



Executable Symbolic Models Of Neural Processes

Sriram M Iyengar¹, Carolyn Talcott²,
Riccardo Mozzachiodi³, Enrico Cataldo⁴,
Douglas A Baxter³

¹School of Health Information Sciences, University of Texas Health Science Center at Houston,

²Computer Science Laboratory, SRI Intl., Menlo Park, CA,

³Dept. of Neurobiology and Anatomy, University of Texas Health Science Center at Houston

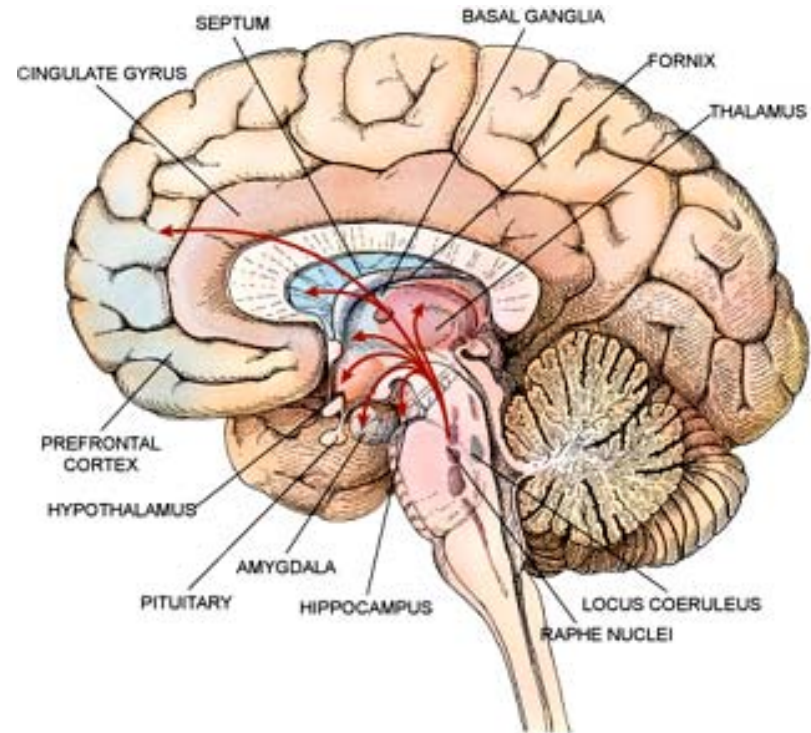
⁴Dept of Biology, General Physiology Unit, University of Pisa

M.Sriram.Iyengar@uth.tmc.edu, ecataldo@biologia.unipi.it, clt@csli.sri.com, Riccardo.Mozzachiodi@uth.tmc.edu,
Douglas.Baxter@uth.tmc.edu

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Modeling in Neuroscience

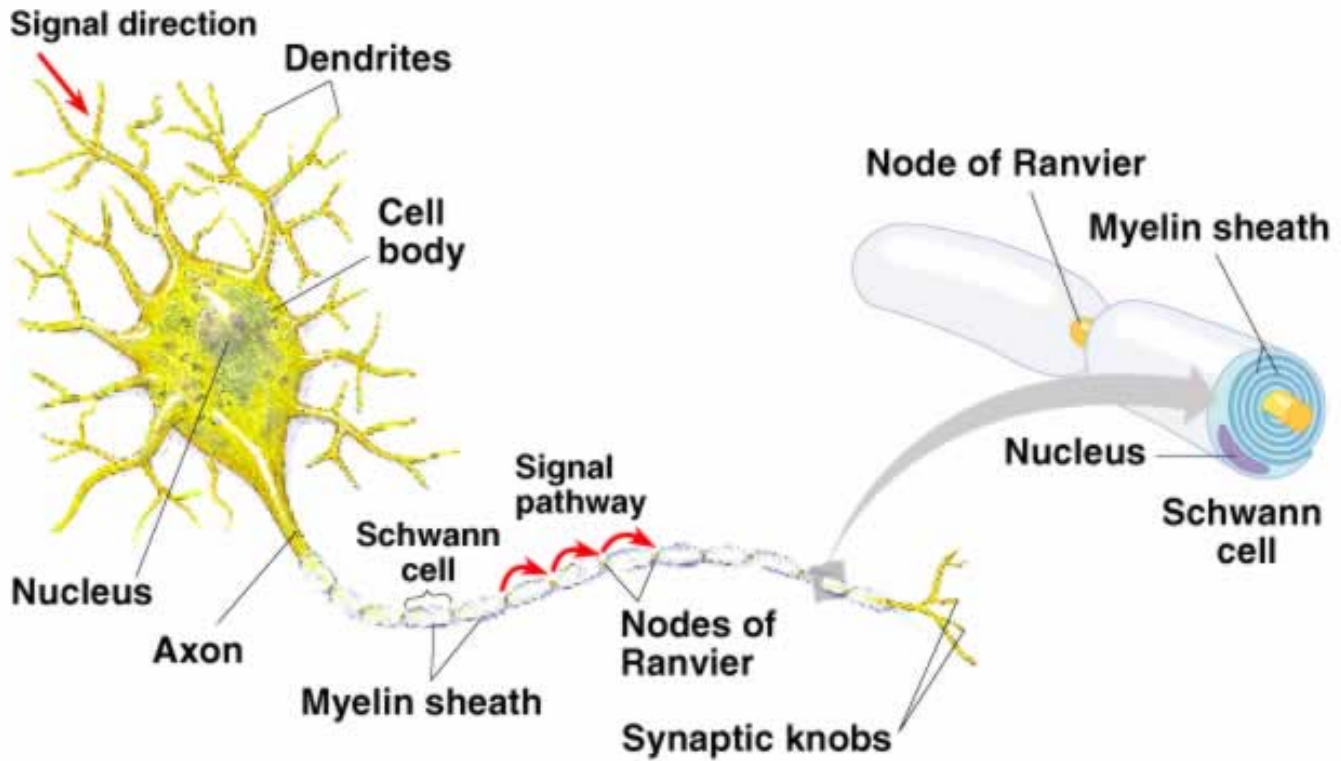
- ❖ Currently, Neuroscience is experiencing explosive growth in the amount of detailed high quality experimental information on neural processes underlying behavior
- ❖ Correspondingly there is enormous interest in models that can help to understand, codify, and unify all this experimental knowledge
- ❖ Highly desirable for models to have predictive capabilities



The Neuron

- ❖ Neurons are highly specialized eukaryotic cells
- ❖ Vast numbers of these form intricate connection networks in the human brain
 - ❖ A cubic centimeter of the human brain can contain up to 50 million neurons
- ❖ They communicate with each other by means of both electrical and chemical signals
- ❖ Electrical signaling occurs through *gap junctions*, in which the membranes of neurons touch at tiny spots
- ❖ Chemical signals involve the release of neurotransmitter chemicals such as acetylcholine, dopamine, glutamate
- ❖ These are released across the synaptic gap from the *pre-synaptic* neuron to the *post-synaptic* neuron

An *action potential* (nerve impulse) travels through the axon up to the nerve terminals and, upon reaching the synapse, it triggers the release of the neurotransmitter



- ❖ While in a resting state, the neuron maintains an electrical polarization of about -70mV across its cell membrane between its interior and the cellular context
- ❖ The movement of an action potential through the cell body and down the axon is accomplished by a sequence of *depolarizations* (up to +40 mV) and *repolarizations*
- ❖ In 1952, Hodgkin and Huxley described the properties of the action potential by a set of simultaneous differential equations based on empirical data on the giant axon of the 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's a need for other models at higher levels of abstraction
 - ❖ Other models (neural networks and integrate-and-fire) also have deficiencies

Invertebrate Nervous Systems

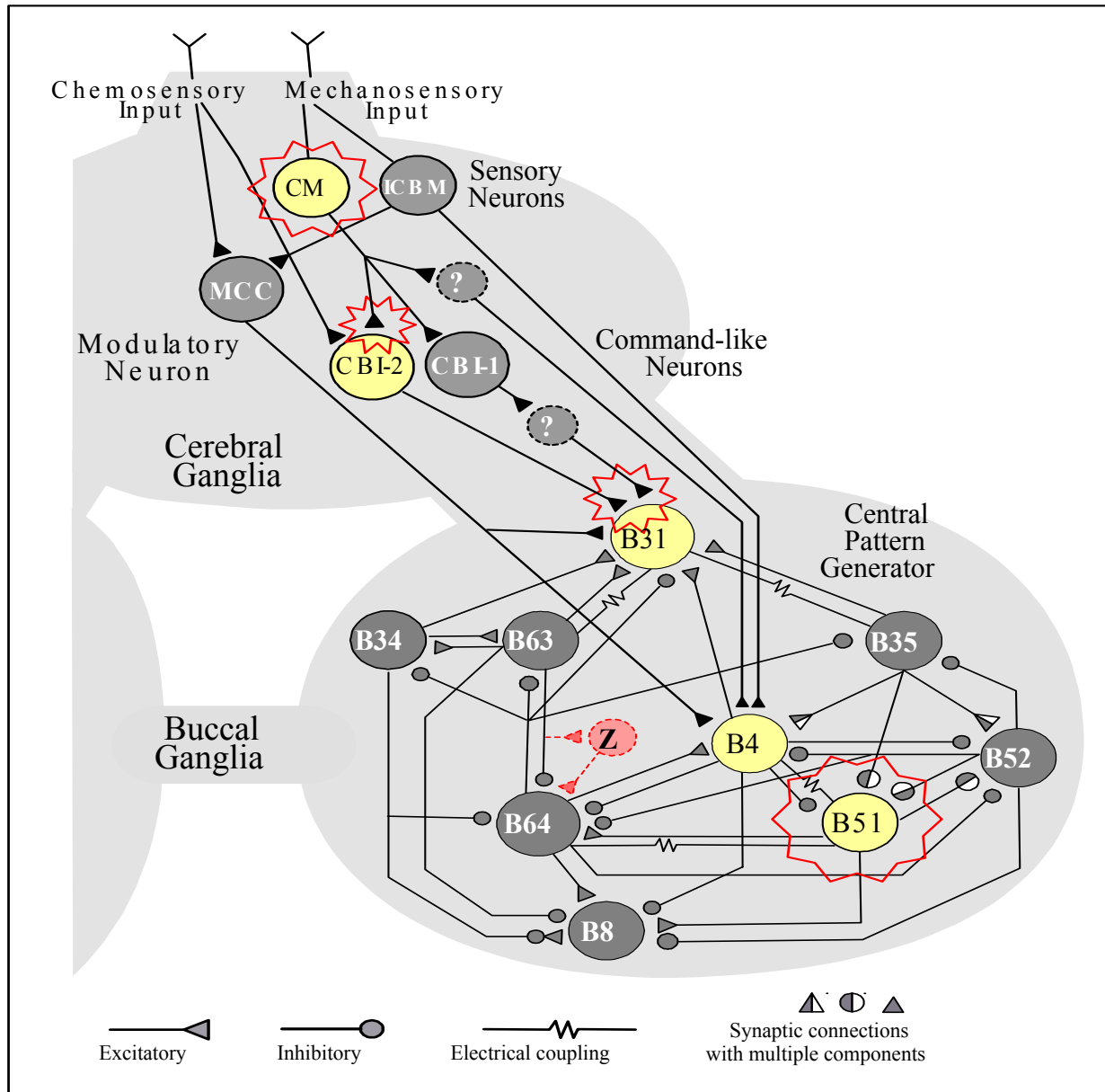
- ❖ Due to the relative simplicity of their nervous systems, as well as their limited range of behaviors, invertebrates are especially attractive as subjects of experimental research in neurobiology
- ❖ The marine snail, *Aplysia Californica*, has proven to be especially useful for the study of learning and memory. One reason is that its neurons are large, with cell bodies up to 1 mm in diameter
- ❖ *Aplysia* exhibits simple behaviors (e.g. defensive reflexes, feeding, mating), which rely on a neural circuitry well characterized and suitable for cellular analyses
- ❖ *Aplysia* behaviors can be conditioned to respond to stimulation in various ways. For example, feeding behavior expresses *instrumental conditioning*, in which the animal is conditioned to exhibit biting behavior 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 Californica



- ❖ 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



New Modeling Methodology: Pathway Logic

- ❖ Pathway Logic is a methodology based on formal logic methods of Computer Science, specifically Rewriting Logic
- ❖ Knowledge is represented at a higher level of abstraction, with biological entities represented as symbols that can be processed by software
- ❖ States of a dynamical system are represented as elements in an algebra
- ❖ Transitions between states are specified by *rewrite rules* that define how one state (element in the algebra) changes into another
- ❖ PL can be viewed as encoding curated knowledge in a way that is amenable to *in silico* reasoning, query, by the creation of executable models
- ❖ Modeling of neural pathways by existing methodologies such as the Hodgkin-Huxley model, neural networks and others have various drawbacks. For example, the H-H models depend for stability on parameters that are frequently unknown
- ❖ PL models are implemented in the language Maude
- ❖ Scalability is a major benefit of this approach

Experimental Neurobiological Results

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

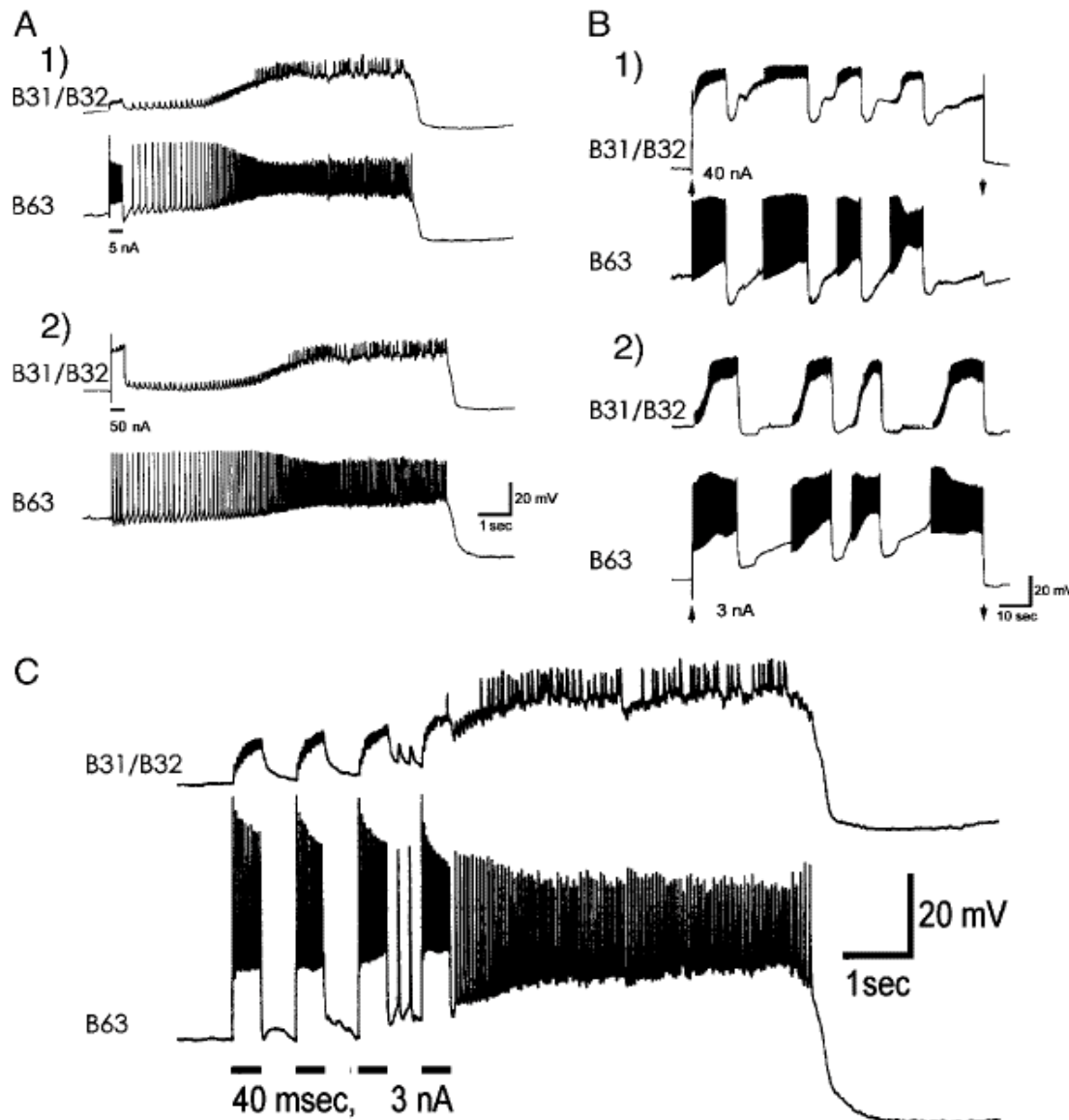


FIG. 2. Recordings from B63 and B31/B32 in the buccal ganglia. *A*: just threshold (400-ms duration) current pulses to both B31/B32 (1) and to B63 (2) induced similar bursts of activity in both neurons, following a delay. However, the threshold for eliciting a burst was higher for B31/B32 than for B63. *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.

Susswein et al, JN 87:2307-23

Elements of PL Model for Neurobiology - 1

- ❖ Model defines the following.
 - ❖ Neurons and types of Neurons
 - ❖ Attributes such as depolarization level, decay times, thresholds
 - ❖ Connections between neurons (ie, neural circuits)
 - ❖ Electrical behavior over time, such as spiking, long bursts, plateaus and so on.
- ❖ Important Sorts (Maude Datatypes) are Neuron, NeuronClass, Msg, Cnx (Connection), Sig (type of axon signal)
- ❖ Model uses Maude operators to specify that neurons can have electrical connections (ECs) and Synaptic Connections (SCs)

`op [SC|from:_,to:_,sig:_] : NeuronId NeuronId Nat -> Cnx [ctor]`

- ❖ Electrical behaviors of a neuron are also represented as ops

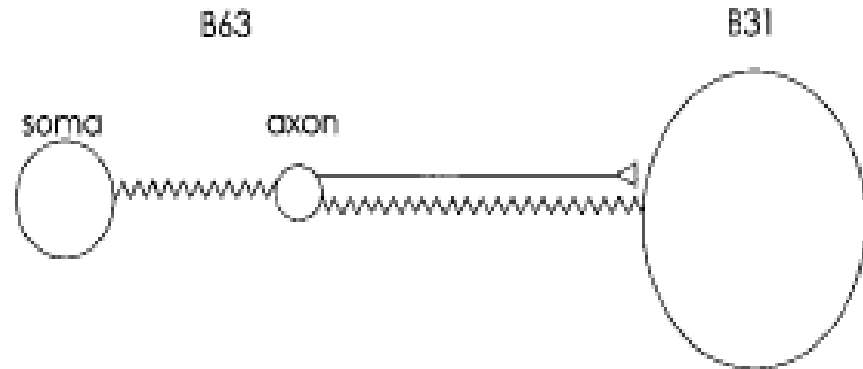
`ops plateau spike burst null : -> Sig .`

Elements of PL Model for Neurobiology - 2

- ❖ Several Maude Sorts and ops enable electrical activity that neurobiologists observe (typically lines and squiggles traced on a paper readout) to be converted into symbolic representations
 - op sig2qid : Sig -> String .
 - eq sig2qid(plateau) = "p" . eq sig2qid(null) = "-" .
- ❖ The 'tick' op causes a neuron to look at its signal input and compute the next state
 - op tick : NeuronId -> Msg .
- ❖ The 'tock' op generates a tick message to all neurons in a configuration
- ❖ Maude rules have been developed that describe how neurons integrate incoming signals and generate output signals. The model runs by alternating two steps:
 1. Process -- each neuron processes its signal input and determines its next state and output
 2. Output is propagated through the electrical and synaptic connections

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 signal propagation via the two kinds of connection is represented in our PL model by means of operators doSC (for synaptic connection) and doEC (for electrical connection). For example, substituting B63 for nid and B31 for nid' the equation below describes transmission of a signal of level I along the synaptic connection from B63 to B31:

```
op doSC : NCCConf NCCConf -> NCCConf .
eq doSC([SC|from: nid, to: nid', sig: I] [nid' : nc | atts, in: j'] nconf,
sconf) =
doSC([nid' : nc | atts, in: max(I,j')] nconf,
sconf [SC|from: nid, to: nid', sig: 0]) .
eq doSC(nconf,sconf) = nconf sconf [owise] .
```

Examples of Rules in the PL Model

- ❖ Maude rules (rl's) are used to express the dynamical behavior of the system, and to express the conditions under which state changes occur. The term in square brackets is a rule descriptor

```
rl[b63.sig.read.spike]:
  tick(nid) [nid : B63 | thresh: i, bthresh: i', decay: d, bdecay: d',
            dplevel: l, ttl: t, out: spike, eout: k, in: j]
=>
  (if j > 0
   then (if l + j < i'
        then [nid : B63 | thresh: i, bthresh: i', decay: d, bdecay: d',
              dplevel: (l + j), ttl: t, out: spike, eout: (max(max(l,j),2) quo 2), in: 0]
        else [nid : B63 | thresh: i, bthresh: i', decay: d, bdecay: d',
              dplevel: i', ttl: d', out: burst, eout: (max(max(l,j),2) quo 2), in: 0]
              fired(nid,i') fi)
   else
    (if t > 1
     then [nid : B63 | thresh: i, bthresh: i', decay: d, bdecay: d',
           dplevel: l, ttl: sd(t,1), out: spike, eout: (max(l,2) quo 2), in: 0]
     else [nid : B63 | thresh: i, bthresh: i', decay: d, bdecay: d',
           dplevel: 0, ttl: 0, out: null, eout: 0, in: 0]
           fi) fi) .
```

Among other things, this rule expresses that if input signal $j > 0$ and $<$ threshold -1 then a spike is emitted. Else B63 outputs a burst.

Results

To simulate the neuron configuration above under various parameters relating to B63 and B31, the Maude reduce (red) command is applied to the Neuron Simulation function, NSim.

Example:

```
red nsim(ici(t,bt,d,bd,t2,d2,on,off,sig),n)
```

causes up to n rewrites of the above configuration of neurons B63 and B31 in which b63 has spike threshold t, burst threshold bt, spike ttl d, burst ttl bd; and a b31 neuron with plateau threshold t2 and ttl d2; and a probe (Cmd pseudo neuron) with on duration on + 1, off duration off, and signal level sig.

By varying the values of these different parameters a rich set of behaviors is obtained. These correspond to the behaviors experimentally observed by *Susswein et al*

Two example results from about 30 obtained by varying parameters

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

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 - - -"]

[b31 : " - - - p p - - - p p - - - p p - - - p p - - -"]

[Cmd : " 1 -----"]

Here, the onset of B31 is delayed because it has a higher threshold

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 seen experimentally and by other simulation methods
- ❖ In contrast to other methods (eg Neural networks) the behaviors observed can be explained by using the Maude Trace facilities.
- ❖ Future work includes adding more neurons to the model, refining the behavior of individual neurons, and making predictions that can be tested experimentally
- ❖ Link between PL formalisms and Semantic Web applications: when the modeling technology matures, we envision that Semantic Web Technology will be useful to develop 'workflow' for test scenario to analyze behavior of proposed neuron circuits under a variety of conditions and parameter settings