

Semantics-based composition of CellML and SBML models



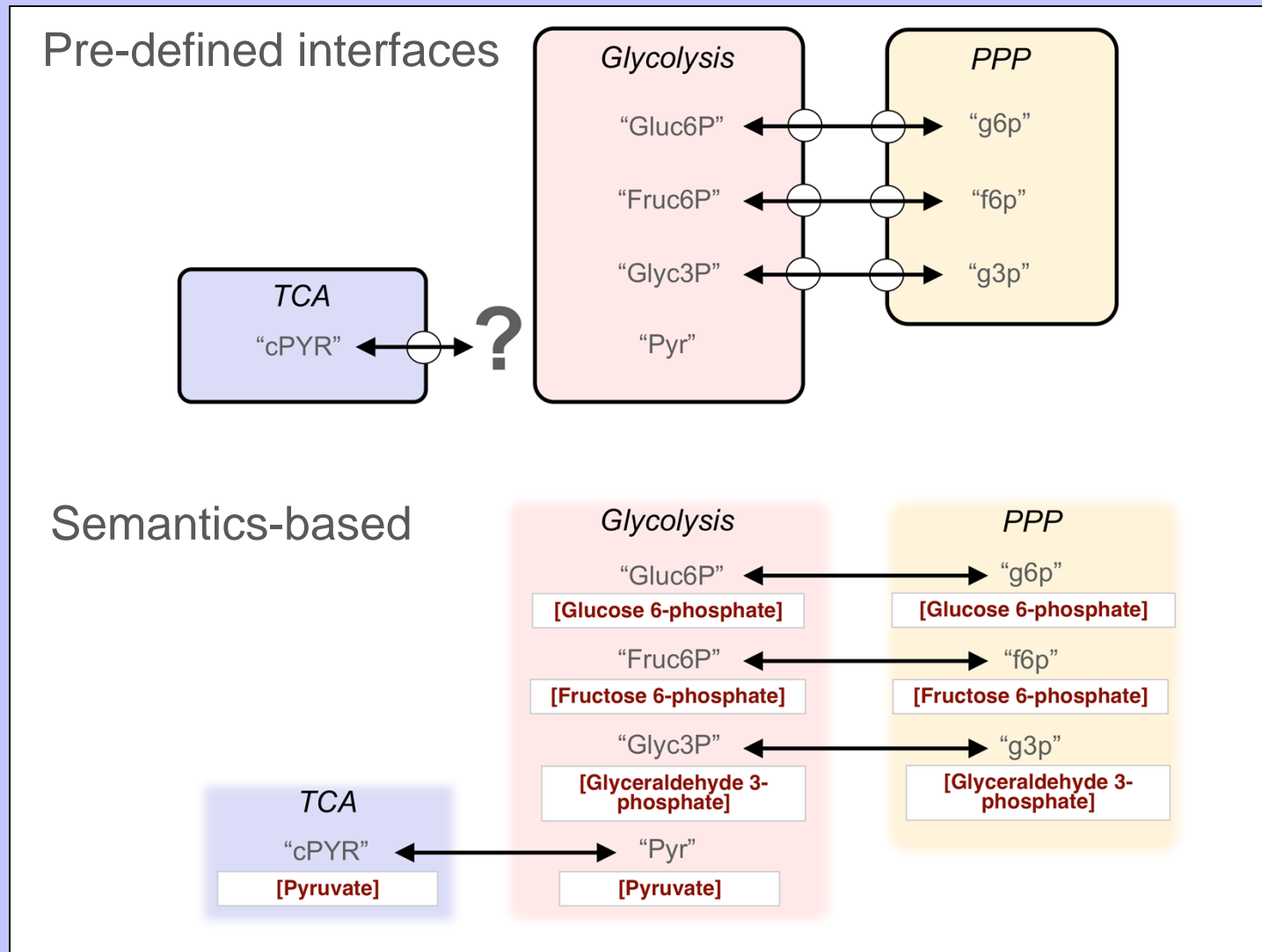
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Composition of physiology models largely occurs at the biological level of abstraction.

Can we better automate these tasks by capturing model biology in a computable form?

Approaches for modular composition of models



Neal ML, Cooling MT, Smith LP, Thompson CT, Sauro HM, Carlson BE, Cook DL, Gennari JH. A reappraisal of how to build modular, reusable models of biological systems. *PLoS Computational Biology*. 2014. 10(10): e1003849.

Pandit-Hinch-Niederer composition

Exp Physiol 93.7 pp 919–929

919

Experimental Physiology

Using Physiome standards to couple cellular functions for rat cardiac excitation–contraction

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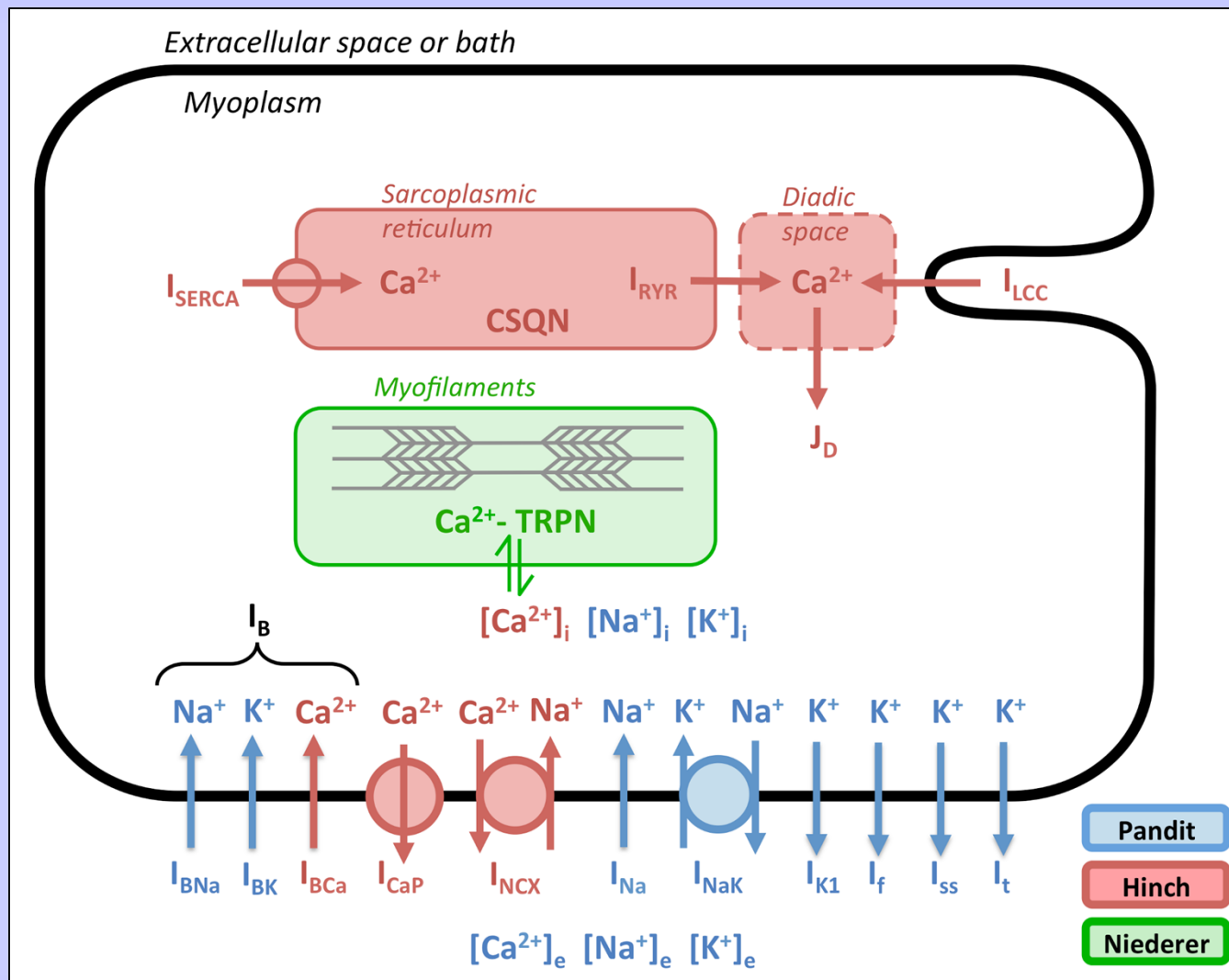
Scientific endeavour is reliant upon the extension and reuse of previous knowledge. The formalization of this process for computational modelling is facilitated by the use of accepted standards with which to describe and simulate models, ensuring consistency between the models and thus reducing the development and propagation of errors. CellML 1.1, an XML-based programming language, has been designed as a modelling standard which, by virtue of its import and grouping functions, facilitates model combination and reuse. Using CellML 1.1, we demonstrate the process of formalized model reuse by combining three separate models of rat cardiomyocyte function (an electrophysiology model, a model of cellular calcium dynamics and a mechanics model) which together make up the Pandit–Hinch–Niederer *et al.* cell model. Not only is this integrative model of rat electromechanics a useful tool for cardiac modelling but it is also an ideal framework with which to demonstrate both the power of model reuse and the challenges associated with this process. We highlight and classify a number of these issues associated with combining models and provide some suggested solutions.

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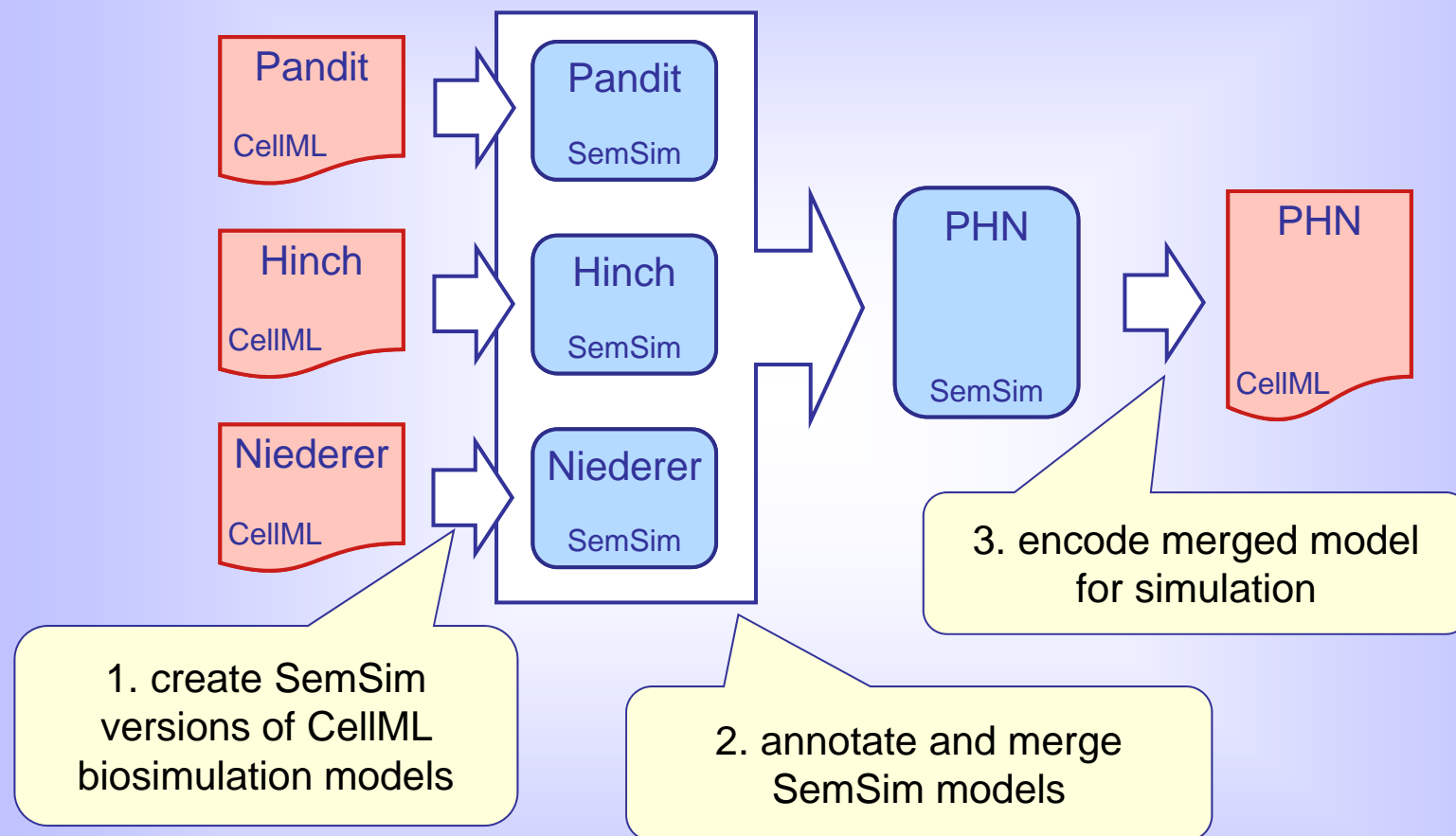
Email: nic.smith@comlab.ox.ac.uk

Pandit-Hinch-Niederer composition



Neal ML, Carlson BE, Thompson CT, James RC, Kim KG, Tran K, Crampin EJ, Cook DL, Gennari JH. Semantics-based composition of integrated cardiomyocyte models motivated by real-world use cases. (submitted)

Pandit-Hinch-Niederer composition



File Tools Help

Hinch

Show imports Sort Options

Reference Terms:

intracellular_ion_concentrations.Ca_i (mM)
 Intracellular calcium (2+) concentration

$$d(\text{Ca}_i)/dt = \text{beta_CMDN} * (\text{I_LCC} + \text{I_RyR} - \text{I_SERCA} + \text{I_SR} + \text{I_NaCa} - \text{I_pCa} + \text{I_CaB} + \text{I_TRPN})$$

Composite annotation

Chemical concentration (OPB)

property_of

calcium(2+) (CHEBI)

part_of

Portion of cytosol (FMA)

part_of

Cardiac myocyte (FMA)

Add Entity

```
<component name="intracellular_ion_concentrations">
  <variable name="Na_i" units="mM" initial_value="10" public_interface="out"/>
  <variable name="Ca_i" units="mM" initial_value="0.0001" public_interface="ou
  <variable name="Ca_SR" units="mM" initial_value="700e-3" public_interface="o
  <variable name="TRPN" units="mM" initial_value="0.0636364" public_interface=
  <variable name="time" units="ms" public_interface="in"/>
  <variable name="V_myo" units="um3" public_interface="in"/>
  <variable name="V_SR" units="um3" public_interface="in"/>
  <variable name="beta_CMDN" units="dimensionless" public_interface="in"/>
  <variable name="I_SERCA" units="mM_per_ms" public_interface="in"/>
  <variable name="I_pCa" units="mM_per_ms" public_interface="in"/>
  <variable name="I_CaB" units="mM_per_ms" public_interface="in"/>
  <variable name="I_TRPN" units="mM_per_ms" public_interface="in"/>
  <variable name="I_SR" units="mM_per_ms" public_interface="in"/>
  <variable name="I_NaCa" units="mM_per_ms" public_interface="in"/>
  <variable name="I_RyR" units="mM_per_ms" public_interface="in"/>
</component>
```

Hinch

- Background_Ca_current
- calmodulin_Ca_buffer
- CaRU
- CaRU_reduced_states
- CaRU_states
- CaRU_Transitions
- cell_geometry
- convert_hinch
- DS_Calcium_Concentrations
- environment
- extracellular_ion_concentrations
- intracellular_ion_concentrations
 - beta_CMDN
 - Ca_i
 - Ca_SR
 - CaSR_plot
 - I_CaB
 - I_LCC
 - I_NaCa
 - I_pCa
 - I_RyR
 - I_SERCA
 - I_SR
 - I_TRPN
 - Na_i
 - time
 - TRPN

Pandit + Hinch: Resolution points automatically identified

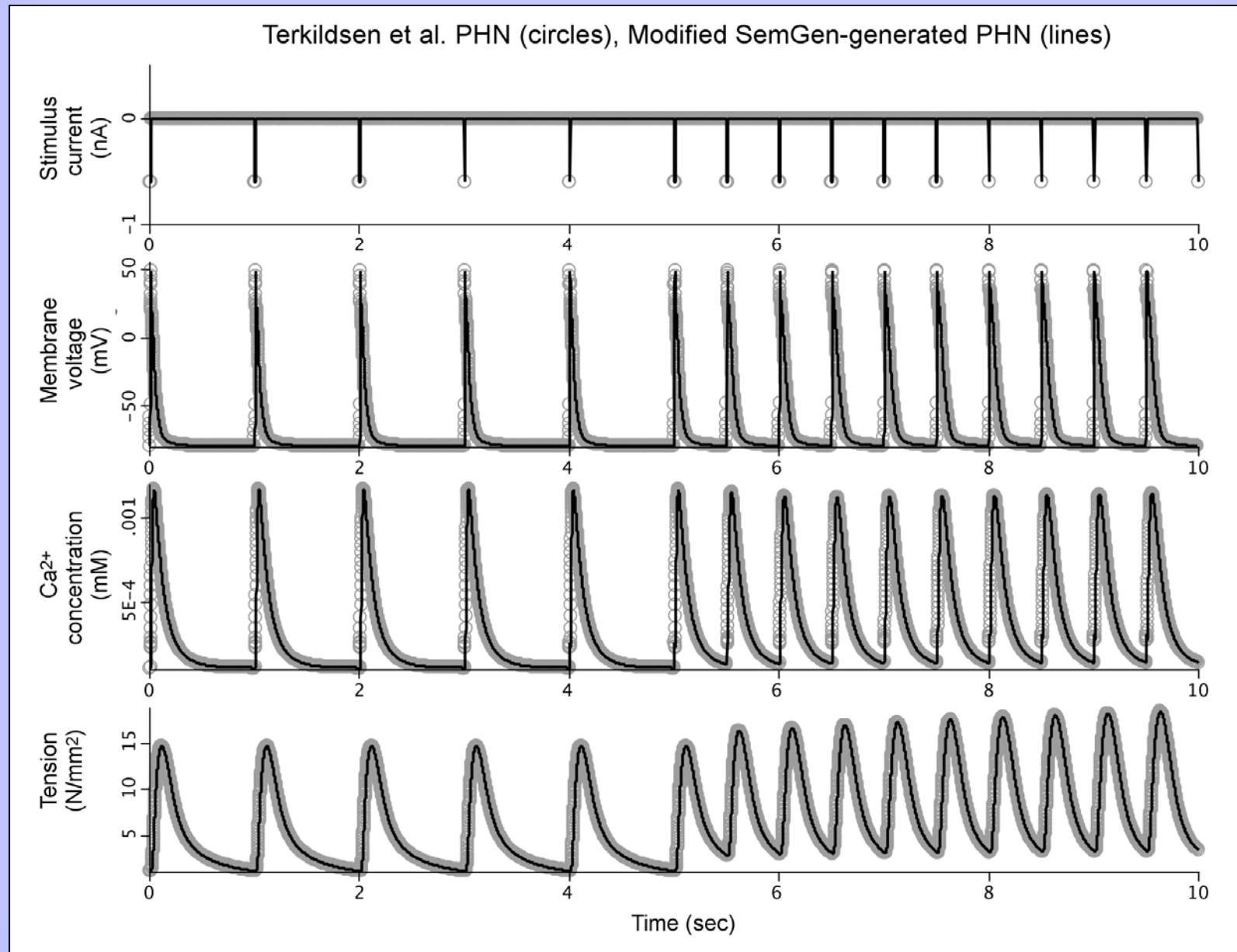
Shared biophysical property	Resolution decision
Background calcium current	Hinch
Calcium-ATPase pump current	Hinch
Sodium/calcium exchanger current	Hinch
Intracellular calcium ion concentration	Hinch
Intracellular sodium ion concentration	Pandit
Extracellular calcium concentration	Pandit
Extracellular sodium concentration	Pandit
Membrane voltage	Pandit
Cytosolic volume	Hinch
Ambient temperature	Hinch
Universal gas constant	Hinch
Faraday constant	Hinch
Temporal solution domain	Hinch

Pandit + Hinch: Resolution points not identified

Shared biophysical property	Resolution decision
* L-type calcium channel current	Hinch
Ryanodine receptor current	Unresolved
SERCA pump current	Unresolved
Troponin-calcium buffering rate	Unresolved
Diadic space calcium concentration	Unresolved
Sarcoplasmic reticulum calcium concentration	Unresolved
Concentration of bound and unbound calmodulin	Unresolved
Concentration of bound and unbound troponin	Unresolved
Troponin-calcium association rate constant	Unresolved
Troponin-calcium dissociation rate constant	Unresolved
Calmodulin-calcium rapid buffer coefficient	Unresolved

* Required manual mapping for biological consistency

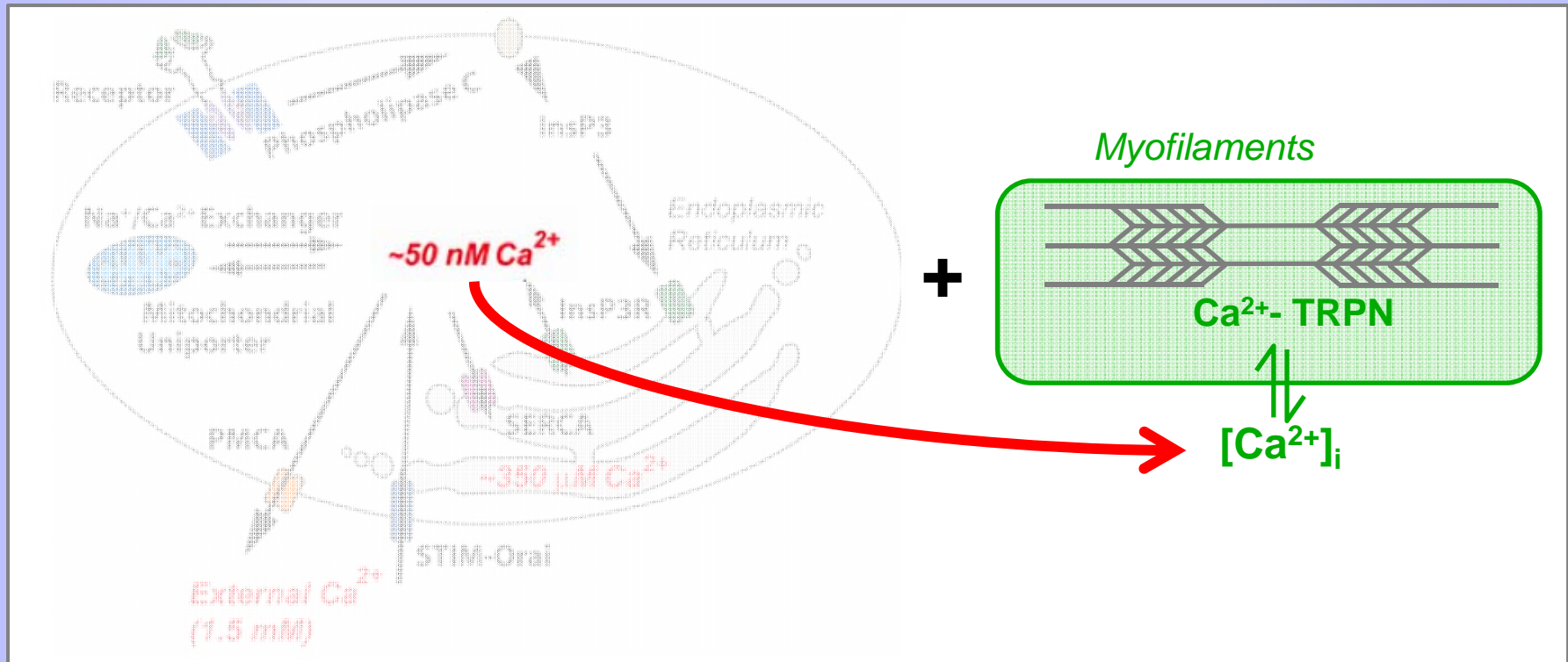
Pandit-Hinch-Niederer modeling task: results



SBML-CellML merge

Abell et al. calcium signaling model

Niederer et al. tension model



BIOMD0000000355.xml



niederer_hunter_smith_2006.cellml

File Tools Help

BIOMD0000000355

Show imports Sort Options

Reference Terms:

Cal (substance_per_volume)

Click to set free-text description

$d(\text{Cal})/d(t) = (J_{\text{Channel}} + \text{mw}bdc6a40_1ae7_4c86_a99f_1fba0b8beaf7 + \text{mw}1c50c3d1_dab9_423a_8373_6a4c75479b54 - J_{\text{Pump}} - \text{mw}530793e3_76b2_4483_bell_e94364306712 - \text{mwa}61047ec_49c1_47b2_b78e_4d84a33d432a)/\text{cytosol}$

Composite annotation

Chemical concentration (OPB)

property_of

Cal

part_of

cytosol

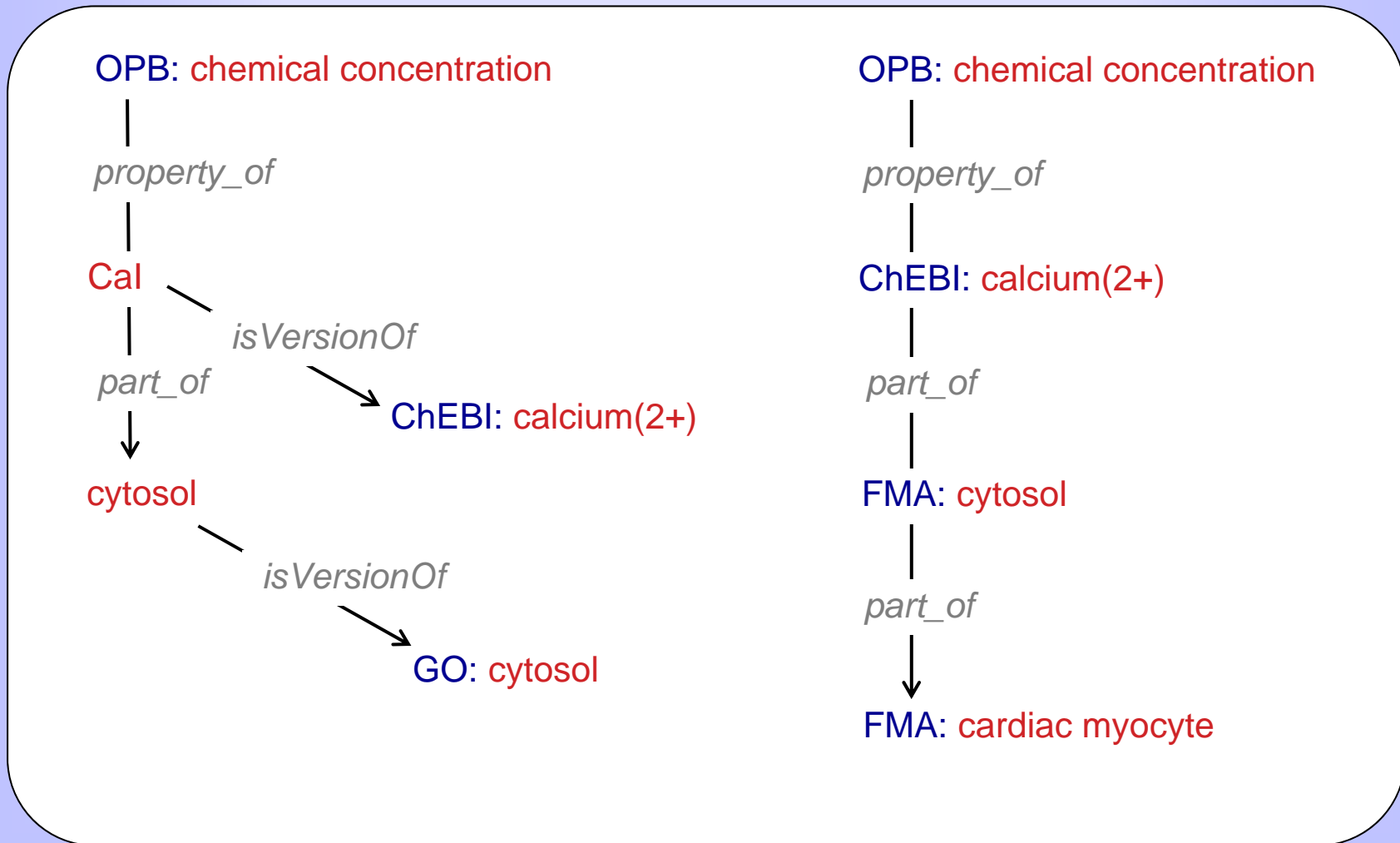
Add Entity

```
<species id="CaI" initialAmount="0.05" name="CaI" metaid="_031974" sboTerm="A"
  <annotation>
    <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xmlns:
      <rdf:Description rdf:about="#_031974">
        <bqbiol:isVersionOf>
          <rdf:Bag>
            <rdf:li rdf:resource="http://identifiers.org/obo.chebi/CHEBI:29
            <rdf:li rdf:resource="http://identifiers.org/kegg.compound/C000
          </rdf:Bag>
        </bqbiol:isVersionOf>
      </rdf:Description>
    </rdf:RDF>
  </annotation>
</species>
<species id="IP3" initialAmount="0" name="IP3" metaid="_031976" sboTerm="SB
  <annotation>
    <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xmlns:
    <rdf:Description rdf:about="#_031976">
```

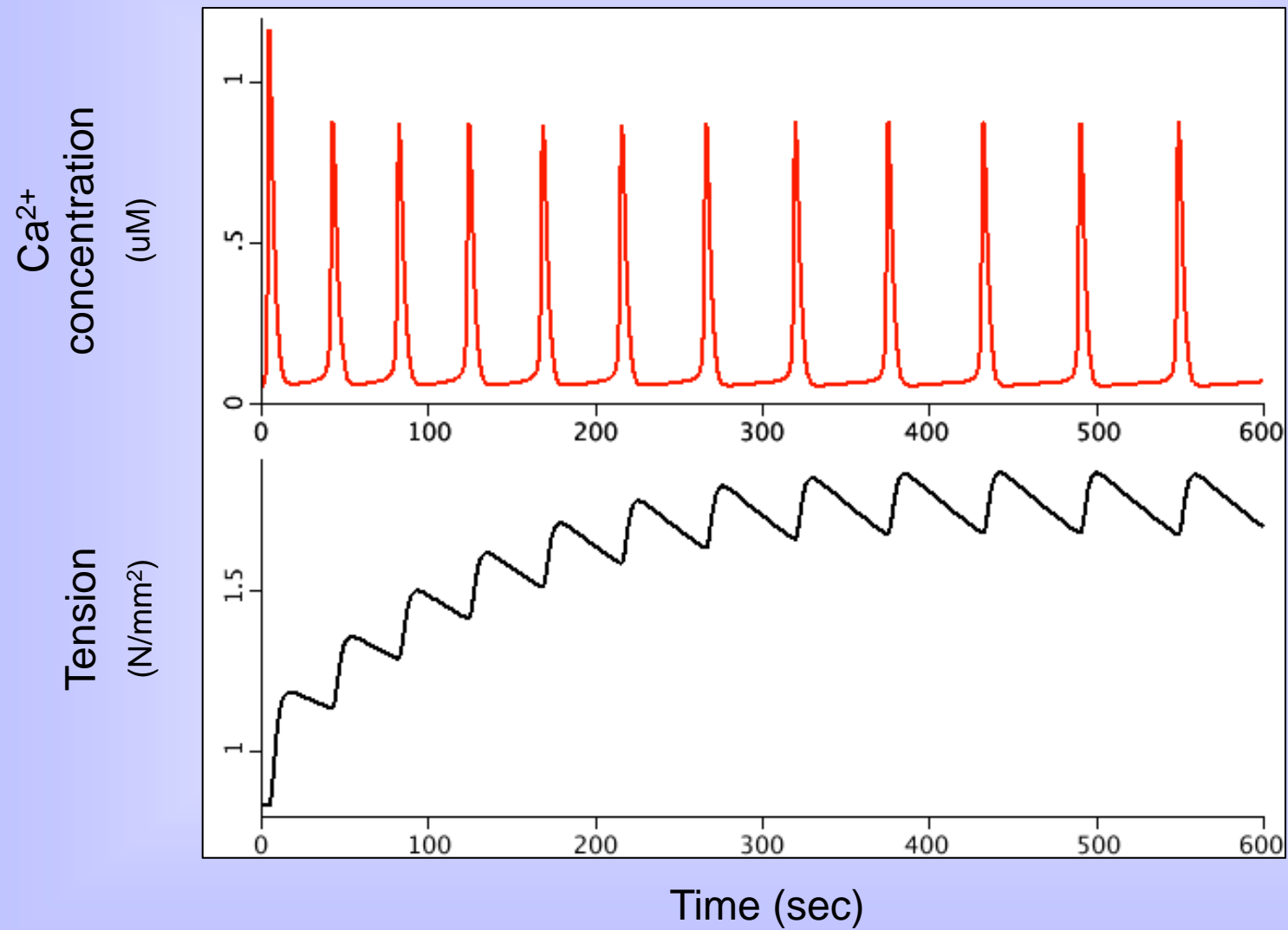
Challenge: identifying $[Ca]_i$ equivalency

Abell et al. calcium signaling model

Niederer et al. tension model



SBML-CellML merge results



Community engagement objectives

- We need a *consensus approach* for semantic annotation to reap full benefits of semantics-based composition
 - We need to understand the annotation policies of the SBML community
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