represent the immediate future and the past, in compressed form



  - **Figure 7.6.** Sequential activation of neuronal assemblies in an episodic memory task. *Center*: The rat was required to
- Intrinsic Dynamics Exist, and may be important.



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Further reading

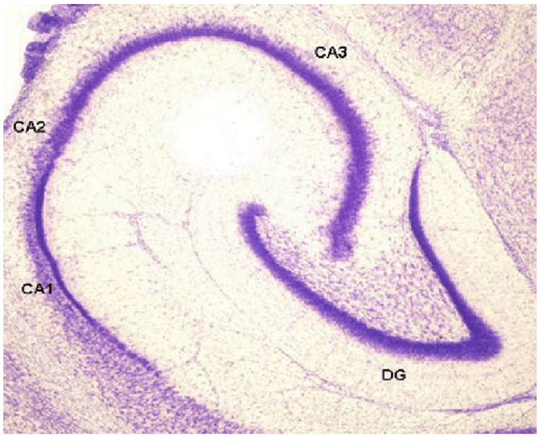
- Cell Assembly Sequences Arising from Spike Threshold Adaptation Keep Track of Time in the Hippocampus
- Who reads temporal information contained across synchronized and oscillatory spike trains?
-

Chapter 8: Internally Organized Activity During Off-Line Brain States

Summary

- Sharp Wave Ripples
  - Combination of two events at different locations:
    - Sharp wave: negative polarity high amplitude deflections in apical dendrites in CA1 (magnitude of synchrony in upstream firing patterns from CA2/3)
    - Ripple: Caused by depolarization of CA1 pyramidal & interneurons -> "tug of war" & fast excitatory/inhibitory oscillations
  - Useful channel to transmit information from HC -> neocortex
  - Palindromic, which indicates this bidirectionality of reading is likely adaptively useful
  - Possibly useful as forward & reverse compressed HC replay
    - Speculation that forward replays used for planning, backward replay recapitulates a prior choice and is modulated by reward strength (e.g. to support credit assignment?)
- Memory and learning
  - SWRs involve repeated re-activation of learned sequences (e.g. during non-REM sleep), which may be useful for consolidation
  - Inside-out perspective on learning: rather than novel sequences being created during exposure to external stimuli, there's a selection phase in which internal sequences are recruited that best match experienced stimuli
  - Facilitation of learning during sleep via SWRs demonstrated by experiments
    - Experimental manipulation of reward association during place cell firing
      - Mouse makes a bee-line for place cell locations linked to reward (brain stimulation) during sleep
    - Abolishing SWRs impairs spatial memory performance
- SWRs for generation / simulation
  - Foraging reward wells in an open field, SWR sequences plotted a path back to home base from the discovered well (a prospective return plan).

  M ay therefore underlie generation of novel sequences via a "stiching" of multiple SWR sequences (forward + reverse)



Question

- Learning & scaffolding of new experience in hippocampus & immune system

Further reading

- Coordinated interactions between hippocampal ripples and cortical spindles during slow-wave sleep.
- https://elifesciences.org/articles/17267

Chapter 9: Enhancing Brain Performance by Externalizing Thought

Summary

- Brain outputs include:
    - Muscle movement
    - Autonomic activity
    - Hormone release
    - Thoughts …?!
- Thoughts are deferred actions that may (or may not) have an advantage to the organism's behavior in the future.
    - Intention, imaged future state (+ valence)
- "The PFC can be considered an internalized offshoot of the motor cortex with a similar neural architecture… the main difference is that while the primary motor cortex sends direct projections to the spinal cord to control the skeletal muscles, the prefrontal cortex instead targets autonomic and limbic sites… these projections can be viewed as corollary circuits through which prefrontal areas inform other higher order cortical areas and motivation or action-preparing structures about pending action plans, similar to the way that motor cortex informs sensory areas about ongoing actions."
- Modern human brains are not really different from early humans, we just externalized a lot of our cognitive processes to technology.
- With large societies and extreme specialization, humanity as a group has stronger cognitive capacities - but as individuals we're actually less capable and more helpless. Without the internet, we'd be pretty screwed.
- Increased specialization at the cellular level with evolution and more complex animals. Representations have to become more and more abstract, to support more complex behavior/cognition.
- Von Economo cells; elephants, whales, macaque monkeys, raccoons have them too!
    - Anterior cingulate and anterior insula in hominids

Questions

- Buzsaki says prefrontal cortex is divided into medial, orbital, and insular areas. What about lateral PFC? [HB]

Further reading

- Techniques for storing notes etc externally - so that they're easy to retrieve: [zettelkasten]()
- Sapiens by Yuval Harari (similar points about the effect of technology on humans/society, but with a more depressing conclusion)
- Buzsaki's comparison of directly evaluating actions vs. comparing and evaluating internal workings of the brain before overt movement reminded me of Wispinski et al's

distinction of good-based (vmPFC) vs action-based (dACC and motor areas) contemplation: http://doi.wiley.com/10.1111/nyas.13973 [HB]

Chapter 10: Space and Time in the Brain

Summary

- Space and time aren't like other senses, we don't have sensors that directly sense them
- Space = time?
    - "Time is a relation of events" ...like space?
- Space is relative to the body. "An image on the retina is not sufficient to perceive space. The brain must also know where the eyes and head are pointing."
- Neural 'clock' systems seem unlikely to exist. More recent idea that time is created in each brain system
- "Timekeeping involves doing". Animals do better in timing experiments when they can keep themselves busy in between tasks
- hippocampal / entorhinal "time cells" perhaps crucial for episodic memory
- Subjective time compression
    - Touching your nose to your toe, or snapping your fingers, seems to all occur at the same time even though the brain receives inputs at different times
    - Hitting the brakes when you see a deer
    - Saccades
    - Imagining you're a mini human in a mini student center
- Car metaphor: The same mechanical movement can be interpreted as speed, distance, or duration as long as we relate it to units of human-invented measuring instruments.
- "Navigation in real or mental space is, by its nature, a succession of events"
    - So sequence is closer than space or time to what the brain does?
    - "The parietal cortex and hippocampal-entorhinal system are general-purpose sequence navigators that continuously tile the gap between events to be linked"
- "The main source of controversy about 'place cells' versus 'time cells' is rooted in the internal contradictions of classical physics"

Further reading

- Eagleman & Sejnowski (2000) [Motion Integration and Postdiction in Visual Awareness]
- Pouget & Sejnowski (1997) https://www.mitpressjournals.org/doi/abs/10.1162/jocn.1997.9.2.222
- Your Brain is a Time Machine (Buonomano, 2017) https://www.goodreads.com/book/show/35187183-your-brain-is-a-time-machine

Chapter 11: Gain and Abstraction

Summary

- Gain modulation can occur through different mechanisms: at the single-neuron level or population, divisive inhibition, neuromodulation
- Gain modulation of different neurons by an external factor (e.g. attention, locomotion, velocity, eye position) can achieve transformation of one coordinate frame to the next; a downstream reader neuron can sum e.g. different neurons that are gain-modulated by eye position, to compute the position of the eye directly.

Questions

- In earlier chapters, Buszaki seems to reject the use of e.g. tuning curves wrt experimenter-defined variables (e.g. in ch 10, ‘space’ and ‘time’). Here, he suddenly uses fairly classical outside-in experimental findings in attention and gain modulation to make his point. Does this weaken his point that the outside-in approach is not that useful for understanding the brain? [AnneU]

Further reading

- Reynolds & Heeger The Normalization Model of Attention
- Heeger & MacKey Oscillatory recurrent gated neural integrator circuits (ORGaNICs), a unifying theoretical framework for neural dynamics

Chapter 12: Everything is a Relationship: The Non-Egalitarian, Log-Scaled Brain

Summary

- It was historically assumed that most things in nature follow a normal distribution. Buzsaki claims that more things in nature follow a log-normal distribution: increasing along orders of magnitude rather than addition
  - Firing rates in the brain are log-normally distributed
  - This gives the appearance of qualitative “types” of neurons (ie fast and slow) when in reality there is a continuum of firing rate
  - Rigid, fast-firing neurons provide stability; plastic, slow-firing neurons are usually quiet but allow change when they do fire
- Lognormal distributions arise from *multiplication* of many underlying factors, rather than *adding* them (which produces a normal distribution)
- As brains scale (i.e. become larger), not all axons are thicker: but the tail subset does, preserving the speed of long-range communication.
- Dendritic spines (a proxy for the strength of synaptic connection between neurons) is lognormally distributed; so there are some neurons that exert a strong influence, and many that exert only a small influence on the postsynaptic neuron. This type of structure is the same for e.g. our social networks. Connection strengths between brain areas span 5 orders of magnitude.
- Fast firing neurons are more connected, and mostly strongly connected to other fast firing neurons: they form a hub that plays an outsized role in distributing information efficiently through networks of cells.
- Distributions of firing rates are intrinsic properties of neurons, stable over time (and maintained during sleep).
  - The distribution of firing rates becomes narrower and sharper during sleep. During waking, sensory drive and run-off STDP may cause more firing in already-high firing neurons.
- Specificity to features (places, contrasts, etc) is also a lognormal continuum, rather than different groups of specialists vs generalizer neurons.
- Social structure in mice has a skewed distribution with a couple of dominant animals. Some depressing parallels with human society and inequality.

Further reading

- The log-dynamic brain: how skewed distributions affect network operations

Chapter 13: The Brain's Best Guess

Summary

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Further reading

- Spontaneous Events Outline the Realm of Possible Sensory Responses in Neocortical Populations
- Spontaneous Cortical Activity Reveals Hallmarks of an Optimal Internal Model of the Environment
- REALITY: THE GREATEST ILLUSION OF ALL

Chapter 14: Epilogue

Summary