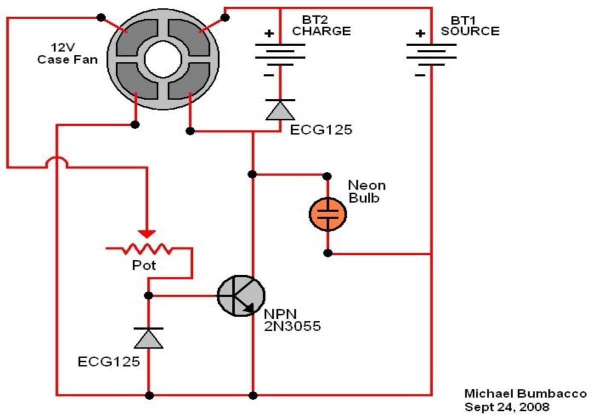
Proposed structure for NeuroML 2.0 and LEMS

- Motivation for LEMS
- Defining Component Types and Components
- Structure of models
- Interpreter
- Under development
- Open issues

Motivation

- From last year's report:
  - *“Discussion focused around two main topics: a possible structure for a more modular and flexible synapse specification; and the wide range of synaptic phenomena that might or might not be expressible in such a structure.”*
  - *“... would need to express a wide range of possible behaviors and could include kinetic scheme elements as for the channel specification, state variables governed by differential equations or reaction networks expressed as SBML”*
- Essentially, how can you keep the clarity and simplicity of domain specific “top level elements”, but also allow it to be easily extended with new types of component?

Electrical Circuit



\+

Shared understanding
Not restated every time

Kirchoff's Laws etc, etc...

$$I_1 + i_2 + i_3 = 0$$

$$I_4 - i_3 + i_5 = 0$$

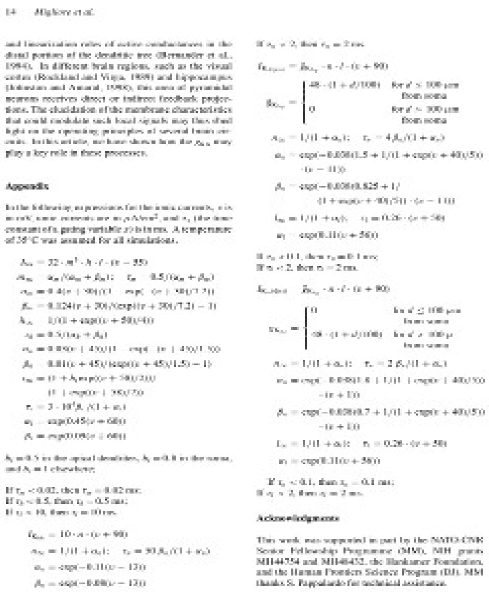
Etc

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

(eg) Hodgkin Huxley ion channel model

? + ?

$$I_{\mathrm{Na}} = 32 \cdot m^3 \cdot h \cdot i \cdot (v - 55)$$
$$m_\infty = \alpha_m/(\alpha_m + \beta_m); \quad \tau_m = 0.5/(\alpha_m + \beta_m)$$
$$\alpha_m = 0.4(v + 30)/(1 - \exp(-(v + 30)/7.2))$$
$$\beta_m = 0.124(v + 30)/(\exp((v + 30)/7.2) - 1)$$
$$h_\infty = 1/(1 + \exp((v + 50)/4))$$
$$\tau_h = 0.5/(\alpha_h + \beta_h)$$
$$\alpha_h = 0.03(v + 45)/(1 - \exp(-(v + 45)/1.5))$$
$$\beta_h = 0.01(v + 45)/(\exp((v + 45)/1.5) - 1)$$
$$i_\infty = (1 + b_i \exp((v + 58)/2))/(1 + \exp((v + 58)/2))$$
$$\tau_i = 3 \cdot 10^4 \beta_i /(1 + \alpha_i)$$
$$\alpha_i = \exp(0.45(v + 60))$$
$$\beta_i = \exp(0.09(v + 60))$$



What not to do...

```
<variable name="F" units="coulomb_per_mole" initial_value="96845" public_interface="out"/>
<variable name="Cm" units="picoF" initial_value="7"/>
<variable name="time" units="millisecond" public_interface="in"/>
<variable name="i_Ca_L" units="picoA" public_interface="in"/>
<variable name="i_Ca_T" units="picoA" public_interface="in"/>
<variable name="i_K_DR" units="picoA" public_interface="in"/>
<variable name="i_K_Ca" units="picoA" public_interface="in"/>
<variable name="i_leak" units="picoA" public_interface="in"/>
<math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply>
    <eq/>
    <apply>
      <diff/>
      <bvar>
        <ci>time</ci>
      </bvar>
      <ci>V</ci>
    </apply>
    <apply>
      <divide/>
      <apply>
        <minus/>
        <apply>
          <plus/>
          <ci>i_Ca_L</ci>
          <ci>i_Ca_T</ci>
          <ci>i_K_DR</ci>
          <ci>i_K_Ca</ci>
          <ci>i_leak</ci>
        </apply>
      </apply>
      <ci>Cm</ci>
    </apply>
  </apply>
</math>
</component>
```

```
<component xmlns="http://www.cellml.org/cellml/1.0#" name="L_type_calcium_current">
  <variable name="i_Ca_L" units="picoA" public_interface="out"/>
  <variable name="phi_Ca" units="millivolt_millimolar" public_interface="out"/>
  <variable name="g_Ca_L" units="nanoS_per_millimolar" initial_value="9"/>
  <variable name="time" units="millisecond" public_interface="in" private_interface="out"/>
  <variable name="V" units="millivolt" public_interface="in" private_interface="out"/>
  <variable name="V_tau" units="millivolt" public_interface="in" private_interface="out"/>
  <variable name="k_tau" units="millivolt" public_interface="in" private_interface="out"/>
  <variable name="R" units="joule_per_kilomole_kelvin" public_interface="in"/>
  <variable name="T" units="kelvin" public_interface="in"/>
  <variable name="F" units="coulomb_per_mole" public_interface="in"/>
  <variable name="Ca_e" units="millimolar" public_interface="in"/>
  <variable name="Ca_i" units="millimolar" public_interface="in"/>
  <variable name="m_L" units="dimensionless" private_interface="in"/>
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <eq/>
      <ci>i_Ca_L</ci>
      <apply>
        <times/>
        <ci>g_Ca_L</ci>
        <apply>
          <power/>
          <ci>m_L</ci>
          <cn cellml:units="dimensionless">2</cn>
        </apply>
        <ci>phi_Ca</ci>
      </apply>
    </apply>
    <apply>
      <eq/>
      <ci>phi_Ca</ci>
      <apply>
        <divide/>
        <apply>
```

```
<connection xmlns="http://www.cellml.org/cellml/1.0#">
  <map_components component_1="leak_current" component_2="environment"/>
  <map_variables variable_1="time" variable_2="time"/>
</connection>
<connection xmlns="http://www.cellml.org/cellml/1.0#">
  <map_components component_1="ER_calcium" component_2="environment"/>
  <map_variables variable_1="time" variable_2="time"/>
  <map_variables variable_1="V_cell" variable_2="V_cell"/>
</connection>
<connection xmlns="http://www.cellml.org/cellml/1.0#">
  <map_components component_1="cytosolic_calcium" component_2="environment"/>
  <map_variables variable_1="time" variable_2="time"/>
  <map_variables variable_1="V_cell" variable_2="V_cell"/>
</connection>
<connection xmlns="http://www.cellml.org/cellml/1.0#">
  <map_components component_1="membrane" component_2="L_type_calcium_current"/>
  <map_variables variable_1="V" variable_2="V"/>
  <map_variables variable_1="i_Ca_L" variable_2="i_Ca_L"/>
  <map_variables variable_1="R" variable_2="R"/>
  <map_variables variable_1="F" variable_2="F"/>
  <map_variables variable_1="T" variable_2="T"/>
</connection>
<connection xmlns="http://www.cellml.org/cellml/1.0#">
  <map_components component_1="membrane" component_2="T_type_calcium_current"/>
  <map_variables variable_1="V" variable_2="V"/>
  <map_variables variable_1="i_Ca_T" variable_2="i_Ca_T"/>
</connection>
<connection xmlns="http://www.cellml.org/cellml/1.0#">
  <map_components component_1="membrane" component_2="voltage_sensitive_K_current"/>
  <map_variables variable_1="V" variable_2="V"/>
  <map_variables variable_1="i_K_DR" variable_2="i_K_DR"/>
  <map_variables variable_1="R" variable_2="R"/>
  <map_variables variable_1="F" variable_2="F"/>
  <map_variables variable_1="T" variable_2="T"/>
</connection>
```

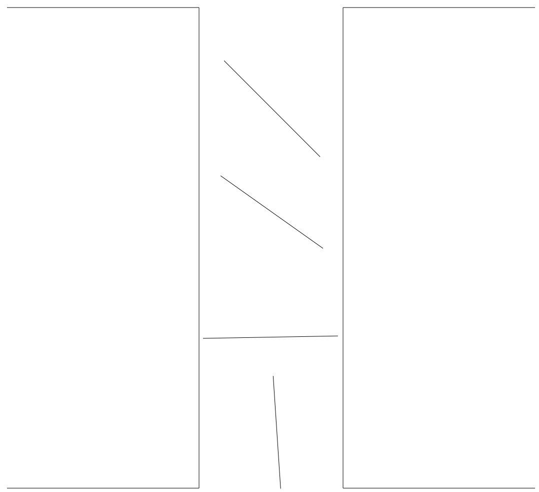
3 of about 30 pages that constitute the CellML representation of a fairly simple HH based cell model.

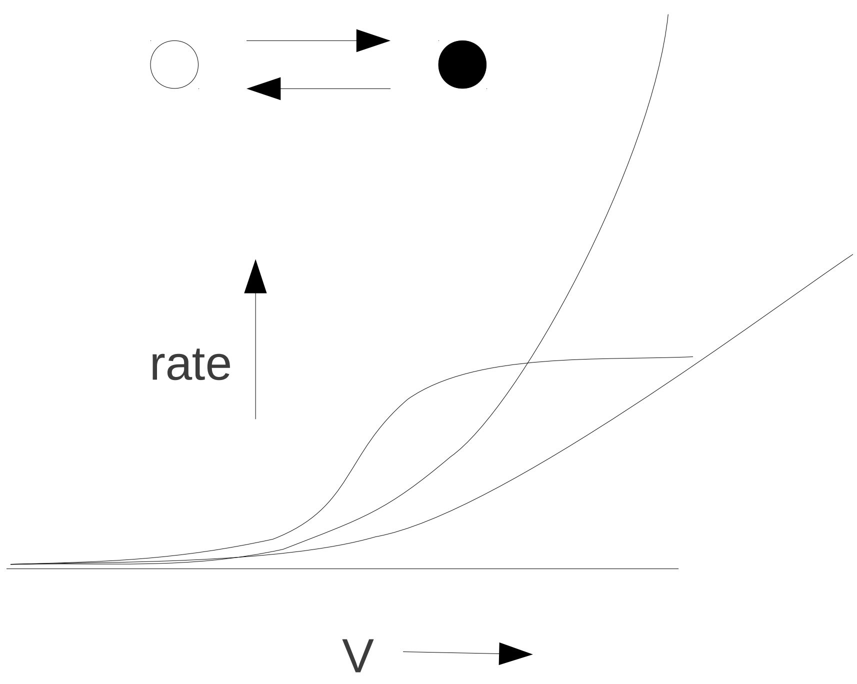
Says $C\, dV/dt = \sum i$,

… but without using $\sum$

All the currents are enumerated explicitly

What actually is the model?





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

NeuroML exploits this structure to allow concise expression of HH style models: (this is actually the PSICS form, but its pretty much equivalent)

```
<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

Without editing the schema/specification every time – neuroscience models are just too diverse.

Similar principle to:
Modelica (mechanical systems)
VHDL (electronic design)
NineML (networks and more)
...and others

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" />

<ComponentType 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>
</ComponentType>

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

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

   </Behavior>
</ComponentType>

<ComponentType 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>

</ComponentType>
```

```
<ComponentType 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>
</ComponentType>


<ComponentType 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>
</ComponentType>
```

With these definitions in place, most of the ion channel models in the modeling literature can be expressed in 10 or 15 lines of XML.

Why “LEMS” - Low Entropy Model Specification?

c.f. Kolmogorov complexity, or algorithmic entropy:

abababababababababababababababababababababababab = 24(ab)
aeagarg89dafgertdfgbsdrgtqewrsae4lgi7hdf89bkfsdsg0efhe (*nothing shorter than itself)*

The first string has lower entropy and the simple coding scheme lets it be expressed in a way that makes this clear.

LEMS is about doing the same thing for biological models.

Several benefits:

1) Easier for people to read and understand the concise form
2) Can be mapped onto other representations (easier to increase entropy than reduce it)
3) Allows a notion of “proximity” on models (“24(ab)” is near “25(ab)” and 24(ac)”)
    - crucial when each model is just a single point in an infinite parameter space
4) Less repetition helps with implementation and validation

What is there so far

- Point process models
  - Dimensions, units, parameters, state variables
  - First order ODEs
  - Event generation and handling
- Hierarchical structures
  - Eg, “a channel has n gates; a gate has children for the forward and reverse rates”
- References between elements
  - Eg “Channels is permeable to Na; the reversal potential of Na in this simulation is 60mV → so, channel reversal potential is 60mV ”
- Elements for defining simulations and outputs
- Expressions with paths and predicates operating on components
  - Selecting and filtering sets of instances
  - Selecting and filtering sets of instance pairs
  - Adding new instances based on sets
  - Per-instance properties

Under development

- Control of model “instantiation”
  - Needed for extended cells and networks
- Selection operators and paths across an “instantiated” model
  - Operating on synapses on a cell, or cells in a population
- Better structures for representing component hierarchies and behaviors

Beyond the horizon

- Spatial structure and PDEs

What can you do with it?

- Reference interpreter - will build and run models defined in LEMS.
- Can retrofit existing NeuroML element types with LEMS component type definitions
- Tools have a choice of recognizing the component type, or processing the LEMS definition

What you can't do

It is tempting to suggest that the behavior definitions say something about the semantics of a model, but they really don't help much. Still need annotations and documentation to express the significance behind a component type.

Component type definitions

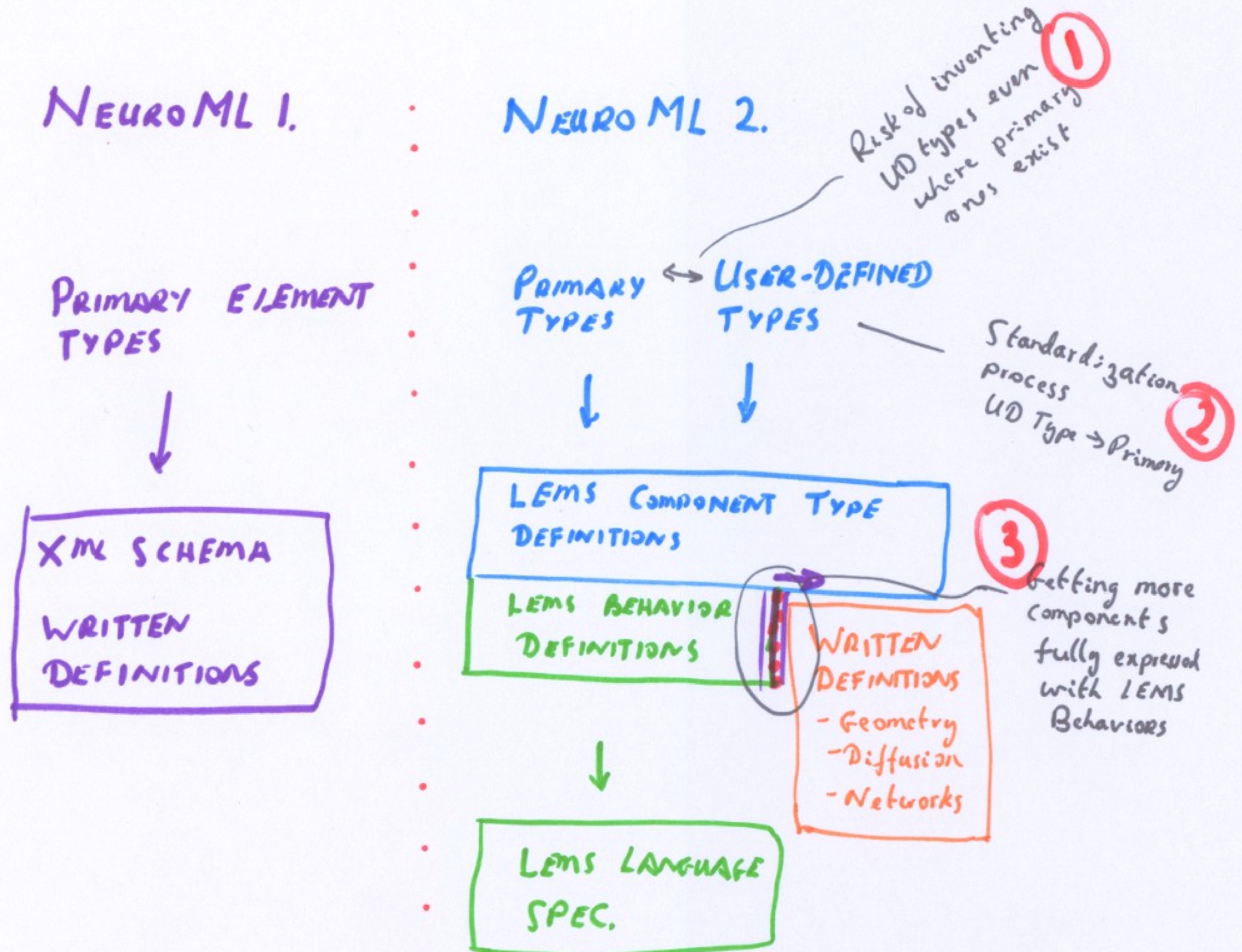
- **Dimensions and Equations**
- Hand-written in XML
- Possibly machine generated in some cases
- Concise, and relatively few of them
- Need referencing and selection mechanisms operating across types.
  - *eg to say the relative conductance of a channel is the product of the relative conductances of its gates*

Component definitions

- **Units and Parameter values**
- Can be hand-written in XML by a modeler, possibly generated
- Need references and selections across a model
  - *Eg to specify the channel model to use for a particular collection of channels*
- **Also** need references and selections across the (hypothetical) instantiated model
  - *Eg to select cells for a particular connectivity pattern (**targets don't exist in the XML**)*

Hypothetical fully-expanded model

- **Simulator state as nesting structure and dimensional quantities**
- One entry for every cell in a network, every state variable in a simulation.
- *Could* be used to simulate a model (but not a very efficient way of doing it)
- In general, may never be generated
- But can still write xpath or equivalent to operate over it



NeuroML 1.
Primary Element Types
XML Schema
Written Definitions
NeuroML 2.
Risk of inventing UD types even where primary ones exist
1
Primary Types
User-Defined Types
Standardization process UD Type → Primary
2
LEMS Component Type Definitions
LEMS Behavior Definitions
3
Getting more components fully expressed with LEMS Behaviors
Written Definitions
- Geometry
- Diffusion
- Networks
LEMS Language Spec.