Neuroscience 201A Reading

Module 3 – Integration

Books/Book Chapters:

Required (PDF): Appendix to *The Synaptic Organization of the Brain* 3rd ed. "Dendritic electrotonus and synaptic integration". Shepherd and Kock.

Review Articles and relevant primary literature:

Dendritic integration:

Reviews:

Required: Silver, R.A. (2010). Neuronal arithmetic. Nature reviews Neuroscience 11, 474-489.

Golding, N.L., and Oertel, D. (2012). Synaptic integration in dendrites: exceptional need for speed. The Journal of physiology 590, 5563-5569.

Yuste, R. (2013). Electrical compartmentalization in dendritic spines. Annual review of neuroscience 36, 429-449.

Tsay, D., and Yuste, R. (2004). On the electrical function of dendritic spines. Trends in neurosciences 27, 77-83.

Papers on dendritic sub- and supralinear integration:

Branco, T., Clark, B.A., and Hausser, M. (2010). Dendritic discrimination of temporal input sequences in cortical neurons. Science 329, 1671-1675.

Smith, S.L., Smith, I.T., Branco, T., and Hausser, M. (2013). Dendritic spikes enhance stimulus selectivity in cortical neurons in vivo. Nature 503, 115-120.

Xu, N.L., Harnett, M.T., Williams, S.R., Huber, D., O'Connor, D.H., Svoboda, K., and Magee, J.C. (2012). Nonlinear dendritic integration of sensory and motor input during an active sensing task. Nature 492, 247-251.

Losonczy, A., Makara, J.K., and Magee, J.C. (2008). Compartmentalized dendritic plasticity and input feature storage in neurons. Nature 452, 436-441.

Abrahamsson, T., Cathala, L., Matsui, K., Shigemoto, R., and Digregorio, D.A. (2012). Thin dendrites of cerebellar interneurons confer sublinear synaptic integration and a gradient of short-term plasticity. Neuron 73, 1159-1172.

Tran-Van-Minh, A., Abrahamsson, T., Cathala, L., and DiGregorio, D.A. (2016). Differential Dendritic Integration of Synaptic Potentials and Calcium in Cerebellar Interneurons. Neuron 91, 837-850.

Papers on the compartmentalization of EPSPs in spines:

Harnett, M.T., Makara, J.K., Spruston, N., Kath, W.L., and Magee, J.C. (2012). Synaptic amplification by dendritic spines enhances input cooperativity. Nature 491, 599-602.

In apparent opposition to:

Tonnesen, J., Katona, G., Rozsa, B., and Nagerl, U.V. (2014). Spine neck plasticity regulates compartmentalization of synapses. Nature neuroscience 17, 678-685.

Popovic, M.A., Carnevale, N., Rozsa, B., and Zecevic, D. (2015). Electrical behaviour of dendritic spines as revealed by voltage imaging. Nature communications 6, 8436.

Acker, C.D., Hoyos, E., and Loew, L.M. (2016). EPSPs Measured in Proximal Dendritic Spines of Cortical Pyramidal Neurons. eNeuro 3.

Axonal integration (papers on spike initiation, AIS plasticity, and analog/digital interplay at boutons):

Reviews:

Kole, M.H., and Stuart, G.J. (2012). Signal processing in the axon initial segment. Neuron 73, 235-247.

Bender, K.J., and Trussell, L.O. (2012). The physiology of the axon initial segment. Annual review of neuroscience 35, 249-265.

Grubb, M.S., Shu, Y., Kuba, H., Rasband, M.N., Wimmer, V.C., and Bender, K.J. (2011). Short- and long-term plasticity at the axon initial segment. The Journal of neuroscience 31, 16049-16055.

Relevant papers:

Shu, Y., Hasenstaub, A., Duque, A., Yu, Y., and McCormick, D.A. (2006). Modulation of intracortical synaptic potentials by presynaptic somatic membrane potential. Nature 441, 761-765.

Hu, W., Tian, C., Li, T., Yang, M., Hou, H., and Shu, Y. (2009). Distinct contributions of Na(v)1.6 and Na(v)1.2 in action potential initiation and backpropagation. Nature neuroscience 12, 996-1002.

Kole, M.H., Letzkus, J.J., and Stuart, G.J. (2007). Axon initial segment Kv1 channels control axonal action potential waveform and synaptic efficacy. Neuron 55, 633-647.

Christie, J.M., and Jahr, C.E. (2008). Dendritic NMDA receptors activate axonal calcium channels. Neuron 60, 298-307.

Kuba, H., Oichi, Y., and Ohmori, H. (2010). Presynaptic activity regulates Na(+) channel distribution at the axon initial segment. Nature 465, 1075-1078.

Grubb, M.S., and Burrone, J. (2010). Activity-dependent relocation of the axon initial segment fine-tunes neuronal excitability. Nature 465, 1070-1074.

Assigned Paper for Discussion:

Poleg-Polsky, A., and Diamond, J.S. (2016). NMDA Receptors Multiplicatively Scale Visual Signals and Enhance Directional Motion Discrimination in Retinal Ganglion Cells. Neuron 89, 1277-1290.

Study Questions for Discussion (led by Ken Burke):

Please take the time to think about all of these questions before class. I ask you to have a fully written and fleshed-out answer to questions 5, 8, 9 and 12; the rest we can discuss together.

1. What cellular computation is being investigated here, precisely? What types of variables would complicate the cell's ability to perform this computation? And how might "synaptic amplification" alleviate some of these complications?

2. Study supplementary figure S1C, and read the first paragraph under "Data Analysis" in the Supplementary Experimental Procedures. The average "DSI" (direction selectivity index) is greater when measured based on action potential firing than when measured using subthreshold postsynaptic potentials. What does this mean, in terms of what "strategy" the cell uses to compute direction selectivity? Would you expect this strategy to be common or rare in the brain for neurons with tuning curves?

3. The authors report that "Consistent with previous reports, inhibitory inputs to DSGCs, recorded under whole-cell voltage clamp, were larger in response to ND stimulation (Figures S1D–S1G)". We can clearly see in Fig S1G that this is true on average. How might this contribute to the direction-selectivity computation?
    a. Fig S1D shows an example of inhibitory and excitatory currents in response to a preferred-direction stimulus (PD), and S1E shows the same for the opposite direction (ND). Other than labelling the traces "IPSC" and "EPSC", how might you know that the upward-deflecting trace is an inhibitory current, and the downward is excitatory? (Hint: look at the holding voltage for the traces)

4. The authors argue that NMDA receptors amplify light-induced potentials in a "multiplicative", rather than "additive", manner. Figure 1D shows an example cell that displays remarkable multiplicative enhancement. How might that figure look differently if the NMDA amplification was ***additive*** instead?

5. The authors suggest that multiplicative enhancement of inputs is actually critical for maintaining direction-selectivity. Find out how they calculate the Direction-Selectivity Index (DSI) and calculate for yourself what the expected DSI should be with:
    i. a multiplicative scaling of inputs by a factor *k*
    ii. an additive scaling of inputs by a factor *x*

What does the difference or similarity between these results and the original DSI formula tell you about the implication of the two different mechanisms for direction selectivity?

6. A numerical simulation of a DSGC developed by the authors shows similar multiplicative amplification of tuning by NMDA receptors. Interestingly, this effect seemed dependent on which type of input was tuned from the beginning; NMDA was multiplicative if inhibition was tuned, but if excitatory inputs were tuned instead, NMDA conductances were additive. With this in mind, what was the rationale behind experimentally testing the effect of increasing intracellular chloride concentration? Which simulation prediction was this experiment trying to test?

7. The authors demonstrate that by removing extracellular magnesium, the NMDA conductances become additive amplifiers because they behave as "Ohmic excitatory synaptic conductances". What exactly do they mean by this term?

8. Their simplified biophysical model that explains why tuned inhibition coupled with voltage-dependent excitatory channels can provide multiplicative amplification, and how most other configurations lead to additive or "sub-additive" amplification instead. Let's walk through it, step by step.
    i. First, they ask you to consider an "ideal" current source. What's the difference between that and a passive leak channel?
    ii. If one assumes that inhibition is tuned to the null direction and is "only shunting", one can prove that an ideal current source will enhance responses in a purely multiplicative sense, without changing DSI (see Fig S8A i-iv). What law demonstrates this, and how?
    iii. Figure S8B and S8C show how "nonideal" channels differ from ideal current sources. Initially, when an ideal current source is replaced by an AMPA conductance, the amplification is nearly multiplicative for small AMPA conductances (see S8Biii). However, as the AMPA conductance and PSP amplitudes get larger the amplification tapers off, approximates additive amplification and direction selectivity suffers. This is less true when NMDA conductances are introduced, where there is a much larger range of conductances and PSP amplitudes that are amplified multiplicatively (though this condition will taper off and degrade direction selectivity as well). What is different about these cases compared to the "ideal current source"? Why does NMDA help "preserve" multiplicative amplification, compared to AMPA's alone?
    iv. Overall, do you think this model is too simplistic, or reasonably complex, with respect to the data it is trying to explain? Do you find it convincing?

9. Spend a little time reading the introduction to the Wikipedia page on Receiver Operating Characteristic (ROC) curves. It's a quantification that is critical to their argument that NMDA conductance enhances true detection of motion in noisy visual environments. Do you think the results in Fig 7C agree with this conclusion?

10. In Figure 8 they decide to test the three conditions (control, 0 Mg++ and AP5) in an intact, spiking cell in order to relate the subthreshold motion detection capabilities to the spiking output. They note that the Direction Selectivity Index (this time measured using spikes and not subthreshold voltage) is ***not*** affected by blocking NMDA receptors (Fig 8E, control blue vs AP5 black). However, the rate of "failures" to detect the preferred direction increases substantially in the NMDA block condition (Fig 8F).

    i. Does it make sense to you that blocking NMDA receptors wouldn't affect DSI? Why?
    ii. How could the rate of failures increase if the DSI is (relatively) unaffected? Feel free to make either mathematical or intuitive arguments

11. The killer experiment that justifies all of this work (at least in my view) is the end of Fig 8 (8G-J). What do these subfigures show on their own? What about in the context of the rest of the paper? Do you find it compelling?

12. Finally, do you think the title of the paper (*NMDA Receptors Multiplicatively Scale Visual Signals and Enhance Directional Motion Discrimination in Retinal Ganglion Cells*) is a fair title? What does it mean to you, having read the paper so carefully now? Does the project seem fleshed-out enough to be published in Neuron? Would you have asked for any specific experiment to enhance the novelty or impact of the paper? Did the paper have to undergo revisions, and how much time elapsed between submission and publication?