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A MONOLITHIC APPROACH TO CELL CONTRACTILITY

***Pradeep Keshavanarayana[1], René de Borst[2] and Martin Ruess[1]**

[1]School of Engineering, University of Glasgow, Glasgow G12 8LT, UK
[2]Faculty of Engineering, University of Sheffield, Sheffield A1 3JD, UK

*p.keshavanarayana.1@research.gla.ac.uk

ABSTRACT

Contraction of cells leads to stress fibre formation in the cytoplasm. They extend along the length of the cell, terminating at focal adhesions. Modelling the growth of stress fibres coupled with focal adhesions, assumed to be made up of high and low affinity integrins, results in a bio-chemo-mechanical problem. Solving the coupled system of equations in a staggered manner restricts the time step used. In this contribution, we present a monolithic approach which relaxes this restriction. The stress fibre is assumed to obey the Hill type growth, where the stress depends on the strain rate, even in non-muscle cells, which we approximate through a non-linear model. We have also implemented the feedback within the system, which is a fundamental nature of all living organisms.

Key Words: *Focal Adhesion, Staggered, Monolithic, Non-linear Hill Model, Feedback*

1. Introduction

Cells are the fundamental units of all cellular organisms. Response of cells to external stimuli is a topic which has been dealt thoroughly, yet not understood completely. The role of mechanics in cellular behaviour has been established almost half a century ago [8]. The advancements in experimental techniques have been successful in quantifying such a role [6]. Bolstering the experimental progress with numerical modelling is the recent trend in various disciplines, including bio-mechanics. With studies emphasising the understanding of the functioning of cells in a mechanical perspective, numerical models are being developed. Such models involve a coupled system of equations, to be solved with boundary conditions matching the experimental observations. The solution schemes used to solve the governing equations play a prominent role in the overall analysis. In this contribution, we consider the continuum model [13] as a base and solve the system of equations with different numerical schemes.

2. Cell motility, contractility and focal adhesion

Cell motility is mainly responsible for processes such as wound healing and growth. Assuming cells to crawl and not swim [12], the process involves continuous reorganisation of the cellular shape and internal skeletal structure [9]. The cellular integrity is maintained by a special structure called the cytoskeleton. Apart from its scaffolding and cell shaping properties, it acts as a dynamic structure which resists, generates and transmits cellular forces. The forces in the cytoskeleton results in contractility of the cell. This in turn decides the connectivity of the cell membrane to the extracellular matrix (ECM), at focal adhesions (FA) [4]. The tension dependent assembly of actin and myosin, forming stress fibres, extend along the length of the cell. The formation of stress fibres involves a series of biochemical activities [11], for which the concentration of calcium ions in the cytoplasm is of utmost importance [10]. At FA, the forces are transferred from and to the cell, resulting in a continuous reorientation of the cytoskeleton. The proteins present at FAs, called integrins, are responsible for sensing the properties of the ECM. Thus, the formation of FAs along with stress fibre growth decides the direction and magnitude of the movement of cells.

3. A bio-chemo-mechanical model

In the recent past, there have been many mathematical models developed to explain the experimental observations of cell contractility. Each of these models could simulate a few set of experiments. Some of the models were developed by assuming the cell as a continuum, while some other modelled it in a discrete sense. Tensegrity models of cells [5], chemo-mechanical models with and without focal adhesions [13] [1] [7] or the modelling of focal adhesions alone [2] are some of the important types of models considered in the past. In this contribution, the mathematical model developed in [13] is considered and the resulting system of equations and its solution scheme is studied.

Noting the importance of calcium in the formation of stress fibres, an ad-hoc signal representing the concentration of calcium activates the system. The stress fibres ending on the cell membrane result in the formation of focal adhesions satisfying the mechanical equilibrium. Focal adhesions are assumed to be made up of high affinity integrins ξ_H and low affinity integrins ξ_L, where only the high affinity integrins form bonds with the ECM, while the low affinity integrins are allowed to diffuse. The integrins are governed by thermodynamic equilibrium, and hence they are interconvertible. The active stress is assumed to follow Hill type growth and passive stress follows from the elastic contribution. In [13] the active stress σ is estimated using a linear piecewise continuous equation:

$$\frac{\sigma}{\sigma_0} = \begin{cases} 0 & \frac{\dot{\varepsilon}}{\dot{\varepsilon}_0} < -\frac{\eta}{\bar{k}_v} \\ 1 + \frac{\bar{k}_v}{\eta}\left(\frac{\dot{\varepsilon}}{\dot{\varepsilon}_0}\right) & -\frac{\eta}{\bar{k}_v} \leq \frac{\dot{\varepsilon}}{\dot{\varepsilon}_0} \leq 0 \\ 1 & \frac{\dot{\varepsilon}}{\dot{\varepsilon}_0} > 0 \end{cases} \tag{1}$$

where, $\dot{\varepsilon}$ is the strain rate, η is the stress fibre concentration, σ_0 is the isometric tension in the stress fibres and $\bar{k}_v$ is a parameter representing the fractional reduction in stress when the strain rate is increased by $\dot{\varepsilon}_0$. Thus, the bio-chemical behaviour is converted to a mathematical problem, where, the mechanical equilibrium and the diffusion equations are solved in a coupled setting. In [13], a staggered solution scheme is used for the solution of the system of equations. It was found that the staggered scheme restricts the time step that can be used. Hence, a monolithic solution approach has been developed which is discussed in the next section.

4. Monolithic solution approach

In the staggered approach, the mechanical equilibrium equation is solved assuming the concentration of high affinity integrins to be constant. Then, the diffusion equation is solved to update the integrin concentration. In the monolithic approach, the equations are coupled to form a larger stiffness matrix. The advantages of the monolithic approach are that the solution involves only one matrix decomposition and the time step being used can be increased without affecting the result.

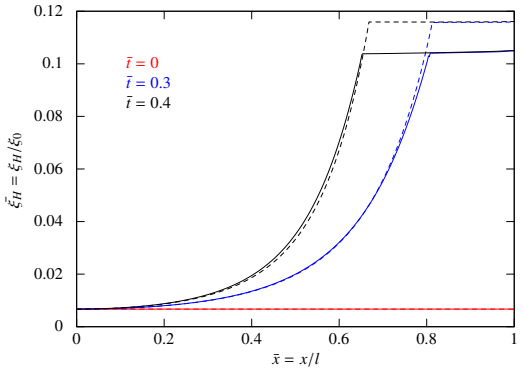

Figure 1: $\Delta_t = 1.0s$

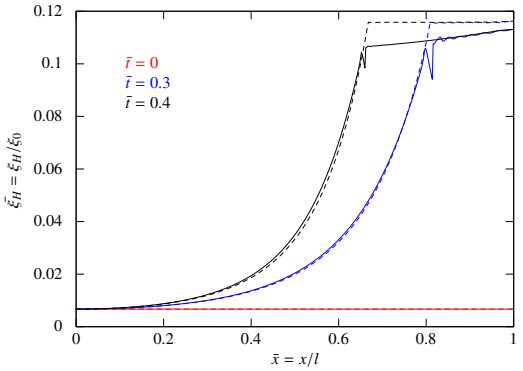

Figure 2: $\Delta_t = 6.0s$

Analysis results according to the monolithic and the staggered solution approach for different time steps Δ_t (— staggered, - - - monolithic).

It can be seen from Fig. 1 and Fig. 2 that, as the time step is increased, the solution of the monolithic approach remains more stable compared to the solution from staggered approach. The values of the reference integrin concentration ξ_0, length of the cell l and other parameters used are taken from [13].

5. Hill model

The Hill model used in [13] provides piecewise continuity, Eq. (1). The computational experiments revealed numerical instabilities when the strain rate conditions changed its regime. Hence in this contribution, we changed to the following non-linear Hill model for the active stress growth :

$$\frac{\sigma}{\sigma_0} = 1 + \frac{\bar{k}_v}{\eta}\left(\frac{\dot{\varepsilon}}{\sqrt{\dot{\varepsilon}^2 + \dot{\varepsilon}_0^2}}\right) \tag{2}$$

which has proven full stability throughout the computations performed. In [13], it has been assumed that the low affinity integrins diffuse along the cell membrane, while high affinity integrins are fixed. In our computations, we found that the growth of focal adhesions shows a similar response even when the diffusion is neglected. In addition, in order to enforce the condition of thermodynamic equilibrium by the interconversion of these integrins and keeping in view the bio-chemical simplifications made in the model, the diffusion of low affinity integrins becomes obsolete. Hence, we have neglected the diffusion of low affinity integrins in further calculations.

6. Feedback cycle

When an external signal acts upon the cell, a series of biochemical reactions results in the release of calcium to the cytoplasm which forms stress fibres. The stress fibres further result in the growth of FAs. The growth of FAs is also a type of stimulus which releases calcium again. Hence, the process becomes cyclic, due to which, there is a need for a feedback loop within the system of equations. This problem of providing feedback has been solved in [3], where the calcium growth is put in a feedback loop. We use this feedback mechanism in combination with the non-linear Hill model to solve the 1-D cell problem as provided in [3].

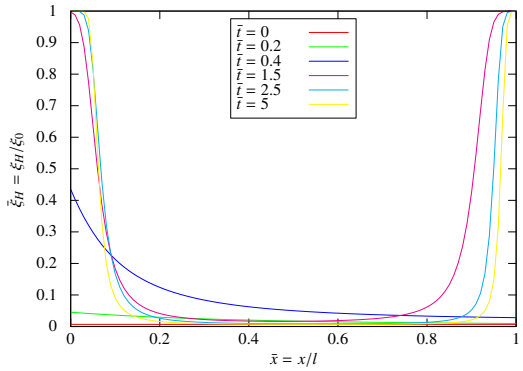

Figure 3: Without feedback

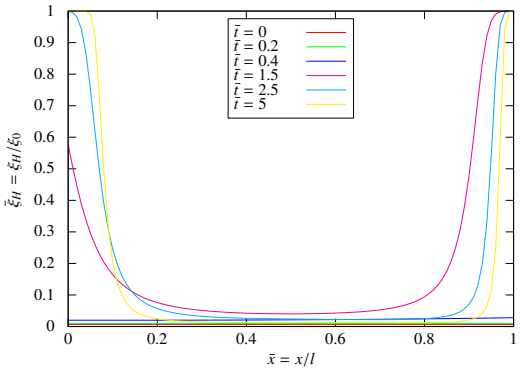

Figure 4: With feedback

A 1-D cell is placed on a substrate and a prescribed displacement is applied to the right end of the cell. Sensing the external stimulus, the focal adhesions start forming near the right end. It can be seen from Fig. 3 that the high affinity integrins are formed on the left end prior to the right end, which do not match the physical observations. In contrast, the results including the feedback mechanism match very well with the experiments, Fig 4. Hence, a feedback mechanism becomes essential for a reliable analysis result.

7. Summary and future work

Most of the models that have been developed to explain the cellular processes are phenomenological models. The solution schemes used to solve the governing system of equations plays a very important role in obtaining the right solution. In this contribution, we have demonstrated that the monolithic solution scheme provides a stable result irrespective of the time step chosen. A continuous non-linear Hill type model has been used for the active stress growth. A Feedback mechanism within the cell was implemented and compared with the system without feedback. In future, the model has to be extended to 2D and different solution schemes are to be compared. Motivated from [11], spiking in calcium signals has to be considered and the effect on the formation of stress fibres will be studied. The current model has to be further developed in order to make it suitable to explain cell motility.

References

[1] A. Besser and U.S.Schwarz. Coupling biochemistry and mechanics in cell adhesion: a model for inhomogeneous stress fiber contraction. *New Journal of Physics*, pp.425, 2007.

[2] A. Besser and Samuel A Safran. Force-Induced Adsorption and Anisotropic Growth of Focal Adhesions. *Biophysical Journal*, 90, 3469-3484, 2006.

[3] A. Pathak, R. M. McMeeking, A. G. Evans and V. S. Deshpande. An Analysis of the Cooperative Mechano-Sensitive Feedback Between Intracellular Signaling, Focal Adhesion Development, and Stress Fiber Contractility. *Journal of Applied Mechanics*, 78, 2011.

[4] B. Geiger, A. Bershadsky, R. Pankov and K. M. Yamada. Transmembrane crosstalk between the extracellular matrixcytoskeleton crosstalk. *Nature Reviews. Molecular Cell Biology*, 2, 793-805, 2001.

[5] D. E. Ingber. Tensegrity I. Cell structure and hierarchical systems biology. *Journal of Cell Science*, 116, 1157-1173, 2003.

[6] G. Bao and S Suresh. Cell and molecular mechanics of biological materials. *Nature materials*, 2, 715-725, 2003.

[7] I. L. Novak, B. M. Slepchenko, A. Mogilner and L. M Loew. Cooperativity between Cell Contractility and Adhesion. *Physical Review Letters*, 93, 2004.

[8] Paul Weiss and Beatrice Garber. Shape and Movement of Mesenchyme Cells as Functions of the Physical Structure of the Medium. *Proceedings of the National Academy of Sciences of the United States of America*, 38, 264–280, 1952.

[9] R. Ananthakrishnan and A. Ehrlicher. The forces behind cell movement. *International journal of biological sciences*, 3, 303-317, 2007

[10] S. Pellegrin and H. Mellor.Actin stress fibres. *Journal of Cell Science*, 120, 3491-3499, 2007.

[11] T. Meyer and L. Stryer. Molecular model for receptor-stimulated calcium spiking. *Proceedings of the National Academy of Sciences*, 85, 5051-5055, 1988.

[12] T. Risler. Cytoskeleton and Cell Motility. *in Encyclopedia of Complexity and System Science*, pp.1738-1774, 2011.

[13] V. Deshpande, M. Mrksich, R. Mcmeeking and A. Evans. A bio-mechanical model for coupling cell contractility with focal adhesion formation. *Journal of the Mechanics and Physics of Solids*, 56, 1484–1510, 2008.