Title:	Role of Myosin Contractility In The Regulation Of Focal Adhesion Dynamics
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Abstract:	ABSTRACT To move is to live, to live is to move. Dynamics is indispensable for life to begin, thrive and proliferate. Forces enable changes in a system's state of motion. A wide range of forces are involved in biological systems – from microscopic biomolecular levels to daily movements of large scale living objects. In the studies of cellular motion, pertinent queries regarding the origin and transmission of such forces arise quite naturally. Myosin motors came to be known as the ubiquitous force generators inside cells, driving plethora of activities leading to cell locomotion. These molecular machines are active, they produce work on their periphery via de-phosphorylation processes. The forces they generate get carried to their intended destinations via elaborate molecular machineries. This begets the question of how active properties of myosin motors affect force generation and transmission during cellular motion. The recent advancements in single molecular studies and molecular force mea- surement techniques allowed for emphasized focus on understanding the myosin active properties better than ever before. The possibility of measuring the effects of modulating the myosin contractility at individual motor level opened up the possi- bilities to comprehend the force fluctuations they produce. Progresses in biophysical modelling allows us to leverage the predictive abilities of biomechanical frameworks in discerning the underlying mechanisms. In this thesis we explore the role of myosin contractility in force fluctuations at focal adhesions and regulations of traction forces via mechanistic model building and validation. Actin polymerization and myosin contractility exert forces on actin which results in a net rearward retrograde flow of the actin network. Focal adhesions which are protein complexes linking the actin to the extracellular matrix, mediates transient interactions between the two, converting the rearward actin flow into forward move- ment of the cell. This is the basis of the 'molecular clutch hypothesis' where the focal adhesions are supposed to act as mechanical clutches. Biophysical modelling of the process has led to important predictions which have been experimentally verified like the biphasic dependence of traction force on substrate rigidity. However, the role of actomyosin contractility in focal adhesion dynamics, both in terms of transient attachment/detachment of myosin to/from the actin filaments and the subsequent movement of bound myosin has not been explored in detail. In this thesis, we build an analytical model based on the motor clutch hypothesis with specific emphasis on myosin motor activity and how it regulates and transmits forces. As a first step, we concentrate solely on the actomyosin and clutch sector, rather ithan the substrate deformation dynamics. Our aim in this work was to understand the mechanistic basis of traction force fluctuations observed in experiments on motile fibroblasts. High resolution traction force microscopy measurements have shown that focal adhesions in a single cell are either in a stable state where traction is spatiotempo- rally static or in a dynamics state where they fluctuate reminiscent of repeated tugging on the extracellular matrix. Could temporal variations in contractility brought about by myosin motors lead to these traction force fluctuations? We show analytically, in an experimentally relevant parameter space, that as the myosin contractility is lowered, effected both by changing the motor velocity and the rate of attachment/detachment, the system goes from decaying oscillations to stable limit cycle oscillations through a supercritical Hopf bifurcation. The system exhibits a wide array of dynamic states as a function of motor activity and the number of clutches. The frequency range of oscil- lations in the average clutch and motor deformation compares well with experimental results. In our next study, we incorporate substrate deformation dynamics in our model. A rigorous study of the equations reveal 'load and fail' or 'stick-slip' behaviour in the traction force dynamics consistent with experiments. Further, our model suc- cessfully reproduces the biphasic relationship between rigidity and force : force first increases and then decreases with rigidity. As the parameters pertaining to molecular determinants are varied, we show that the system traverses between diverse states of stabilities - from decaying oscillations to self-sustaining limit cycles. Modulating myosin activity in our model via different pathways exhibits striking shifts in optimal stiffness. A reduction in the number of myosin motors leads to a shift of traction force maxima towards higher stiffness maxima. An equivalent trend has been observed in experiments where myosin motors were inhibited using blebbistatin. A reduction in clutch number in our model shifts the traction force maxima towards lower substrate rigidities. This is also in agreement with experimental studies where clutches were inhibited. Our study therefore provides excellent agreement with experiments and additional testable predictions. Biological systems are inherently noisy, and their stochastic nature plays a significant role in shaping cellular functionalities and determining cell fate. While the motor and clutch turnover dynamics in our analytical model ensures stochasticity via their on and off rates, we develop a computational model using overdamped Langevin dynamics that explicitly includes a Gaussian noise. Performing stochastic simulations using the Euler-Maruyama method, we show that the predictions from the first study are reproduced, along with qualitative and quantitative matches. ii
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