Continuum modeling of neuronal cell under blast loading: Supplementary Materials

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Supplementary Materials A: Finite element setup complementary information

A-1 Nanoindentation finite element setup

The tremendous variability in geometry, function and structure of neurons [1], as well as the complexity of the cell structure evolution by protein deformation/reorganization and/or by the action of molecular motors and ionic gates [2, 3] cannot possibly be fully taken into account. As a consequence, simplifications for the model morphology coupled to an experimental setup chosen so as to *a priori* simplify the deformation mechanisms should be used. Bernick *et al.* proposed the use of a continuum semi-ellipsoid as a representative body of a cerebral cortex rat neuron [4]. The model was subjected to a series of *in vitro* indentations at different rates (in one unique

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run). The results were compared to an average of experimental results with the same loading conditions. Note that by inversing the order of the applied indentation velocities and observing the same rate effect experimentally, the authors confirmed the operating deformation mechanisms as passive mechanisms, *i.e.* without active remodeling of the cytoskeleton. The constitutive model chosen in this reference consists of a hyperelastic network and a set of Hooke and Newton models in parallel and series [4].

In our model, the chosen modeled continua are the nucleus, the cytoplasm and the cortex plus membrane. The nucleus envelope is composed of two bilipid membranes, pierced by multiple proteins and pores, supported by an underlying dense network of proteins (mainly lamina and chromatin) [5, 6]. However, the membrane stiffness can be considered as insignificant when compared to the nuclear lamina and interior stiffness [6]. As a consequence, the nucleus is modeled here as a unique continuum with 3D finite elements for the blast simulations (2D axisymmetric elements for the nanoindentations) without envelope. Note that Vaziri *et al.* emphasized the need to model the nuclear envelope when sharp perturbations on the nucleus are considered [5]. However, all the nucleus (indirect) loadings observed in this work involve relatively diffuse nucleus deformation patterns, thus supporting our modeling assumption. The "cortex plus cell membrane" region, on the other hand, is significantly stiffer than the rest of the cytoplasm and intricately connected [7], and thus needs to be modeled independently [8]. In the approach followed here, we model cortex and membrane together by means of shell elements (or 1D axisymmetric shell elements for nanoindentation). Finally, the cytoplasm and its constituents are modeled with 3D finite elements (or 2D axisymmetric

elements for nanoindentation).

The membrane/cortex is discretized with 54 linear axisymmetric shell elements (SAX1), the cytoplasm with 702 bilinear axisymmetric quadrilateral elements with hybrid, constant pressure, reduced integration, and hourglass control formulation (CAX4RH), and the nucleus with 905 of the same elements and 14 linear axisymmetric triangle with hybrid and constant pressure formulation (CAX3H).

A-2 Blast finite element setup

The membrane/cortex is discretized with 1761 linear triangular shell elements (S3), the cytoplasm with 16,949 linear tetrahedra (C3D4), and the nucleus with 7,948 linear tetrahedra (C3D4). The Eulerian finite element mesh of the box is constituted of 125,000 cubic elements (EC3D8R). Fluid material mass is assigned to each element as a function of its intersection with the solid Lagrangian mesh and a frictionless"hard contact" algorithm between the Eulerian mesh and the Lagrangian mesh is used [9]. In order to account for visco-hyperelasticity and volumetric equation of state, the solid elements were duplicated while keeping the same nodes and the constitutive models were adequately distributed.

The fluid box has frictionless reflective boundary conditions on all sides, except on the top face where a pressure loading is imposed. The cell bottom is constrained to the bottom of the box.

A-3 Artificial Viscosity

Originally proposed by von Neumann and Richtmyer [10], the artificial viscosity aims at spreading the shock front over several elements in order to

enable the simulations of strong shocks of thickness smaller than the mesh size. The viscosity introduced in the calculations vanishes when the mesh size decreases and conserves the fundamental features of the shock, such as the shock speed or the jump conditions, while avoiding the high frequency spurious mode otherwise observed. The commercial software used in this work (Abaqus [9]) is using a similar formulation. An artificial bulk viscosity P_{av} term composed of a linear and quadratic terms is added to the pressure terms with

$$P_{av} = \rho l_e \dot{\epsilon}_v \left(b_1 c_d + l_e b_2^2 \dot{\epsilon}_v \right) \tag{1}$$

where b_1 and b_2 are damping coefficients, l_e is the characteristic element size, ϵ_v is the volumetric strain, and $c_d = \sqrt{\frac{\lambda+2\mu}{\rho}}$ is the dilatational wave speed, λ and μ being the Lamé constants. Note that P_{av} must be substracted to P in the energy and momentum conservation equations not to affect the dynamics of the problem.

Finally, it must be noted that, all these models being already embedded in Abaqus [9], implementations in additional subroutines were not necessary.

The default parameters taken by Abaqus are:

$$\begin{cases} b_1 = 0.06 \\ b_2 = 1.2 \end{cases} \tag{2}$$

By checking that the artifical viscosity energy remains well below the other energies of the problem, those values have been found to be a good compromise.

Supplementary Materials B: Model parameters literature review

B-1 Cortex and membrane

As discussed above, both the bilipid membrane and the cortex are modeled by a unique layer of shell elements of 200 nm thickness. The cortical tension in neutrophils during phagocytosis has been intensively studied by Herant and coworkers and has been evaluated (before phagocytosis) to be approximatively 0.03 $mN.m^{-1}$ [11, 12, 13], which amounts to a membrane/cortex Young modulus of roughly $\sim$100 Pa. Red blood cells seem to have a slightly higher value of $\sim$300 Pa [14]. Overall though, putting aside the confusion that is often made by calling membrane what is in reality the cortex plus the membrane, and taking into account the fact that different cells have different properties, literature values seem to converge towards a Young Modulus of 1000 Pa [15, 16], reaching close to 7,000 Pa for myoblasts [17]. Additionally, the elastic modulus of the F-action network (and thus cortex) in the excitation range of 0.1—1 Hz has also been reported to range from hundreds to thousands of pascals for neurons and neutrophils, and fibroblasts respectively. Note finally that cortex bending stiffness is of the order of $10^{-18}N.m$ and $10^{-19}N.m$ for neutrophils and red blood cells respectively [8], which, using the area moment of inertia of a plate, leads to Young moduli of the order of 1000 Pa and 100 Pa respectively.

For neutrophils, the surface tension viscosity has been evaluated to 75 $poise.cm$=75.10^{-3} $Pa.s.m$ (*i.e.* η_1^{mem}=375.10^3 $Pa.s$) with a relaxation time of 3000 s [11, 12].

B-2 Nucleus and cytoplasm

The long term Young modulus of cell nucleus has been directly estimated to be of the order of $E_0^{nuc} = 1\ kPa$ for articular chondrocytes [18], and 5 kPa for myoblasts [17]. However, as reported by Vaziri *et al.*, other references diverge on this value, thus leading to the rather wide range of $E_0^{nuc} \sim 10$—10^4 Pa [19, 20, 21, 5, 22]. Note that recent work on crosslinked/bundled actin filaments network by Lieleg *et al.* have reported values in the lower range (~ 10—$100\ Pa$) of these estimations [23].

The cytoskeleton[2] Young modulus has been evaluated to be 1.4 times lower than the one of the nucleus according to Ofek *et al.* [22], 3 to 4 times according to Guilak *et al.* [18], and 5 to 10 times according to Friedl *et al.* [6]. It was directly evaluated to be of the order of 500 Pa for endothelial cells by Caille *et al.* [19], but based on the nuclear stiffness range and the "rule-of-factor-3/10" between nucleus and cytoplasm, the acceptable range should be of $E_0^{nuc} \sim 1$—$10^3\ Pa$, one more time rather unreliable.

The typical viscoelastic time constant $\tau_1^{nuc/cyto}$ seem to vary widely depending on the way the cell or cell component is tested (*e.g.* nucleus aspiration or cell compression with time constant of the order of tens of seconds [18, 24, 25], full glial cell stretch with time constant of the order of tenths of seconds [26], and seconds in neutrophil phagocytosis [13]). In the recent work of Lieleg *et al.* on crosslinked/bundled actin filaments network, converting their frequency domain viscosity values to time domain values yield time constants ranging from hundredths of seconds to seconds [23].

[2]protein networks, organelles and cytosol surrounding the nucleus and enclosed by the membrane

Finally, cytoplasmic viscosity has been evaluated to be in the range of 300—600 $Pa.s$ for neutrophils by Herant *et al.* [11, 13]. The work of Lieleg *et al.* on crosslinked/bundled actin filaments network reports values in the range ∼1—500 $Pa.s$ [23]. The nucleus has been estimated to be nearly twice as viscous as the cytoplasm [18]. A fibroblast nucleus viscosity of 52 $Pa.s$ was directly measured by Tseng *et al.* [21].

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