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Long-Term Three-Dimensional Simulation of Cytoskeletal Rearrangement During Adipogenic Differentiation

Manoochehr Rabiei and Alan Bowling

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Manoochehr Rabiei*, Alan Bowling#

Department of Mechanical and Aerospace Engineering
University of Texas at Arlington
701 S. Nedderman Drive, Arlington, TX, 76019, USA
* manoochehr.rabiei@mavs.uta.edu , # bowling@uta.edu

Abstract

The long-term simulation of cytoskeletal rearrangement during adipogenic differentiation, or adipogenesis (the lineage change from stem cells to adipose(fat) cells), modeled in three dimensions is presented herein. Obtaining long-term dynamic simulation of cellular processes has been infeasible even with the employment of supercomputers[1]. A scaling approach based on the method of multiple scales (MMS)[3] is employed to produce the 5-day time history of this process on a desktop computer in less than **40 minutes**.

Studies suggest that the stem cells cytoskeleton, consisting mostly of actin microfilaments, rearranges in the first phase of adipogenesis before any appreciable production of lipid droplets[5]. The microfilaments around the nucleus are observed to vanish corresponding to a large reduction in nuclear area. The experimental data of the process are produced by analyzing two-dimensional fluorescent images of the subcellular elements taken every two days[2].

The stem cell model consists of the nucleus, the cytoskeletal actin microfilaments structure, and the cellular membrane actin cortex. This model has 2088 spherical particles with 5.06 nm diameter and 0.0741 fg weight, connected through massless springs with the appropriate stiffness to represent the connected structures. The equations of motion will take the form of:

$$m\,\ddot{\mathbf{q}} + \beta\,\dot{\mathbf{q}} + K(\mathbf{q})\,\mathbf{q} = \Gamma \tag{1}$$

where m is the mass of the particles, β is the damping coefficient derived from Stoke's drag of particles in cytoplasm, $K(\mathbf{q})$ is the stiffness matrix based on the actin microfilaments and nuclear membrane stiffnesses, and Γ contains all other large forces (gravity and buoyancy, volume conserving reaction forces, and reaction forces of the substrate). Generalized coordinates, speeds, and accelerations, $\mathbf{q}$, $\dot{\mathbf{q}}$, and $\ddot{\mathbf{q}}$, are the three-dimensional cartesian coordinates of the particles and their respective time differentials.

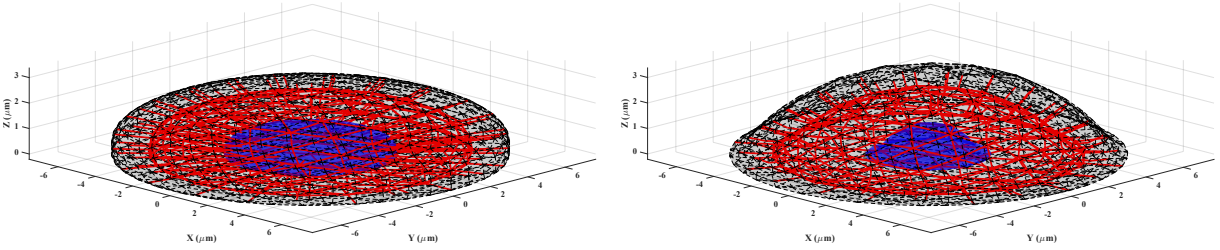

Figure 1: The cellular model situated on top of the substrate. Left: At the start of the simulation. Right: At the end of the simulation. The nucleus is in blue, Cytoskeletal microfilaments are in red, and the cellular membrane actin cortex is in black.

The large disparity between the inertial, damping, and stiffness terms results in very small integration time step sizes, making the computational time of acquiring the simulation prohibitively large. Herein a scaling approach based on the method of multiple scales (MMS) is employed to balance these disparities in larger time scales[4]. This method employs two small dimensionless numbers, ε_1, and ε_2, at the characteristic time unit of 1 ks for the multi-day adipogenesis process.

$$\varepsilon_1\ (1ks) = \left(\frac{m}{\beta}\right) = 1.41 \times 10^{-13} \qquad \varepsilon_2\ (1ks) = \left(\frac{\beta}{k}\right) = 2.24 \times 10^{-14} \tag{2}$$

These scaling factors are used to decompose the time variable into multiple scales, where $T_i = \varepsilon_j^i t$, to produce asymptotic expansion of the equations of motion. Organizing the resulting equations into powers

of the dimensionless numbers allows for the isolation of accelerations to the selected time unit of 1 ks. This results in the scaling of the equations of motion with two dimensionless scaling factors, a_2 and b_2 in the form of:

$$m\,\ddot{\mathbf{q}} + a_2\,\beta\,\dot{\mathbf{q}} + a_2\,b_2\,K(\mathbf{q})\,\mathbf{q} = a_2\,b_2\,\Gamma \tag{3}$$

where $a_2 > \varepsilon_1 \frac{1}{1ks}$ and $b_2 > \varepsilon_2 \frac{1}{1ks}$. The values of $a_2 = b_2 = 1.13 \times 10^{-12}$ are used in this study.
The integration of the cellular model simulation is performed using the ODE45 solver of MATLAB 2023b on a desktop computer with an Intel Core i7-8700 processor and the data is recorded every 100s. The computational time required for obtaining the 5-day time history of the scaled system was 39' 27". The unscaled system required 26 minutes of computational time to produce 1ps (10^{-12})s of time history. The use of the scaling method thus results in **computational time reduction in the order of** 10^{17}.

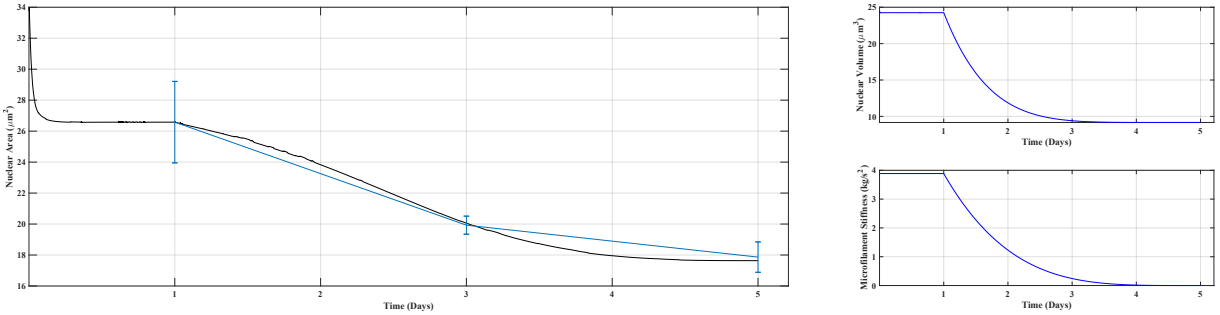

Figure 2: Left: The change in the nuclear area, computational data in black and experimental data[2] in blue. Top right: Change in nuclear volume. Bottom right: change in the stiffness of actin microfilaments connected to the nucleus.

Cytoskeletal rearrangement is modeled as a reduction in stiffness of actin microfilaments connected to the nucleus. The rate of this change and the change in nuclear volume can be found by the agreement between the computational and experimental[2] data:

$$\mathrm{k}_t = \mathrm{k}_0 \left(1 - \frac{t}{t_r}\right)^4 \qquad \mathrm{V}_t = \mathrm{V}_5 + (\mathrm{V}_1 - \mathrm{V}_5) \left(1 - \frac{t}{t_r}\right)^6 \tag{4}$$

where k_t denotes the time-dependent microfilaments stiffnesses, k_0 denotes the starting stiffnesses, t_r denotes the rearrangement time period if four days, V_t is the current volume of the nucleus, V_1 is the starting volume, and V_5 is the volume at day 5. The exponential decrease in stiffness, with the power order of 4, signifies a rapid rearrangement of the cytoskeletal structure at the beginning of the adipogenesis process. The change in the nuclear volume has been found to follow an even more rapid decrease with the power value of 6. Both of these results signify the importance of the dynamic simulation of the cellular processes where the computational data can reveal some characteristics of the process in the absence of observational data.

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