論 文 の 内 容 の 要 旨

論文題目　　Mesoscopic deconstruction and reconstruction of multicellular organizations: Towards a nonequilibrium phase transition theory of complex adaptive systems

(多細胞組織のメゾスコピックレベルでの分解と再構成：複雑適応系の非平衡相転移理論に向けて)

氏　　名　　楼　玉婷

Complexity has been the main challenge for the traditional scientific paradigm, which is hypothesis-driven and reductionist. For dealing with the complexity of the modern scientific themes, new paradigms using data-driven or system-theoretic approaches have been developed and applied in complex-system-related sciences. Nevertheless, these new approaches still suffer from fundamental problems that impair their scientific values. Particularly, the data-driven approaches tend to establish phenomenological models that only be faithful to the microscopic details but lacking in pinpointing the testable theories; by contrast, system-theoretic approaches produce mechanistic models by throwing away much microscopic information, thus lacking in its representativeness for the real targeted complex phenomena.

To improve these new system approaches, a mesoscopic bridge between the data-driven models and the system-theoretic models is in demand. The objective this thesis is twofold: 1) to draw testable theories of multicellular homeostasis by mesoscopic approaches and 2) to generalize some methodological formalism for a broader variety of systems on the mesoscopic deconstruction and reconstruction of systems.

Multicellular homeostasis is a typical phenomenon resulted from multi-scale multifactorial complexities. The stability and functionality and the resistance against external damages of tissues are well preserved by multicellular homeostatic mechanisms, the violation of which will lead to severe chronic diseases in tissues. Both data-driven complicated and system-theoretic simple models exist for multicellular homeostasis, and I attempt to set up mesoscopic model to link the two extremes. One of the most successful data-driven models for multicellular homeostasis is Immersed Boundary Cell model (IBcell) for epithelial acini formation. IBcell incorporates multi-scale information about cells: the cell morphology is controlled by hydrodynamics and the cell behaviors are controlled by the receptor dynamics inside each cell. IBcell can simulate epithelial acini formation as precisely as in the experiments, however, at the cost of huge computational resources and of lack of analyzability.

For facilitating long-time simulation and model analysis, I simplify this model to a cell-based form with discrete time and space and transform the complex fluid dynamics to simplest equivalent cell movement principles. On each node of the 2D regular lattice, at least one cell can exist and the presence of the cell is represented by a configuration of five kinds of receptors. The simulation is implemented at the cell level with all the sub-cellular, inter-cellular and extracellular information encompassed into the rules of receptor dynamics(Fig.1). For simplicity, this mesoscopic model is briefed as discrete receptor dynamics model (DRDM) hereafter.

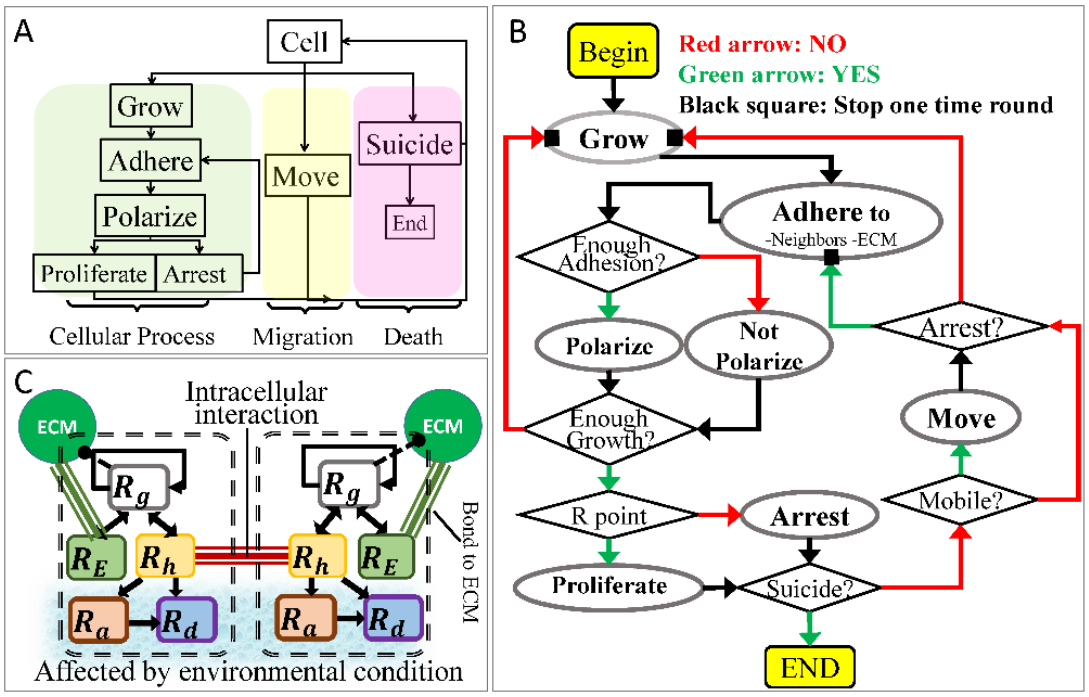

Fig. 1 Model construction of DRDM. (A) Cell behaviors. The behaviors are divided into three paralleled modules: cellular process, migration and death, which are executed during each time step. (B)The flowchart of the single cell behaviors for one simulation time step: The blue circles stand for the cell behaviors and the white diamonds serve as checkpoints. The cellular process begins from *Grow* function for the first time step; during one time round after the first time step, the cell starts from either *Grow* or *Adhere* function according to the finishing state in the last time round. The cell executes cell behaviors sequenced in the flowchart until it hits the black squares and stops for a time round. If the cell commits suicide, the process will end. (C) The receptor transformation of two interacting cells. The transformation to arrest and death receptors is affected by environmental conditions.

The basic results in IBcell model can be qualitatively reproduced by DRDM even with much microscopic information lost. The original long-time simulations of DRDM show that homeostatic states are quasi-stable and, more particularly, normal homeostatic states tend to evolve to tumorigenic states and degenerate states. Moreover, the tumorigenic states are accompanying a decrease in average cell age (the times of cell division), i.e., rejuvenation and the degenerate states are accompanying an increase in average cell age, i.e., aging. These shift among homeostatic states are non-mutational and irrelevant of environmental stress. By embracing some prototype mutations in DRDM, one can confirm that the non-mutational self-organization of different homeostasis can have a profound influence on the mutational paths of individual cells.

To pinpoint the mechanisms and to propose testable theories for the quasi-stable homeostasis found in DRDM and experiments, a mechanistic model is required. I with my collaborators in the Department of Medicine conducted a modified wound healing experiments to investigate the time-

dependent healing phenomena. The results show that healing processes were slowed down in relation to the waiting time before the wound creation (Fig.2), the same as in the DRDM simulation using normal-to-degenerate parameter settings (Fig.3).

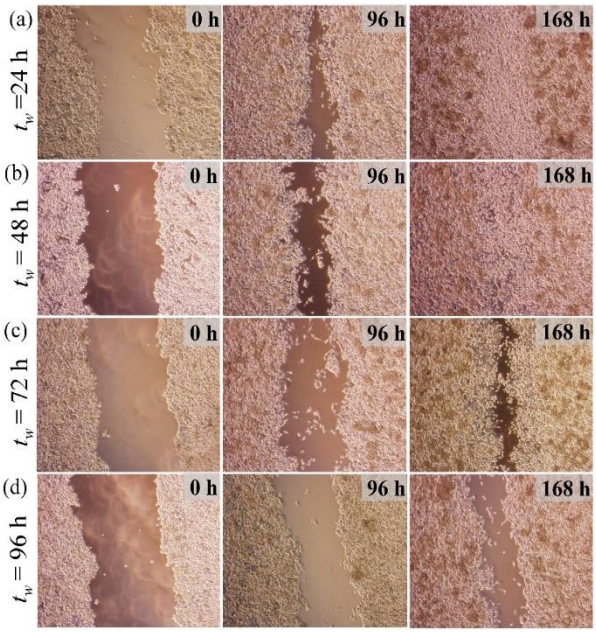

Fig.2 Slowdown of healing in relation to the waiting time t_w before wound creation in vitro.

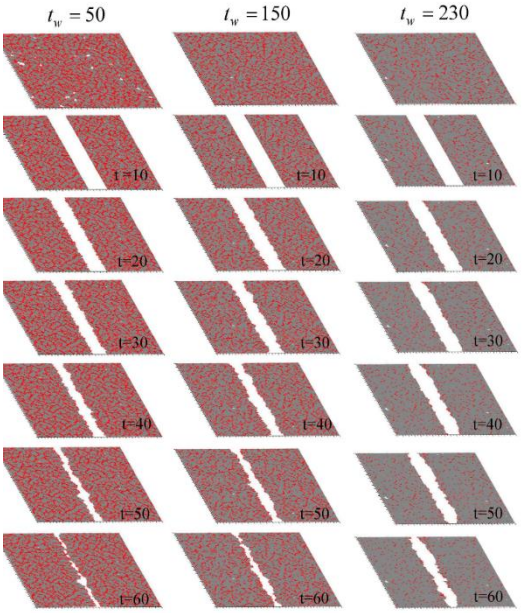

Fig.3 Slowdown of healing in relation to the waiting time t_w before wound creation in DRDM.

The reconstruction of a complex system from a mesoscopic model to its macroscopic phenomenon needs simpler mechanistic models that stand in between. For our multicellular aging in DRDM and in vitro, such a mechanistic model is found to reproduce macroscopic experimental results and to link the details of the meso- and microscopic models. The model is a modified version of Fisher-Kolmogorov model with delayed "wake-up" from cell cycle arrest (Eq. 1-3).

$$\frac{\partial u(x,t)}{\partial t} = d\frac{\partial}{\partial x}D(u)\frac{\partial u}{\partial x} + mM(u)u \tag{1}$$

$$D(u) = p/(p+u) \tag{2}$$

$$\begin{cases} M(t) = 1-u(t) & \text{if } 1-u(t) \le M(t-\Delta t) \\ M(t) = \delta(1-u(t)) + (1-\delta)M(t-\Delta t) & \text{if } 1-u(t) > M(t-\Delta t) \end{cases} \tag{3}$$

The delay fraction δ, ranging from 0 to 1, in the cell proliferation term $M(t)$ describes how fast the cell can transition from cell cycle arrest to cell growth as a response to the wound. Numerical simulations show that the value of δ controls the speed of aging and the simple model reproduces all macro-phenomena observed in our experiments. Meanwhile, criticality analysis reveals that the healing time is divergent with the decrease in δ and this critical role coincides with the receptor

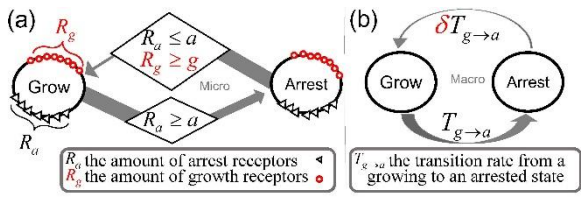

Fig.4 The essence of control parameter *restriction asymmetry* represented in two models of different scales: (a) in DRDM and (b) in modified Fisher-Kolmogorov model.

threshold g in the critical analysis of DRDM. By comparing the meaning of δ and g, the essence of the control parameter for the aging phenomena can be interpreted as the asymmetry in the cell cycle regulation, i.e., the delayed recovery from cell cycle arrest to cell growth compared with the cell growth inhibition.

By setting up a simpler mechanistic model standing between DRDM and the experiments, a clear description of the control parameter with its concrete biological correspondence can be found and tested. This break of symmetry in cell cycle regulation indicates an intrinsic dissipation can be further linked to some universality class with the absorbing phase transition which facilitates system theories for multicellular aging.

To conclude, in this thesis I practice the methodology of mesoscopic modelling (DRDM) to link data-driven phenomenological model (IBcell) and the macroscopic mechanistic models (modified Fisher-Kolmogorov model). These efforts help establish an absorbing phase transition theory for multicellular homeostasis. Meanwhile, this practice also serves as a good example for engineering other complex adaptive systems and suggests that the self-organization under cooperative dynamics should be studied in prior to that under adaptive dynamics. Also, the slow transition from normal homeostasis to tumor or degeneration may also be one instance of the absorbing phase transitions that prevails in many kinds of systems. Very little detailed system-specific demonstration has been done for pragmatic system engineering due to the lack of scientific tools. Yet, the practice in this thesis shows that mesoscopic modelling can be a powerful tool to integrate the merits of data-driven and system-theoretic models and to improve their scientific utility in many other complex adaptive systems.