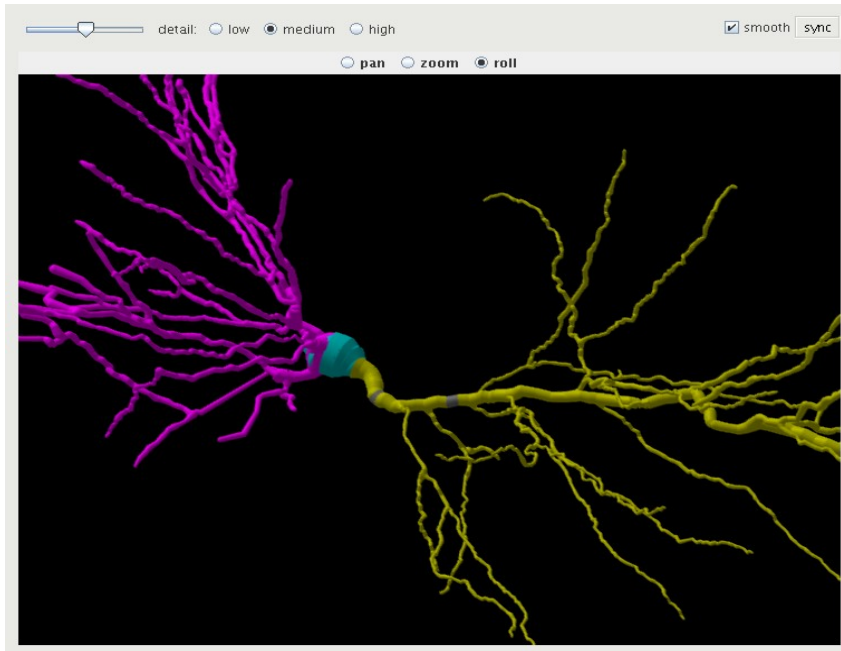
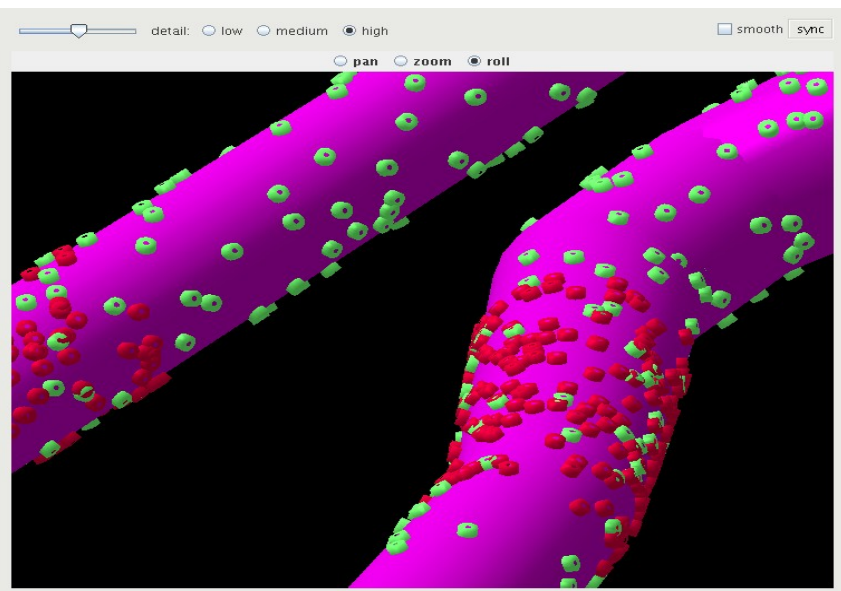


A perspective from Neuroscience



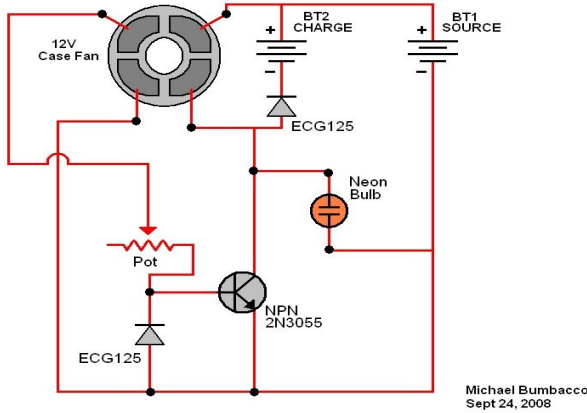
- NeuroML
 - www.neuroml.org (examples)
- NineML
 - www.nineml.org
- ...*PSICS*
 - www.psics.org



Physically extended systems
Tools implement problem-specific
methods
Initial focus on what the tools can
do, not what the model is

- Works OK(ish) for neurons, ion channels, possibly networks.
- Extension to synapse models risks an explosion of component types and unmanageable specifications.
- → shift to a catalog of user-defined types
- But want to keep the simple top-level specification and avoid duplicating the maths

Electrical Circuit



+

**Kirchoff's
Laws**

Shared understanding
Not restated every time



$$\begin{aligned}
 i_1 + i_2 + i_3 &= 0 \\
 i_4 - i_3 + i_5 &= 0 \\
 \text{Etc}
 \end{aligned}$$

Abstracting Kirchoff's laws as shared knowledge allows a mode to be communicated at the diagram level rather than the equation level.

Hodgkin Huxley ion channel model

?

+

?



$$\begin{aligned}
 I_{Na} &= 32 \cdot m^3 \cdot h \cdot i \cdot (v - 55) \\
 m_\infty &= \alpha_m / (\alpha_m + \beta_m); \quad \tau_m = 0.5 / (\alpha_m + \beta_m) \\
 \alpha_m &= 0.4(v + 30) / (1 - \exp(-(v + 30) / 7.2)) \\
 \beta_m &= 0.124(v + 30) / (\exp((v + 50) / 4) + 1) \\
 \tau_h &= 0.5 / (\alpha_h + \beta_h) \\
 \alpha_h &= 0.03(v + 45) / (1 - \exp(-(v + 45) / 10)) \\
 \beta_h &= 0.01(v + 45) / (\exp((v + 58) / 2) + 1) \\
 i_\infty &= (1 + b_i \exp((v + 58) / 2)) / (1 + \exp((v + 58) / 2)) \\
 \tau_i &= 3 \cdot 10^4 \beta_i / (1 + \alpha_i) \\
 \alpha_i &= \exp(0.45(v + 60)) \\
 \beta_i &= \exp(0.09(v + 60))
 \end{aligned}$$

14 *Hopfner et al.*

and simulation rates of order combinations in the distal portion of the dendritic tree (Stressman et al., 1994). In different brain regions, such as the visual cortex (Rockland and Vitek, 1989) and hippocampus (Kobayashi and Arai, 1990), the rates of pyramidal neurons receive direct or indirect feedback projections. The elucidation of the membrane characteristics that could coordinate such local inputs may thus shed light on the operation principles of several brain circuits. In this article, we have shown how the β_{Na} may play a key role in these processes.

Appendix

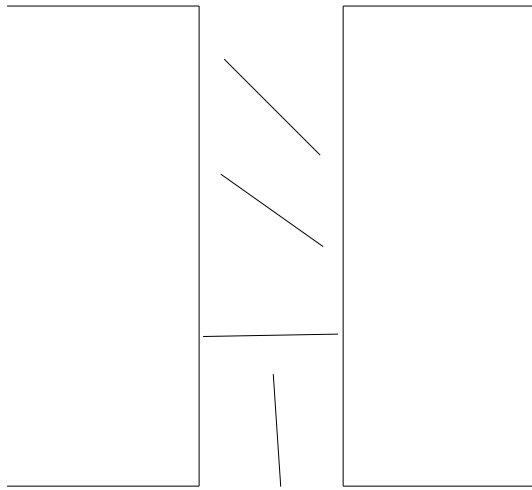
In the following expressions for the ionic currents, v is in mV, v_m is in mV, v_{rest} is in mV, and v_{th} is in mV. The constants of a gating variable x is in ms. A temperature of 35°C was assumed for all simulations.

$I_{Na} = 32 \cdot m^3 \cdot h \cdot i \cdot (v - 55)$
 $\alpha_m = 0.4(v + 30) / (1 - \exp(-(v + 30) / 7.2))$
 $\beta_m = 0.124(v + 30) / (\exp((v + 50) / 4) + 1)$
 $\tau_h = 0.5 / (\alpha_h + \beta_h)$
 $\alpha_h = 0.03(v + 45) / (1 - \exp(-(v + 45) / 10))$
 $\beta_h = 0.01(v + 45) / (\exp((v + 58) / 2) + 1)$
 $i_\infty = (1 + b_i \exp((v + 58) / 2)) / (1 + \exp((v + 58) / 2))$
 $\tau_i = 3 \cdot 10^4 \beta_i / (1 + \alpha_i)$
 $\alpha_i = \exp(0.45(v + 60))$
 $\beta_i = \exp(0.09(v + 60))$

$I_{Kd} = 10 \cdot (v - 55) \cdot n^4$
 $\alpha_n = 1.1(1 + \exp(-(v + 30) / 10)) / (1 + \exp(-(v + 30) / 10) + \exp(-(v + 30) / 10))$
 $\beta_n = \exp(-0.008(v + 10)) / (1 + \exp(-(v + 30) / 10))$
 $\tau_n = 1 / (\alpha_n + \beta_n)$
 $I_{Ks} = 0.5 \cdot (v - 55) \cdot s^2$
 $\alpha_s = 1.1(1 + \exp(-(v + 30) / 10)) / (1 + \exp(-(v + 30) / 10) + \exp(-(v + 30) / 10))$
 $\beta_s = \exp(-0.008(v + 10)) / (1 + \exp(-(v + 30) / 10))$
 $\tau_s = 1 / (\alpha_s + \beta_s)$
 $I_{CaT} = 0.5 \cdot (v - 55) \cdot t^2$
 $\alpha_t = 1.1(1 + \exp(-(v + 30) / 10)) / (1 + \exp(-(v + 30) / 10) + \exp(-(v + 30) / 10))$
 $\beta_t = \exp(-0.008(v + 10)) / (1 + \exp(-(v + 30) / 10))$
 $\tau_t = 1 / (\alpha_t + \beta_t)$
 $I_{CaL} = 0.5 \cdot (v - 55) \cdot l^2$
 $\alpha_l = 1.1(1 + \exp(-(v + 30) / 10)) / (1 + \exp(-(v + 30) / 10) + \exp(-(v + 30) / 10))$
 $\beta_l = \exp(-0.008(v + 10)) / (1 + \exp(-(v + 30) / 10))$
 $\tau_l = 1 / (\alpha_l + \beta_l)$
 $I_{A} = 0.5 \cdot (v - 55) \cdot a^2$
 $\alpha_a = 1.1(1 + \exp(-(v + 30) / 10)) / (1 + \exp(-(v + 30) / 10) + \exp(-(v + 30) / 10))$
 $\beta_a = \exp(-0.008(v + 10)) / (1 + \exp(-(v + 30) / 10))$
 $\tau_a = 1 / (\alpha_a + \beta_a)$

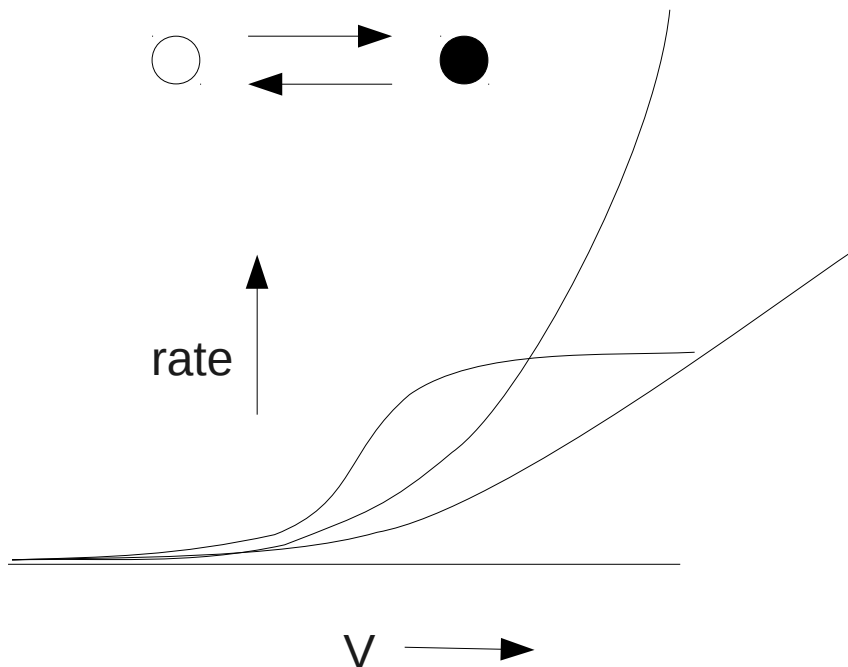
Acknowledgments

This work was supported in part by the NATO (CRK Senior Fellowship Program) (M.M., 5018 grants M144754 and M144642), the Shokar Foundation, and the Human Frontiers Science Program (H.F.S.). We thank S. Poppele for technical assistance.



Original HH model and almost all derivatives have:

- Serial independent gates
- Gate opening and closing governed by a rate expression with one of three forms:
 - $\exp(V)$
 - $\exp(V) / (1 + \exp(v))$
 - $V / (1 - \exp(-V))$
- Each rate expression has three parameters – V scale, Rate scale, V offset



PSICS exploits this structure to allow concise expression of HH style models:

```
<KSChannel id="HH_Na" permeantIon="Na" gSingle="20pS">
  <KSComplex id="m" instances="3">
    <ClosedState id="c"/>
    <OpenState id="o"/>
    <ExpLinearTransition from="c" to="o" rate="1.per_ms" midpoint = "-40.mV" scale="10mV"/>
    <ExpTransition from="o" to = "c" rate="4.per_ms" midpoint="-65.mV" scale="-18mV"/>
  </KSComplex>
  <KSComplex id="h">
    <ClosedState id="c"/>
    <OpenState id="o"/>
    <ExpTransition from="c" to="o" rate="0.07per_ms" midpoint="-65.mV" scale="-20.mV"/>
    <SigmoidTransition from="o" to="c" rate="1per_ms" midpoint="-35mV" scale="10mV"/>
  </KSComplex>
</KSChannel>

<KSChannel id="HH_K" permeantIon="K" gSingle="20pS">
  <KSComplex id="n" instances="4">
    <ClosedState id="c"/>
    <OpenState id="o"/>
    <ExpLinearTransition from="c" to="o" rate="0.1per_ms" midpoint = "-55.mV" scale="10mV"/>
    <ExpTransition from="o" to = "c" rate="0.125per_ms" midpoint="-65.mV" scale="-80mV"/>
  </KSComplex>
</KSChannel>
```

But this depends on external definitions for the element types.
What if we want to express the whole lot from scratch?

Need a way to express -

- The structures shared by many models, once
- For a particular model, just the parts unique to that model, with a reference to the shared structure

XML shorthand for as yet undefined canonical form

Desired content of the top layer of the model specification

Syntactic fiddles:

“<XXX .../>”

is shorthand for

“<Component type='XXX'/>”

“a='value unit'”

is shorthand for

“<value parameter='a'
size='val'
unit='unit'/>”

```
<Include file="hhchannel.xml" />  
<Unit symbol="mV" dimension="voltage" powTen="-3" />  
<Unit symbol="per_ms" dimension="per_time" powTen="3" />  
<Unit symbol="pS" dimension="conductance" powTen="-12" />
```

```
<HHChannel id="na" conductance="20pS">  
  <HHGate id="m" power="3">  
    <Forward type="HHExpLinearRate" rate="1.per_ms" midpoint="-40mV" scale="10mV" />  
    <Reverse type="HHExpRate" rate="4per_ms" midpoint="-65mV" scale="-18mV" />  
  </HHGate>  
  <HHGate id="h" power="1">  
    <Forward type="HHExpRate" rate="0.07per_ms" midpoint="-65.mV" scale="-20.mV" />  
    <Reverse type="HHSigmoidRate" rate="1per_ms" midpoint="-35mV" scale="10mV" />  
  </HHGate>  
</HHChannel>
```

```
<HHChannel id="k" conductance="20pS">  
  <HHGate id="n" power="4">  
    <Forward type="HHExpLinearRate" rate="0.1per_ms" midpoint="-55mV" scale="10mV" />  
    <Reverse type="HHExpRate" rate="0.125per_ms" midpoint="-65mV" scale="-80mV" />  
  </HHGate>  
</HHChannel>
```

```

<Dimension name="voltage" m="1" l="2" t="-3" i="-1" />
<Dimension name="time" t="1" />
<Dimension name="per_time" t="-1" />
<Dimension name="conductance" m="-1" l="-2" t="3" i="2" />
<Dimension name="capacitance" m="-1" l="-2" t="4" i="2" />
<Dimension name="current" i="1" />

<Type name="HHRate">
  <Parameter name="rate" dimension="per_time" />
  <Parameter name="midpoint" dimension="voltage" />
  <Parameter name="scale" dimension="voltage" />
  <Behavior>
    <IndependentVariable name="v" dimension="voltage" />
    <DerivedVariable name="r" dimension="per_time" />
  </Behavior>
</Type>

<Type name="HHExpRate" extends="HHRate">
  <Behavior inherit="variables">
    <DerivedVariable name="r" value="rate * exp((v - midpoint)/scale)" />
  </Behavior>
</Type>

<Type name="HHSigmoidRate" extends="HHRate">
  <Behavior inherit="variables">
    <DerivedVariable name="r" value="rate / (1 + exp(0 - (v - midpoint)/scale))" />
  </Behavior>
</Type>

<Type name="HHExpLinearRate" extends="HHRate">
  <Behavior inherit="variables">
    <DerivedVariable name="x" value="(v - midpoint) / scale" />
    <DerivedVariable name="r" value="rate * x / (1 - exp(0 - x))" />
  </Behavior>
</Type>

```

```

<Type name="HHGate">
  <Parameter name="power" dimension="none" />
  <Child name="Forward" type="HHRate" />
  <Child name="Reverse" type="HHRate" />
  <Behavior>
    <IndependentVariable name="v" dimension="voltage" />
    <StateVariable name="q" dimension="none" />
    <ExternalVariable name="rf" dimension="per_time" select="Forward/r" />
    <ExternalVariable name="rr" dimension="per_time" select="Reverse/r" />
    <TimeDerivative variable="q" value="rf * (1 - q) - rr * q" />
    <DerivedVariable name="fcond" dimension="none" value="q^power" />
  </Behavior>
</Type>

```

```

<Type name="HHChannel">
  <Parameter name="conductance" dimension="conductance" />
  <Children name="gates" type="HHGate" min="0" max="4" />
  <Behavior>
    <IndependentVariable name="v" dimension="voltage" />
    <ExternalVariable name="gatefeff" dimension="none"
      select="product(gates[*]/fcond)" />
    <DerivedVariable name="g" value="conductance * gatefeff" />
  </Behavior>
</Type>

```


Status

- Part of NeuroML 2.0 development project. Docs at www.psics.org/lems
- Provides a set of elements and an interpreter for building and running models using user-defined types.
- Early days – mainly experimental at present
- Can retrofit many NeuroML elements so that some models can be run on the generic interpreter
- Some success retrofitting SBML and SED-ML
- The INCF NineML project is aiming to develop a standard for this type of model specification
 - Focus on simple cells and networks but should generalize