Executable Symbolic Modeling of Neural Processes

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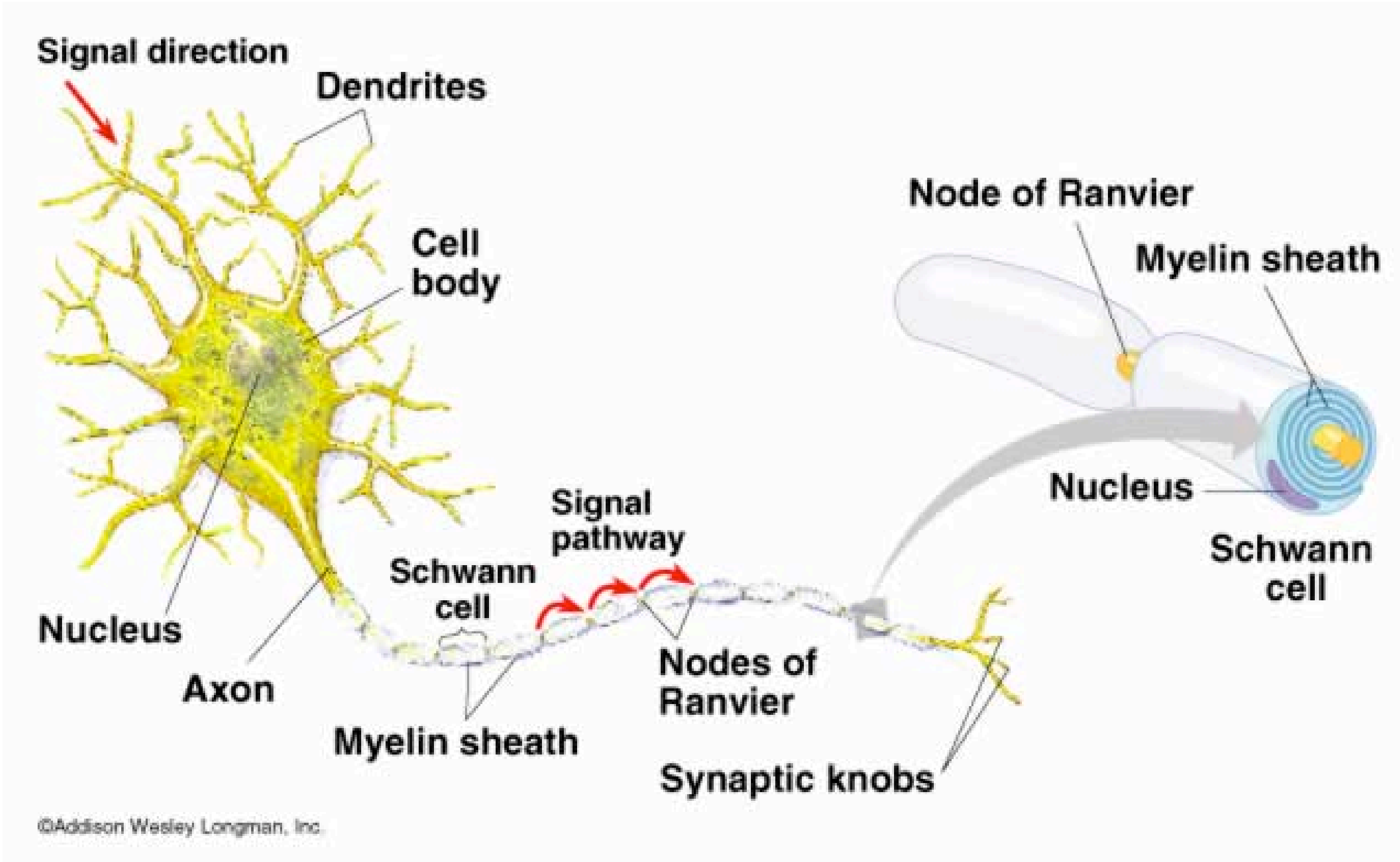
The Neuron

- Neurons are highly specialized eukaryotic cells. Vast numbers of these form intricate connection networks in the human brain--up to 50 million neurons in a cubic centimeter.

- Neurons communicate using electrical and chemical signals
  - Electrical signaling occurs at membrane contact points called *gap junctions*
  - Chemical signals involve the release across synaptic gaps of neurotransmitters: serotonin, dopamine, glutamate ...

- In a resting state, the neuron maintains an electrical polarization of -70mV across its cell membrane.

- An *action potential* (nerve impulse) travels along an axon via a sequence of *depolarizations* (upto +40 mV) and *repolarizations*. Upon reaching the synapse, chemical signaling occurs.


Signal direction
Dendrites
Cell body
Nucleus
Axon
Schwann cell
Signal pathway
Myelin sheath
Nodes of Ranvier
Synaptic knobs
Node of Ranvier
Myelin sheath
Nucleus
Schwann cell
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- In 1952, Hodgkin and Huxley described these *membrane potentials* by a set of simultaneous differential equations based on a study of axons in the neurons of the giant squid

- The Hodgkin-Huxley model expresses complex non-linear dynamics and contains coefficients that must be measured experimentally depending on the type and origin of the neural system being studied. It is not always easy to get accurate measurements of these constants.

- Studying signaling in large numbers of interconnected neurons becomes intractable very quickly

- There is a need for new alternative models at higher levels of abstraction.

Invertebrate Nervous Systems

❖ Due to the relative simplicity of their nervous systems, as well as their limited range of behaviors, invertebrates are especially attractive as subjects of experimental research in neurobiology.

❖ The California sea snail, *Aplysia Californicus,* has proven to be especially useful for the study of learning and memory. One reason is that its neurons are large, with cell bodies up to 1 mm in diameter.

❖ Its behavior can be conditioned in various ways, for example to exhibit biting behavior -- *fictive feeding* --when a stimulus is applied

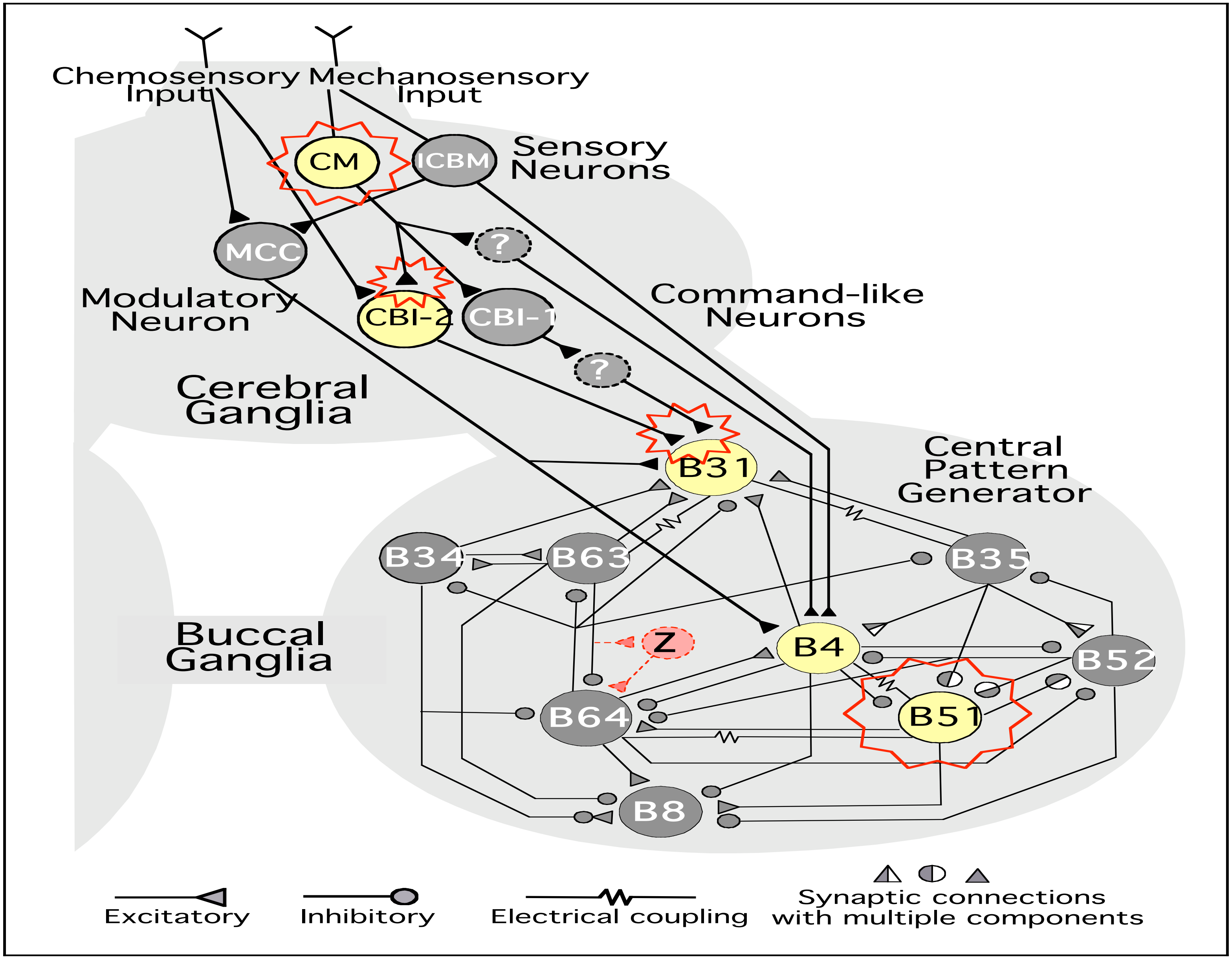
❖ *Neural plasticity* refers to the changes in neural pathways that occur due to conditioning. To study these, neurobiologists need to understand the neural pathways underlying the different behaviors involved in the execution of a cycle such as Stimulus-Response-Outcome.

Aplysia Californicus

❖Even in a simple invertebrate like Aplysia, the feeding circuit can be complex.

❖The mix of neurons, their multiple types of connections and the nonlinearity of electrical signaling results in complex patterns of activity and non-intuitive behaviors.

Selected portions of circuit involved in feeding in Aplysia



Experimental Neurobiological Results

(Example from Susswein, Hurwitz, Thorne, Byrne, Baxter, 2002)

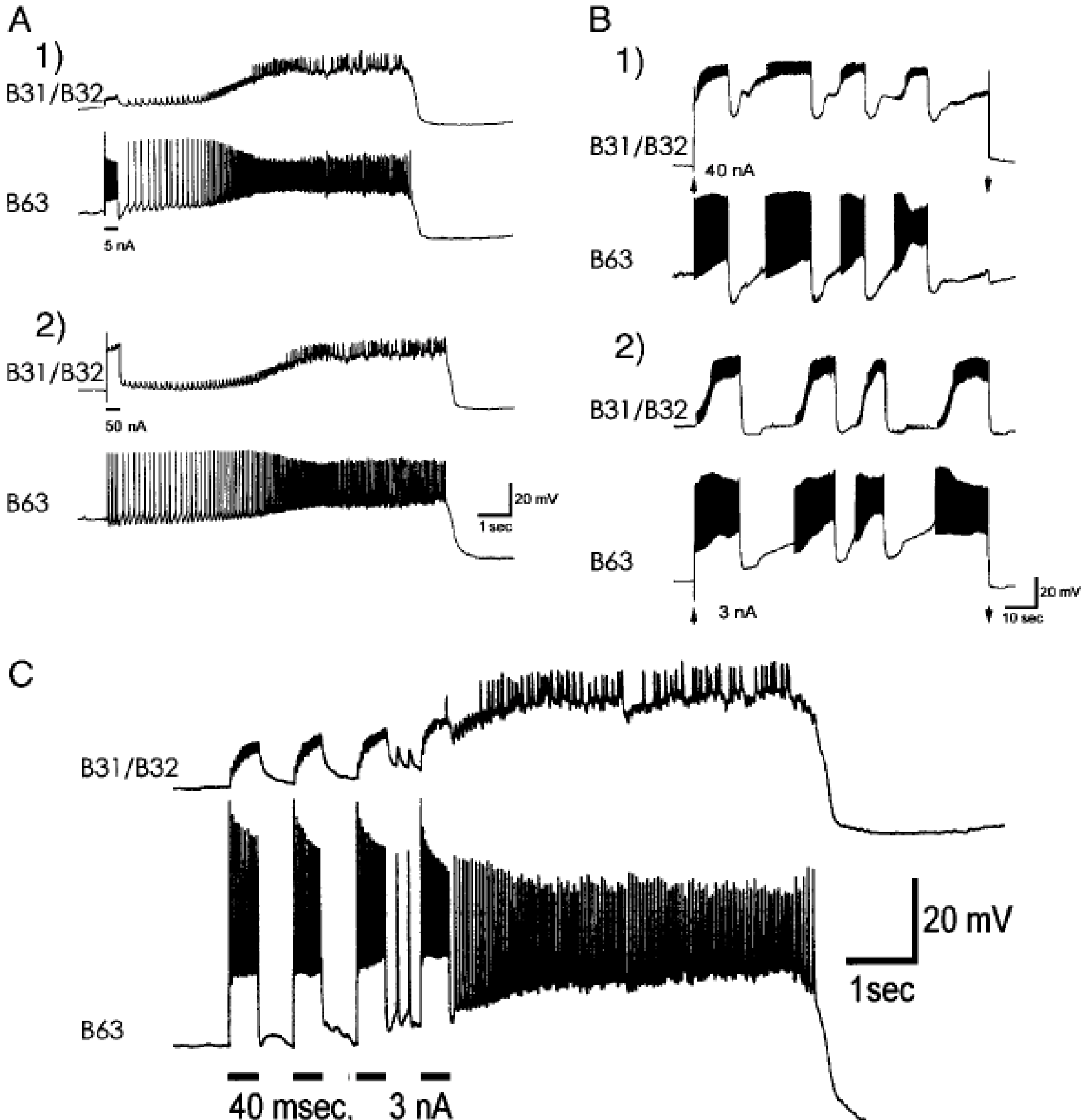


FIG. 2. Recordings from B63 and B31/B32 in the buccal ganglia. *A*: just threshold (400-ms duration) current pulses to both B31/B32 (*1*) and to B63 (*2*) induced similar bursts of activity in both neurons, following a delay. However, the threshold for eliciting a burst was higher for B31/B32 than for B63. *B*: in the buccal ganglia, continuous depolarization of either a B31/B32 neuron (*1*) or a B63 neuron (*2*) induced continuous bursting for as long as the stimulus was maintained. For this figure, the amplitude of the stimulus was adjusted so bursting was maintained at a rate of ~4 per 100 s. Note the difference in the current amplitudes to the two neurons that were needed to elicit this rate. *C*: a series of subthreshold depolarizations to B63 also elicited a burst in the buccal ganglia.

New Modeling Approach: Pathway Logic

- ❖Pathway Logic (PL) is an approach to modeling biological processes based on rewriting logic and its realization in the Maude system.

- ❖Knowledge is represented symbolically in a way that is amenable to *in silico* reasoning: execution, search, checking formal properties.
  - ❖States of a dynamical system are represented as elements of an algebra
  - ❖Transitions between states are specified by local *rewrite rules* that define how one state (element in the algebra) changes into another.

- ❖PL models are modular and scalable
  - ❖Individual neuron types can be modeled and analyzed alone or in the larger systems
  - ❖Models can be developed at multiple levels of abstraction

Elements of a PL model for neuron circuits

- Neurons are modeled as objects (data structures) with an id, a class id, and attributes representing the neuron's parameters and state.
- Neuron attributes include:
  - depolarization levels, decay times, thresholds
  - signaling mode (null/rest, spiking, bursting, plateau)
- Synaptic connections have the form
  [SC|from: transmitterId, to: receiverId, sig: level]
- Electrical connections have the form
  (transmitterId EC receiverId)

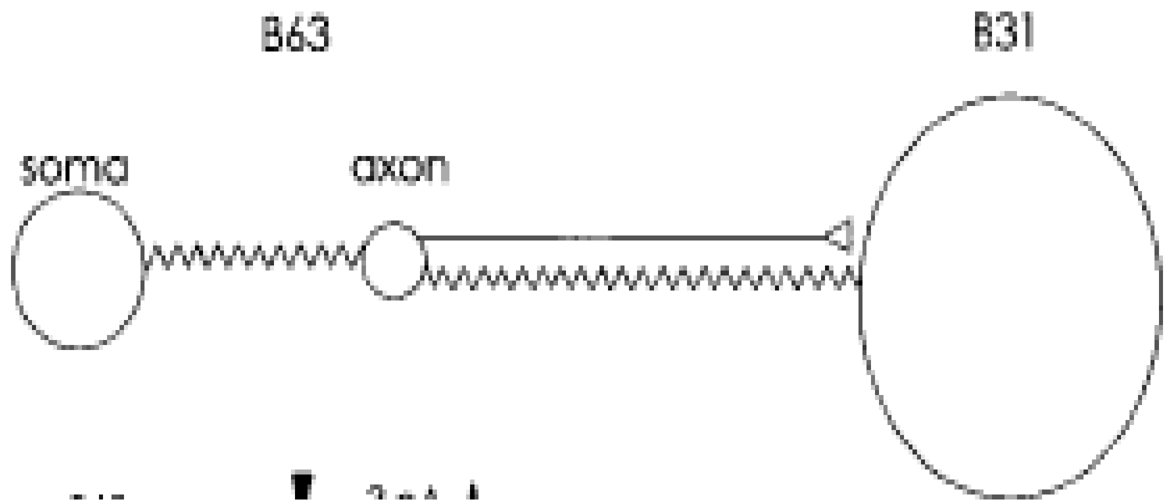
Example Maude Rule for B31 Neurons

```
rl[b31.sig.read.plateau]:
   tick(nid)  [ nid : B31 | thresh: i,  decay: d, dplevel: l, ttl: t,
                                out: plateau, eout: k, in: j ]
 =>
  (if t > 1
   then [ nid : B31/2 | thresh: i,  decay: d,  dplevel: l, ttl: t - 1,
                             out: plateau, eout: eo31(l), in: 0 ]
   else [ nid : B31/2 | thresh: i,  decay: d,  dplevel: 0, ttl: 0,
                             out: null, eout: 0, in: 0 ]
   fi) .
```

This rule models an observed behavior where, in plateau mode (out: plateau), a B31 neuron ignores signal input (presence of tick(nid)) until the plateau duration time (ttl: t) expires.

Modeling A Neuron Configuration in PL

Baxter *et al* studied this configuration from the feeding circuit of Aplysia with two neurons having one synaptic connection and two electrical ones. Input stimuli are applied to B63



This system is represented in our PL model as a multiset consisting of 2 neurons, a synaptic connection from b63 to b31, an electrical connection between b63 and b31, and an electric probe (called Cmd) connected to b63.

[b31 : B31 | b31-attributes] [b63 : B63 | b63-attributes]
[SC|from: b63, to: b31, sig: 0] (b31 EC b63)
[Cmd : SG | probe-attributes] (Cmd EC b63)

Simulation of a neuron system

- A configuration is initialized by applying a function `tock' which propagates existing signals, then creates a message tick(nid) for each neuron in the system to activate it. Execution proceeds by applying rules for each neuron to respond to its tick message. When all messages have been processed, tock is again applied to the configuration to initiate another round.

- To experiment with the effects of different initial values for the neuron attributes, a readout object is added to the configuration. Each application of the tock function adds a reading to the readout object, recording the signaling mode of each neuron (value of the out: attribute).

In Silico Experiments

- Test configurations are constructed by a function

  ici(t,bt,d,bd,t2,d2,on,off,sig)

  In the resulting configuration b63 has spike threshold t, burst threshold bt, spike duration d, burst duration bd; b31 has plateau threshold t2 and duration d2; and Cmd (a pseudo neuron) has on duration on + 1, off duration off, and signal level sig.

- The function nsim(conf,n) runs the system for up to n rewrites and returns the final readout.

- By varying the values of these different parameters, a variety of behaviors can be obtained. Many correspond to the behaviors experimentally observed by Susswein et al.

Two example in silico experiments

reduce in NEURON-MTEST : nsim(ici(1, 2, 1, 2, 1, 3, 0, 1000, 1), 100) .

result Readings:

```
[b63: "- s b b - - - - - - - - - - - - - - - - - - -"]
[b31: "- p p p - - - - - - - - - - - - - - - - - - -"]
[Cmd: "1 - - - - - - - - - - - - - - - - - - - - - -"]
```

b63 spikes once and bursts twice. b31 has a plateau of duration 3

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reduce in NEURON-MTEST : nsim(ici(1, 2, 1, 2, 3, 2, 0, 1000, 1), 100) .

result Readings:

```
[b63: "- s b b - s b b - s b b - s b b - s b b - s b"]
[b31: "- - - p p - - p p - - p p - - p p - - p p - -"]
[Cmd: "1 - - - - - - - - - - - - - - - - - - - - - -"]
```

Here, the onset of B31 is delayed because it has a higher threshold, feedback keeps the signalling going.

Conclusions and Future Work

- Pathway Logic is capable of representing neurons of various types and neuron configurations containing multiple connections, electrical and synaptic
- Our model is expressive: it can represent a wide range of neuron behaviors such as spikes, bursts, and plateaus as well as effects of feedback.
- Models can be executed/simulated or subjected to logical analysis.
- PL models can also serve as a framework for integrating more detailed computational models of subsystems
- Future work includes
    - refining the representation of signal integration and propagation mechanisms
    - fitting the parameters to experimental conditions
    - modeling additional neuron types
    - making predictions that can be tested experimentally

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