

Extracellular reaction-diffusion modeling in NEURON

Adam Newton

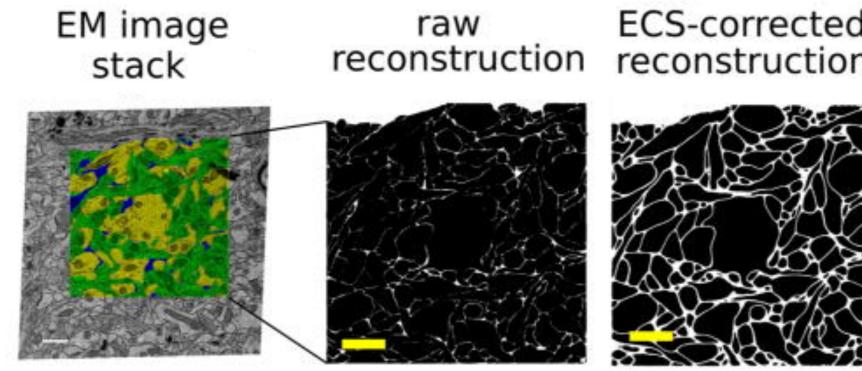
*William Lytton
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Outline

- ♦ Macroscopic model of extracellular space
- ♦ Extracellular reaction-diffusion in NEURON
- ♦ Example models of ischemic stroke

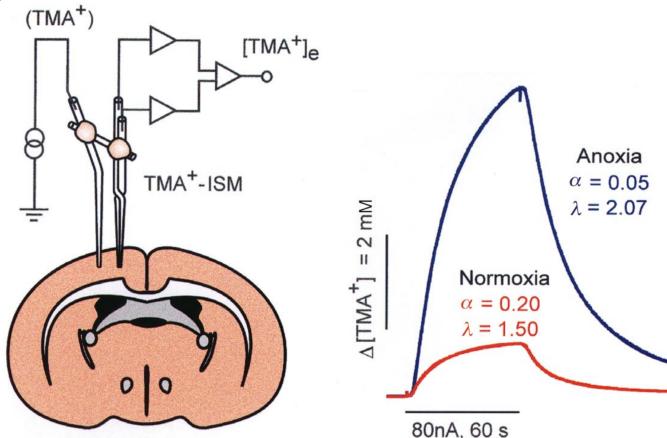
Extracellular reaction-diffusion

- Extracellular space (ECS) composed of sheets and tunnels



(Kinney et al. Journal of Comparative Neurology 2013)

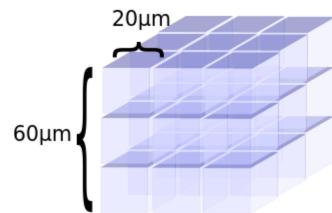
- Coarse-grained volume averaged approximation
 - Tortuosity (λ)
 - Porosity (α)



(Nicholson and Syková Trends in neurosciences 1998)

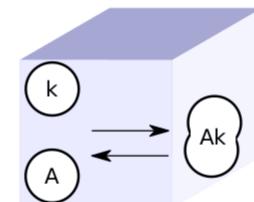
Extracellular rxd in NEURON

- Uses the same simple Python interface



```
ecs = rxd.Extracellular(xlo=-30,ylo=-30,zlo=-30,  
xhi=30,yhi=30,zhi=30,dx=20,  
tortuosity=1.6,volume_fraction=0.2)
```

```
astrocytic_buffering = rxd.Reaction(A + k, AK, kf, kb)
```



(Newton et. al. Frontiers in neuroinformatics 2018)

- Rectangular cuboid grid

- Supports
 - anisotropy
 - heterogeneous tissue characteristics

Extracellular rxd in NEURON

- Initial conditions and boundary conditions

```
k = rxd.Species(ecs, name='k', d=2.62, charge=1,  
initial=lambda nd: 40 if nd.x3d**2 + nd.y3d**2 + nd.z3d**2 < 100**2 else 3.5,  
ecs_boundary_conditions=3.5
```

- Accessing and recording concentrations

```
k[ecs].states3d
```

```
ecs_vec = h.Vector()  
ecs_vec.record(k[ecs].node_by_location(0,0,0)._ref_value)
```

Extracellular rxd in NEURON

- Inhomogeneous diffusion characteristics

Lx, Ly, Lz = 1000, 1000, 1000

alpha0, alpha1 = 0.07, 0.2

tort0, tort1 = 1.8, 1.6

r0 = 100

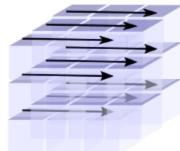
```
def alpha(x, y, z) :  
    return alpha0 if x**2 + y**2 + z**2 < r0**2  
    else min(alpha1, alpha0 +(alpha1-alpha0)  
        *((x**2+y**2+z**2)**0.5-r0)/(Lx/2))
```

```
def tort(x, y, z) :  
    return tort0 if x**2 + y**2 + z**2 < r0**2  
    else max(tort1, tort0 - (tort0-tort1)  
        *((x**2+y**2+z**2)**0.5-r0)/(Lx/2))
```

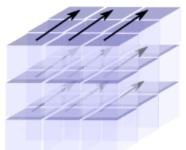
```
ecs = rxd.Extracellular(-Lx/2.0, -Ly/2.0,  
-Lz/2.0, Lx/2.0, Ly/2.0, Lz/2.0, dx=10,  
volume_fraction=alpha, tortuosity=tort)
```

Extracellular rxd in NEURON

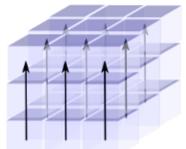
- Douglas-Gunn Alternating Direction implicit method



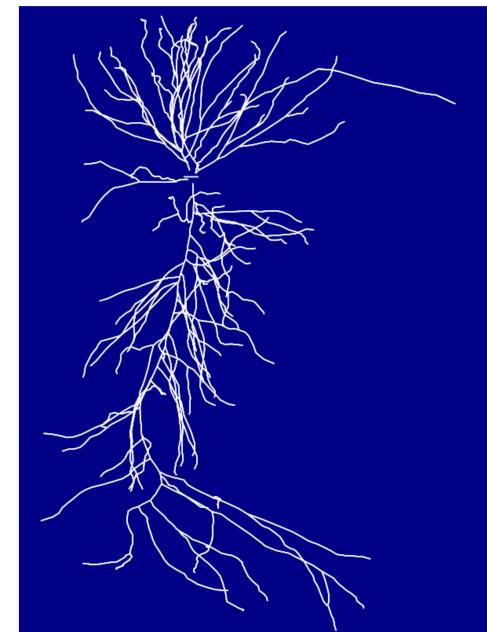
$$1 - \frac{r_x}{2} \nabla_x^2 \phi^{(t+\frac{1}{3})} = \left(\frac{r_x}{2} \nabla_x^2 + r_y \nabla_y^2 + r_z \nabla_z^2 \right) \phi^{(t)}$$



$$1 - \frac{r_y}{2} \nabla_y^2 \phi^{(t+\frac{2}{3})} = -\frac{r_y}{2} \nabla_y^2 \phi^{(t+\frac{1}{3})}$$

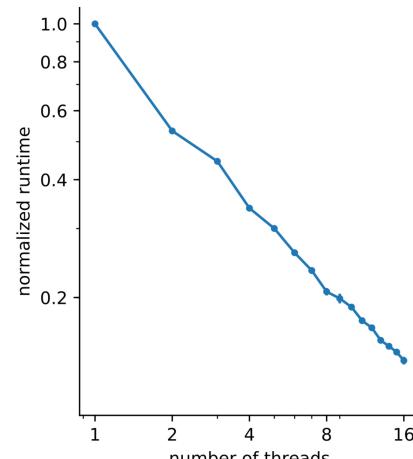


$$1 - \frac{r_z}{2} \nabla_z^2 \phi^{(t+1)} = -\frac{r_z}{2} \nabla_z^2 \phi^{(t+\frac{2}{3})}$$

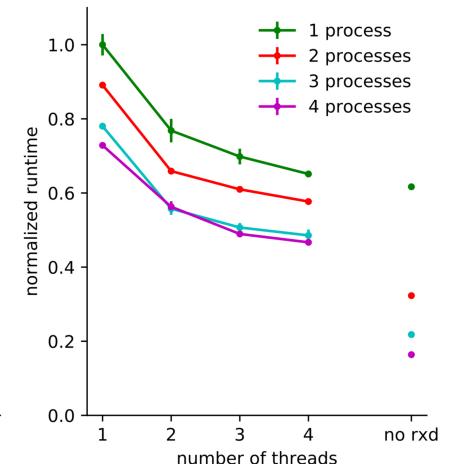


- Calculations via compiled C-code
- Parallelized with a thread pool
- Benefits from multiprocessor parallelization of electrophysiology

rxd only

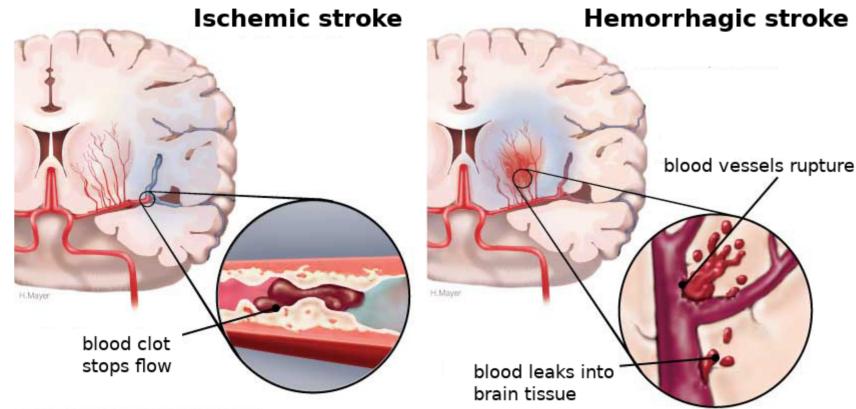


electrophysiology
and *rxd*

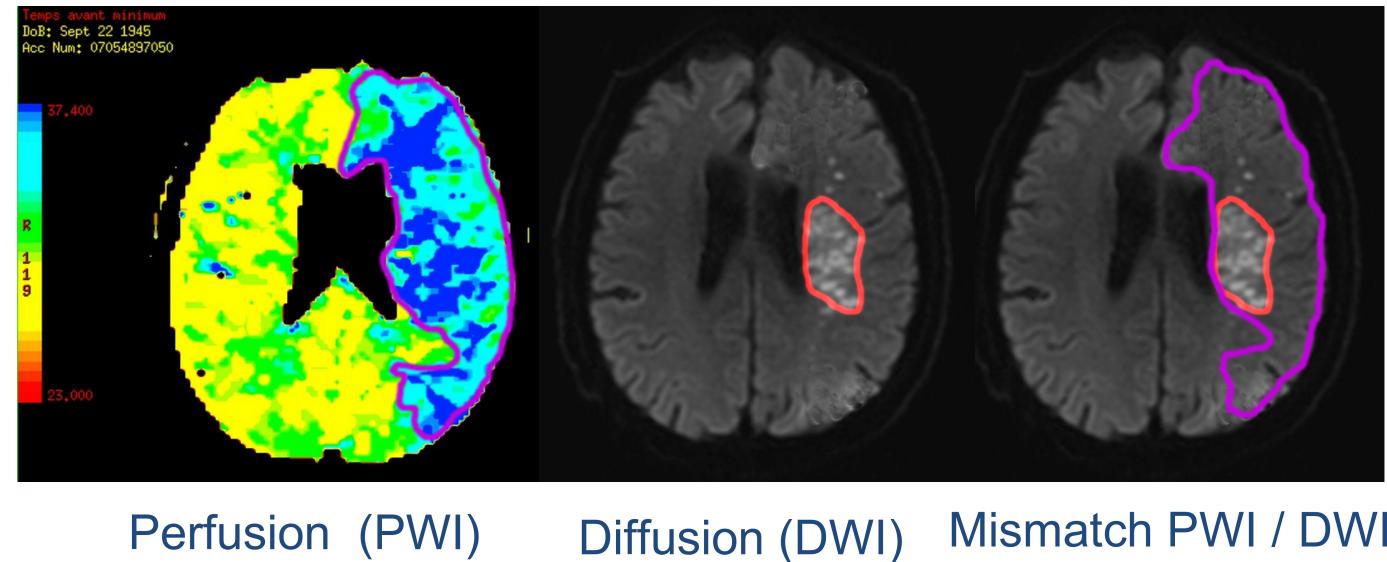


Ischemic stroke

- ◆ Occlusion of a blood vessel in the brain
- ◆ Three regions of tissue
- ◆ Treatment by reperfusion
- ◆ Neuroprotective therapies are still in preclinical development



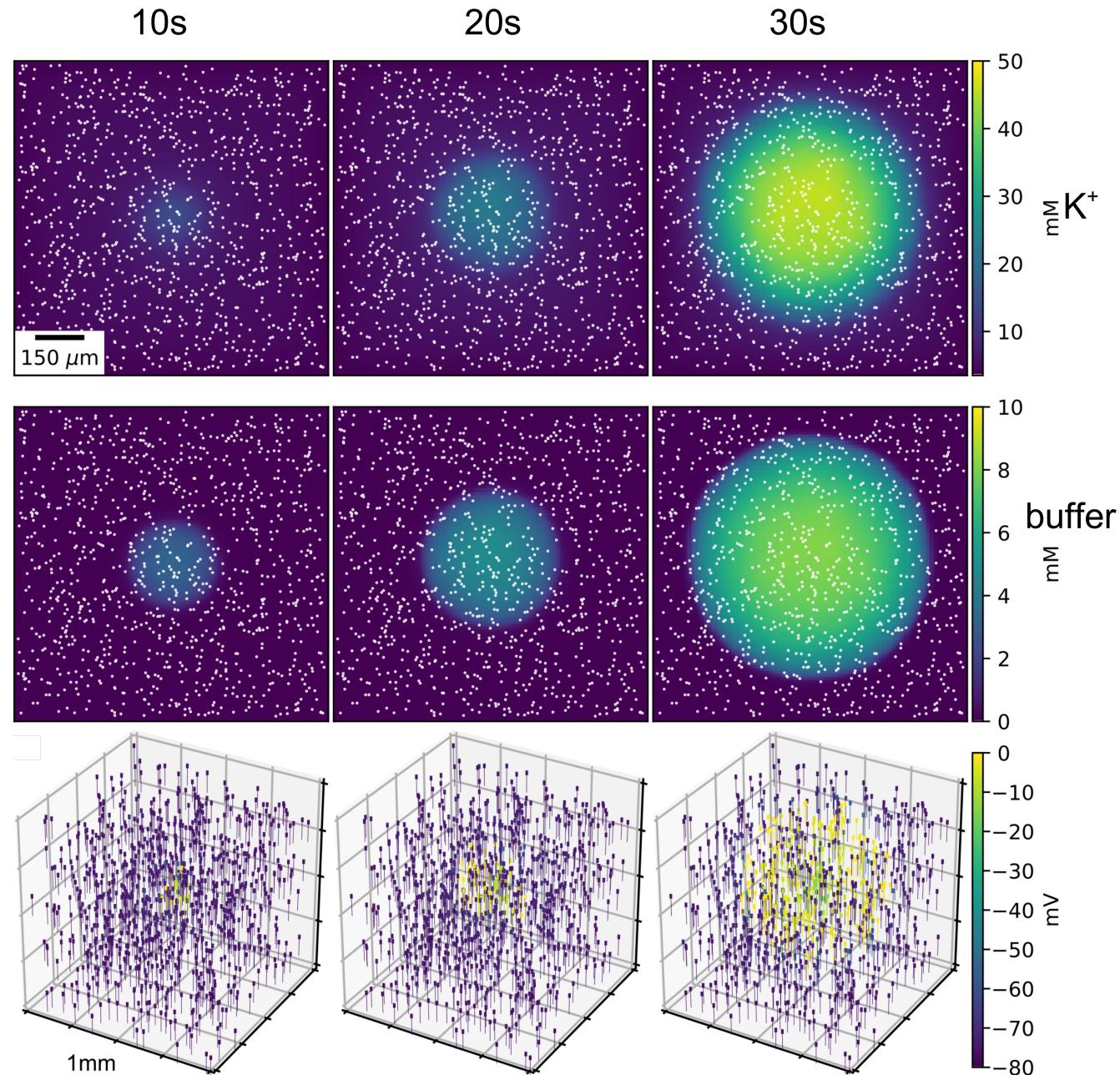
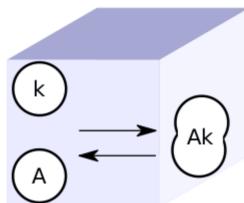
(neurowiki2013.wikidot.com)



(Drier et al. Proc. Intl. Soc. Mag. Reson. Med. 2011)

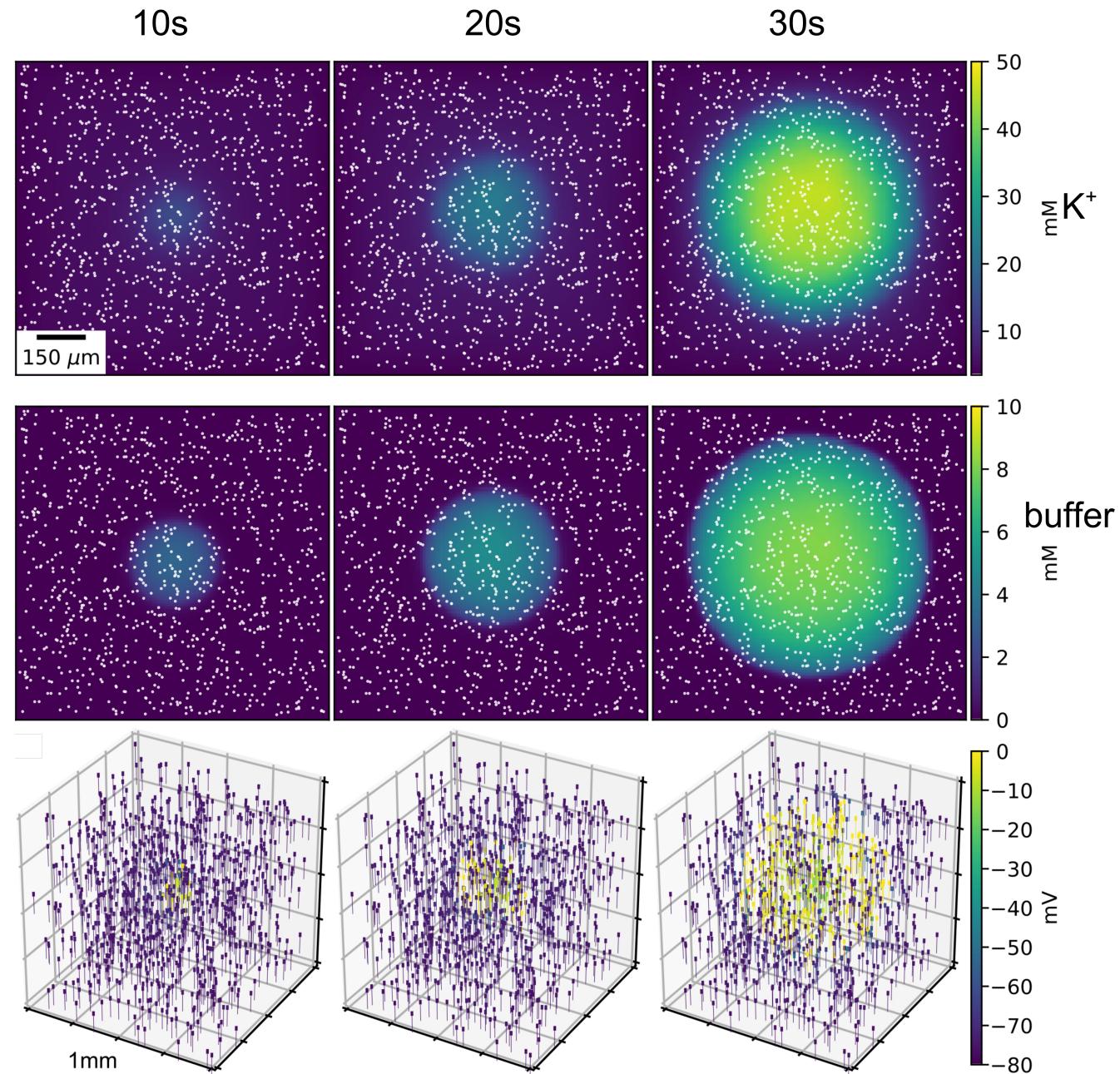
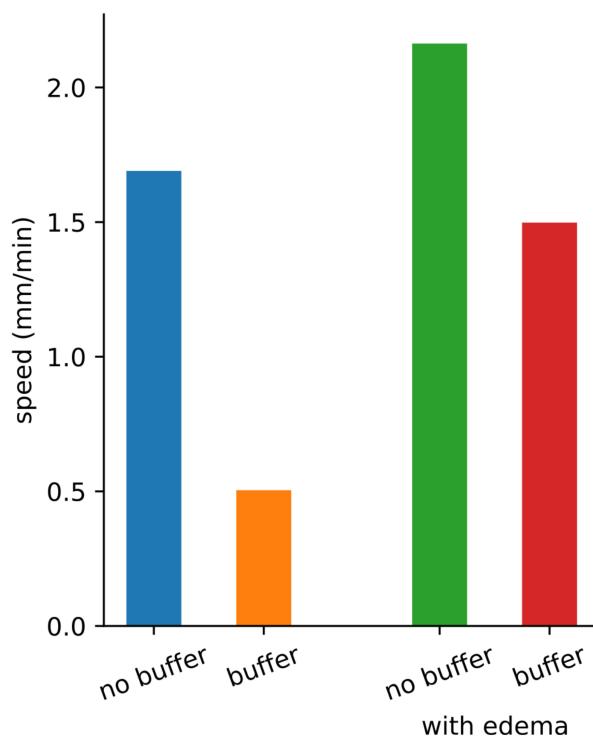
Spreading depression

- 90,000 neurons in 1 mm^3 of extracellular space.
- Model K^+ and Na^+
- Astrocytic buffering with a phenomenology model.



Spreading depression

- Altered tissue characteristics to simulate edema



Spreading depression

```
from neuron.crx import rxdmath
```

```
k = rxd.Species(ecs, name='k', d=2.62, charge=1,  
    initial=lambda nd: 40 if nd.x3d**2 + nd.y3d**2 + nd.z3d**2 < 100**2 else 3.5,  
    ecs_boundary_conditions=3.5)
```

```
na = rxd.Species(ecs, name='na', d=1.78, charge=1,  
    initial=133,  
    ecs_boundary_conditions=133)
```

#Glia buffering parameters

```
kb = 0.0008
```

```
kth = 15.0
```

```
kf = kb / (1.0 + rxdmath.exp(-(k - kth)/1.15))
```

```
Bmax = 10
```

#Free buffer

```
A = rxd.Species(ecs, name='buffer', charge=1, d=0, initial=Bmax)
```

#Bound buffer

```
AK = rxd.Species(ecs, name='bound', charge=1, d=0, initial=0)
```

```
buffering = rxd.Reaction(A + k, AK, kf, kb)
```

Summary

- Macroscopic modeling of extracellular space
- Extracellular support in the NEURON crxd module
- Example applications to ischemic stroke

Poster P269

Extracellular reaction-diffusion in the NEURON simulator: modeling ischemic stroke

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Reaction-diffusion

NEURON has been extended to include coarse-grained macroscopic models of the extracellular space.

Ischemic stroke

Ischemic stroke is a metabolic phenomena, with temporal scales from minutes to hours. It is a spatially heterogeneous process, leading to regions of brain damage.

Spreading depression

The coarse-grained model describes the spread of extracellular metabolic depression across the extracellular space.

Cellular and sub-cellular scales

We can now "zoom-in" to a detailed cellular and sub-cellular scale to study mechanisms of cell death.

Performance

Performance is improved by using a hybrid approach where the extracellular space is modeled with reaction-diffusion and the intracellular space with multiprocessor parallelism.

NetPyNE

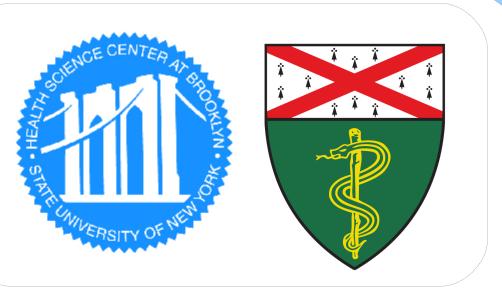
NetPyNE facilitates research towards development and analysis, working with multiple models.

References

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