



PROCEEDINGS OF SIMAI 2016
THE XIII BIENNIAL CONGRESS OF SIMAI
13-16 SEPTEMBER 2016
MILAN, ITALY

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Multiscale Numerical Model of the Strain-Based Permeability of the Nuclear Envelope

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A basic recent understanding in stem cell differentiation is that the cell is able to translate its shape (e.g. roundish or deformed) into a fate decision. However, the mechanisms by which phenotype expression is regulated by cell shape are complex and poorly understood. Our hypothesis is that cell deformation induces nuclear deformation, which in turn causes strains in the nuclear envelope (NE). These strains cause a change in porosity/permeability of the NE to the traffic of transcription factors involved in stem cell differentiation [1]. To demonstrate this hypothesis, we set-up a numerical model of the interaction between the nuclear pore complexes (NPC) and the NE. It is worth mentioning that the NPC is assumed as a multiprotein structure with a "basket shape" in the nuclear side that plays a significant role in the transport of solutes through the NE [2, 3].

In parallel to the computational modeling and analysis, we recreated in the laboratory the two extreme deformation conditions for the NE by using mesenchymal stem cells (MSC) derived from the bone marrow of adult rat; the cells were seeded and grown on two different substrates: i) a glass flat surface, and ii) a 3D nanoengineered synthetic niche. The flat surface leads to the deformed nuclear configuration, whereas the niche induces the roundish nuclear shape. MSC were incubated at 37°C with 0.1 μ M of Hoechst 3342, a vital and fluorescent little (615 Dalton) molecule, that can freely diffuse inside the cells and bind stably to the DNA. After 10 minutes cells were washed in PBS three times and then placed on a fresh cell culture medium. Samples were mounted into the FluoView10i laser scanning confocal microscope (Olympus) to acquire images (with 30 μ m depth and step 1 μ m) of the cells in both configurations. The nuclear intensity/pixel of each cell is

calculated by manual segmentation of the nuclei and by measurement of the fluorescence intensity of the region of interest.

In order to couple a change in permeability of the NE at the microscale with a change in configuration of a single NPC at the nanoscale (in response to the deformation applied to the NE), we incorporated the measured data of the nuclei main axis from [1] into a computational model of the NPC-NE mechanical interaction. Such experimental measurements were taken inside and outside the aforementioned niches. Considering that the NPC is directly attached to the nuclear lamina, the effect of the nuclear deformation due to mechanotransduction will directly open or close the effective area of the pores, thus increasing or decreasing the permeability of the NE. Here we propose a numerical model that defines the permeability as the areal ratio between the whole nucleus surface area and the total area of the pores. A value of diffusion is then calculated as the product of the permeability and the maximum diffusion coefficient in the cytoplasm (free diffusion) of Hoechst 33342 calculated by means of the Stokes-Einstein law and its molecular weight [4]. Using the continuum mechanics theory for thin lamina, we calculate the pore opening as a function of the local Green-Lagrange deformation tensor at every point on the nuclear surface. We considered an equispaced distribution of NPC's on the NE so that a local permeability is then calculated by dividing the occupied area of a deformed pore by the corresponding NE local area. To do that, we considered the cell as incompressible, that means, the final ellipsoidal volume from [1] will be equal to its corresponding "zero-stress" spherical configuration. Finally, a strain-dependent value of diffusion was calculated and directly applied to a passive transport finite element simulation following the Fick's laws of diffusion.

Our preliminary simulation results show a faster transport of solutes on the deformed NE as compared to the roundish nucleus (a ratio of 7,66:1 faster in the deformed nucleus with respect to the roundish configuration). These results correlate well with experiments performed with Hoechst 33342 where a significantly higher intensity per pixel was found in highly deformed nuclei (cells on the flat surface), suggesting a faster transport through the NE with respect to less deformed nuclei. These results indicate the strain dependence of the passive diffusion process of nucleocytoplasmic transport of solutes. In addition, the computational model is able to recreate such passive transport dependency with respect to the deformation of the nucleus.

This project has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (grant agreement No 646990 - NICHOD).

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