Cerebellar Timing and Classical Conditioning

Computational Models of Neural Systems
Lecture 2.4

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September, 2013
Feedback vs. Feedforward Control

High latency
Residual errors
Subject to oscillations if gain too high

Anticipatory response gives low latency
Better accuracy (lower error)
Sensors tell us the system state
Control requires an internal model
Pavlovian Eyeblink Conditioning
Eyeblink Conditioning in Humans

- Measure cognitive development
- Impaired by mental disorders:
  - Schizophrenia
  - OCD
  - Fetal alcohol syndrome

Eyeblink Conditioning System
from San Diego Instruments
Delay vs. Trace Conditioning

- **Delay conditioning**: CS stays on until US arrives

- **Trace conditioning**: CS comes on and then goes off again. US must be associated with the *memory trace* of the CS.

- Trace conditioning takes about 5x as many trials to learn

- Trace conditioning (but not delay conditioning) is disrupted by lesions of hippocampus or medial prefrontal cortex.
Effect of Inter-Stimulus Interval (ISI)

- ISI must be 100-3000 msec (ideal is 200-500 msec)
- The learned CR (blink) is timed to just precede the UCS (air puff).
- Several hundred trials required for long ISIs
- Long ISIs also generate a broader response
Mixing 200 ms and 700 ms ISI Trials

Two responses

Two responses

Two responses
Eyelid Conditioning Circuitry
Effects of Lesions

- Lesioning the cerebellar cortex disrupts response timing but does not abolish the response entirely.
- Associative learning can still occur, but responses have very short latency (timing is off).

Conclusion: two sites of Pavlovian learning in the cerebellum:
- Interpositus nucleus learns to respond to the CS (mf → nuc)
- Cerebellar cortex fine tunes the temporal response (pf → Pk)
Theories of Cerebellar Response Timing

a) Delay lines

b) Spectral timing

c) Conjunctions of oscillators

d) Liquid state machines
Medina & Mauk Simulation

600 mossy fibers
10,000 granule cells
900 Golgi cells
60 basket cells
20 Purkinje cells
6 nucleus cells
> 300,000 synapses
More Simulation Details in the J.Neurosci. Paper

Realistic mossy and climbing fiber inputs based on experimental data.
Response Timing in the Model
LTP + LTD

- Granule cells exhibit a variety of broad temporal responses
- LTD alone produces an overly broad CR (right).
- But LTP + LTD together produces a precisely timed response by combining inputs from multiple Purkinje cells to keep the DCN inhibited until just before the US is expected to arrive.
Time Course of Learning and Response Shaping

a) Nuclear cell

b) Simulated Purkinje cell

10
5
2
NAIVE
Early Late

Nucleus Activity [Hz]

10
5
2
NAIVE
Early Late

10
5

Training Day

0 2 4 6 8 10

Purkinje Activity [Hz]

0 20 40 60 80 100

Late in CS
Early in CS

Early LTP + Late LTD
Learning With LTP Disengaged: Response Timing is Poor
Recovery After Partial Lesion to Cerebellar Cortex

**Simulation**

- **a)** Simulation graph showing nucleus activity over time with different post-lesion periods.

**Rabbit**

- **b)** Graph showing eyelid position in a rabbit with different post-lesion periods.
Recovery After Lesioning Cerebellar Cortex

a) Simulation

b) Rabbit

c) Plot showing Purkinje Activity over time with data points labeled 'Early in CS' and 'Late in CS'.

d) Image of a brain with an arrow pointing to a specific area.
Why Do Long ISIs Prevent Learning?
Hypothesis: Too Much LTP Overwhelms LTD
Summary: there could be a set of delay lines built into every Purkinje cell's dendritic tree.
Metabolic Transmission Pathway in Purkinje Cell Dendrites

\[ \text{DAG} = \text{diacylglycerol} \]
\[ G = \text{guanine nucleotide-binding protein} \]
\[ mGluR1 = \text{metab. glutamate receptor} \]
\[ PKC = \text{phospholipase C} \]
\[ PIP_2 = \text{phosphatidylinositol} \]
\[ IP_3 = \text{inositol 1,4,5-triphosphate, a second messenger} \]
\[ IP_3R = \text{IP}_3 \text{ receptor} \]
Basic Story

- Glutamate binds to \textit{mGluR1} receptors, causing second messenger IP$_3$ to bind to IP$_3$R receptor.
- IP$_3$R receptor causes release of calcium from storage in the endoplasmic reticulum (ER).
- Ca$^{2+}$ activates calcium-dependent potassium channels, hyperpolarizing the dendrite.
- When Ca$^{2+}$ concentration gets too high, the IP$_3$R receptor closes again.

![IP$_3$R Open Probability Graph]
Spectral Timing

- Calcium level in the dendrite builds slowly as IP$_3$ accumulates.
- Positive feedback on IP$_3$ production and IP$_3$ R channel opening results in a rapid rise in calcium level.
- But when Ca$^{2+}$ level high enough, IP$_3$ R channels close again.
- The speed at which this happens depends on the number of mGluR1 receptors in the synapse.
- Different concentrations of mGluR1 receptors produce different timing characteristics.
- High calcium level hyperpolarizes the dendrite through calcium-dependent potassium channels and inhibits firing.
Spectral Timing: Calcium Concentration Profiles

Fiala et al. simulation: responses to 50 msec glutamate application produced by varying \( B_{\text{max}} \) parameter.
Learning Performance for the Model

30 trials; ISI = 500 msec
Learning in Purkinje Cell Dendrites
Cerebellar Cortex As a Liquid State Machine

Rich Variety of Granule Cell Activity Patterns
Similarity Index: Granule Cell Activity Patterns Evolve Over Time

Correlation of LSM activity patterns at times $t_1$ and $t_2$.

Slices through the graph at left at $t=200$, $t=500$, and $t=800$ show that similarity changes smoothly.
Cerebellum = Liquid State Machine + Perceptron
Summary

- Two sites of cerebellar learning for eyeblink conditioning:
  - Cells in interpositus nucleus learn to respond to tone CS
  - Purkinje cells in cerebellar cortex learn timing of the response
- Purkinje cells require both LTP and LTD to produce temporally accurate responses.
- Multiple hypotheses about how the cerebellum keeps time: delay lines, spectral timing, oscillators, liquid state machines
- Two hypotheses for why learning fails at long ISIs:
  - Medina et al: long period of LTP overwhelms LTD
  - Medina & Mauk recurrent network (= LSM) model: granule cell activity sequence gradually diverges