Modeling the Neuroanatomic Propagation of ALS in the Spinal Cord

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Abstract. Recent hypotheses of amyotrophic lateral sclerosis (ALS) progression have posited a point-source origin of motor neuron death with neuroanatomic propagation either contiguously to adjacent regions, or along networks via axonal and synaptic connections. Although the molecular mechanisms of propagation are unknown, one leading hypothesis is a "prion-like" spread of misfolded and aggregated proteins, including SOD1 and TDP-43.

We have developed a mathematical model representing cellular and molecular spread of ALS in the human spinal cord. Our model is based on the stochastic reaction-diffusion master equation approach using a tetrahedral discretized space to capture the complex geometry of the spinal cord. Domain dimension and shape was obtained by reconstructing human spinal cord from high-resolution magnetic resonance (MR) images and known gross and histological neuroanatomy. Our preliminary results qualitatively recapitulate the clinically observed pattern of spread of ALS thorough the spinal cord.

Introduction

Amyotrophic lateral sclerosis (ALS or "Lou Gehrigs disease") is a progressive neurodegenerative disease that affects motor neurons in the brain and the spinal cord. The progressive degeneration of motor neurons in the spinal cord causes patients to lose their ability to control their muscle movement. As the disease progresses they lose the ability to move their limbs, speak, eat, and eventually breath, leading to death. There are over 25,000 cases in the US with more than 6,400 new cases each year. It is the most lethal of the common neurodegenerative disorders, and has thus far been refractory to all treatments.

To better understand this devastating disease, we have begun to develop a cellular and molecular model of the spread of ALS in the spinal cord. Recent studies have shown that there is a stochastic component to the initiation and propagation of ALS [1]. This is consistent with the hypothesis that the molecular mechanism of ALS is prion-like, i.e. a self-proliferating infectious agent consisting of misfolded protein[2]. Recent work [3] has shown that in mice a prion-like particles composed of aggregates of the human SOD1 protein transmit a templated, spreading aggregation process through the spinal cord, resulting in a fatal ALS-like disease.

ALS is a progressive disease. Recent studies have shown that the disease progresses by contiguous neuroanatomical propagation [1]. Analysis has shown that the motor neuron death within the spinal cord starts at a single anatomic site of outbreak and spreads contiguously to adjacent regions. It has also been shown to propagate between the upper motor cortex and the lower motor cortex, suggesting propagation through synaptic connections along the neuronal network. The molecular mechanism of propagation and cellular death in ALS is unknown. Currently, we are working with the hypothesis of a prion-like misfolding and aggregation of one or more proteins within the motor neurons [2]. One candidate is the protein TDP-43, which is thought to have prion-like properties and has been associated with sporadic as well as some forms of familial ALS [4].

Model

We have developed a stochastic reaction-diffusion model of ALS progression in the spinal cord. This model uses a prion-like process for the molecular mechanism of ALS. We assume that a random event causes a protein to transform into a prion (shown in red in figure 2). When the prion molecule encounters a neuron (shown in blue), the prion infects the cell and propagates its

misfolded template to other proteins in that cell. Prion molecules escape the cell and diffuse throughout the extra-cellular space to infect nearby neurons. The aggregation of prion molecules within the neuron eventually leads to cell death.

The fundamental question we seek to answer with our model is the mechanism of initiation and progression of ALS within the spinal cord and brain. ALS progression has two possible modes of transmission: diffusive and network. In diffusive transmission, neuronal cells transmit the pathogenic compound to the cell bodies of their neighbors. In the movement mechanism, the geometric shape of the domain is critical to the understanding of the progression patterns. In network transmission, the pathogenic compound is transmitted via axonal transport along the synaptic connections[5]. In this movement mechanism the network connectivity of the regions of the spinal cord are important for understanding the progression patterns.

To accurately simulate the complex domain of the spinal cord, we reconstructed a section of the cervical spinal cord from images of a stained cross section. Figure 1A shows the stained image of the spinal cord, and figure 1B shows the 3D domain constructed from tetrahedral elements, with the gray matter and white matter subdomains. We developed this spatial stochastic model in our advanced computational software environment, StochSS (Stochastic Simulation as a Service)[6], making use of the spatial stochastic simulation from PyURDME [11].

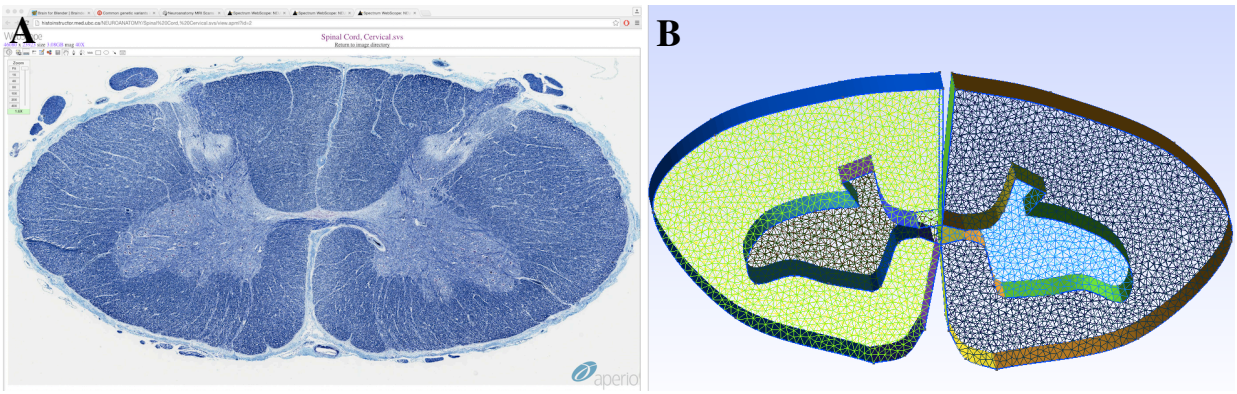

FIGURE 1. 3D reconstruction of cervical spinal cord from stained cross sections **(A)** Image of a stained cross section of the cervical spinal cord [7]. **(B)** 3D mesh of cervical spinal cord (created with [8]).

Our model describes the direct interaction of the ALS prion molecules with the neurons in a stochastic reaction-diffusion formulation. The model contains two species: ALS prion molecules ("Toxin" or T), and Neurons (N). The neurons are distributed uniformly within the gray matter of the spinal cord, this can be see as the lighter interior region in figure 1A. As an initial condition, 100 ALS prion molecules are placed randomly at a single location within the spinal cord. These molecules diffuse about the gray and white matter regions of the spinal cord. When ALS prion molecules encounter a neuron, they interact to create additional prion molecules by propagating their misfolded template to naïve proteins. ALS toxin molecules interacting with neurons also result in neuronal death. This system can represented mathematically by:

$$\frac{\partial T}{\partial t} = D_T \nabla^2 T + k_1 T N \tag{1}$$

$$\frac{\partial N}{\partial t} = -k_2 T N. \tag{2}$$

We have parameterized our model with $k_1 = 0.1$, $k_2 = 0.1$, and the toxin diffuses at rate $D_T = 0.01$. The time units are arbitrary.

Preliminary Results

Figure 2 shows four frames from our simulation of ALS propagation. Our model appears to realistically recapitulate the clinical and pathological spread of ALS in human spinal cord [1]. Of note, the speed of longitudinal spread remains constant despite an exponential increase in the amount of misfolded protein. This matches the predictions from mathematical models of epidemiological systems [9]. The geometric shape and physical dimensions of spinal cord white and gray matter regions constrain the lateral spread of pathogenic particles and mitigate what would be symmetric spread. Our results also identify key parameters that require quantification, including the rate of spread of misfolding proteins and the growth rate of protein aggregates.

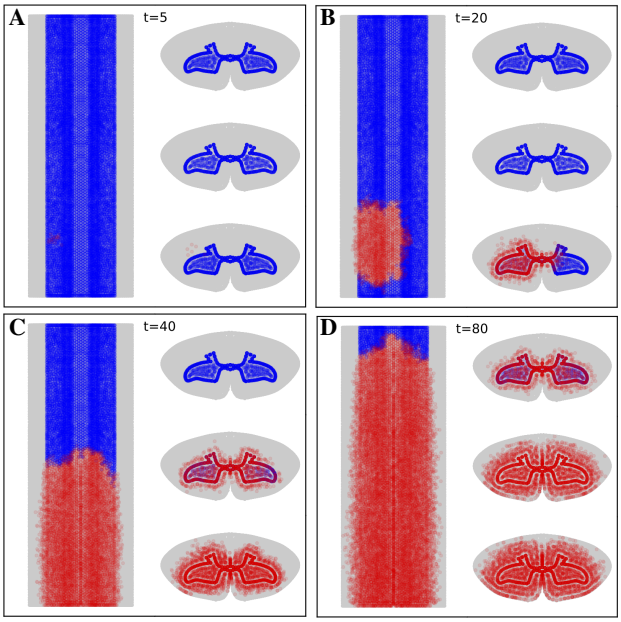

FIGURE 2. Spatial stochastic simulation of ALS progression in the cervical spinal cord. Blue: healthy neurons, red: ALS molecules. Left: Vertical projection, right: three horizontal cross sections. **(A)** ALS molecule spontaneously forms and infects neurons in the gray mater region of the spinal cord **(B)** Infected neuron produce ALS molecules via prion-like misfolding and aggregation, and lead to neuron death. **(C)** ALS molecules spread via diffusion to infect neurons in nearby regions. **(D)** ALS molecules cross to left side and spread contiguously up the spinal cord. The unstructured tetrahedral mesh has 37,745 vertices and 107,370 independent neurons.

Discussion

We aim to develop and expand this model of ALS propagation to better explain the complexity of this disease, as well as to address additional open questions in the field. These include: (1) the validity and consequences of the prion hypothesis of ALS, as well as searching for the biochemical and genetic mechanisms that underly the misfolding and aggregation process, (2) understanding the cellular level biological process that result in cell death in ALS, and (3) determination of the selective vulnerability of motor neurons versus other neurons.

We will employ advanced computational techniques to accurately model the dynamics of this disease. These include: parameter estimation, parameter sweeps, and Bayesian inference of kinetic rate parameters and biochemical reaction network structure [10]. These computational and data analysis techniques necessitate a large number of simulated realizations of the model system, exploring thousands of parameter points each requiring an ensemble of thousands of stochastic simulations. We are well positioned to address this challenge with our newly developed advanced computational framework StochSS [11] that allows us to harness the nearly unlimited capacity of cloud computing infrastructures for simulation of these large scale analytical techniques.

We will fit our model to data obtained from radiological, and clinical assessment data. This will be challenging, since both the disease data and the model are stochastic, thus even if the parameters are fit properly the random trajectories may not follow the same progression pattern. Radiological data, such as that from MRI scans, will provide maps of the progression of the disease throughout the spinal cord. Comparison to clinical assessment data, such as the Pro-ACT database[12], will require an analysis that maps the clinical progression markers, such as handwriting, swallowing, and walking stairs to physical regions within the spinal cord. Additionally, neural plasticity and neuronal reinnervation compensation[13] will need to be accounted for.

Future studies will extend our model to: (1) examine spread of misfolded proteins in the cerebral cortex, (2) superimpose spinal and cortical spread, (3) predict the relative contributions of network and contiguous spread to ALS progression, (4) determine whether different initiation locations and distributions lead to disease variability, and (5) examine differential cellular vulnerability in various topographical CNS regions. We will also fit the model parameters to additional MR imaging data that we anticipate to emerge in parallel with our work. Finally we anticipate our modeling framework of disease progression will be useful in developing pharmacotherapies (e.g., that inhibit production and/or accelerate degradation/clearance of abnormal proteins) in ALS and possibly other neurodegenerative disorders.

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