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COMPUTATIONAL MODEL OF INTRACELLUAR STRUCTURE FOR SIMULATION OF MECHANICAL TESTS OF CELLS

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Living cells in a human body are constantly subjected to mechanical stimulations due to its external environmental and inter physiological conditions. Depending on the magnitude, direction and distribution of these mechanical stimuli, cells can respond in different ways that generate stresses and strains [3]. Recently various innovative experimental techniques have been developed to mechanically probe a single cell with forces in piconewtons and displacements in microns. Experimental techniques are classified on the basis of its operating principle, force and displacement maxima, resolution, and extent of deformation. The experimental tests of single cells are designed to understand intracellular and extracellular mechanotransduction of an individual cell, whereas cell population approaches are designed to understand the role of mechanics in regulating the structure and functions of tissues that comprise organs [1].

Ingber has hypothesised that the cytoskeleton and nucleoskeleton networks of a cell behaves as multi-functional tensegrity structures that influence the cell motility and intracellular regulation of mechanical signals cascades. Both computational models of a cell discussed here are based on finite element method [3]. The hybrid of continuum and microstructural approaches has been applied to design the complete cell model. The cytoskeleton was designed with microstructural approach, cytoplasm as well as nucleus with continuum approach and plasma membrane as a shell on the cell surface [2].

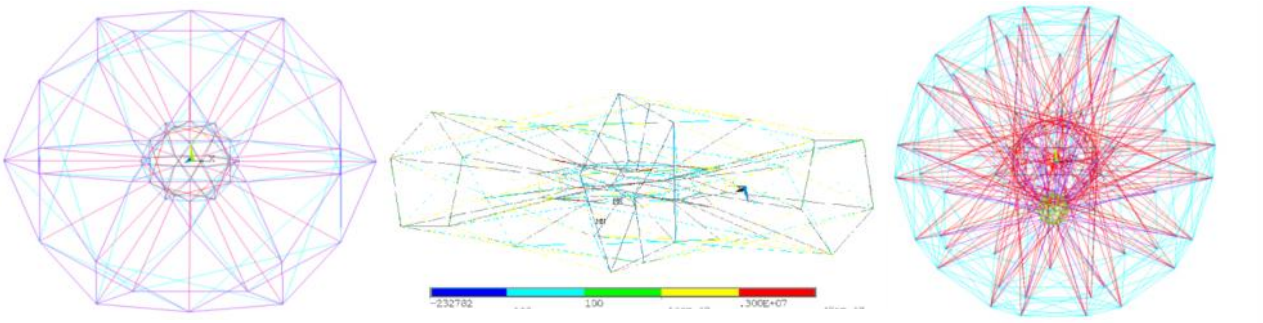

Fig. 1: (a) Tensegrity based previous computational model of intracellular structure with 210 members & (b) Distribution of axial stresses in intracellular tensegrity simulated in tension test with micropipettes [2]. (c) New tensegrity based computational model of intracellular structure with 862 members.

The previous computational model of cell depicted in Fig. 1(a) has a lot of deficiencies compared to living cell from biological structure perspectives, although it brought some relevant global results [2]. It was an initial and sincere attempt based on the information

available at that time. First, the major drawback of this model is it consists of interlinked microtubules with equal lengths in submembrane region which cannot form a 'star' topology. Second, membrane skeleton and nucleoskeleton are interlinked via intermediate filaments but do not have a dense network of these filaments either in peripheral region of nucleus or spread through the intracellular region. Third, the microfilaments are of equal lengths and not cross-linked, consequently there is a spare network of actin filaments in the surface region. Fourth, this model does not contain integrins which transfer mechanical signals from focal adhesions located on cell membrane surface to cytoskeleton. Finally, nucleoskeleton designed with regular icosadodecahedron tensegrity disables to maintain its shape stability at higher stresses; moreover, both intracellular skeletons have same tensegrities [2].

On the basis of literature available on intracellular structure, the new model presented here (see Fig. 1(c)) is able to overcome the above drawbacks. Nucleus and centrosome are modelled with tensegrities designed using form-finding technique to provide self-stabilisation and high stiffness structures. The membrane skeleton also called as cortical membrane is a dense network of tensed microfilaments in surface region constructed by cross-linking of these filaments [5]. Numbers of intermediate filaments (connecting membrane cytoskeleton to nucleoskeleton tangentially) provide a dense network in peripheral region of nucleus [4]. Microtubules are constructed with unequal lengths, emerging from centrosome and linked to membrane skeleton, to form a star shape as that of a real cell. The focal adhesions on plasma membrane are connected with cytoskeleton through integrins being in tension [5]. The material properties, dimensions and prestrain values required for modelling are obtained from literature survey.

The results obtained in simulation of tension test with the older model are depicted in Fig. 1(b) and with the new model maximum axial stresses are expected to be in dense network of intermediate filaments located in the peripheral region of nucleus playing a key role in mechanotransduction. The optimisation of the new cell model will be achieved by performing computational simulations of different mechanical tests and comparing the results obtained (force-displacement curves) with published experimental data. In this way, a more realistic computational model could be obtained enabling us a better understanding of cell mechanics.

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