Long Term Simulation of Adipogenic Differentiation

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EXTENDED ABSTRACT

1 Introduction

Simulation of cellular processes in biomolecular definition for large time periods are still outside of reach, even with the aid of supercomputers. The multiscale nature of the constituent structures of the cells, from nano- to microscale, increases the computational cost of obtaining the solution of the dynamic model of the cell. A scaling approach, based on the method of multiple scales, has been employed to drastically reduce the computational time and make it feasible to obtain the solution of the dynamic model. Herein this method is further developed to account for the difference, and change, in masses of the constituent cellular structures in a tensegrity model of the cellular dynamics. This results in substantial reduction in computational time from the previous works. The test case is the process of adipogenic differentiation of a mesenchymal stem cell into an adipocyte. This process, lasting 15 days, was simulated in less than 2 hours on a typical desktop computer. This reduction in computational time allows for the study of the cellular structures' dynamics during the process which is very difficult to observe due to experimental constraints.

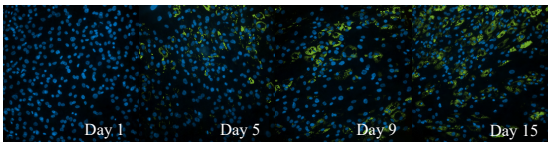

Figure 1: Fluorescent images of adipogenesis. Nuclei (DAPI blue) and lipids (LipidTox, green) are fluorescently dyed. A sample is shown at days 1, 5, 9, and 15.

2 Test Case and Model

Stem cells can differentiate into multiple phenotypes such as bone, cartilage, and adipose tissue [1]. The cocktail of biological factors, substrate stiffness, and external forces affect the phenotype commitment [2]. Adipogenesis is the process of transformation of stem cells into adipocytes, i.e. fat storing cells. The process was observed for 15 days. The nucleus size, and lipid droplet accumulation was visualized by bio-staining the cell with fluorophore dyes (Fig. 1).

The fluorescent images were processed by employing K-means clustering for nuclei morphology, size, and numbers [3]. The aggregate size of the lipid droplets were analyzed by processing the images in MATLAB 2021b by binarizing the image after applying a Wiener filter.

The tensegrity model [4] is chosen to describe the dynamics of cytoskeletal structure rearrangement during adipogenesis. This model divides the cytoskeleton into distinct tensile and compressive members [5]. The thin actin microfilaments are the tensile members. The microtubules constitute the compressive elements due to their thickness allowing them to withstand bending.

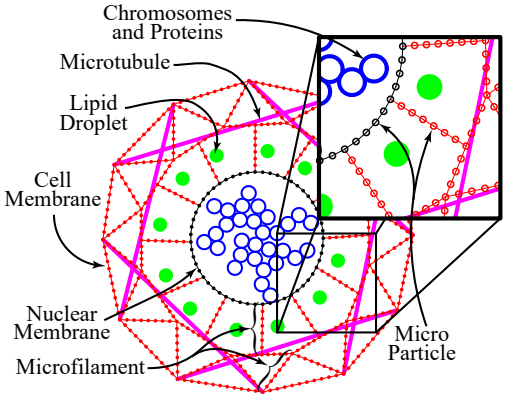

Figure 2: Schematic of the cellular model showing the nuclear, cytoskeletal, and lipid elements.

The cellular structures are coarse-grained in a two-dimensional model to account for the two-dimensional nature of the experimental results. The nuclear membrane, and cytoskeletal members, are dissected into rigid circular particles connected with springs with possible changing stiffness and unstretched lengths. The lipid droplets are modeled as circular rigid particles changing in mass and size. The cytoplasm is the viscous media surrounding the cytoskeleton and the lipid droplets. The intranuclear chromosomes and proteins are modeled as circular rigid particles surrounded by the viscous nucleoplasm (Fig. 2). The appropriate viscous drag is applied to the particles and The contact between them are modeled as elastic.

There is a large discrepancy between the size of the spring and viscous forces and the mass of the particles. This difference results in large accelerations in short time intervals necessitating very small integration step sizes to obtain the solution. This is the basis of the problem in the simulation of the biomolecular systems for long time periods. A scaling method, based on the

method of multiple scales [6], has been employed to bring these forces into the same scale as the mass term [7]. This results in a large increase in integration step size and drastic reduction in computational time. Employing this method changes the standard equation of the motion into the form:

$$M(\mathbf{q})\ddot{\mathbf{q}} = a_2\, D(\mathbf{q})\dot{\mathbf{q}} + a_2 b_2\, K(\mathbf{q}) + a_2 b_2\, \mathbf{\Gamma}_l \tag{1}$$

where a_2 and b_2 are scaling factors in the order of m/β and β/K respectively.

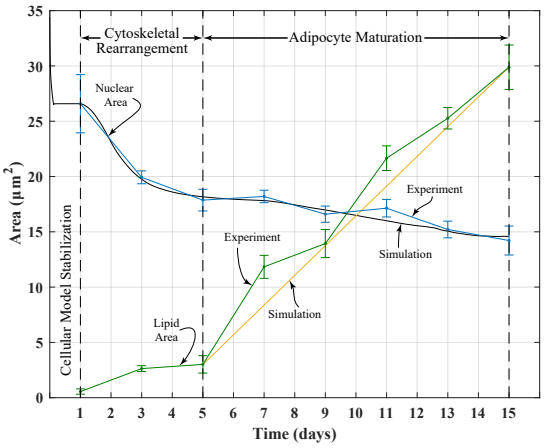

Figure 3: Experimental and simulation results corresponding to different stages of adipogenic differentiation.

Herein, this scaling approach is further developed to include the effects of increasing mass of the lipid droplets, for which the equation of motion will take the form of:

$$m\ddot{\mathbf{x}} = -(a_2\beta\, \dot{\mathbf{x}} + a_2 b_2 k\, \mathbf{x}) + a_2 b_2 \mathbf{F} - \dot{m}\dot{\mathbf{x}} \tag{2}$$

The difference in the mass of different particles limits the values of a_2 and b_2 in eqn. 1 to the largest possible values of m/β and β/K in the system, respectively. The scaling method has been enhanced with addition of a third scaling factor c_2 in the order of the m_{small}/m_{large}. The expanded equation of motion will take the form of:

$$\begin{cases} m_{small}\ddot{\mathbf{x}} = -(a_2 c_2 \beta\, \dot{\mathbf{x}} + a_2 b_2 c_2 k\, \mathbf{x}) + a_2 b_2 c_2 \mathbf{F} \\ m_{large}\ddot{\mathbf{x}} = -(a_2\beta\, \dot{\mathbf{x}} + a_2 b_2 k\, \mathbf{x}) + a_2 b_2 \mathbf{F} \end{cases} \tag{3}$$

3 Results and Conclusion

The adipogenic differentiation was simulated in three phases. In the cellular model stabilization the initial condition of the model is stabilized to align with the experimental results. The cytoskeletal rearrangement phase is modeled to show the effects of dissolution of the compressive microtubules and cellular membrane connection to microfilament structure. The adipocyte maturation phase is modeled by the linear increase in the area of lipid droplets. The agreement between the experimental and simulation results validates the scaling approach (Fig. 2). The further development of the scaling approach shown in eqn. 3 results in 40% reduction in computational time from the scaling approach shown in eqn. 1 to 2 hours. This faster than real-time computational speed allow for the study of the dynamic rearrangement of the cytoskeletal structure during adipogenesis.

Acknowledgments

This work was supported by the National Institutes of Health (NIH) National Institute of Biomedical Imaging and Bioengineering (NIBIB) award number 1R15EB030842-01. The authors thank Dr. Andrew McCulloch, and Mr. Vatsal Joshi for his aid in this research.

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