博士論文（要約）

Statistical-mechanical field theory of self-renewing tissues: tissue homeostasis and tumor formation

（生体組織における自己複製の統計力学的場の理論：恒常性と腫瘍形成）

山口　裕樹

Competition between populations of biological species is ubiquitously observed in nature, across various scales from RNA viruses in sub-cellular systems to groups of animals. Progresses in various experimental techniques developed in different cell populations, ranging from strains of bacteria cultured on a dish to stem cell populations in living animals, have shown many examples for cell competitions beyond the well-mixed approximation, where the fluctuations due to stochastic events as well as local cell-to-cell interactions play significant roles. These experimental progresses not only open up the frontier of life science by providing fresh insights into various fields of biology such as development, stem cells, and cancer, but also are appealing to physicists, due to the intrinsically non-equilibrium nature of such systems. Specifically, from the point of view of statistical physics, the cell competition dynamics lead to interesting phenomena characteristic to out-of-equilibrium systems such as pattern formations, genetic segregation, coarsening, phase separation, and scale invariant growth, which can be compared to theoretical models of interacting particle systems.

This thesis is devoted to the theoretical studies on the cell populations that undergo turnover in adult animal tissues, which play a key role in maintaining the tissue homeostasis. Tissue homeostasis here refers to the realization of a steady state of the cell population in tissues, where the production and loss of cells due to cell division and death are balanced so that the cell density is regulated around a stationary value. The maintenance of tissue homeostasis relies on certain feedback mechanism through the fate coordinations of individual cells. Elucidating the mechanism of tissue homeostasis is particularly important, since its breakdown would lead to tissue disruption or the initiation and further progressions of tumors.

The genetic labeling experiments have enabled to track the stem cell populations in, for example, mouse skin tissues, and have revealed that the fates of individual stem cells (i.e., self-renewal or differentiation) are chosen randomly with balanced rates. The statistics of the clone size, (i.e., the number of progenies of initially labeled stem cells) showed a remarkable dynamical scaling law, which matches with a simple stochastic kinetics called the voter model in statistical physics. The appearance of such robust statistics in the maintenance of tissue homeostasis implies that simple and robust mechanisms may exist behind the seemingly complex feedback structure. The emergence of the voter model behavior in the stem cell population is particularly interesting from the point of view of statistical physics, because the experimental realization of the voter model has not yet been reported due to the difficulty of preparing $\mathbb{Z}_2$-symmetric states.

In the first part of this thesis, we consider the density feedback dynamics of cell populations that undergo turnover and stochastic fate coordination around the steady state of tissue homeostasis. We specifically focus on the genetically labeled cell density in homeostatic tissues that gives rise to the experimentally observable clone size statistics and show that its effective dynamics exhibit the voter model behavior at sufficiently long time and length scales. To show this, we introduce a stochastic interacting particle model of the cell population with generic forms of feedback in cell fate coordination, and develop a field-theoretic description for the cell density fields based on the particle-based model. The seemingly robust appearance of the voter model behavior is generically explained as a consequence of the time scale separation in the density feedback dynamics, which is in fact guaranteed by the assumption of the linear stability of the homeostatic steady state due to feedback from the density fluctuation. Using the scaling argument and the dynamical renormalization group analysis, we show that the effective dynamics of the labeled density robustly exhibit the voter model kinetics in the limit of long time and length scales, suggesting that the emergence of the voter model kinetics in the experimental clone size statistics is a natural consequence of the universal characteristics of the generic feedback dynamics in tissue homeostasis. Our

result suggests a scenario for the voter-model kinetics to appear naturally in genetically labeled cell populations in homeostatic tissues, though the experimental realization of the voter model, for example in liquid crystal systems, has been challenging owing to the difficulty in preparing the $\mathbb{Z}_2$-symmetric directors. We also find the existence of minimum time and length scales that are required for the voter-model scaling to show up, which are tissue-specific quantities and thus would be inversely used to infer the length and time scales of feedback from experimental observations. We then demonstrate a method to estimate these feedback length and time scales, by using a specific example of the density feedback mechanism mediated by the growth factor concentration, which has been recently proposed for the tissue homeostasis in mouse seminiferous tubules. Such non-universal characteristics that underlie the feedback dynamics would be tissue specific quantities and thus would provide biologically instructive insights. This result shows that even though the underlying mechanisms is unknown in some specific tissues, it would be possible to infer the spatio-temporal scales associated with the density feedback dynamics from observations of long term clonal labeling experiments.

In the second part of the present thesis, we consider the clonal expansion of mutant cells in the early stage of the tumor formation. Specifically, we consider the extension of the model of homeostatic tissues to the case of two inhomogeneous populations with density-dependent fate coordination, in which the newly introduced mutant population has slightly perturbed parameter values. In the setup of the two-population model, the homeostatic steady state is realized within each population, but the difference in the parameters describing the cell fate coordination would tilt the balance between two competing populations and drive the expansion of one population. In order to investigate how the competition between the mutant and normal populations will lead to the spatial expansion of the mutant, we consider, as a specific example, small perturbations in the turnover rate, feedback strength, and fate balancing density. Applying the field-theoretic description developed in the homeostatic case to the two-population setup, we show that the dynamics of the fraction of mutant follow the stochastic Fisher-Kolmogorov equation, which describes the propagation of the mutant population in space and time. By making use of the growth speed formula in the strong noise limit, we derive the condition for a given mutant population to win the competition against the normal population, and the expression of its speed with respect to the perturbative parameters introduced in the density feedback dynamics. These results demonstrate that whether or not and how fast a given mutant would compete out the normal cell population could be predicted from experimentally measurable quantities, which would be potentially testable in future experiments. Our model is based upon the scenario of the clonal expansion driven by the interaction at the interfaces of competing cell populations, which has been also suggested in recent studies based on the deep sequencing data in human epidermis.

In summary, we have developed the statistical-mechanical field theory of homeostatic and competing population dynamics in adult animal tissues. The present works have elucidated not only the universal laws that would be shared with various tissues, but also the non-universal characteristics that would provide biologically relevant tissue specific insights. Our field-theoretic framework is derived from stochastic interacting particle models and thus takes into account the stochastic nature of cell fate coordination and the cell-to-cell interaction at the single-cell level, which would be useful also in more complex situations such as development and cancer.