Morphologically realistic computational models of rat hindlimb motoneurons and the effects of spinal cord injury

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... to promote adaptation in neural systems

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Neuroscience 2008

Introduction & Specific Aims

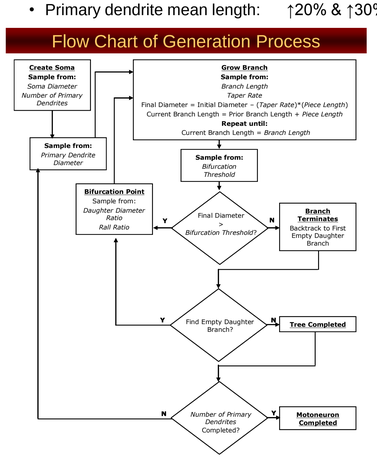
- Motoneuron morphology determines connectivity and influences motor output[1] while changes in motor behavior patterns affect morphology[2] (*form ↔ function*)
- Motoneuron morphology[3,4,5] and electrophysiology[6] are altered following chronic spinal cord injury (SCI)
  - Primary dendrites: mean number decreases, mean diameter and length increase
  - Measures of overall dendritic arborization decrease greatly
  - Motoneurons become hyper-excitable, exhibit prolonged self-sustained firing
  - Relationship between morphology and electrophysiology is poorly understood
- Neuronal morphology can be parsimoniously described with a small number of measured basic parameters and a stochastic recursive "growth" algorithm[7,8,9]
  - Morphology exhibits fractal properties: *self-similarity* and *recursive branching*[10]
  - With empirical measurements from a small number of reconstructed neurons, an algorithm can generate unlimited numbers of unique virtual neurons

Aims: develop algorithms to generate and analyze populations of morphologically realistic virtual motoneurons; explore the role of the changes in basic parameters after SCI in changes on overall dendritic arborization

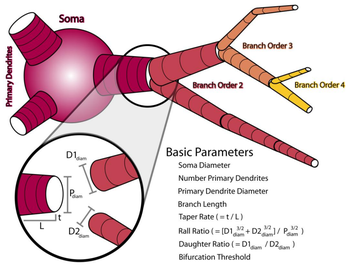
Methods

- Generated virtual motoneurons with morphometrics statistically similar to normal rat hindlimb motoneurons[11]
  - Fitted basic parameter distributions with probability distributions
  - Developed algorithms to generate morphologies and analyze morphometrics
  - Compared single vs multiple distributions for significant differences across branch orders
    - Branch length: three distributions (1°, 2°, ≥3°)
    - Taper rate: two distributions (1°, ≥2°)
- Examined role of changes in basic parameters on dendritic arborization
  - Altered basic parameter distributions to mimic known effects of SCI[3,4,5]
    - Primary dendrite mean number: ↓10% & ↓20%
    - Primary dendrite mean diameter: ↑10% & ↑20%
    - Primary dendrite mean length: ↑20% & ↑30%

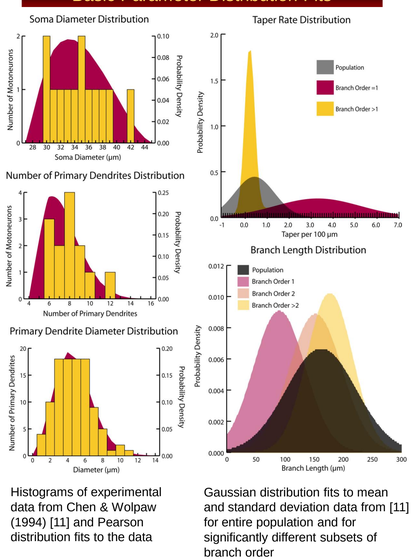
Flow Chart of Generation Process



Basic Parameter Definitions



Basic Parameter Distribution Fits



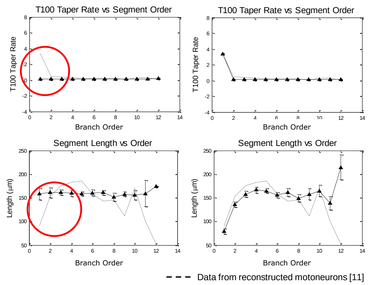
Histograms of experimental data from Chen & Wolpaw (1994) [11] and Pearson distribution fits to the data

Gaussian distribution fits to mean and standard deviation data from [11] for entire population and for significantly different subsets of branch order

Results – Normal Motoneurons

Basic Parameters by Branch Order

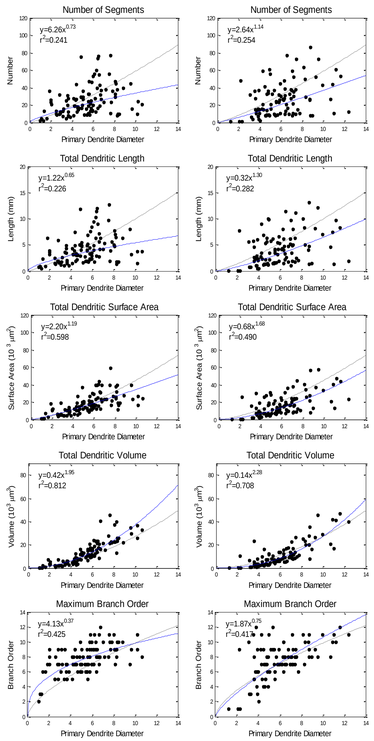
Single Distribution | Multiple Distributions



Use of multiple distributions greatly improves taper rate and branch length as a function of branch order

Diameter Analysis

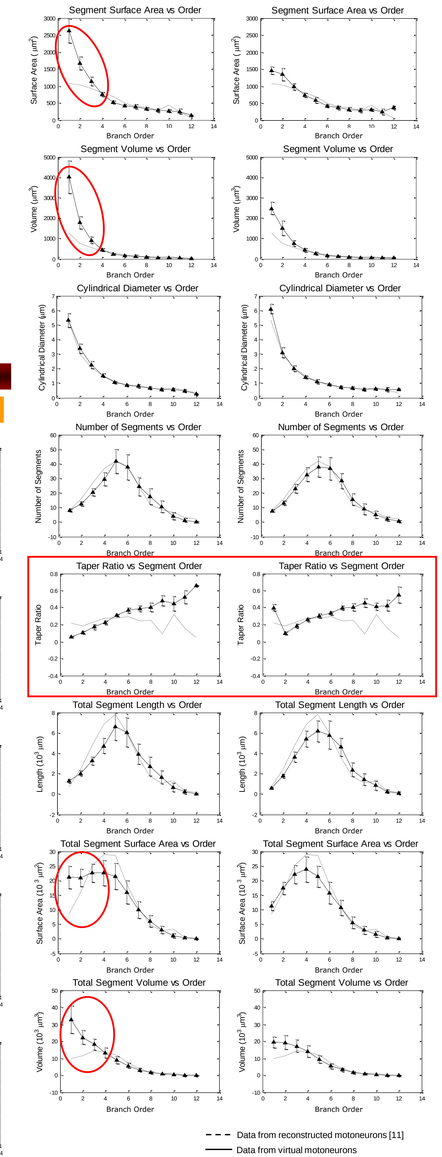
Single Distribution | Multiple Distributions



- Measurements of dendritic arborization as a function of primary dendrite diameter are similar to those from reconstructed motoneurons
- Use of multiple distributions improves quality of fits of emergent parameters as a function of primary dendrite diameter

Branch Order Analysis

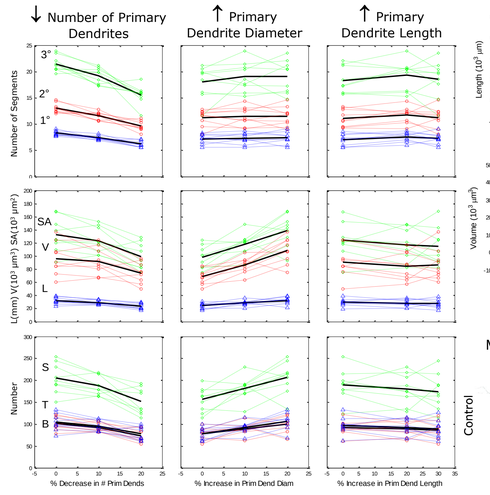
Single Distribution | Multiple Distributions



- Morphometrics versus branch order are generally similar to those of reconstructed motoneurons
- Lower branch order surface areas and volumes are much too large, but improved by use of multiple distributions
- Despite good similarity of taper rate and branch length as a function of branch order with multiple distributions:
  - Lower branch orders have too much surface area and volume
  - Taper ratio trend is inappropriate

Results – Spinal Cord Injury

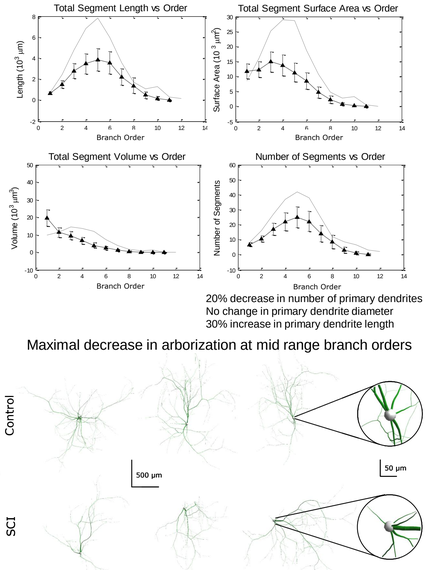
SCI Primary Dendrite Parameters



1°, 2°, 3° : First, second and third order branches
SA, V, L : Total surface area, total volume and total length
S, T, B : Segments, terminations and bifurcations

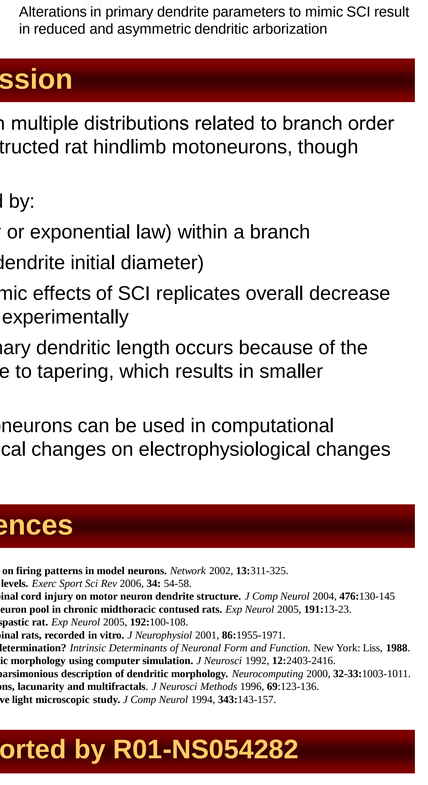
- ↓ in number of primary dendrites reduces overall arborization
- ↑ in primary dendrite diameter increases arborization
- ↑ in primary dendrite length slightly reduces arborization

SCI Branch Order Analysis



20% decrease in number of primary dendrites
No change in primary dendrite diameter
30% increase in primary dendrite length

Maximal decrease in arborization at mid range branch orders



Alterations in primary dendrite parameters to mimic SCI result in reduced and asymmetric dendritic arborization

Discussion

- Stochastic recursive "growth" algorithm with multiple distributions related to branch order improves morphometric similarity to reconstructed rat hindlimb motoneurons, though primary dendrites are still too large
- Morphometric measures could be improved by:
  - Taper Rate = *f* (local diameter via power or exponential law) within a branch
  - Primary Dendrite Length = *f* (1/primary dendrite initial diameter)
- Altering basic parameter distributions to mimic effects of SCI replicates overall decrease in dendritic arborization following SCI seen experimentally
- Decreased arborization with increased primary dendritic length occurs because of the reduced final primary dendrite diameter, due to tapering, which results in smaller daughter branch initial diameters
- These morphologically realistic virtual motoneurons can be used in computational models to explore the effects of morphological changes on electrophysiological changes (*form ↔ function*)

References

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Acknowledgment: Supported by R01-NS054282