Applications of multisource data-based dynamic modeling to cell-cell signaling and infectious disease spreading

Chen, D.

English summary

Complex disease closely linked to abnormal cell-cell signaling, and infectious disease stand as significant long-term threats to mankind. In this thesis, we studied cell-cell signaling and infectious disease transmission, demonstrating how the methodology based on dynamic modeling can be applied in each respective area.

In **Part I** of this thesis, we studied Notch signaling, Notch signaling-mediated cell fate decision and cell motility in angiogenesis. Notch signaling is activated by the binding of Notch receptor in one cell to Notch ligand in a neighboring cell (tans-activation), which is counterposed by the binding of Notch receptor to ligand in the same cell (cis-inhibition). Based on the experimental evidence, we proposed a new model of Notch signaling, in Chapter 2, where Notch receptor cis-inhibition is mediated by ligand dimer and Notch receptor trans-activation is mediated by ligand monomer. The general applicability and reliability of our model is demonstrated by the fact that it can recapitulate the results of experimental research at both the cellular as well as the tissue level.

In Chapter 3, we studied endothelial cell fate decision in angiogenesis and proposed a model centered on Dll4-Notch signaling. A similar model has been investigated in the past; however, experimental evidence that Notch signaling is a paradoxical component in regulating the expression of Dll4 has been overlooked. Our research predicts that increasing Notch signaling promotes down-regulation of Dll4 expression in endothelial cells when Notch signaling is less than a threshold level, and up-regulates Dll4 expression when Notch signaling is higher than the threshold level. This model better explains published observations in angiogenesis.

In Chapter 4, we explore cell fate decision in angiogenesis in greater detail by considering Jag1 dynamics in our general model described in Chapter 3, with the aim of explaining the critical question: why do Dll4 and Jag1 have opposing effects on angiogenesis. Experimentation and mathematical modeling predicts that Dll4-

Jag1 heterodimerization generates a switch between high Dll4/low Jag1 state and low Dll4/high Jag1 state of cells. Therefore, high levels of Dll4 triggers intercellular Notch signaling which limits angiogenesis. Increasing the expression of Jag1 reduces the level of Dll4 via Dll4-Jag1 dimerization, thereby limiting Dll4-mediated Notch signaling. Moreover, low affinity of Notch for Jag1 means that Jag1 in endothelial cells does not mediate high level of Notch signaling.

In Chapter 5, we proposed a multi-scale model of vasculogenesis by integrating the model of endothelial cell fate into the Cellular Potts model. Previous computational models have reproduced the multi-cellular network formation, but do not faithfully match the behaviour of individual cells. Numerical simulations of the multi-scale model show that our new model can recapitulate the dynamics of both individual cells and collective cell behaviour in vasculogenesis. Moreover, the research predicts that Notch signaling affects vasculogenesis by involving the polarization of cell motility, which sheds new light on our understanding of vasculogenesis and the role of Notch signaling during this process.

In **Part II** of this thesis, we first studied the effect of air pollution on respiratory infection. In Chapter 6, we presented evidence for a causal relationship between air pollution and respiratory infection, where air pollution is a driving factor of respiratory infection. Based on this, we proposed a model coupling the dynamics of air quality index and respiratory infection, where the incidence of respiratory infection is an increasing function of air quality index. Theoretical analysis and numerical simulations of the model predict that timely interventions against air pollution reduces the basic reproduction number of respiratory infection, which highlights new approaches to control respiratory infection.

In Chapter 7, we proposed a method to explore the trade-off between mobility restriction and infectious disease transmission. The problem that we want to solve is how to design a reopening strategy in response to mobility restrictions in epidemic areas. We first determined the location and time of reopening based on epidemic data, and then estimated the movement rate of population between these selected locations at 'correct' moment. The applicability of this method is supported by a retrospective prediction of COVID-19 that lifting the lockdown in mainland China with this strategy does not result in a second outbreak.

The application areas studied in Parts I and II of this thesis are different, however, we show that similar mathematical techniques, based on dynamic models, can be used to tackle each problem. This demonstrates that mathematical models can be applied to address a wide range of biological problems.