Normalized cortical depth (NCD) as a primary coordinate system for cell connectivity in cortex: experiment and model

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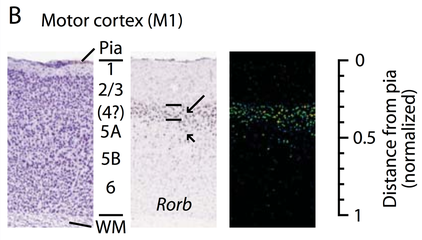
NCD in Experimental Datasets

Traditionally, cortical microcircuits have been described using layers. Here we argue that there are several advantages to using normalized cortical depth (NCD) instead of layers as a primary reference system.



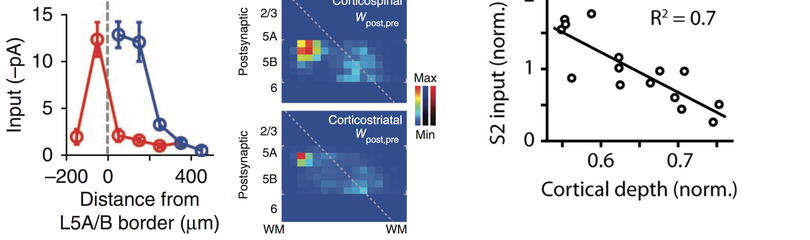
NCD provides a well-defined, consistent and continuous reference system, depending only on two readily-identifiable landmarks: pia (NCD=0) and white matter (NCD=1).

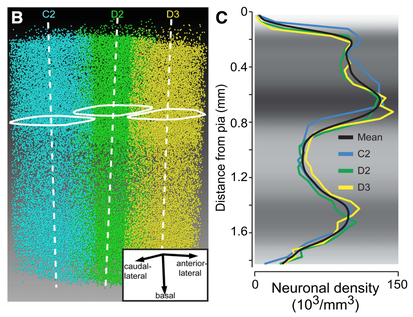
By contrast, layer identity will differ across laboratories and over time. For example, L4 has recently been identified in M1, classically considered to lack this layer.
(Yamawaki, 2015)

NCD better suited to represent cortical connectivity and cell density: both vary systematically within and across layers. This has motivated the use of sublayers such as L5A and 5B, or L4A, 4B and 4C.

The strength of input from L2/3 to L5B corticospinal cells in M1 depends on the cortical depth of cell soma.
(Anderson, 2010)

The strength of input from S2 to L5B corticospinal cells in M1 depends on the cortical depth of cell soma.
(Suter, 2015)

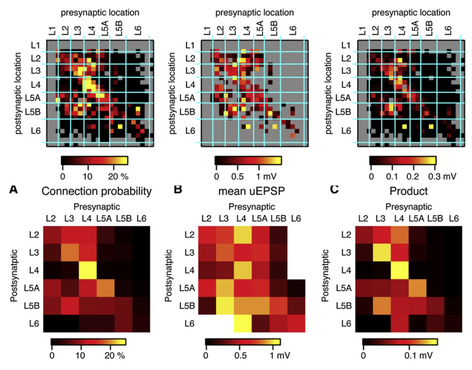




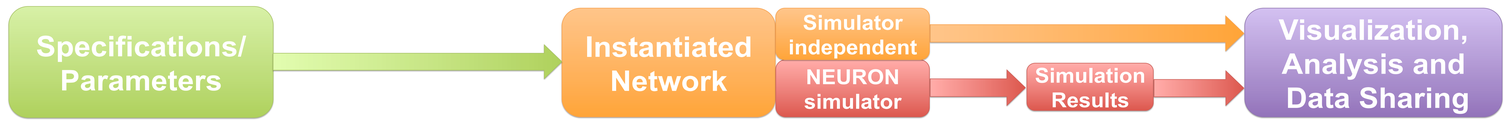
Neuronal density in rat somatosensory cortex depends on cortical depth, and exhibits intralaminar differences and gradual transitions between layers.
(Kleinfeld, 2011)

Experimental data is typically recorded using the NCD or absolute depth for each cell.
Absolute depth can be converted to NCD if know cortex thickness.
Data is then binned based on grid (eg. 50 um) and/or layers.
(Lefort et al, 2009)

Using NCD to model experimental data preserves original granularity/resolution, preventing loss of information.



Multiscale Modeling Framework based on NCD



Simulator-independent full specifications of network (cell properties, populations and connectivity rules) using standardized but flexible and extensible format.

Populations:
- Defined using flexible tags/attributes
- Easy to swap cell models (eg. point neuron vs multicompartment)
- Can include NCD dependent density function

```
# L2/3 IT
netParams['popParams'].append({
    'popLabel':     'IT_L23',
    'cellModel':    'Izhi2007',
    'cellType':     'IT',
    'yfracRange':   [0.1, 0.26],
    'density':      lambda y:1e5*y})


# L5B PT
netParams['popParams'].append({
    'popLabel':     'PT_L5B',
    'cellModel':    'HH',
    'cellType':     'PT',
    'yfracRange':   [0.56, 0.77],
    'density':      1e5})
```

IT L2/3 point neuron

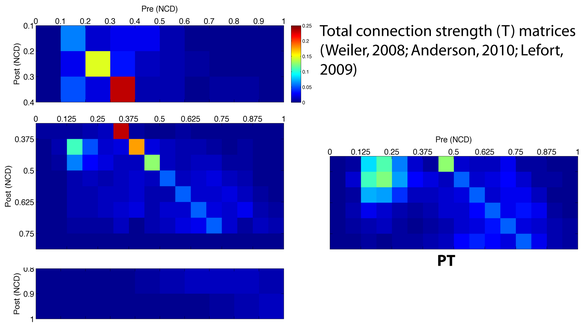
PT L5B multicompartmnet neuron

Connectivity rules:
- Applied conditionally based on arbitrary set of presyn- and postsyn- cell tag values
- Can include NCD dependent connectivity function

```
# IT->PT
netParams['connParams'].append({
    'preTags':      {'cellType': 'IT',
                     'yfrac': [0.12,0.31},
    'postTags':     {'cellType': 'PT'},
    'connFunc':     'yfracConn',
    'probability': lambda y: 0.15/y,
    'weight':       0.71,
    'delay':        5,
    'synReceptor': 'AMPA'})
```

```
# SOM->ALL
netParams['connParams'].append({
    'preTags':      {'cellType': 'SOM',
                     'yfrac': [0.31,0.77]},
    'postTags':     {yfrac: [0.31,0.77},
    'connFunc':     'distConn',
    'probability': lambda d: 1*e(d/100),
    'weight':       0.92,
    'delay':        6,
    'synReceptor': 'GABAB'})
```

- Can combine NCD data from multiple papers with different granularities

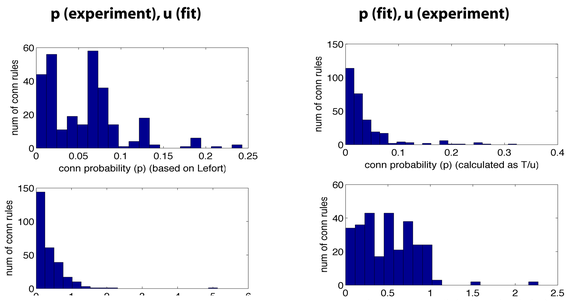


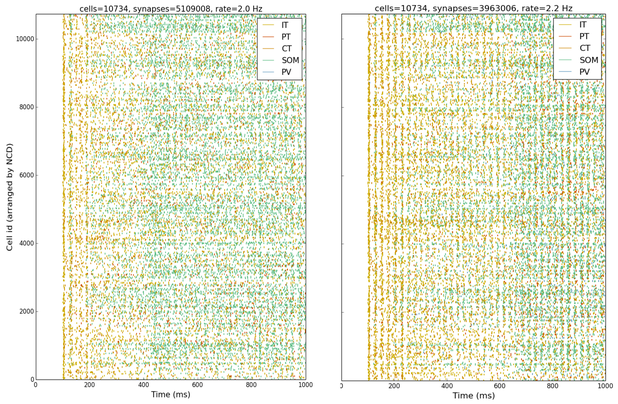
Total connection strength (T) matrices (Weiler, 2008; Anderson, 2010; Lefort, 2009)

Simulator-independent instantiation of network (all cells, connections, ...), and NEURON specific instantiation of network ready for simulation.

Example: mouse motor cortex (M1) model of 300 um x 300 um x 1350 um with 10,734 Izhikevich cells, of 5 cell types (IT, PT, CT, SOM, PV), distributed in 5 layers (2/3, 4, 5A, 5B, 6), with NCD-based connectivity.

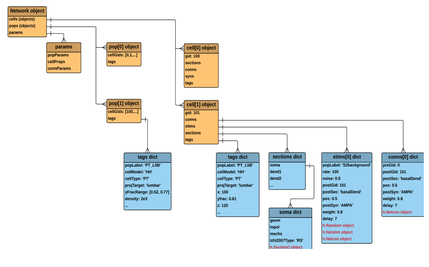
Constraining unknown connectivity by simulation:
total conn strength (T) = probability of conn (p) · unitary conn strength (u)



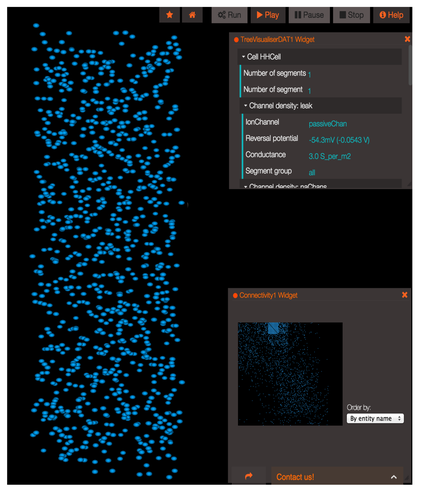


Despite having the same total connection strength (T) matrices, the networks firing patterns were different as a consequence of differences in connection probability (p) and unitary weights (u)

Analysis, visualization and data sharing (pickle, mat, JSON, NeuroML) of parameters, network and simulation results



Model shared on OpenSourceBrain.org in NeuroML format; OSB 3D explorer enables 3D visualization of network,



References

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Anderson CT, Sheets PL, Kiritani T, Shepherd GMG (2010) Sublayer-specific microcircuits of corticospinal and corticostriatal neurons in motor cortex. *Nat Neurosci* 13:739-744.
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Conclusions

1. NCD is better suited than layers to describe cortical microcircuits, given that connectivity and density varies systematically within layers.

2. We developed a modeling framework to facilitate incorporating NCD-based experimental data, with the following features:
a) Simulator-independent full specifications of network using standardized but flexible and extensible format.
b) Support for hybrid networks combining point neurons and detailed multicompartment neurons.
c) NEURON-specific instantiation of network ready for simulation.
d) Analysis, visualization and data sharing (mat, pickle, JSON, NeuroML, OSB 3D) of parameters and simulation results.

3. The framework was used to build a 10k cell M1 network model and explore different combinations of connection probabilities vs. unitary conn strengths.