

Summary

Cancer is a complex disease that is characterized by multiple and diverse genetic alterations (mutations), affecting cellular molecules and the functions that they regulate. The most important goal of studying complex diseases is to better understand how mutations cause disease initiation and development.

The thousands of molecules in a cell are interconnected in different types of networks that work together to regulate the numerous cellular functions and thereby the cellular behaviour. Thus, altered cellular molecules may lead to altered networks, which in turn may cause disease progression. Investigating these altered networks may therefore lead to a better understanding of the molecular cause of complex diseases. However, investigation of these networks is often only possible with computational efforts due to their complexity.

In this thesis, we present our research, where we use computational modeling and analyses to explore altered cellular networks. A computational model of a cellular network can be used to demonstrate and predict how it behaves in a healthy or diseased condition. Additionally, we clearly describe our computational frameworks so they can be easily understood and reused by other researchers.

Colorectal cancer is one of the most common types of cancer, causing 8.5% of the cancer related deaths in the developed world (694,000 per year). In the initial steps of colorectal cancer development, hyperactivated cell growth turns healthy cells into non-cancerous tumor cells due to specific mutations. At a later stage, these cells can transform into cancerous tumor cells and from there on spread. In the initial steps, the Wnt protein plays an important role. In healthy cells, the Wnt protein activates the ‘Wnt/ β -catenin signaling pathway’ leading to accumulation of the β -catenin protein. Specific mutations, however, provide deregulated (misleading) Wnt/ β -catenin signaling, in the absence of the Wnt protein, leading to increased β -catenin levels and formation of non-cancerous tumor cells. In Chapter 2, we created a computational model of the Wnt/ β -catenin signaling pathway. By simulating healthy and deregulated Wnt/ β -catenin signaling with this model, we could explore the differences in their molecular interactions leading to different levels of β -catenin.

In the next step of colorectal cancer progression the non-cancerous tumor cells further progress to cancerous tumor cells due to deregulation of additional signaling pathways such as the ‘Ras-MAPK signaling pathway’. In the majority of colorectal cancer this is associated with ‘chromosomal aberrations’, where large portions of chromosomal DNA are gained (copied) or lost (removed). Aurora kinase A, or AURKA, is a gene that is frequently gained and subsequently overexpressed (the protein product occurs in higher levels than normal) because of these events. In Chapter 3, we investigated the molecular interactions of the effect of AURKA-gain on Wnt/ β -catenin and Ras-MAPK signaling in two colorectal cancer cell lines by applying a network analysis. Here, we combine gene expression data with protein-protein interaction data to identify genes that were deregulated by

AURKA. Although most of these genes differed between the two cell lines, genes in the Wnt/ β -catenin and Ras-MAPK signaling pathways were enriched in both.

In complex diseases, mutations in multiple genes lead to functional deregulation that cannot be described by the additive effects of each individual mutation. This is due to ‘genetic interactions’, where mutations in two different genes cause unexpected phenotypes compared to the phenotypes of the individual mutations. In Chapter 4, we studied possible molecular networks for the genetic interaction pattern called inversion, where the phenotype of two combined mutations is the opposite of the two single mutations. To that end, we created all possible computational models of inversion. By analysing these models we observed that a combination of strong and weak interactions is a crucial component for the molecular networks underlying inversion.

In Chapter 5, we described how we generated the computational framework used in Chapter 4 to investigate all the possible genetic interactions models. Here, we described model creation, parameter definition, model simulation, assignment of specific genetic interaction patterns to each model and further analysis of possible molecular interactions for the different genetic interaction patterns. In Chapter 6, we described a different framework that converts descriptive biological models from a database to executable models that can be simulated. Using this framework, amongst other things, we repeated our simulation of Wnt/ β -catenin signaling from Chapter 2.