**SFB1315** Mechanisms and Disturbances in Memory Consolidation: from Synapses to Systems

Lecture Series 2019–2020

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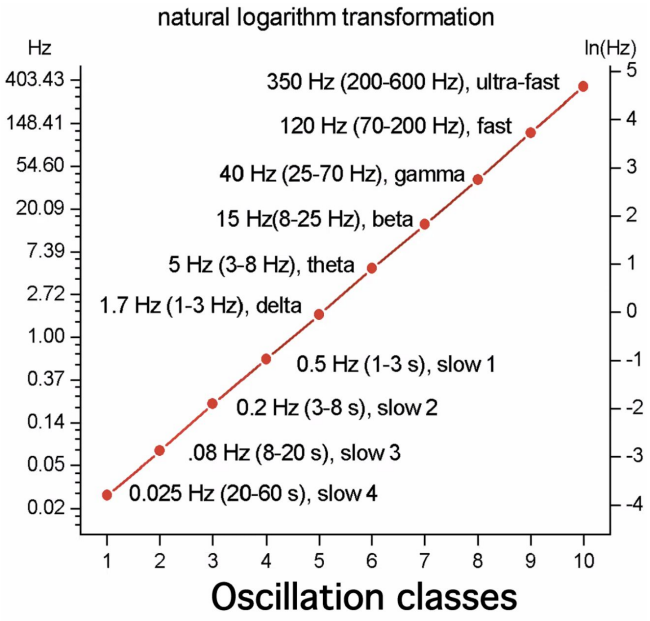
| Speaker | György Buzsáki, Buzsáki Lab, New York University, School of Medicine |
| Host | Richard Kempter, subproject B01 |
| Talk | **"Ways to think about the brain"** |
| Date/Time | March 16, 2021 - 4pm CET |
| ZOOM | Zoom-Meeting beitreten<br>https://hu-berlin.zoom.us/j/7754910236<br><br>Meeting-ID: 775 491 0236<br><br>max. 491 participants; 59 in meet-the-speaker |

## Notes:

**Major theme of lecture: The major preoccupation of the brain is to maintain its own dynamics**

- Dominant thinking in neuroscience
  - Random connections
  - Hebbian plasticity
  - E/I balance
  - Noise
  - Engram (separate writing and reading)
- Egalitarian, blank slate
- Log rules in the non-egalitatiran brain
  - Fundamental rule of psychophysics, the Weber-Fechner (log) 'law', describes subjective perception as proportional to the logarithm of the simulus intensity (also applies to perception of both distance and duration)
  - wide dynamic range of synaptic weights, firing rates and pop synchrony (lognormal dist)
  - dynamics occur on an anatomica substrate




- Buzsaki and Draguhn Science 2004
- Ho et al., Nature 2014 - lognormal distribution of brain connectivity
    - Lots of weak connectivity from many areas
    - Strong inputs from a small number of areas
- Busaki, Mizuseki, Nat Rev Neurosci 2014 - log-normal dist of axon diameters
- Lowenstein, Kuras, Rumpel, J Neurosci 2011 - dist of spine sizes also log-normal
- Mizuseki Buzsaki Cell Rep 2013 - Spike transmission strength also log-normal
- Firing rates are log-normal across classes of neurons and within the same classes of neurons
- Log-normal firing rates of neurons carries over from one state to another
- Preexisting firing rates predict firing rates in *any* situation (familiar or novel)
- Population level
    - magnitude of neuronal syncrony follows lognormal stats
- Relationship between structural features and firing patterns
    - Ciocchi, Passecker, Malagon-Vina, Mikus, Klausberger Science 2015
    - Larger axonal arbors -> more firing
    - “Rich club” network (or “good enough brain”)
- These observations are not just statistical curiosities
- Reconcile conflicting demands
    - stability
    - robustness
    - plasticity
    - redundancy, resilience
    - degeneracy
    - homeostasis
    - Renart, Song, Way Neuron (2013)
    - Buzsaki, OUP (2019)
- Albert Lee at Janelia Farm
    - 50 m track = many place fields
    - What is the prob that a neuron fires in many different regions?

    - Royer Buzsuak J Neurosci 2010 - Skewed dist
    - Alme Moser PNAS 2014 - same but some neurons firing in all places
- Buzsaki Science (2015)
    - How do downstream 'readers' interpret messages sent by skewed populations?
    - Do post-synaptic neurons evaluate the change in firing of pre-synaptic neurons dep on plasticity? Need to know.
    - One group of synapses are 'generalizers' the others are 'specifiers'
- Prob: measuring synaptic weights in a freely moving animal
    - Don't have good measures of synaptic weight changes
- Weber-Fechner rules also applies to proportional firing to baseline firing rates (Svoboda)
- Slow-firing neuron spikes = saying something important, vice versa for fast-spiking neurons

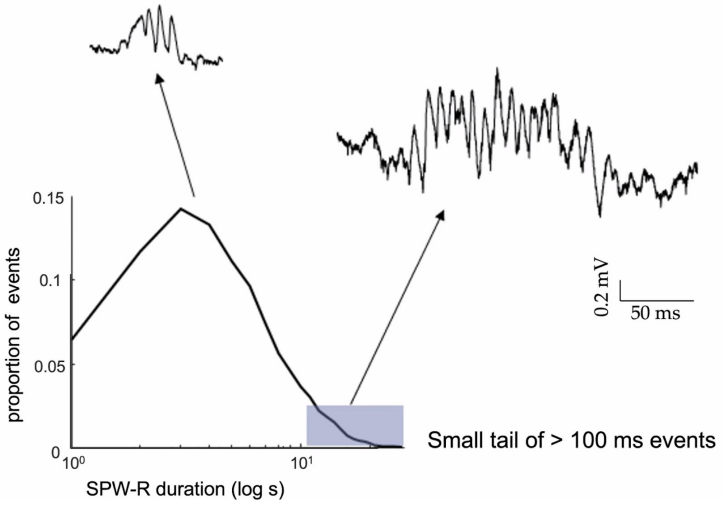
The maintenance problem

- Watson Buzsaki Neuron (2016), Levenstein Buzsaki Curr Op Neurosci (2017)
- Maintenance carried out by non-REM sleep
- Steriade et al J Neurosci (1993) - stable sequences
- Neurons with higher firing rates function as the leaders for up-down state transitions
    - This rule has far-reaching consequences
- Fast and slow neurons are anti-correlated (good news for spike timing dependent plasticity)

Is the maintenance important for learning?

- Grosmark, Buzsaki Science (2016) - Low firing rate neurons are affected by learning
    - These are the plastic neurons (low firing ones)

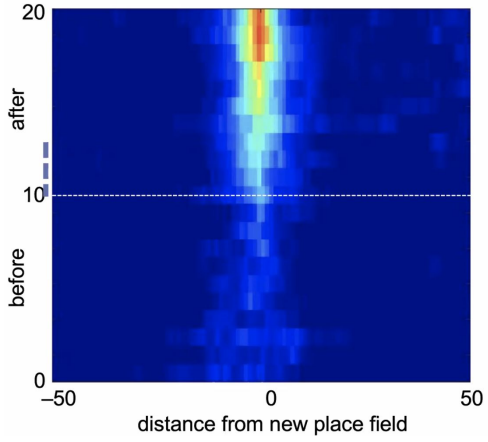
Skewed distributions constraint 'representations'

- half of spikes are emitted by minority of fast firing ('rigid') neurons
- Two tails of the dist correspond to specific vs general and novel vs familiar features
    - Fernandez-Ruis, Oliva, Oliveira, Rocha-Almeida, Tingley, Buzsaki Science (2019)
    - 

    - "Sharp wave 'first cousins' of up-state in the cortex"
    - Ripples are longer in novel environments and memory tasks
    - SPW-Rs longer in familiar vs novel environment
- Prolongation of the sharpwave ripple

- Found improvements in memory on hippocampus-dependent task
- A SPW-R is a trajectory determining a sequence of travel
- Adding more ripples extends the trajectory

How is experience incorporated into brain dynamics?

- Tabula rasa (information-absorbing device) versus brains coming with a preconfigured dynamic and a realm of possible neuronal sequences
- Brain is not just an information-absorbing device
- Alan Turing: "Presumably the child brain is something like a notebook as one buys it from the stationer's" - an endorsement of Tabula rasa
- Magee, Grienberger ARN (2020) - support for the Tabula rasa idea
  - "Give me a neuron and I can make it a place cell anywhere"
- Drogoi Harris Buzsáki Neuron (2003)
  - Place field plasticity is constrained
  - Hypothesis: alteration of syn connectivity modifies firing relationship among neurons and their behavioral correlations
  - Similar rational in: Rich Lee Science (2014), Bittner Magee Nat Neurosci (2015)
  - We found that neurons with strong place cells didn't change, but neurons with bad place fields could change
- Luczak, Bartho, Harris Neuron (2009) - induced patters are selected from a preexisting rich repertoire of internally organized dynamics
  - Dragoi Tonegawa Nature (2009), Stark Buzsaki PNAS (2015), Grosmark Buzsaki Science (2016), Liu Dragoi Hippocampus (2019)
- Stark Rous Eiler Buzsaki PNAS (2015)
  - Neurons which participated with high prob in ripples were most susceptible to recruitment
- McKenzie, Huszár, English, Kim, Yoon, Buzsáki, Neuron (2021)
  - Optogenetically induced place fields are 'unmasked' from preconfigured dynamic
  - Large gain in excitation in the E/I ratio
  - 

  - Do these neurons fire together during sleep? Do they fire with manipulated neurons?
    - Neurons willing to change (part of place field) were already part of cell assembly

    - Monosynaptic P-I transmission prob is rearranged after optogenetic remapping of place fields

Reject the blank slate!

- brains come with preconfigured connectivity and dynamics
    - Karmos, Martin, Czopf (1979)
    - Chomsky (1980)
    - Edelman (1987)
    - Kenet, Buzsaki (2006; 2019)
    - Dragoi Tonegawa (2013)
    - Sadtler Batista (2014)
    - Golub Yu (2018)
    - Farooq Dragoi (2019)
- Brains are preconfigured spaghetti
    - “Neurons that wire together will fire together”
- Learning is matching process
- Meaning is acquired by adding utility to preexisting patterns by experience

Do you agree-support brain enhancement via biohacking techniques? What is your belief on brain enhancement?

See The Brain from

## Questions:

1) Is György familiar with Robert Rosen’s work and if so, could he share some remarks?
2) What does György think about BigData and the Neural Network hype?
   A: Always better than small data - lots of q’s in the field could be answered with more data. Serious issue. Used to have many open q’s because of lack of neurons. visit homepage - sharing >1000 datasets with everyone.
3) What would be the postsynaptic readout mechanism to normalize synaptic inputs (to distinguish changes from high-firing vs. low-firing presynaptic cells)?
   A: I’d love to know that! Good exp for Matthew. Does a neuron know if the spikes came from neighboring neuron or far away? Could do maybe. Nearby = cell body. Don’t know what normalization is for a synapse.
4) What is the mechanism of learning during SPW-Rs?
   A: There is no learning during SPW-Rs that happens in the awake animal. SPW-Rs are replay events. Replayed 2000X / night.
5) What do you think about spontaneous activity ?
   A: Spont act is the most important thing the brain does! Maintains its own dynamic. HPC SWR deprivation = seizures!
6) Is there evidence of plasticity in fast-firing neurons in ‘more general’ learning, ie. not just a new instance of a familiar context (new maze)

A: Correction: firing is a fingerprint that correlates with many other things. Used as a generalizer everywhere.

7) Perhaps I missed it: Was there evidence of the fast-firing/rich club neurons corresponding to the 'generalizers' e.g. in the novel room case, or is that a speculation?
   A: Not speculation. Rich club members are fast firing, longer axons, fast firing awake = fast firing in the night.
8) In Fernandez-Ruiz et a. 2019, optogenetic stimulation prolonged SPWRs and improved memory. Improvement seems to occur on day 1 already. Is stimulation on day 1 sufficient for improvement?
   A: Assume so. Haven't done exp. Animal in novel environment, Sharp waves longer.
9) Do you think that awake and sleep SW-ripples are under a different generation mechanism?
   A: Much discussed in the field. David Foster: waking ripples everything reversed. But then found same thing in waking. Seems to be a pattern visiting the possibilities. Can be biased. More reversed replays needs bigger reward (Foster). Behrens in humans: things being replayed don't correspond to physical presentation sequence but rather the prioritization.
10) (Nina Soto) if novel environments and experiences prolong the duration of the ripple, would a 'dry period' during which no new experiences are obtained affect the formation of new trajectories (i.e. SWR of new experiences in that animal will still be shorter in comparison to an animal which constantly learns new things)?
    A: If we shorten SW-R memory suffers.
    Q: What if we just stop animal learning new things?
    A: Assume because of homeostasis that long will become shorter.
11) If place fields are not created but selected from predefined options, is it also possible to do the reverse test, to fail to create a place field with a specific subset of cells? Or are all options still possible in every ensemble and we would never find such failing ensembles? If so, how would the consequences of this framework (all options are still possible) differ from a blank slate?
    A:
12) Can optogenetic manipulation on specific neurons during SWR change the animal decision(it could be a wrong or correct choice)?
    A: Trying to do this. Answer so far - we failed. Potential reason: HC trying to explore possibilities. Need to record from more neurons.
    JS: Maybe this paper did something similar: https://doi.org/10.1016/j.neuron.2020.01.021
13) Is the repertoire of "spontaneous" sequences built-in genetically? Are the underlying structures fixed during development and unchanged for life?
    A: Good question: HC-theta is controlled by a few genes. T channels attract spindles. What about a newborn mouse with externally generated rhythms? Don't know.
14) Does it irk/bother you when neuroscientists plot oscillation frequency in linear coordinates i.e. in a periodogram?
    A: Have a preference but it doesn't really matter, it's just a transformation. Most important thing is you know it's skewed. Forget linear statistics, t-test, ANOVA when log rules apply. Or do a log-transform before
15) Does this ripple prolongation rule apply to spindles too?
    A: Don't know. Some exps showing coupling between spindles and ripples helps memory.

16) Which do you think is more energy consuming? Changing preconfigured connections or making new connections?
    A: Non-existing connections don't cost anything.
17) Those data suggest that less pruning during development leads to higher chances of learning/"highlighting" new information. I would love a comment on this.
    A: Less pruning occurs in a tissue culture! Not necessarily good.