Reaction-Diffusion in the NEURON Simulator

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11 November 2016

Getting Started

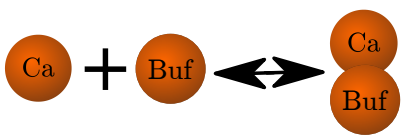
What is a reaction-diffusion system?

"Reaction–diffusion systems are mathematical models which explain how the **concentration** of one or more substances distributed in space changes under the influence of two processes: **local chemical reactions** in which the substances are transformed into each other, and **diffusion** which causes the substances to spread out over a surface in space."[1]

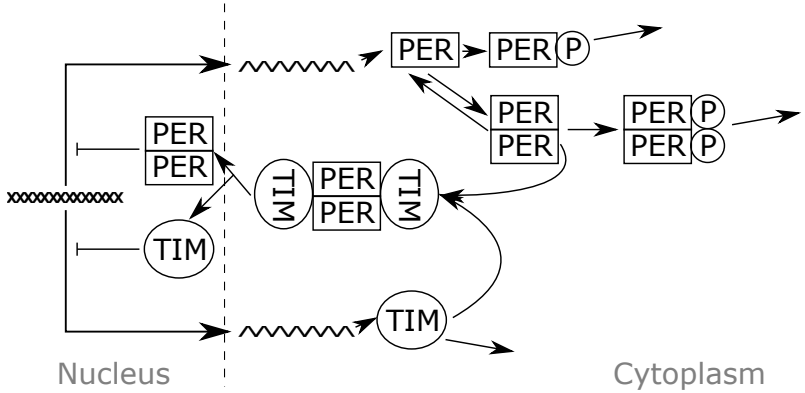
[1] http://en.wikipedia.org/wiki/Reaction%E2%80%93diffusion_system

Examples

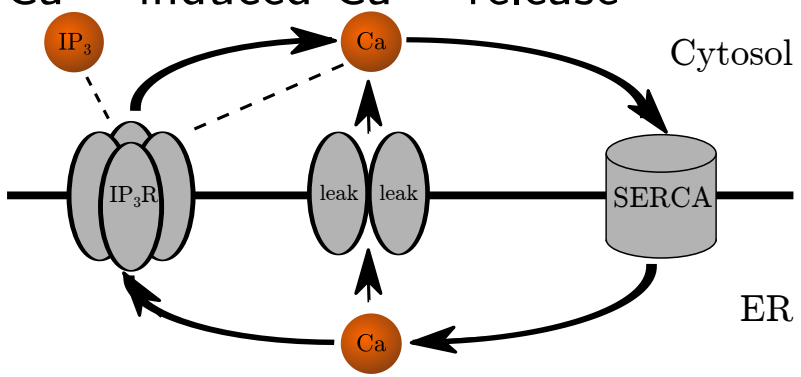
- Pure Diffusion
- Protein Degradation
- Buffering



- Circadian Oscillator



- Ca^{2+}-induced Ca^{2+} release



Circadian oscillator model adapted from Tyson et al 1999; CICR adapted from Neymotin et al 2015.

What does the rxd module do?

Reduces typing

- **In 2 lines:** declare a domain, then declare a molecule, allowing it to diffuse and respond to flux from ion channels.

```
all = rxd.Region(h.allsec(), nrn_region='i')
ca = rxd.Species(all, name='ca', d=1, charge=2)
```

- **Reduces** the risk for **errors** from typos or misunderstandings.

Allows arbitrary domains

NEURON traditionally only identified concentrations just inside and just outside the plasma membrane. The rxd module allows you to **declare your own regions** of interest (e.g. ER, mitochondria, etc).

The three questions

- **Where** do the dynamics occur?
  - Cytosol
  - Endoplasmic Reticulum
  - Mitochondria
  - Extracellular Space
- **Who** are the actors?
  - Ions
  - Proteins
- **What** are the reactions?
  - Buffering
  - Degradation
  - Phosphorylation

Declare a region with rxd.Region

Basic Usage

cyt = rxd.Region(seclist)

seclist may be any iterable of sections; e.g. a SectionList or a Python list.

Identify with a standard region

cyt = rxd.Region(seclist, nrn_region='i')

nrn_region may be i or o, corresponding to the locations of e.g. nai vs nao.

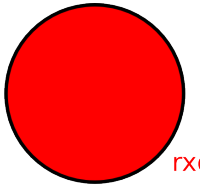
Specify the cross-sectional shape

cyt = rxd.Region(seclist, geometry=rxd.Shell(0.5, 1))

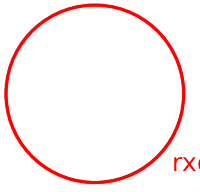
The default geometry is rxd.inside.

The geometry and nrn_region arguments may both be specified.

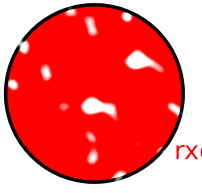
geometry:



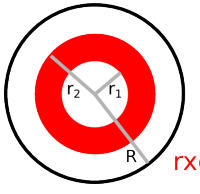
rxd.inside



rxd.membrane



rxd.FractionalVolume(
volume_fraction=f_1,
surface_fraction=f_2)



rxd.Shell(r_1/R, r_2/R)

Adapted from:
McDougal et al 2013.

rxd.Region tips

Specify nrn_region if concentrations interact with NMODL

If NMODL mechanisms (ion channels, point processes, etc) depend on or affect the concentration of a species living in a given region, that region must declare a nrn_region (typically 'i').

To declare a region that exists on all sections

```
r = rxd.Region(h.allsec())
```

Use list comprehensions to select sections

```
r = rxd.Region([sec for sec in h.allsec() if 'apical' in sec.name()])
```

Declare proteins and ions with rxd.Species

Basic usage

protein = rxd.Species(region, d=16)

d is the **diffusion constant** in $\mu m^2/ms$. region is an rxd.Region or an iterable of rxd.Region objects.

Initial conditions

protein = rxd.Species(region, initial=value)

value is in mM. It may be a constant or a function of the node.

Connecting with HOC

ca = rxd.Species(region, name='ca', charge=2)

If the nrn_region of region is "i", the concentrations of this species will be stored in cai, and its concentrations will be affected by ica.

Specifying dynamics: rxd.Reaction

Mass-action kinetics

$$\mathrm{ca} + \mathrm{buffer} \underset{kb}{\overset{kf}{\longleftrightarrow}} \mathrm{cabuffer}$$

buffering = rxd.Reaction(ca + buffer, cabuffer, kf, kb)

kf is the forward reaction rate, kb is the backward reaction rate. kb may be omitted if the reaction is unidirectional.
In a mass-action reaction, the reaction rate is proportional to the product of the concentrations of the reactants.

Repeated reactants

$$2\mathrm{H} + \mathrm{O} \underset{kb}{\overset{kf}{\longleftrightarrow}} \mathrm{H2O}$$

water_reaction = rxd.Reaction(2 * H + O, H2O, kf, kb)

Arbitrary reaction formula, e.g. Hill dynamics

$$\mathrm{a} + \mathrm{b} \longrightarrow \mathrm{c}$$

hill_reaction = rxd.Reaction(a + b, c, a ^ 2 / (a ^ 2 + k ^ 2), mass_action=False)

Hill dynamics are often used to model cooperative reactions.

rxd.Rate and rxd.MultiCompartmentReaction

rxd.Rate

Use rxd.Rate to specify an explicit contribution to the rate of change of some concentration or state variable.

```
ip3degradation = rxd.Rate(ip3, -k * ip3)
```

rxd.MultiCompartmentReaction

Use rxd.MultiCompartmentReaction when the dynamics span multiple regions; e.g. a pump or channel.

```
ip3r = rxd.MultiCompartmentReaction(ca[er], ca[cyt], kf, kb,
                                    membrane=cyt_er_membrane)
```

The rate of these dynamics is proportional to the membrane area.

Manipulating nodes

Getting a list of nodes

- nodelist = protein.nodes

Filtering a list of nodes

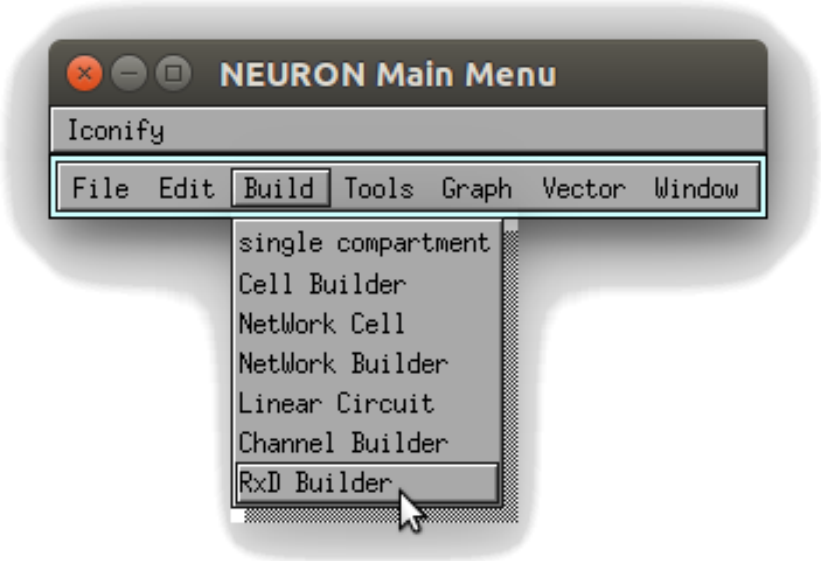
- nodelist2 = nodelist(region)
- nodelist2 = nodelist(0.5)
- nodelist2 = nodelist(section)(region)(0.5)

Other operations

- nodelist.concentration = value
- values = nodelist.concentration
- surface_areas = nodelist.surface_area
- volumes = nodelist.volume
- node = nodelist[0]

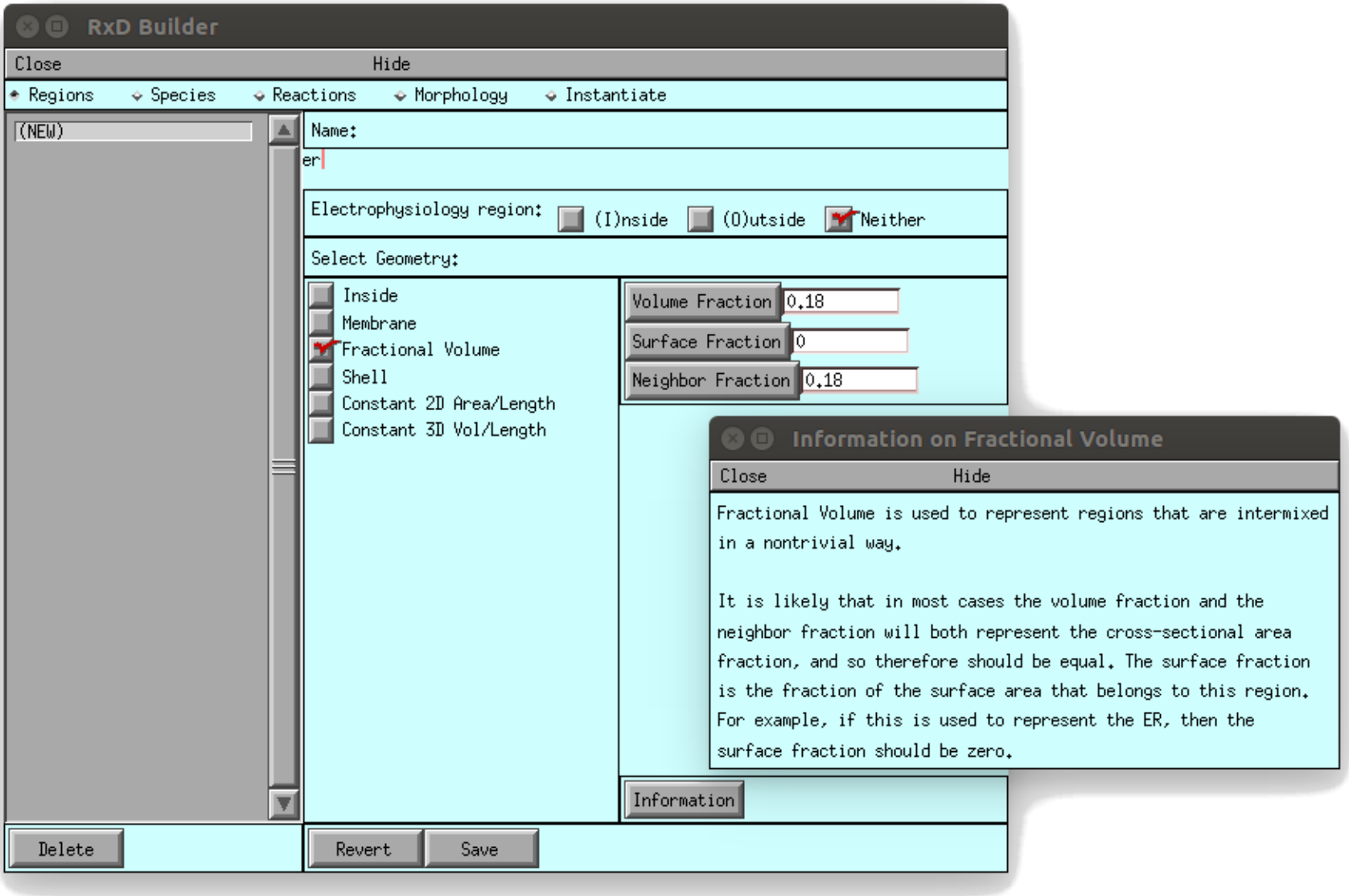
GUI

Reaction-diffusion dynamics can also be specified via the GUI. This option appears only when rxd is supported in your install (Python and scipy must be available).

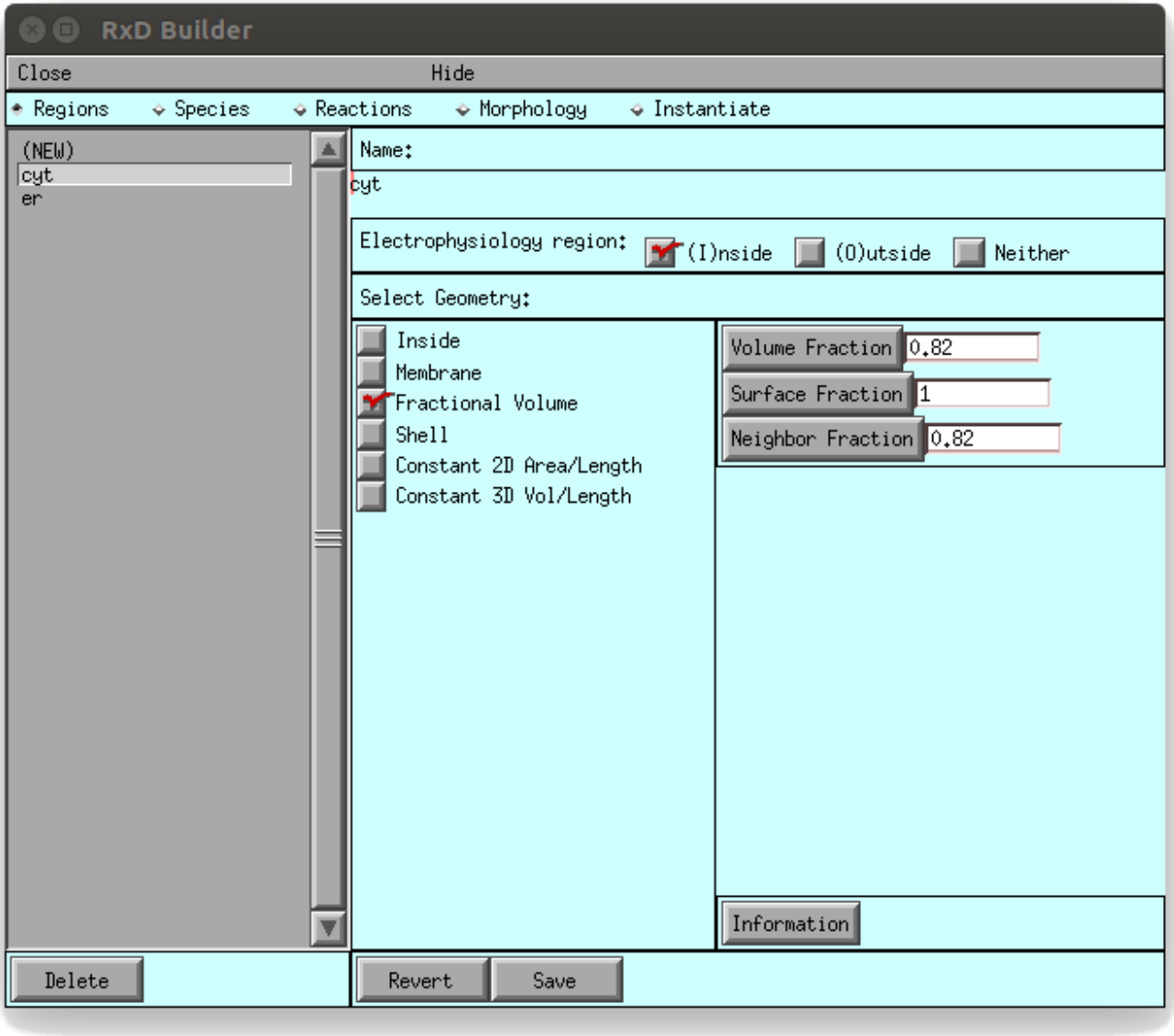


An experimental version without a scipy dependency is under development.

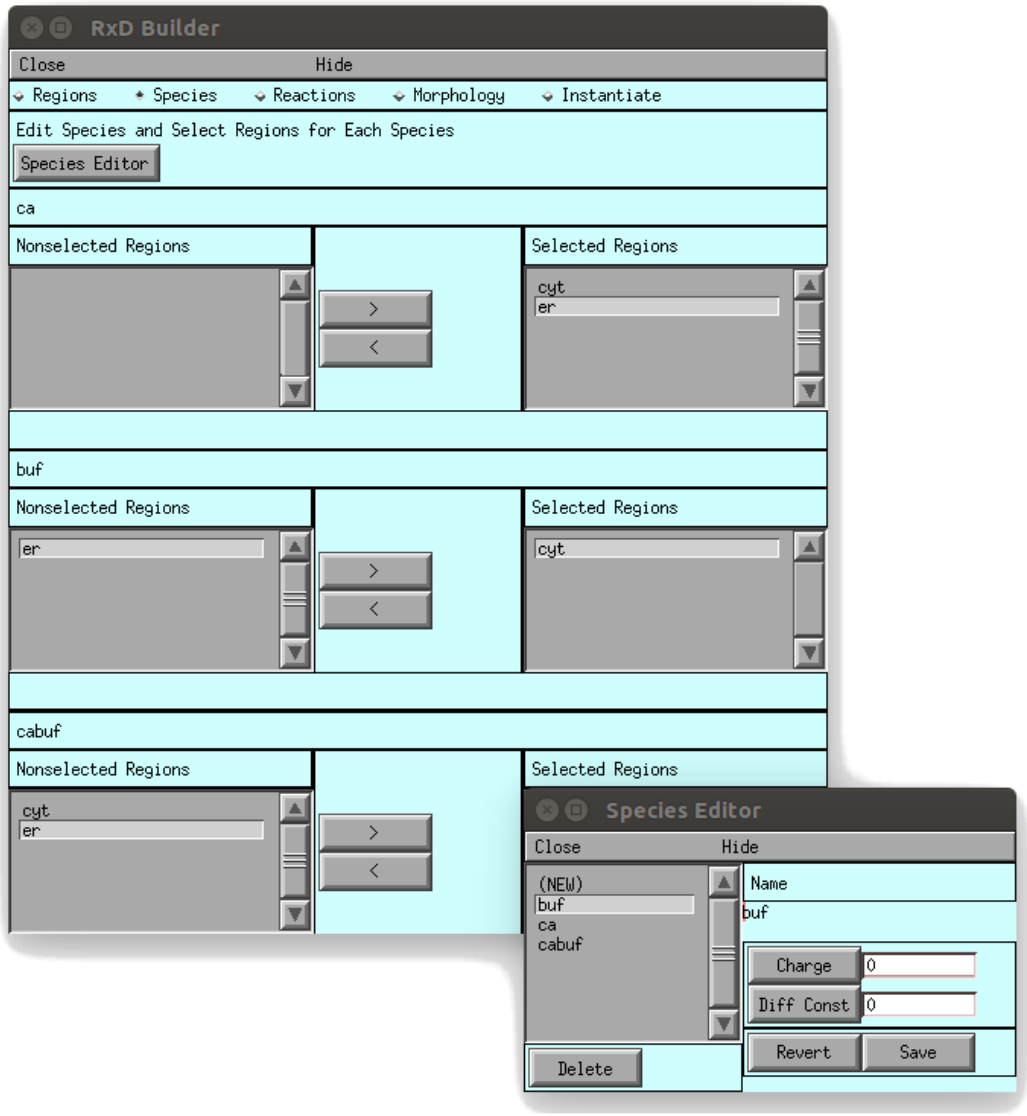
GUI


RxD Builder
Close
Hide
Regions
Species
Reactions
Morphology
Instantiate
(NEW)
Name:
er
Electrophysiology region:
(I)nside
(O)utside
Neither
Select Geometry:
Inside
Membrane
Fractional Volume
Shell
Constant 2D Area/Length
Constant 3D Vol/Length
Volume Fraction
0.18
Surface Fraction
0
Neighbor Fraction
0.18
Information
Delete
Revert
Save
Information on Fractional Volume
Close
Hide
Fractional Volume is used to represent regions that are intermixed in a nontrivial way.
It is likely that in most cases the volume fraction and the neighbor fraction will both represent the cross-sectional area fraction, and so therefore should be equal. The surface fraction is the fraction of the surface area that belongs to this region. For example, if this is used to represent the ER, then the surface fraction should be zero.

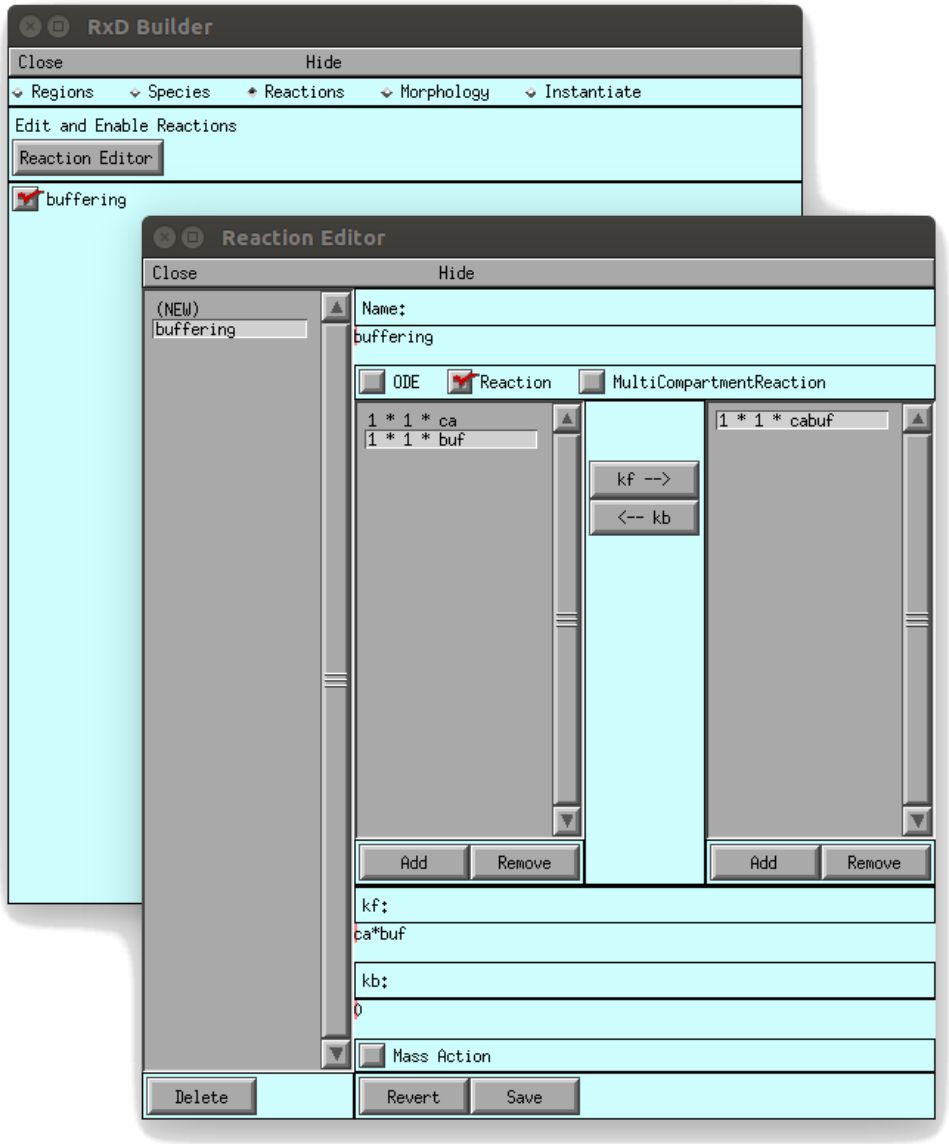
GUI


RxD Builder
Close
Hide
Regions
Species
Reactions
Morphology
Instantiate
(NEW)
cyt
er
Name:
cyt
Electrophysiology region:
(I)nside
(O)utside
Neither
Select Geometry:
Inside
Membrane
Fractional Volume
Shell
Constant 2D Area/Length
Constant 3D Vol/Length
Volume Fraction
0.82
Surface Fraction
1
Neighbor Fraction
0.82
Information
Delete
Revert
Save

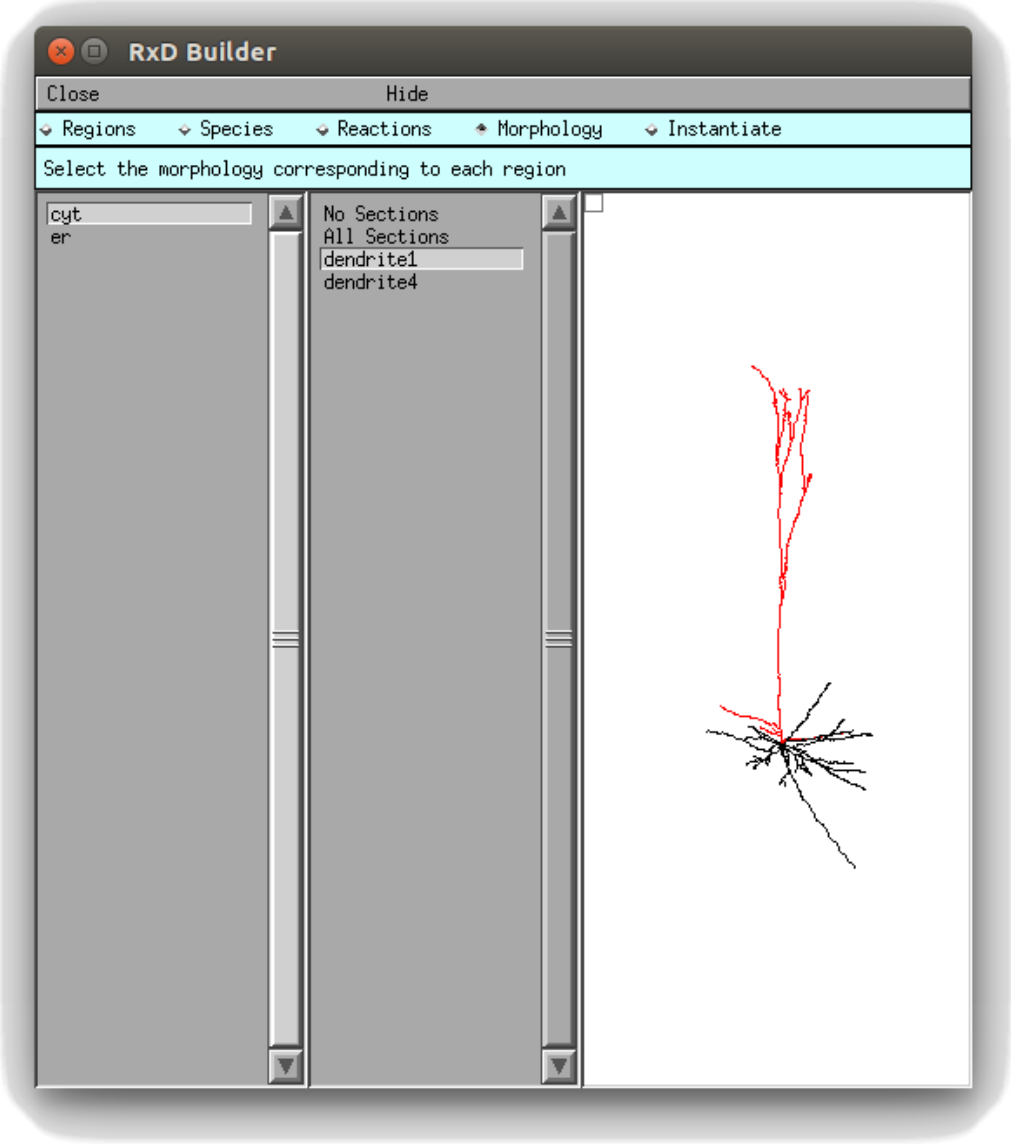
GUI


RxD Builder
Close
Hide
Regions
Species
Reactions
Morphology
Instantiate
Edit Species and Select Regions for Each Species
Species Editor
ca
Nonselected Regions
Selected Regions
cyt
er
buf
Nonselected Regions
Selected Regions
er
cyt
cabuf
Nonselected Regions
Selected Regions
cyt
er
Species Editor
Close
Hide
(NEW)
buf
ca
cabuf
Name
buf
Charge
0
Diff Const
0
Delete
Revert
Save

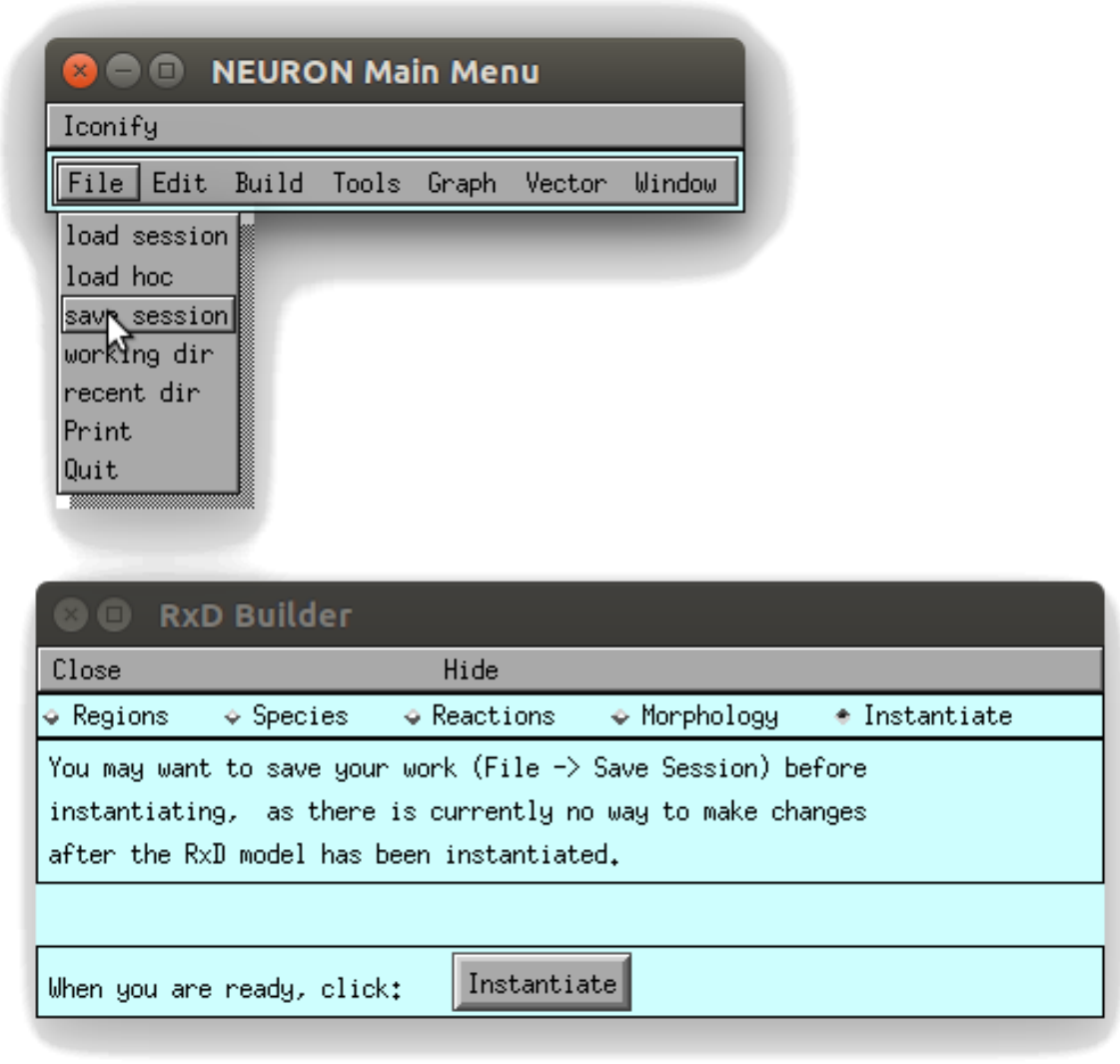
GUI


RxD Builder
Close
Hide
Regions
Species
Reactions
Morphology
Instantiate
Edit and Enable Reactions
Reaction Editor
buffering
Reaction Editor
Close
Hide
(NEW)
buffering
Name:
buffering
ODE
Reaction
MultiCompartmentReaction
1 * 1 * ca
1 * 1 * buf
kf -->
<-- kb
1 * 1 * cabuf
Add
Remove
Add
Remove
kf:
ca*buf
kb:
0
Mass Action
Delete
Revert
Save

GUI


RxD Builder
Close
Hide
Regions
Species
Reactions
Morphology
Instantiate
Select the morphology corresponding to each region
cyt
er
No Sections
All Sections
dendrite1
dendrite4

GUI

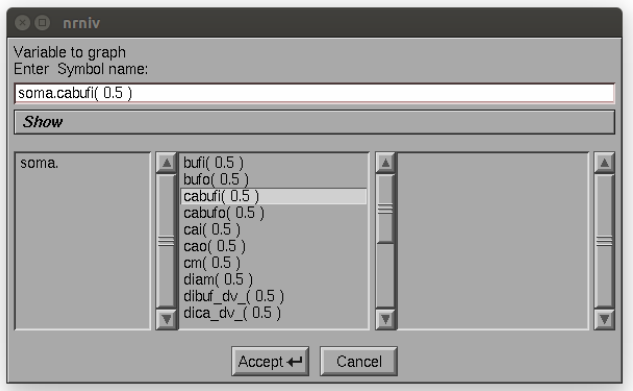

NEURON Main Menu
Iconify
File Edit Build Tools Graph Vector Window
load session
load hoc
save session
working dir
recent dir
Print
Quit
RxD Builder
Close Hide
Regions Species Reactions Morphology Instantiate
You may want to save your work (File -> Save Session) before
instantiating, as there is currently no way to make changes
after the RxD model has been instantiated.
When you are ready, click: Instantiate

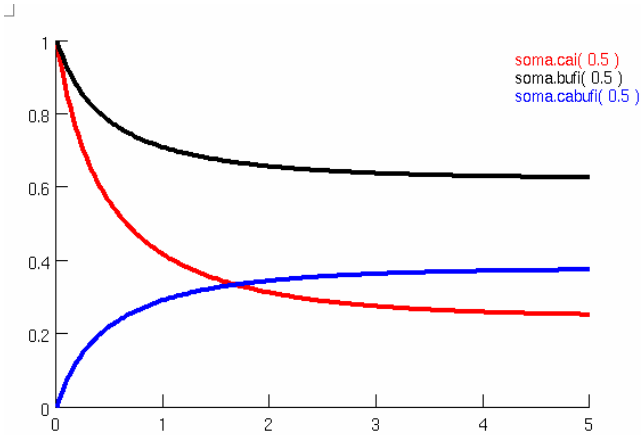
Example: Calcium buffering

```
from neuron import h, rxd, gui

h('create soma')
soma_region = rxd.Region([h.soma], nrn_region='i')

ca = rxd.Species(soma_region, initial=1,
                 name='ca', charge=2)
buf = rxd.Species(soma_region, initial=1,
                  name='buf')
cabuf = rxd.Species(soma_region, initial=0,
                    name='cabuf')

buffering = rxd.Reaction(2 * ca + buf, cabuf, 1, 0.1)
```

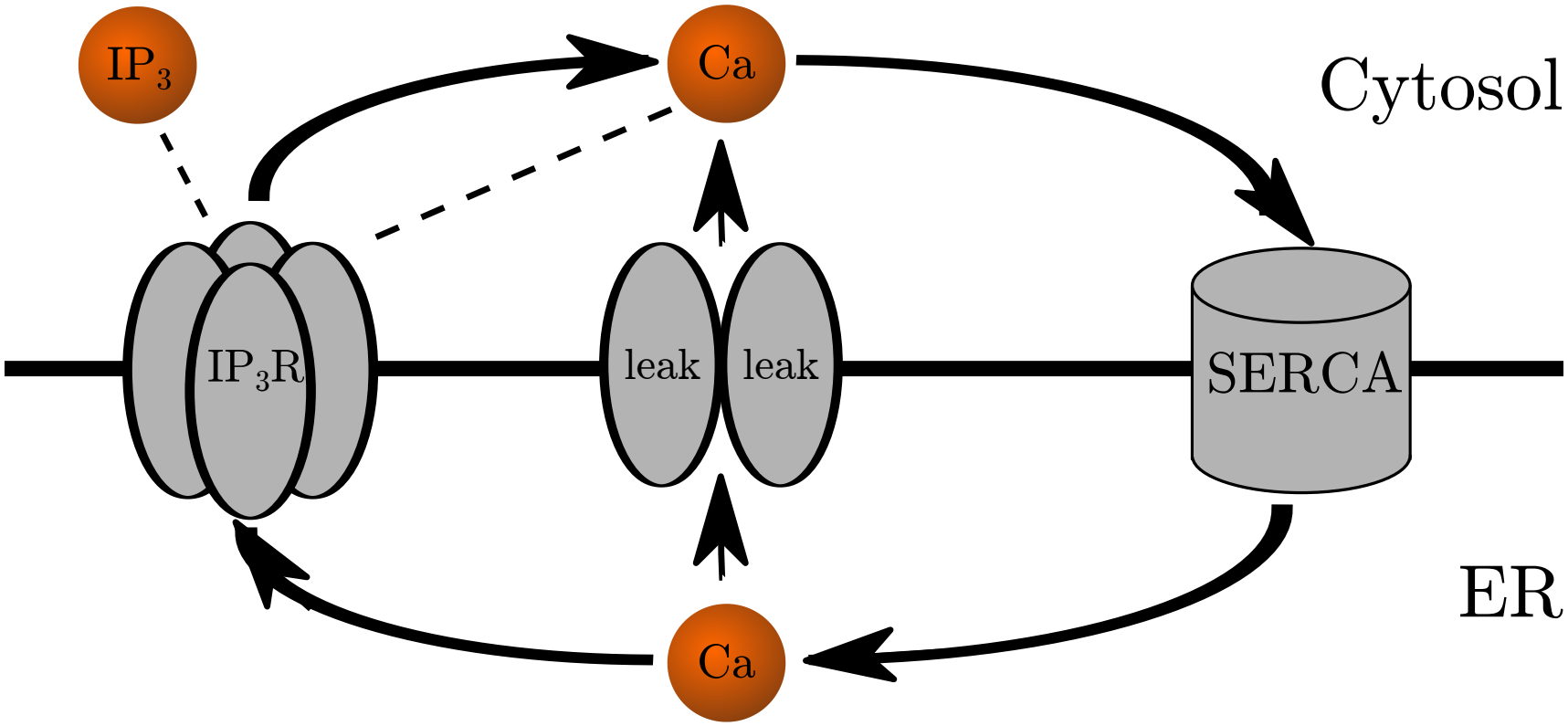
In this example, we suppose each buffer molecule binds two molecules of calcium. Other buffers have different properties.

Use the GUI to create a graph and run the simulation.





Example: Calcium wave dynamics



Wagner et al. 2004. *Cell Calcium*. DOI: 10.1016/j.ceca.2003.10.009
Neymotin et al. 2015. *Neural Computation*. DOI: 10.1162/NECO_a_00712

ModelDB: 168874

There are three regions:

Cytosol:

```
cyt_geom = rxd.FractionalVolume(0.83, surface_fraction=1)
cyt = rxd.Region(h.allsec(),
                 nrn_region='i',
                 geometry=cyt_geom)
```

Endoplasmic Reticulum (ER):

```
er = rxd.Region(h.allsec(),
                geometry=rxd.FractionalVolume(0.17))
```

The ER membrane:

```
er_membrane = rxd.Region(h.allsec(),
                         geometry=rxd.ScalableBorder(1))
```

There are two species:

Calcium:

```
def ca_init(node):
    return ca_cyt0 if node.region == cyt else ca_er0

ca = rxd.Species([cyt, er],
                 d=caDiff,
                 name='ca',
                 charge=2,
                 initial=ca_init)
```

Inositol trisphosphate (IP3):

```
ip3 = rxd.Species(cyt,
                  d=ip3Diff,
                  initial=ip3_init)
```

Each pump and channel corresponds to its own "reaction":

Leak:

```
leak = rxd.MultiCompartmentReaction(
    ca[er],
    ca[cyt],
    gleak,
    gleak,
    membrane=er_membrane)
```

SERCA:

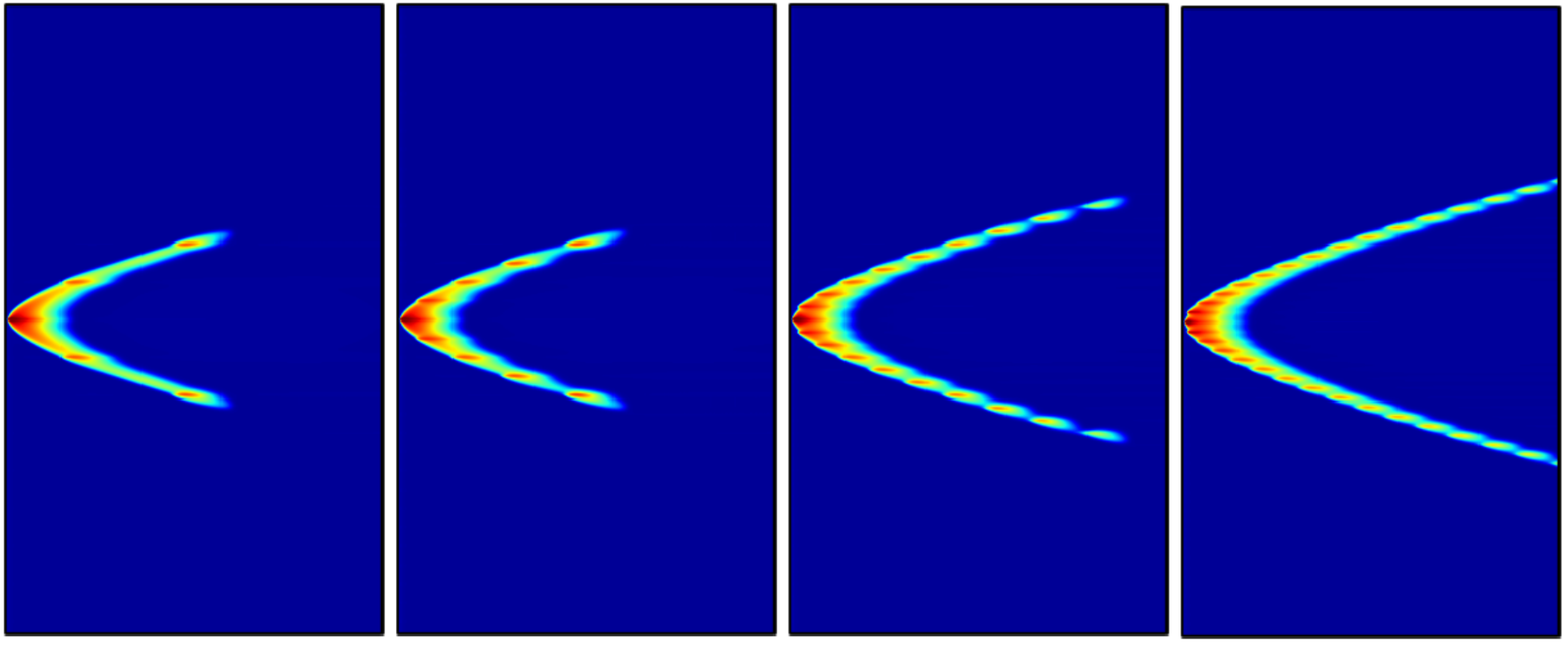
```
serca = rxd.MultiCompartmentReaction(
    ca[cyt],
    ca[er],
    gserca * (ca[cyt])**2 / (Kserca**2 + (ca[cyt])**2),
    membrane=er_membrane,
    mass_action=False)
```

The IP_3R is more complicated because it is essentially a channel that opens and closes slowly as a function of calcium concentration.

IP_3R:

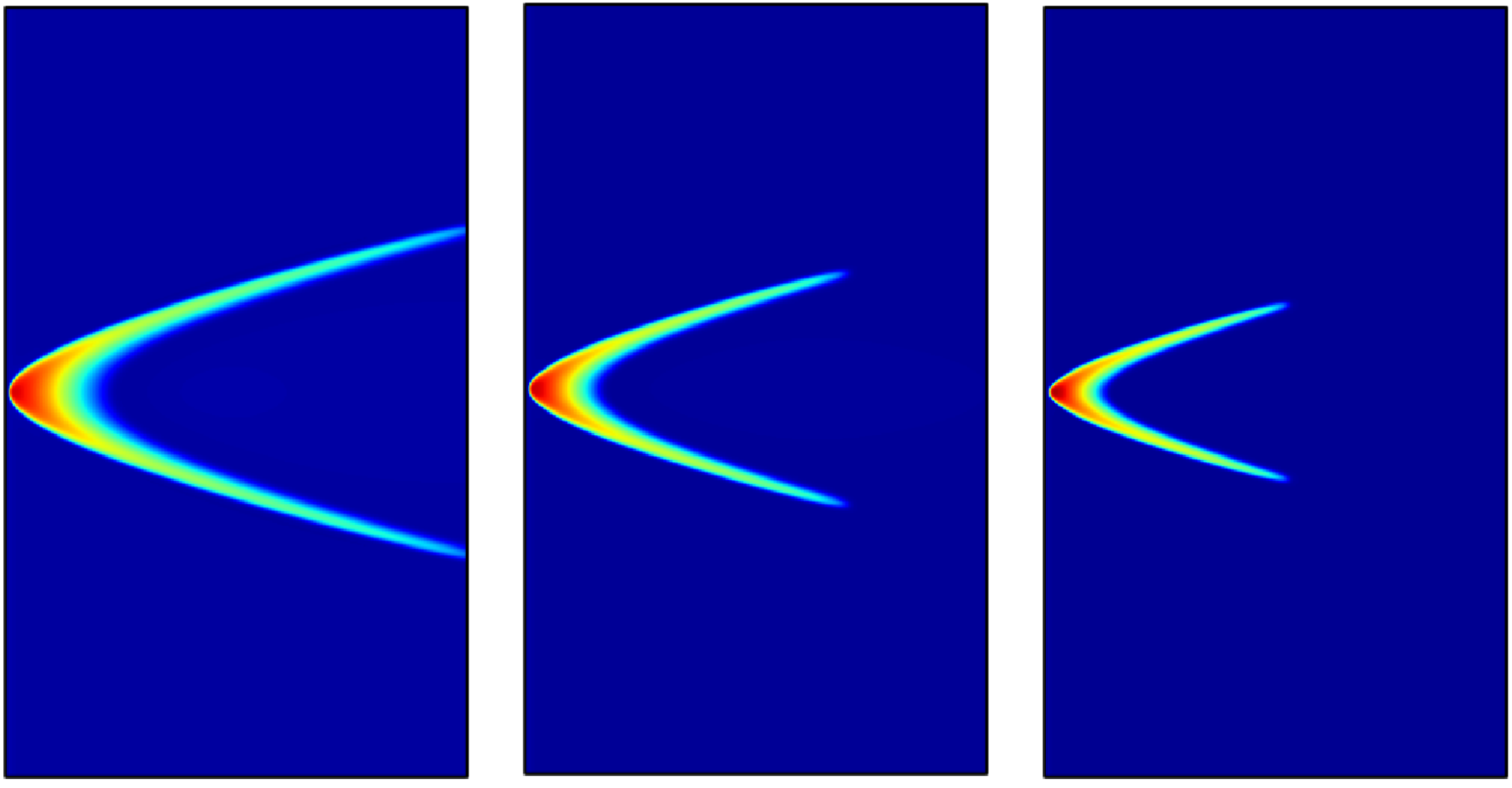
```
# slow gating due to calcium
ip3r_gate_state = rxd.State(er_membrane, initial=0.8)
h_gate = ip3r_gate_state[er_membrane]
ip3rg = rxd.Rate(h_gate,
                 (1. / (1 + ca[cyt] / scale) - h_gate) / tau)

# fast gating due to calcium and IP3
minf = ip3[cyt] * ca[cyt] / (ip3[cyt] + Kip3) / (ca[cyt] + Kact)

# same permeability for either direction of flow
k = gip3r[cyt] * (minf * h_gate) ** 3

# the actual channel
ip3r = rxd.MultiCompartmentReaction(
    ca[er], ca[cyt], k, k, membrane=er_membrane)
```

Reducing IP_3R spacing facilitates wave propagation



More closely spaced $IP_3R \longrightarrow$

Increasing SERCA activity weakens wave propagation



Increasing SERCA activity $\longrightarrow$

Interacting with the rest of NEURON

node._ref_concentration or node._ref_value returns a pointer.

Recording traces

```
v = h.Vector()
v.record(ca.nodes[0]._ref_concentration)
```

Plotting

```
g = h.Graph()
g.addvar('ca[er][dend](0.5)', ca.nodes(er)(dend)(0.5)[0]._ref_concentration)
h.graphList[0].append(g)
```

Tips

dir(·)

To find out what methods and properties are available, use dir:

```
dir(ca.nodes)
```

CVode and atol

NEURON's variable step solver has a default absolute tolerance of 0.001.

Since NEURON measures concentration in mM and many cell biology concentrations are in μM, this tolerance may be too high. Try lowering it:

```
h.CVode().atol(1e-8)
```

3D Simulations

The Third Dimension

Specifying 3D Simulations

Just add one line of code[2]:

```
rxd.set_solve_type(dimension=3)
all = rxd.Region(h.allsec())
ca = rxd.Species(all, d=1)
ca.initial = lambda node: 1 if node.x3d < 50 else 0
```

Plotting

Get the concentration values expressed on a regular 3D grid via nodelist.value_to_grid()

```
values = ca.nodes.value_to_grid()
```

Pass the result to a 3d volume plotter, such as Mayavi's VolumeSlicer:

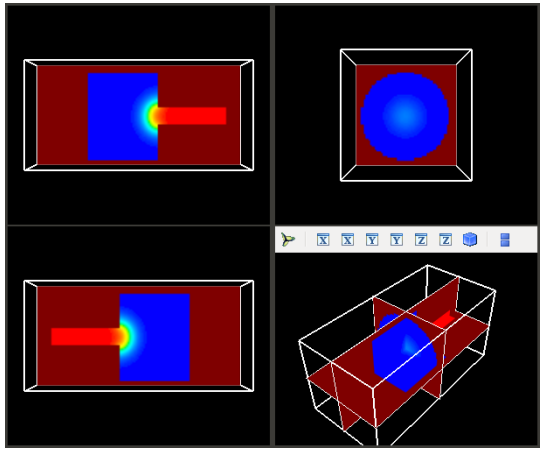
```
graph = VolumeSlicer(data=ca.nodes.value_to_grid())
graph.configure_traits()
```

[2] `rxd.set_solve_type` can optionally take a list of sections as its first argument; in that case only the specified sections will be simulated in three dimensions.

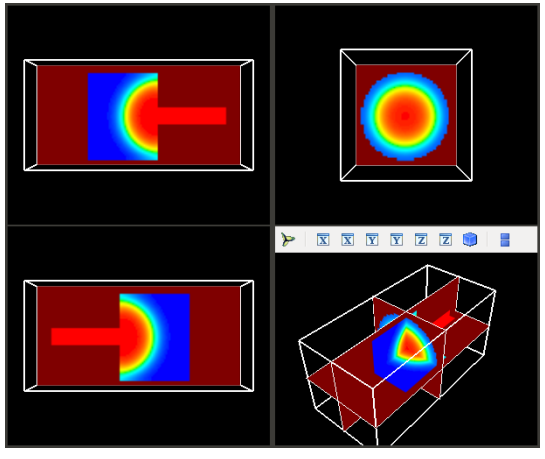
Example: wave curvature

```
from neuron import h, gui, rxd
import volume_slicer

sec1, sec2 = h.Section(), h.Section()
h.pt3dadd(2, 0, 0, 2, sec=sec1)
h.pt3dadd(9.9, 0, 0, 2, sec=sec1)
h.pt3dadd(10, 0, 0, 2, sec=sec1)
h.pt3dadd(10, 0, 0, 10, sec=sec2)
h.pt3dadd(18, 0, 0, 10, sec=sec2)

def do_init(node):
    return 1 if node.x3d < 8 else 0

all3d = rxd.Region(h.allsec(), dimension=3)
ca = rxd.Species(all3d, initial=do_init, d=0.05)
r = rxd.Rate(ca, -ca * (1 - ca) * (0.1 - ca))

def plot_it():
    graph = volume_slicer.VolumeSlicer(
        data=ca.nodes.value_to_grid(),
        vmin=0, vmax=1)
    graph.configure_traits()

h.finitialize()
for t in [30, 60]:
    h.continuerun(t)
    plot_it()
```

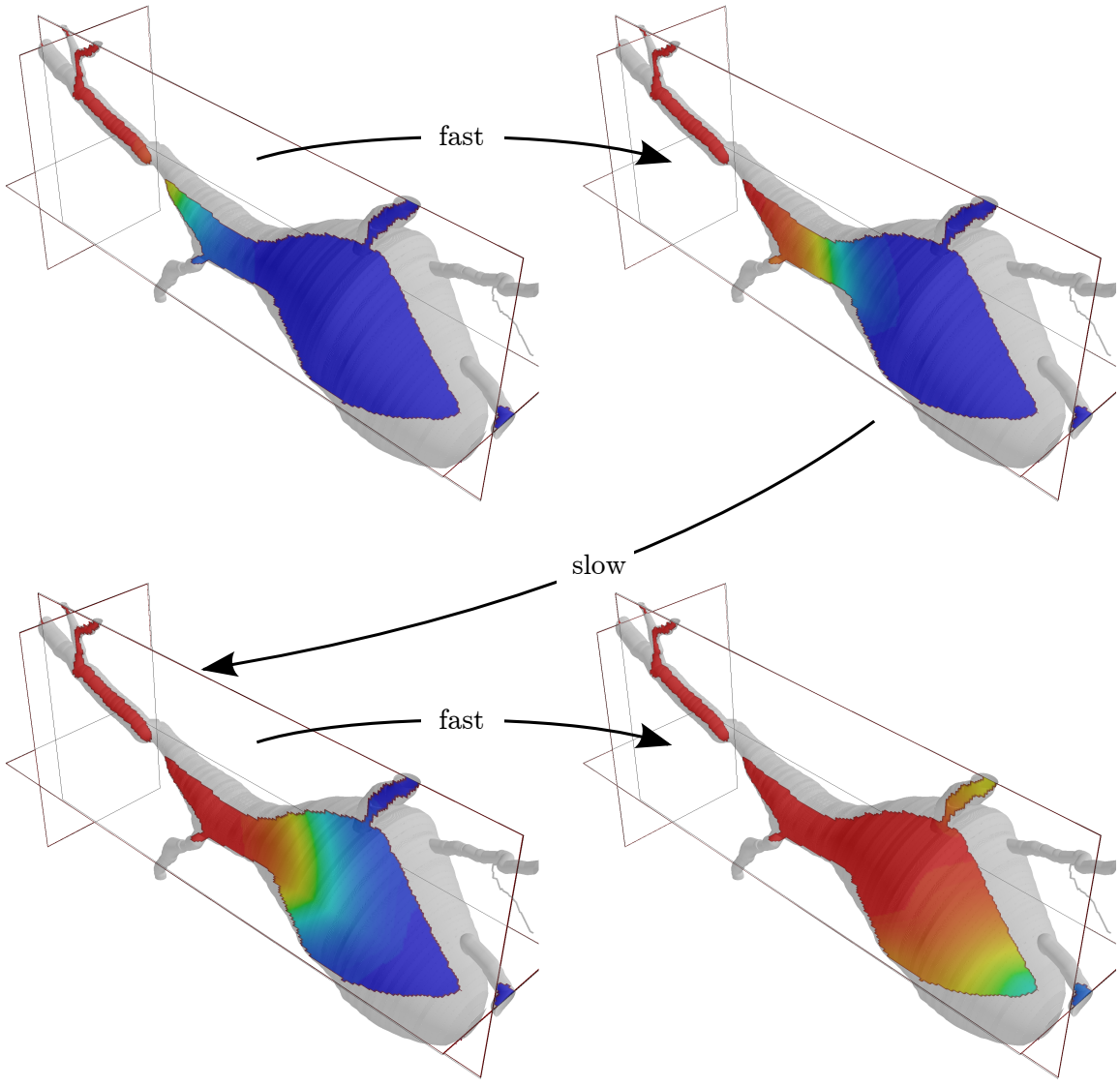
t = 30



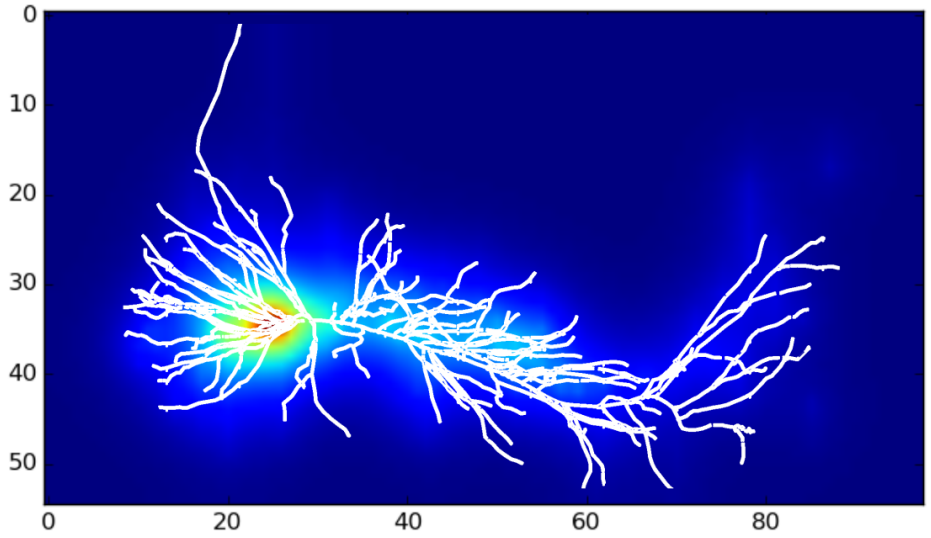
t = 60



Example: wave curvature at soma entry



Coming soon



- Extracellular diffusion
- Stochastic reaction-diffusion
- SBML support
- Better reaction-diffusion performance
- Parallel reaction-diffusion

For more information, see:

Journal Articles on Reaction-Diffusion in NEURON

- McDougal, R. A., Hines, M. L., Lytton, W. W. (2013). Reaction-diffusion in the NEURON simulator. *Frontiers in Neuroinformatics*, 7.
- McDougal, R. A., Hines, M. L., Lytton, W. W. (2013). Water-tight membranes from neuronal morphology files. *Journal of Neuroscience Methods*, 220(2), 167-178.

Online Resources

- NEURON Forum
- Programmer's Reference
- NEURON Reaction-Diffusion Tutorials