Neuronal Integration:

• Cable theory
• Passive integration in dendrites
• Orthodromic and antidromic (bAP) spike propagation
• “Active” properties of dendrites
  – Intrinsic & synaptic mechanisms
• Synapse localization, EPSPs vs IPSPs
• Axonal integration
  – Analog vs. Digital components of AP-evoked release
  – Determinants of AP initiation
Passive spread of voltage along a leaky cable

\[ V = \frac{r_m}{r_i} \cdot \frac{d^2V}{dx^2} \]

\[ \lambda^2 \left( \frac{d^2V}{dx^2} \right) - V = 0; \quad \lambda = \sqrt{\frac{r_m}{r_i}} \]

\[ \lambda = \sqrt{\frac{r_m}{r_i}} = \sqrt{\frac{R_m}{R_i}} \cdot \frac{d}{4} \]
\[ \lambda \propto d, r_m \]

Tight cable = Long space const.

Note: we're currently ignoring membrane capacitance
Let’s stop ignoring capacitance:

\[ \tau = r_m C_m \]

Membranes take time to charge.

Distal synaptic inputs appear slower at the soma.
EPSPs are spatiotemporally filtered
Real life example: cerebellar stellate interneurons

Is this a pre- or postsynaptic effect?

PPR changing with distance?

Abrahamsson et al., 2012
PMID: 22445343
If they uncage, they see the same PPR differences

Abrahamsson et al., 2012
PMID: 22445343
Neuronal “exploitations” of passive cable properties
Exploit #1: encoding broadband auditory chirps
Octopus cells need to be extremely fast integrators. Therefore, very low time constant. Mechanism?
Octopus cells need to be extremely fast integrators. Therefore, *very low* time constant. Mechanism?

Golding and Oertel 2012
There is a synaptic component to coincidence detection, too. 

*Synaptic currents are unusually brief in auditory brainstem*.

In part due to channel properties (AMPA subunit GluR4\_flop desensitize quickly). What other mechanisms could speed PSPs in auditory brainstem?
Exploit #2: Interaural timing difference coding
(nucleus laminaris in birds, medial superior olive in mammals)

ITD: Interaural timing difference
IID: Interaural intensity difference

Knudsen 2002
Auditory coincidence detection is done by convergence of binaural signals onto bipolar neurons
ITD detection in chick nucleus laminaris (NL)

Interaural time difference (ITD)

Axonal conduction delay

Jeffress model for ITD coincidence detection (1948)
Evidence for axonal delay lines in owl.

Carr & Konishi 1990
Accurate coincidence detection in post-hatch chick (40°C)

Kuba et al., 2003
Properties of bipolar coincidence detector cells

[B] MSO principal cell

ipsilateral VCN

40µm

contralateral VCN

Sub-optimal ITD  Best ITD

Ipsi Contra

Sum

MSO cell

10 mV 20 ms

1 mV 0.5 ms

τ = 0.37 ms
Why are the dendrites so short in neurons that encode high frequencies?

Small, slow EPSPs

Large, fast EPSPs
It’s not just dendrites. Position of spike initiation zone in axon also contributes to proper ITD processing.

Kuba, Ishii & Ohmori, 2006
Exploit #3? Sublinear integration of neighboring inputs in cerebellar stellates.

NB: $r_{\text{input}} = 1 \text{ G}\Omega$!
Passive properties make voltage clamp difficult in dendritic cells
Active properties make voltage clamp a nightmare

Voltage clamp is really good for local currents

Williams & Wozny 2008
Practical consideration for interpreting somatic voltage-clamp data

Voltage clamp is really bad for distal currents

b

Current clamp

Dendrite (500 μm)

Voltage clamp

\[ V_{\text{site}} \]

\[ V_{\text{escape}} \]

\[ I_{\text{dclamp}} \]

\[ I_{\text{vclamp}} \]

[c]

Fast dEPSC

Percentage

\[ V_{\text{escape}} \]

\[ I_{\text{recovered}} \]

Distance (μm)

Soma

0

200

400

600

100

80

60

40

20

0

e

Current step

Percentage

\[ V_{\text{escape}} \]

\[ I_{\text{recovered}} \]

Distance (μm)

Soma

0

200

400

600

100

80

60

40

20

0

Williams & Wozny 2008
Branch points affect voltage propagation through trees

this holds true for voltage propagation from soma → out

common

most common

WTF?

what about voltage → soma?
AP propagation down axon is generally reliable

Khaliq and Raman, 2005
Dendritic backpropagation is quite variable

Vetter, Roth, Hausser, 2005
Now on to active properties:
Recruitment/inactivation of channels and receptors

NDMAR: Jahr and Stevens, 1990
**Ca\(^2+\)** channel types respond differentially to depolarization

Antagonist:
- Nifedipine, nimodipine
- \(\omega\)-agatoxin
- Conotoxin-MVIIC
- SNX-482
- TTA, mibefradil

**Ca\(_V\)3.2** (T-type)

- Graphs showing current-voltage relationships for different test potentials.
  - **A**: Ca\(_V\)1.3
  - **B**: Ca\(_V\)1.2
  - **C**: Test potential vs. normalized current (I/Imax) graph.
Dendritic spike trigger zones in cortical pyramidal cells

Tuft PSP alone

bAP alone

Pair the two

Big tuft PSP is enough
(and at times, a bAP burst)

Larkum Sakmann, 1999
Active properties of dendritic branches

Branco Hausser 2010
Why is “in” better than “out”?

Branco Hausser 2010
Mechanism here: boosting by NMDAR activation

what other mechanisms could support dendritic supralinearities?
Integration in axons—

Postsynaptic EPSP amp can increase if presynaptic soma is depolarized. Why?

Shu, Hasenstaub, McCormick 2006
Potential mechanism #1: subthreshold depolarizations propagate down axon (aka, analog axonal signaling)

Shu, Hasenstaub, McCormick 2006
What’s that depolarization doing in the axon?

1st IPSP amplitude increases, PPR decreases.
Depolarizations activate VGCCs in boutons?

Note that this is in 1 GOhm stellate cells.
What would you expect in leakier cells?
What about cells with much longer axons?

Christie Jahr 2011
What else can depolarization do?
What about activation states of spike-associated channels?

\[ \text{DTX-I applied to soma or AIS} \]
What else can depolarization do?
Affects spike shape by inactivating AIS Kv1 channels

Kole Stuart 2007
AP is very wide at AIS, so that might affect release. It does, but very modestly. Why?
Spike initiation zone has 2 $\text{Na}_\text{V}$ isoforms — $\text{Na}_\text{V}1.2$ proximal, 1.6 distal

Hu Shu 2009
Na\textsubscript{V} activation kinetics differ by location — What does this mean for spike initiation?

Hu Shu 2009
Remove prox 1.2’s, no backpropagation

**a**
With proximal AIS Na\(_\text{v}\)1.2

**b**
Without proximal AIS Na\(_\text{v}\)1.2

**Action potentials**

**Soma**

-73 mV

**Axon**


<table>
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<tr>
<th>50 mV</th>
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<td>10 ms</td>
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| 1 nA |

Hu Shu 2009
Modulatory mechanisms that alter integration

Too many to list, really. But some are:

— modulation of membrane resistivity near $V_{\text{rest}}$
  • HCN channels
  • K channels

— modulation of channels that contribute to dendritic nonlinearities
  • Ca channels
  • K channels
  • NMDA receptors

— modulation of spike initiation
  • K channel inactivation in AIS
  • Na channel inactivation
  • “supporting” channels in AIS: KCNQ, VGCCs
  • Position and length of AIS relative to soma

— modulation of plasticity (a.k.a., plasticity of plasticity: metaplasticity)