**Nutritional Systems Biology**

“Prevention is better than cure” and when it comes to human health, this strategy translates into many socioeconomic benefits. Practically all the cellular processes, including every step in the flow of genetic information from gene expression to protein synthesis and degradation, can be affected by diet and lifestyle. Similar to the role of pharmaceuticals, nutrients contain a number of different compounds that act as modifiers of network function and stability. However, the level of complexity in nutrition studies is further increased by the simultaneous presence of a variety of nutrients, with diverse chemical structures that can have numerous targets with different affinities and specificities. Obviously, this differentiates the nutritional from the pharmacological studies, where single elements are used at low concentrations and with a relatively high affinity and specificity in a small number of thoroughly selected targets. Our need for fundamental understanding of the building blocks of the complex biological systems had been the main reason for the reductionist approach that was mainly applied in the past to elucidate these systems. Nowadays, it is widely recognized that systems and network biology has the potential to increase our understanding of how small molecules affect metabolic pathways and homeostasis, how this perturbation changes at the disease state, and to what extent individual genotypes contribute to this. A fruitful strategy in approaching and exploring the field of nutritional research is, therefore, to borrow methods that are well established in medical and pharmacological research.

In this thesis, we use advanced data-mining tools for the construction of a database with available, state-of-the-art information concerning the interaction of food and its molecular components with biological systems and their connection to health and disease. The database will be enriched with predicted interactions between food components and protein targets, based on their structural and pharmacophore similarity with known small molecule ligands. Further to this, the associations of bioactive food components with metabolic pathways will be investigated from a chemical-protein network perspective, while their effects in network robustness will be further confirmed by proteome analyses and high-throughput genotype-phenotype characterization.

The first chapter of the thesis is about the development of our data resource. In this work, we applied text mining and Naive Bayes classification to assemble the knowledge space of foodphytochemical and food-disease associations, where we distinguish between disease prevention/amelioration and disease progression. We subsequently searched for frequently occurring phytochemical-disease pairs and we identified 20,654 phytochemicals from 16,102 plants associated to 1,592 human disease phenotypes. We selected colon cancer as a case study and analyzed our results in three directions; i) one stop legacy knowledge-shop for the effect of food on disease, ii) discovery of novel bioactive compounds with drug-like properties, and iii) discovery of novel health benefits from foods. This works represents a systematized approach to the association of food with health effect, and provides the phytochemical layer of information for nutritional systems biology research. The paper also shows as a proof-of-concept that a systems biology approach to diet is meaningful and demonstrates some basic principles on how to work with diet systematic.

The second chapter of this thesis we developed the resource NutriChem v1.0. A foodchemical database linking the chemical space of plant-based foods with human disease phenotypes and provides a fundamental foundation for understanding mechanistically the consequences of eating behaviors on health. Dietary components may act directly or indirectly on the human genome and modulate multiple processes involved in disease risk and disease progression. The database has been created from text mining. The database and its content have been made available to the public from our webserver NutriChem: http://cbs.dtu.dk/services/NutriChem-1.0

The third chapter of the thesis is on developing a molecular roadmap of drug-food interactions. Our main hypothesis in the current work is that the complex interference of food on drug pharmacokinetic or pharmacodynamics processes is mainly exerted at the molecular level via natural compounds in food that are biologically active towards a wide range of proteins involved in drug ADME and drug action. Hence, the more information we gather about these natural compounds, such as molecular structure, experimental and predicted bioactivity profile, the greater insight we will gain about the molecular mechanisms dictating drug-food interactions, which will help us identifying, predicting and preventing potential unwanted interactions between foods and marketed- or novel drugs. Unlike drug bioactivity information that has already been made available for system-level analyses, biological activity data and source origin information of natural compounds present in food are scarce and unstructured. To this end, we integrate proteinchemical interaction networks, gene expression signatures and molecular docking to provide the foundation for understanding mechanistically the effect of eating behaviors on therapeutic intervention strategies.

The fourth chapter of the thesis is a case study on diet-colon cancer through candidate molecular interaction networks. The study shows a holistic examination of the dietary components for exploring the mechanisms of action and understanding the nutrient-nutrient interactions. In this paper we used colon cancer as a proof-of-concept for understanding key regulatory sites of diet on the disease pathway. We propose a framework for interrogating the critical targets in colon cancer process and identifying plant-based dietary interventions as important modifiers using a systems chemical biology approach.

The fifth chapter of the thesis is on discovering of novel anti-ovarian cancer compounds from our diet. Ovarian cancer is the leading cause of death from gynecological disorders with an increasingly high incidence, especially in the western world. Epidemiological studies suggest that some dietary factors may play a role in the development of ovarian cancer; so far most studies have shown up inconclusive. In the present study we disclose novel anti-ovarian cancer compounds from our diet with activity against ovarian cancer, through text mining and a systemwide association of phytochemicals, foods and health benefits on human ovarian cancer. We selected several compounds that where predicted to have anti-ovarian cancer activities, using chemoinformatics approaches and evaluated and confirm their activities in vitro.

**General information**