論 文 の 内 容 の 要 旨

論文題目 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）

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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 the 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 through the fate coordination 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, for example, in 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 was matched with a simple stochastic kinetics called the voter model in statistical physics. The appearance of such a robust statistics in the maintenance of tissue homeostasis implies that simple and robust mechanisms may exist behind the seemingly complex feedback structures. The emergence of 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 focus on the density feedback dynamics in the cell fate coordination that underlies the maintenance of tissue homeostasis. We show that the effective dynamics of the genetically labeled population in homeostatic tissues exhibits 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 feedback in their fate coordination, and develop a field-theoretic description that is 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. Specifically, we show that the voter behavior appears universally only beyond certain minimum scales in space and time that characterize the detail of the feedback dynamics. We then demonstrate a method to estimate these feedback length and time scales that are required for the universal voter behavior to show up, 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.

Secondly, motivated by the tumor formation, we consider the extension of the model of homeostatic tissues to the case of two inhomogeneous populations, in which the homeostatic balance is possibly broken down due to the competition between the two cell populations. We here use the particle based setup as in the homeostatic case, with the local density dependent feedback, in which the newly introduced mutant population has slightly perturbed parameter values. In order to investigate how the competition between the mutant and the 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 follows 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 measurable parameters introduced in the density feedback.

In summary, we have here developed the statistical-mechanical field theory of homeostatic and competing population dynamics in 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.