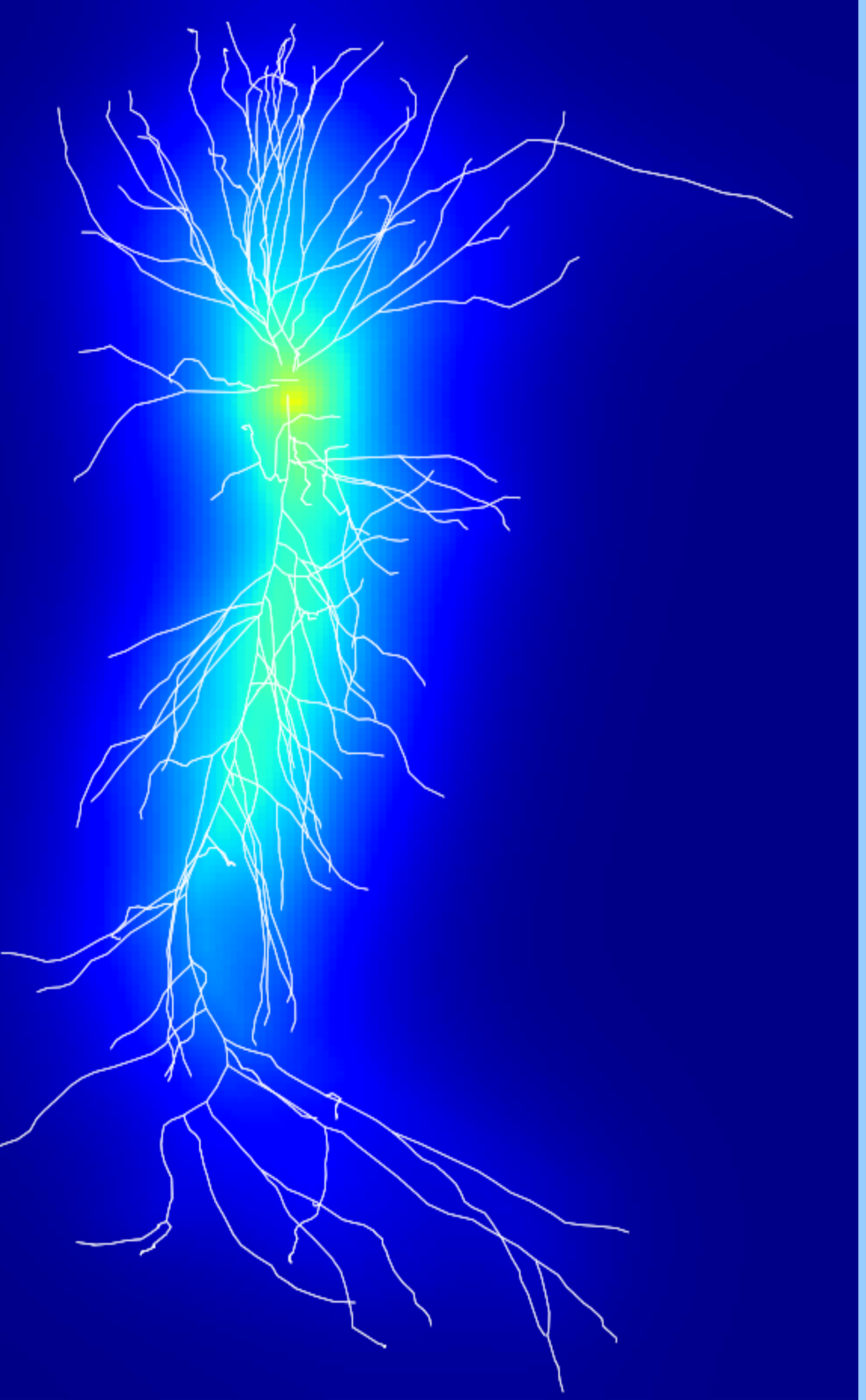


Extracellular reaction-diffusion modeling in NEURON

Adam Newton

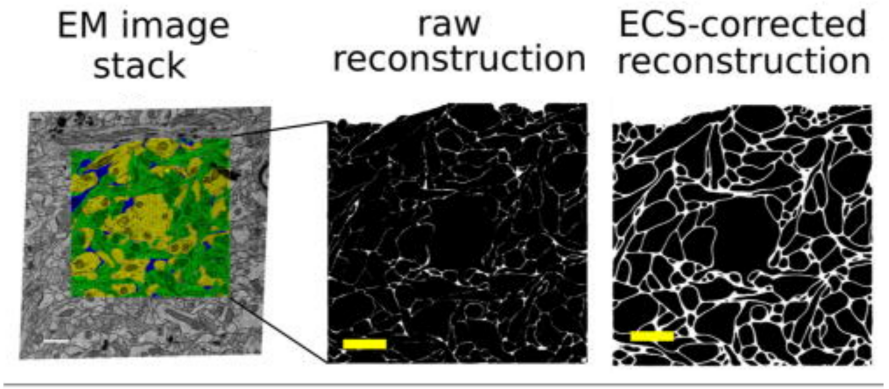
William Lytton
Robert McDougal

Outline

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

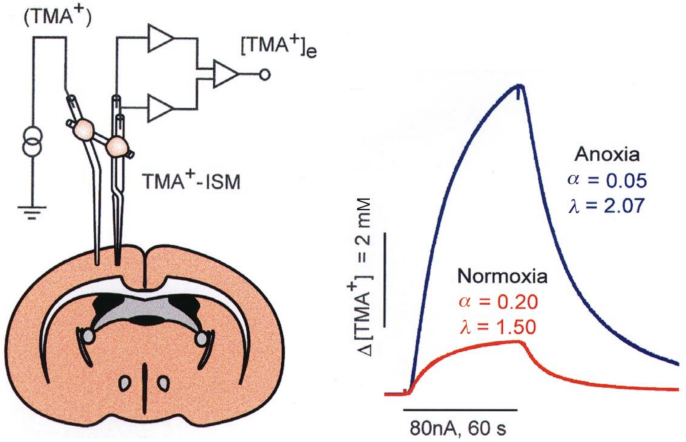
Extracellular reaction-diffusion

- Extracellular space (ECS) composed of sheets and tunnels



(Kinney et al. Journal of Comparative Neurology 2013)

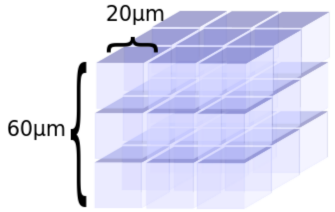
- Coarse-grained volume averaged approximation
  - Tortuosity (λ)
  - Porosity (α)



(Nicholson and Syková Trends in neurosciences 1998)

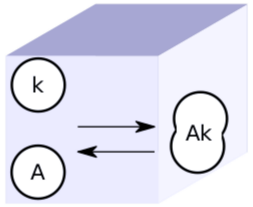
Extracellular rxd in NEURON

- 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)
```

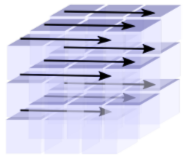
Extracellular rxd in NEURON

- Inhomogeneous diffusion characteristics

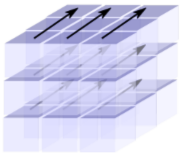
```
Lx, Ly, Lz = 1000, 1000, 1000
alpha0, alpha1 = 0.07, 0.2
tort0, tort1 = 1.8, 1.6
r0 = 100

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

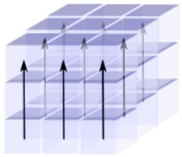
- Douglas-Gunn Alternating Direction implicit method



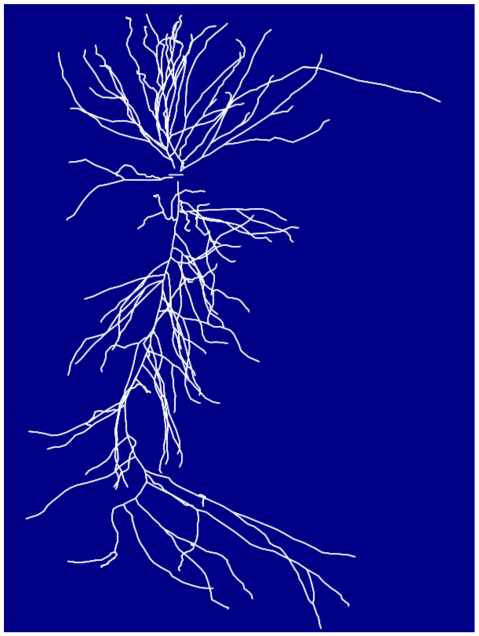
$$1 - \frac{r_x}{2}\nabla_x^2\phi^{\left(t+\frac{1}{3}\right)} = \left(\frac{r_x}{2}\nabla_x^2 + r_y\nabla_y^2 + r_z\nabla_z^2\right)\phi^{(t)}$$



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

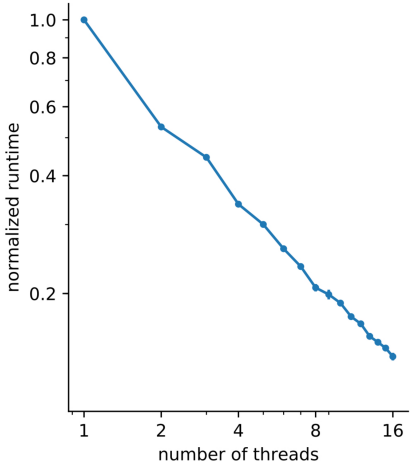


$$1 - \frac{r_z}{2}\nabla_z^2\phi^{(t+1)} = -\frac{r_z}{2}\nabla_z^2\phi^{\left(t+\frac{2}{3}\right)}$$

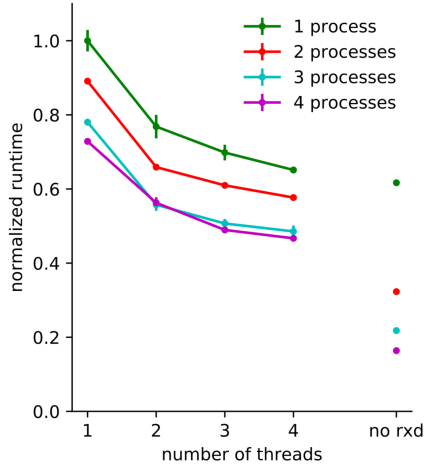


- Calculations via compiled C-code
- Parallelized with a thread pool
- Benefits from multiprocessor parallelization of electrophysiology

rxd only

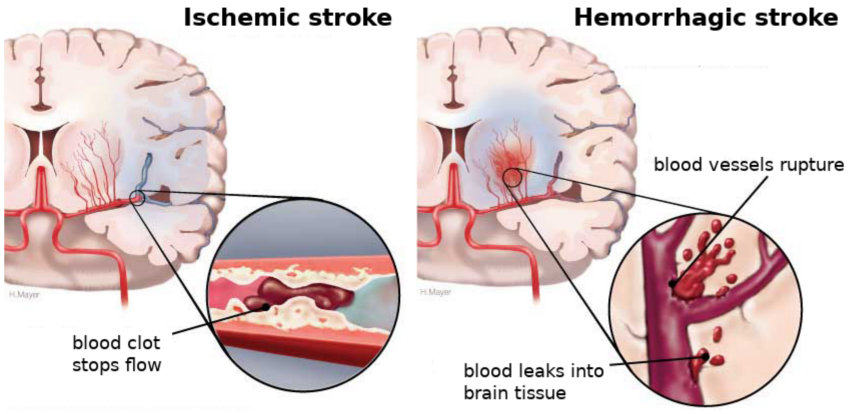


electrophysiology and *rxd*

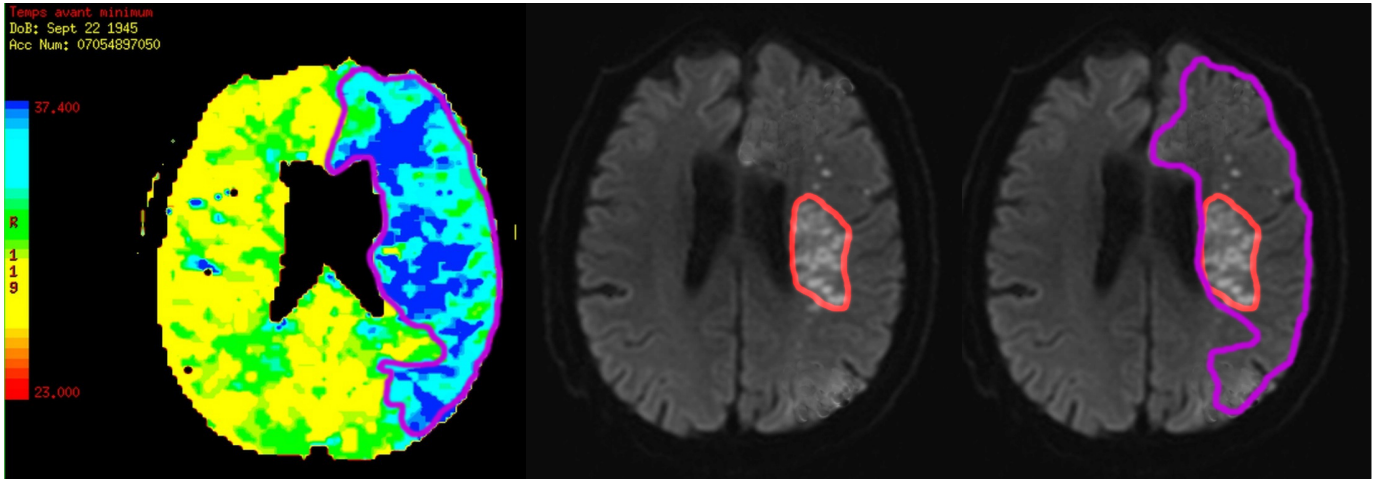


Ischemic stroke

- 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)

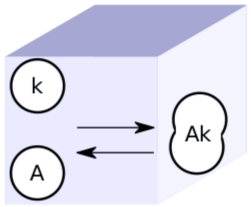


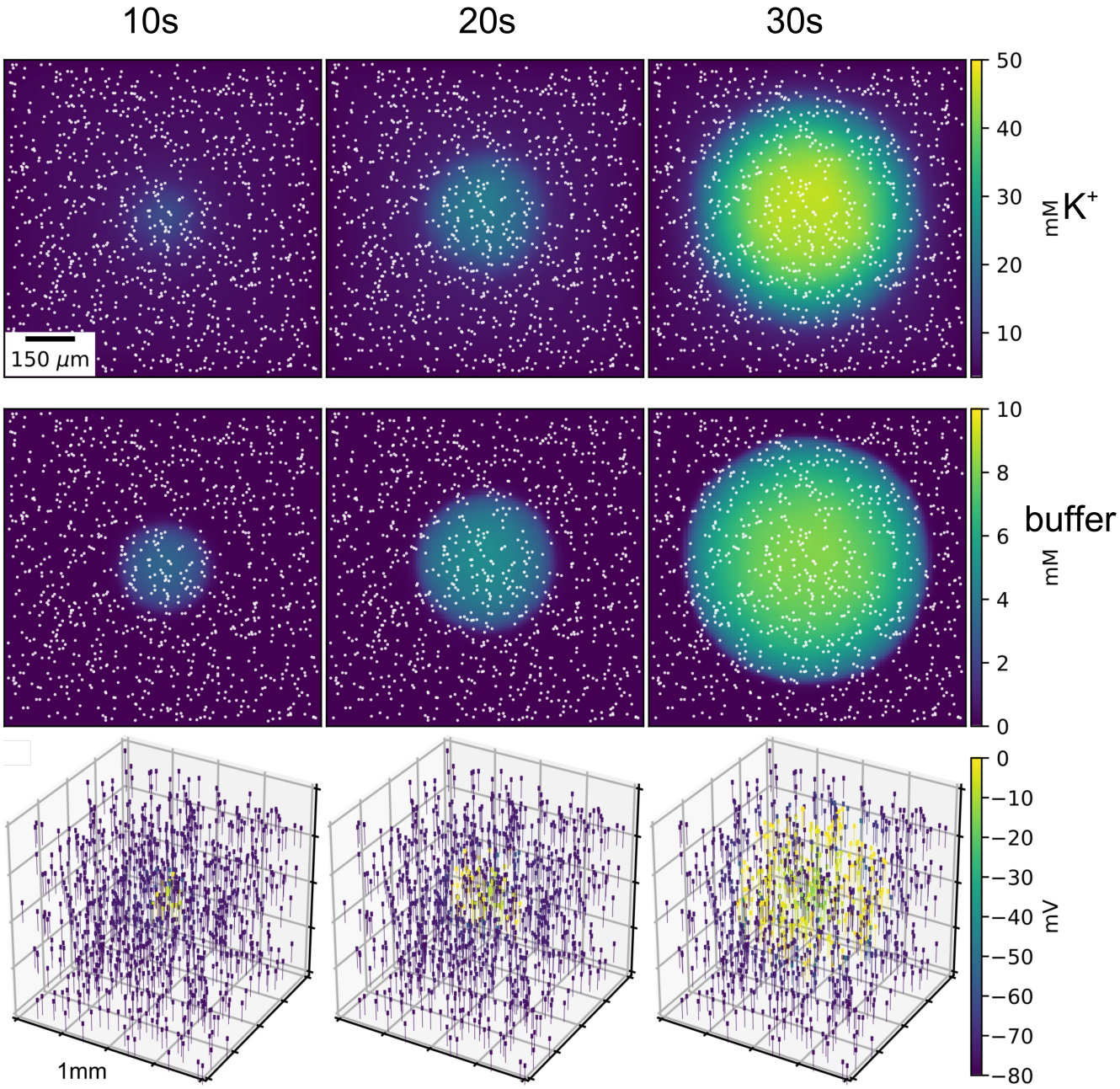
Perfusion (PWI) Diffusion (DWI) Mismatch PWI / DWI

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

Spreading depression

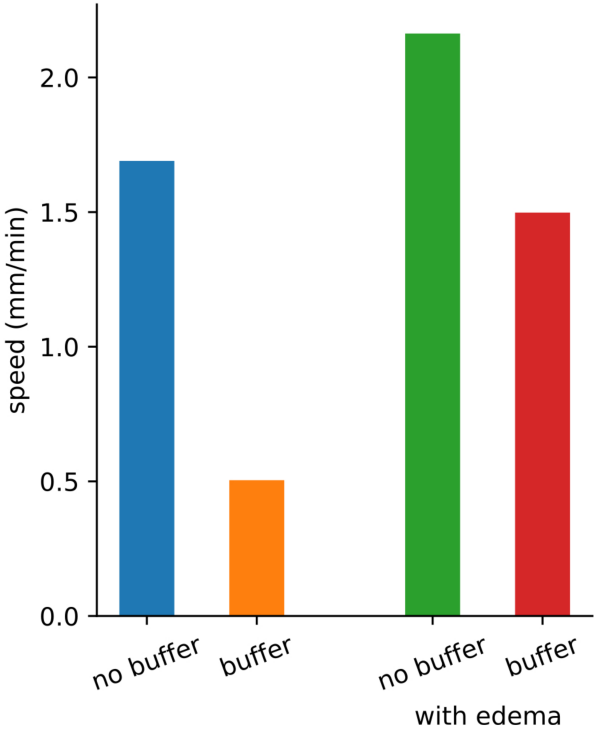
- 90,000 neurons in 1 mm^3 of extracellular space.
- Model K^+ and Na^+
- Astrocytic buffering with a phenomenology model.

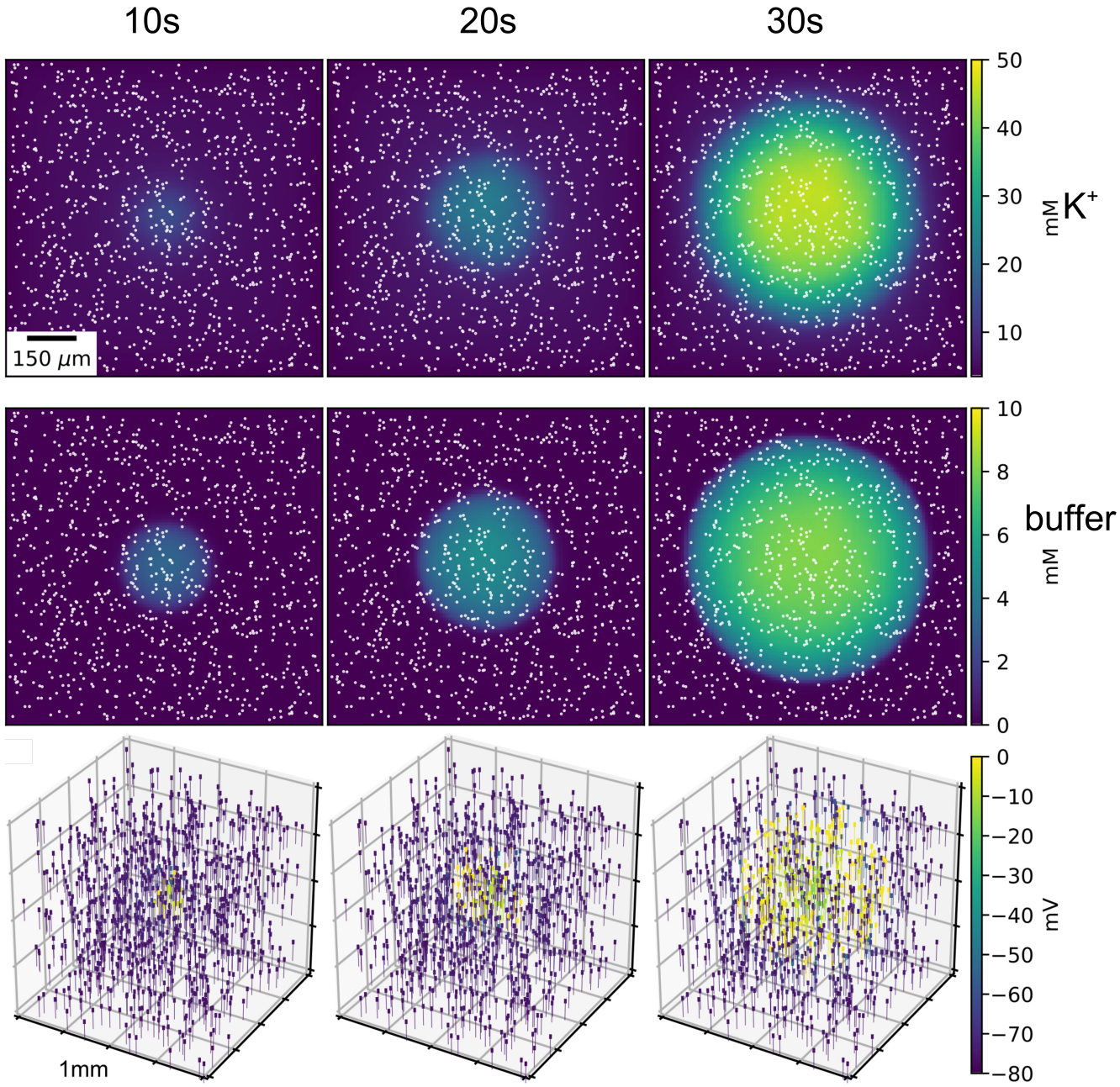




Spreading depression

- Altered tissue characteristics to simulate edema





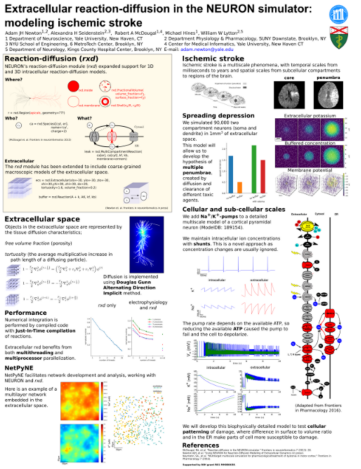
Spreading depression

```
from neuron.crxd 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



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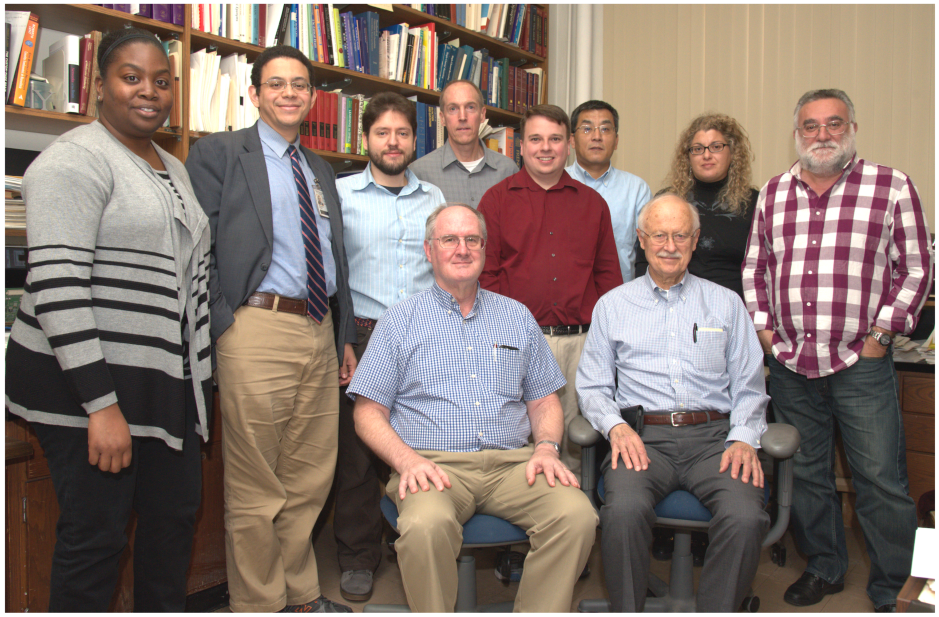

Thank you for your time.

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NIH National Institutes of Health