Towards a Multiscale Model of the Brain ECM

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Brain is one of the softest tissue in the body, yet its stiffness increases in the presence of cancer. Glioblastoma (GBM) is one of the most common and malignant brain tumors with a very low survival rate. Mechanical cues are known to be important in progression of GBM via a process called mechanotransduction. This process involves remodeling of the matrix around cells, i.e. extracellular matrix (ECM), and change in its mechanical properties [1]. To understand the relationship between ECM remodeling and the increased stiffness of the brain, we are developing a multiscale computational model of the brain ECM.

In contrast to the protein-based ECM of most tissues, the brain ECM is mainly based on polysaccharides with a hyaluronic acid (HA) backbone, decorated by chondroitin sulfate proteoglycans and crosslinked by tenascins. We have developed a one-bead-per-saccharide (1BPS) model for hyaluronic acid and chondroitin sulfates [2]. Despite being “super” coarse-grained from a molecular perspective, the 1BPS model makes predictions that match experimental observations in length scales relevant to the brain ECM without any fitting parameters.

Proteoglycans are brush-like polymers with a protein backbone and polysaccharide side chains. To model the conformation of proteoglycans, we have combined the 1BPS model with a one-bead-per-aminoacid (1BPA) model developed in our group [3] and an elastic network model. This model has been validated for aggrecan (a well-studied proteoglycan) in terms of radius of gyration, and is being used now for predicting the structure–property relationship of brain-specific proteoglycans, such as brevican and neurocan.

An intermediate validation of the approach is currently carried out by means of a network of HA to model the stiffness of crosslinked HA gels [4]. Subsequently, this model will be extended by including brain-specific proteoglycans and tenascin cross linking proteins, aspects of which will be highlighted in the talk. Eventually, the developed tools will allow us to predict the stiffness of brain ECM from its composition and architecture.

References

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