論文内容の要旨

論文題目：Biophysical Study on Cell Motility and Division
Using Traction Force Microscopy

（力測定法を用いた細胞運動と分裂に関する生物物理学的研究）

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Likewise in non-living matter physics, connecting micro and macro scales is also essential in living matter physics. In the context of cellular biological phenomena, 'micro' implies molecular scale and 'macro' implies cellular scale. Since these two scales are exceedingly apart, it is impossible to directly connect them and thus descriptions in intermediate hierarchies must be needed. This kind of awareness of the issues is not so modern but has been shared among pioneers in both biology and biophysics for a long time with commonly expressed as 'Structure and Function'. The motivation throughout this thesis is to perform modern quantitative studies inspired by this old-fashioned, but still impressive concept and to describe cell biological phenomenon with cell level quantities. Therefore, we have combined quantitative measurement and analysis of various cell level quantities, motion, shape and forces, to attack two major issues in cell biology, cell motility and division.

This thesis is composed by one chapter for Introduction (Chapter 1), four for Results (Chapter 2, 3, 4 and 5), one for Conclusion (Chapter 6) and one for Appendix (Chapter 7).

In Chapter 2, we measured traction stresses of migrating *Dictyostelium discoideum* cell using improved Traction Force Microscopy. We quantified spatio-temporal dynamics of fine structures in stress field and found that the mechanism of cell motility is an inchworm-like one with front-rear asymmetric adhesion anchoring. And furthermore, we introduced multi-pole analysis for traction stresses and investigated dynamic nature of the lowest two moments, force dipole and quadrupole, having a tight relationship to cellular motion (Fig.1). This is the first report about a relationship between traction stress dynamics and cellular motion and gives a cellular level description of cell migration.

In Chapter 3, using the setup constructed in Chapter 2, we measured traction stresses of dividing cell, to our knowledge, for the first time. Dividing cell was found to exert much larger forces comparing to ordinary migrating cell and a large part of this force was tensile forces acting on cleavage furrow, suggesting a role of traction forces on cytokinesis. We also analyzed spatial dynamics of traction stresses and found the agreement of traction stress asymmetry and cellular division axis (Fig.2). This result supports a recently raising hypothesis that adhesion or force pattern at the beginning or even before Mitotic phase determines later division axis. Taken together, these results give a description of cell division using cellular level quantities, traction stresses and cellular shape, and demonstrate a vital importance of measuring mechanical properties in the studies of cell division.

In Chapter 4, we focused on another interesting cell level quantity, cellular shape, of motile cell and investigated its spatio-temporal dynamics under various experimental conditions. We found that ordered cellular shape mode depended on cell-substrate adhesiveness and became more ordered and oscillating in time with increasing adhesion strength. We also found that under some culturing condition, *Dictyostelium* cell showed a migratory behavior much like *Keratocyte*. Although *Dictyostelium* and *Keratocyte* are thought to be largely different organisms adopting different mechanisms for their motility, this observation indicates that there might underlies principles behind this diversity. Cellular shape dynamics is expected to contain fruitful information of many aspects of cell. Thus the experimental systems established in this Chapter would uncover mechanisms of ordered shape mode and universal principle underlying apparently diverse cellular migratory behaviors.

Finally, in Chapter 5, we investigated relationship between fluctuations of cellular shape and centroid motion with a help of simple mathematical theory. We measured shape fluctuations and centroid motion of cells in different developmental stages and, based on the experimental results, introduced a simple Langevin model with multiplicative noises. We then tested the prediction of the model; asymmetry of shape noise would grow with development proceedings. Although theories must be indispensable to understand natural phenomenon, there are few successes of such theoretical studies in the area of cell biology. In this Chapter, we demonstrated an experiment-theory feedback with constructing theory from experiment and testing its prediction in further experiment. We expect that this study will be a reference for following quantitative studies which combine experiment and theory.

To summarize the thesis, we obtained cellular level descriptions for cell motility and division using cellular level quantities like motion, shape and forces. Since these quantities can appear in studies of various area, for example, as quantitative phenotypes in molecular biology and as clues for mathematical modeling, we expect that our result will motivate further studies by people with various backgrounds, which are essential to understand cell biological phenomena as physics.

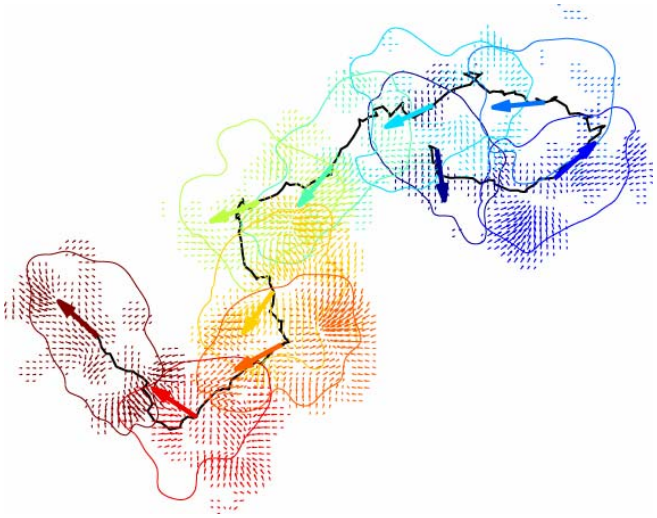

Fig.1 'Directed force dipole' and cell migration. Cellular shape (color solid line) and traction stress vectors (thin arrow) for 15 min data are superimposed on the centroid trajectory (black solid line). Adding to them, the main axis of force dipole is also plotted with bold arrows. The direction of dipole axis is set such that the (1,1,1) component of force quadrupole is positive. This plot shows that cell migrates with a direction of 'directed' force dipole.

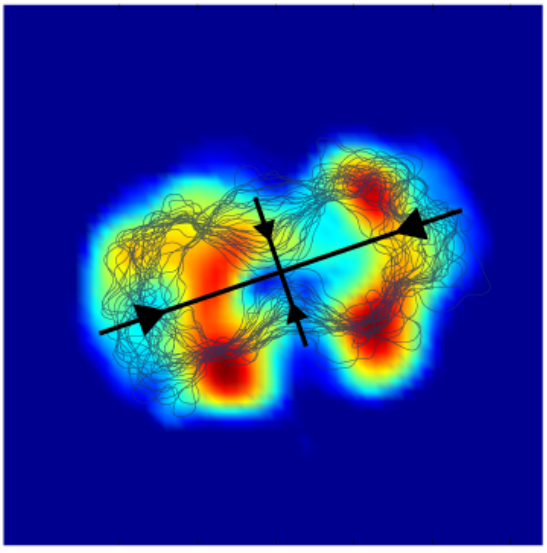

Fig.2 Angular relationship between division axis and traction stress asymmetry. Integrated stress field, cellular outlines and force dipole during cytokinesis were plotted. This plot shows that the dipole axis and division axis are well consistent.