Ira A. FULTON school of engineering
ARIZONA STATE UNIVERSITY
CENTER FOR ADAPTIVE NEURAL SYSTEMS

Morphologically realistic computational models of rat hindlimb motoneurons after spinal cord injury

Joe Graham[1,2] & Ranu Jung[1,2]

[1]Center for Adaptive Neural Systems, [2]Department of Bioengineering, Arizona State University, Tempe, AZ, USA,

designing adaptive engineered systems
… to promote adaptation in neural systems

76.5
GG26

CENTER FOR
ADAPTIVE NEURAL SYSTEMS

Neuroscience 2007

Introduction

Recent studies have reported that following a spinal cord injury (SCI), motoneurons below the level of injury undergo significant morphological and electrophysiological changes. When compared with uninjured controls, SCI motoneurons have on average a larger soma, fewer and thicker primary dendrites, and less dendritic branching.[1,2] Electrophysiologically they are more excitable and exhibit altered rhythmic firing and reflex properties.[3]

Motoneurons are the "final common pathway" for motor control, their dendrites play an active role in shaping motor output, and motoneuron morphology (form) is an important determinant of motoneuron behavior (function).[4,5,6] While neuronal morphology and neuronal behavior are clearly linked, to date it is not clear to what extent the morphological changes in motoneurons following SCI result in altered electrical behavior.

Motoneuron morphology is complex, and variability within a population is important for motor control. Obtaining 3-D digital reconstructions from experimental data is time-consuming and data-intensive and limited data can be obtained. Computational models that capture features of realistic individual motoneuron morphology as well as variability in the properties of the motoneurons (population distributions) would allow an exploration of the relationship between morphology and behavior in individual motoneurons and motoneuron populations.

Specific Aims

- Generate a population of virtual "normal" motoneurons with individual motoneuron morphology and population characteristics similar to an actual population of rat hindlimb motoneurons
- Alter key motoneuron morphology parameters from "normal" virtual motoneurons (mimicking changes observed after SCI) to generate a population of virtual "SCI" motoneurons, thus predicting their emergent properties.

Future aims:

- Utilize the virtual SCI morphologies in computational models to explore the effects of altered morphology on individual intrinsic electrical and reflex behavior
- Arrange virtual populations of motoneurons into pools to explore the effects of altered morphology on motor output to a muscle

Methods

A small number of measured "basic" parameters in combination with a recursive growth algorithm is sufficient to describe motoneuron morphology ("emergent" parameters).[7,8,9] (Table 1)

Such an algorithm can be used to "grow" virtual motoneurons in 3D from the soma outward. (Figs. 1,3)

The program L-Neuron is used to implement such an algorithm, using basic parameters taken from rat motoneurons.[9,10] (Fig. 1)

The program L-Measure is used to extract quantitative spatial information from the virtual populations.[9]

Custom Matlab code is used to format the data from L-Measure and to generate tables and plots.

Basic Parameters	Emergent Parameters
Soma diameter	Rostral-caudal extent
Number of primary dendrites	Dorsal-ventral extent
Diameter of primary dendrites	Medial-lateral extent
Dendritic taper rate	Dendritic length
Contraction and Fragmentation	Dendritic surface area
Length between bifurcations	Dendritic volume
Bifurcation threshold	Number of segments
Bifurcation angles	Number of terminations
Rall Power	Number of branch points
Poliko Constant	Maximum branch order
Daughter diameter ratio	Distance Analysis
Terminal branch pathlength	Segment Analysis

Table 1. Left: Basic parameter distributions needed to generate digital motoneuron morphologies using L-Neuron and the Hillman algorithm. Right: Emergent parameters quantified in L-Measure for comparison with actual motoneuron reconstructions.

Methods (continued)

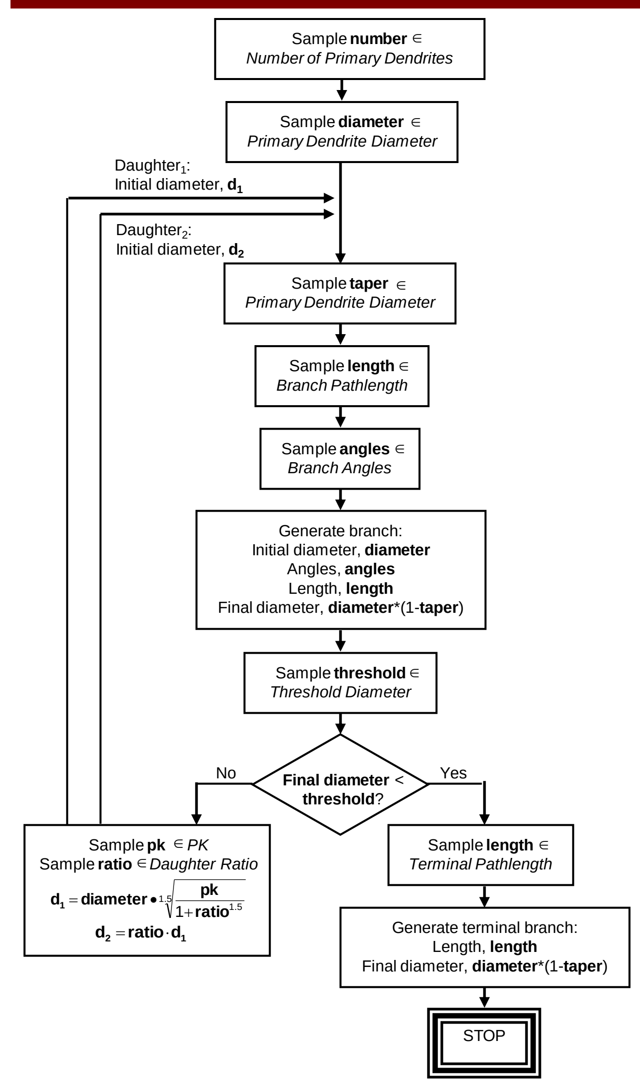

Fig 1. Algorithm and basic parameters used to generate morphologies in L-Neuron. Modified from [9].

Normal virtual motoneuron generation procedure:

- Quantify basic parameter distributions (Fig 2A)
- Represent the distributions as combinations of Gaussian, uniform across a range, and constant distributions (Fig 2B)
- Generate a population of motoneurons
- Compare the "emergent" parameters (not specified in the input to the algorithm) to actual parameters (Fig 4 and Table 2)
- Refine the basic parameter distributions and repeat until virtual motoneurons are statistically similar to actual rat motoneurons

SCI virtual motoneuron generation procedure:

- Modify the basic parameter distributions to mimic the effects of chronic SCI
  - Increase soma size (18% from [2])
  - Decrease number of primary dendrites (22% from [1])
  - Increase diameter of primary dendrites (10% and 20% to mimic qualitative report in [1])
- Use the same algorithm to generate SCI virtual motoneurons
- Predict emergent parameters for SCI rat motoneurons
- Explore effects of varying the altered basic parameters

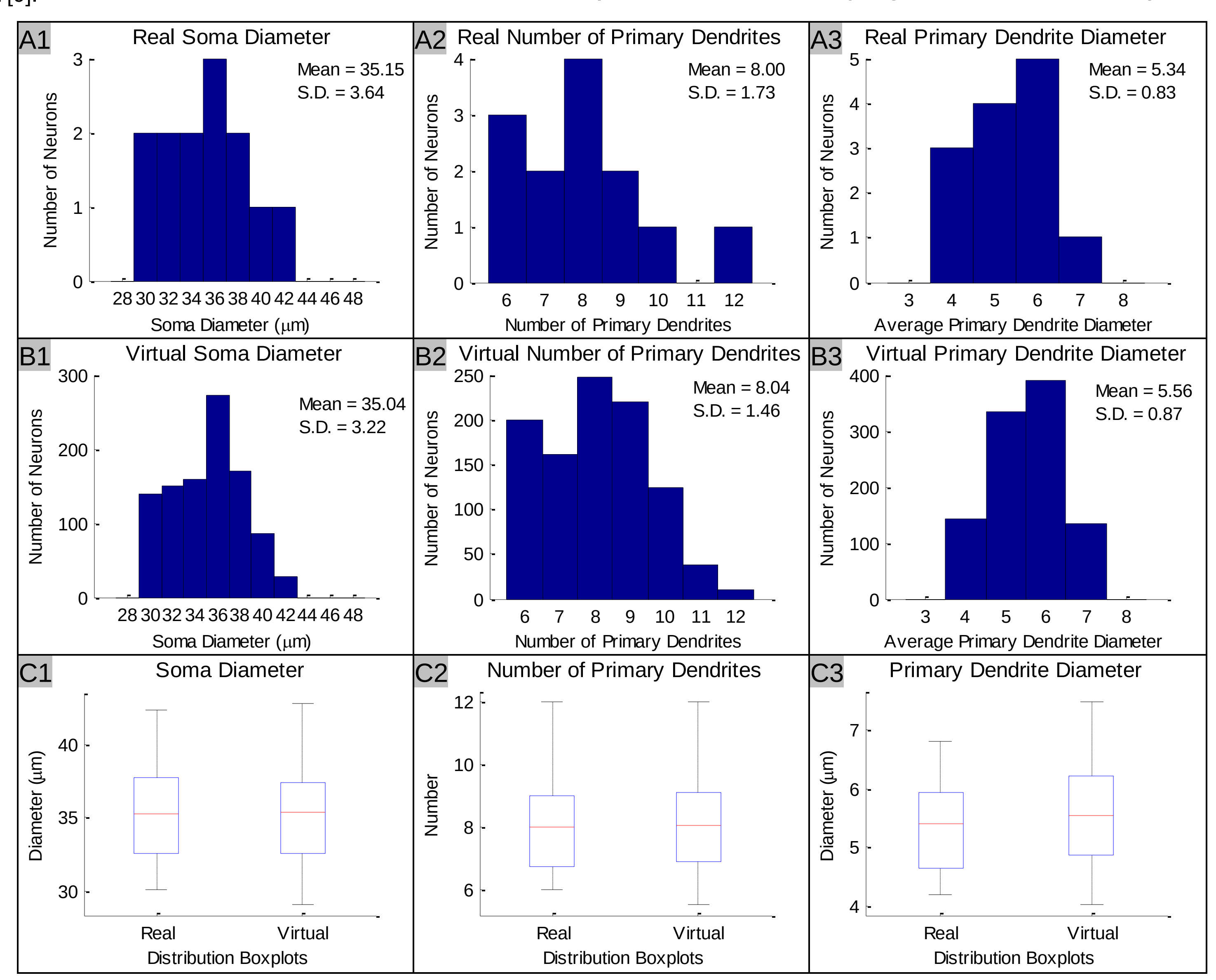

Fig 2. ***A***. Data from reconstructed rat motoneurons from [10]. ***B***. Virtual representations of distributions from A used to create normal virtual motoneurons. ***C***. Box plot comparisons of real and virtual parameter distributions. ***1***. Distribution of soma sizes. ***2***. Distribution of the average number of primary dendrites. ***3***. Distribution of the average primary dendrite diameter.

Results

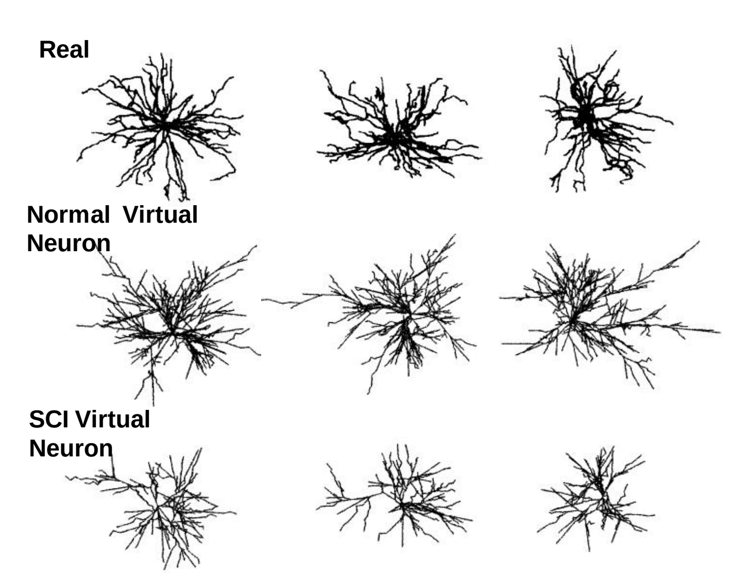

Fig 3. Orthogonal views of representative motoneuron morphologies.

Top row: Reconstructions of experimentally obtained rat triceps surae motoneurons illustrated in [10].

Middle row: L-Neuron generated virtual morphologies for normal motoneurons.

Bottom row: L-Neuron generated virtual morphologies for SCI motoneurons, with mean soma diameter increased by 18%, number of primary dendrites reduced by 22%, and primary dendrite diameter increased by 10%, as seen experimentally in [1,2,11].

Supported in part by NIH NS054282-01

Results (continued)

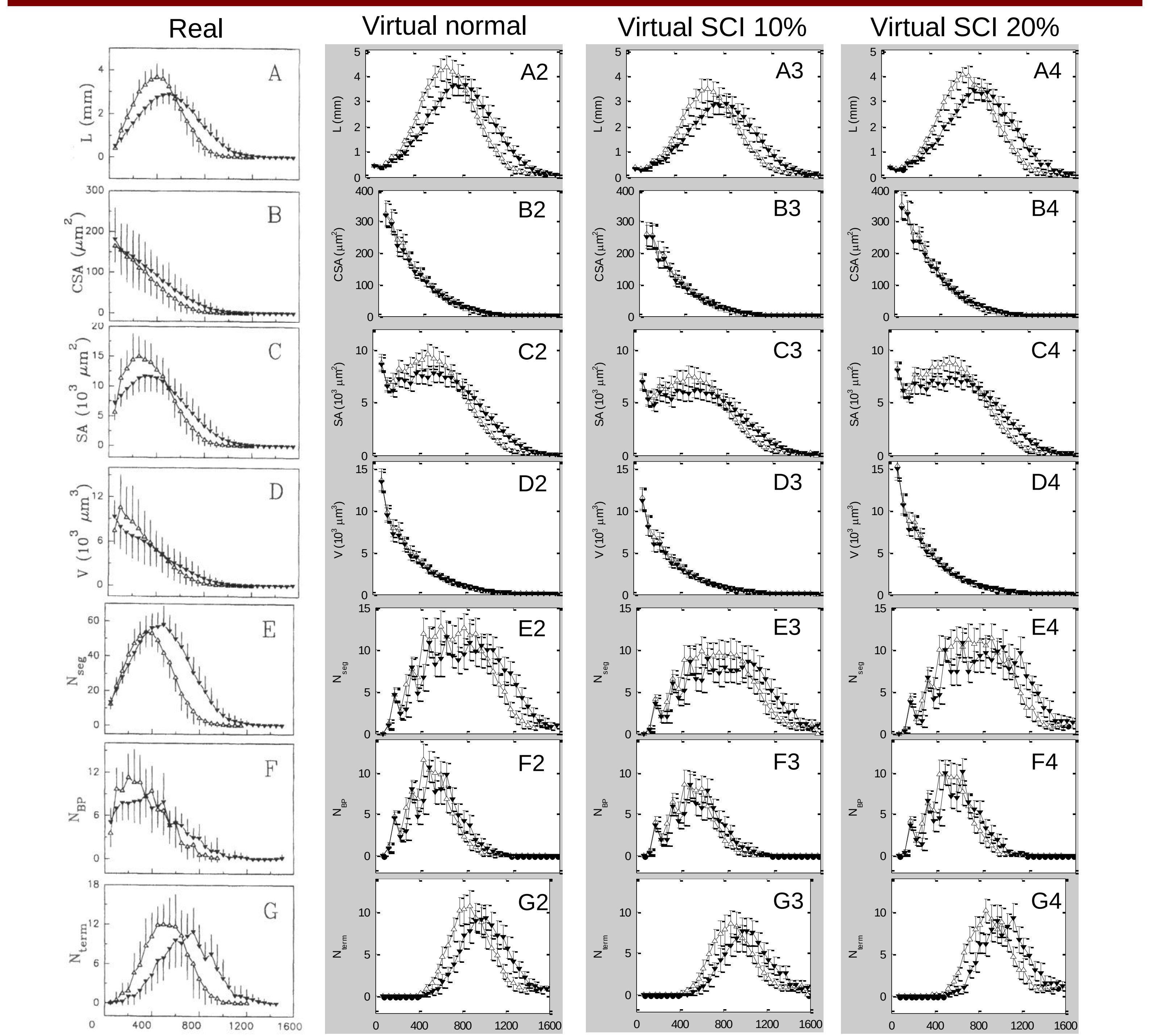

Fig 4. Emergent parameters (distance analysis) of populations of motoneurons. ***Column 1*** is from real motoneurons from [10] (n=13 neurons). ***Column 2*** is from the normal population of virtual motoneurons. ***Column 3*** is from an SCI population of virtual motoneurons with primary dendrite diameter increased by 10%, ***Column 4*** is from an SCI population of virtual motoneurons with primary dendrite diameter increased by 20%. ***A***. Dendritic length. ***B***. Dendritic cross-sectional area. ***C***. Dendritic surface area. ***D***. Dendritic volume. ***E***. Number of segments. ***F***. Number of branch points. ***G***. Number of terminations. X-axis is either the Euclidean distance from soma center (open triangles) or the dendritic pathlength from soma perimeter (closed triangles). For all virtual SCI motoneurons soma size ↑ by 18%, # of primary dendrites ↓ by 22%. Mean ± SD. (n=100 virtual motoneurons per population)

Population Parameters	Real	Virtual Control	Virtual SCI - 10%	Virtual SCI - 20%
Basic Parameters				
Soma diameter (μm)	± 3.5	35.4 ± 2.6	38.8 ± 2.0	39.7 ± 1.6
Number of Primary Dendrites	8.0 ± 1.7	7.6 ± 1.2	5.8 ± 1.2	5.9 ± 1.2
Primary Dendrite Diameter (μm)	± 0.8	6.1 ± 0.4	6.4 ± 0.4	7.4 ± 0.5
Emergent Parameters				
Rostrocaudal Extent (mm)	1526 ± 236	1678 ± 240	1604 ± 298	1661 ± 284
Dorsoventral Extent (mm)	1351 ± 231	1423 ± 223	1379 ± 263	1398 ± 251
Mediolateral Extent (mm)	849 ± 139	1473 ± 230	1421 ± 302	1444 ± 285
Total Dendritic Length (mm)	35.7 ± 4.2	51.2 ± 10.4	40.8 ± 9.6	47.4 ± 9.1
Total Dendritic Surface Area (μm^2)	± 40	143 ± 28	114 ± 27	137 ± 24
Total Dendritic Volume (μm^3)	± 36	74 ± 15	62 ± 15	82 ± 15
Number of Dendritic Segments	216 ± 27	196 ± 39	155 ± 36	180 ± 34
Maximum Branch Order	9.9 ± 1.4	6.7 ± 0.7	6.5 ± 0.9	6.7 ± 0.8
Number of Terminations	113 ± 13	859 ± 170	682 ± 159	789 ± 149
Number of Branch Points	104 ± 13	91 ± 19	72 ± 17	84 ± 16

Table 2. Scalar basic and emergent parameter values for real, virtual normal, and virtual SCI populations of motoneurons with soma size ↑ by 18%, # of primary dendrites ↓ by 22% and primary dendrite diameter increased by 10% and 20%.

Conclusions

1. Populations of virtual motoneurons statistically similar to real rat motoneurons created
2. Populations of virtual SCI motoneurons 'grown' from altered basic parameters
3. Emergent properties from virtual SCI motoneuron populations predict :
   a. Dendritic arborization after injury is pruned (e.g. total path length, total extent (95% of all dendritic segments), # of branches) due to decrease in # of primary dendrites
   b. Decreased arborization is partially compensated by increase in primary dendrite diameter
   c. More than 20% increase in diameter is likely to be necessary to adequately compensate for the decrease

References

1. Bose P, Parmer R, Reier PJ, Thompson FJ: **Morphological changes of the soleus motoneuron pool in chronic midthoracic contused rats.** *Exp Neurol* 2005, **191:**13-23.
2. Kitzman P: **Alteration in axial motoneuronal morphology in the spinal cord injured spastic rat.** *Exp Neurol* 2005, **192:**100-108.
3. Bennett DJ, Li Y, Siu M: **Plateau potentials in sacrocaudal motoneurons of chronic spinal rats, recorded in vitro.** *J Neurophysiol* 2001, **86:**1955-1971.
4. van Ooyen A, Duijnhouwer J, Remme MW, van Pelt J: **The effect of dendritic topology on firing patterns in model neurons.** *Network* 2002, **13:**311-325.
5. Zengel JE, Reid SA, Sypert GW, Munson JB: **Presynaptic inhibition, EPSP amplitude, and motor-unit type in triceps surae motoneurons in the cat.** *J Neurophysiol* 1983, **49:**922-931.
6. Friedman WA, Sypert GW, Munson JB, Fleshman JW: **Recurrent inhibition in type-identified motoneurons.** *J Neurophysiol* 1981, **46:**1349-1359.
7. Hillman D: **Parameters of dendritic shape and substructure: intrinsic and extrinsic determination?** In *Intrinsic Determinants of Neuronal Form and Function*. Edited by Lasek RJ BM. New York: Liss; 1988: 83-113
8. Burke RE, Marks WB, Ulfhake B: **A parsimonious description of motoneuron dendritic morphology using computer simulation.** *J Neurosci* 1992, **12:**2403-2416.
9. Ascoli GA, Krichmar JL: **L-neuron: A modeling tool for the efficient generation and parsimonious description of dendritic morphology.** *Neurocomputing* 2000, **32-33:**1003-1011.
10. Chen XY, Wolpaw JR: **Triceps surae motoneuron morphology in the rat: a quantitative light microscopic study.** *J Comp Neurol* 1994, **343:**143-157.
11. Gazula VR, Roberts M, Luzzio C, Jawad AF, Kalb RG: **Effects of limb exercise after spinal cord injury on motor neuron dendrite structure.** *J Comp Neurol* 2004, **476:**130-145.