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Research projects for the Bioinformatics track within the Data Engineering MSc program

General information

In the first section, general Data Engineering projects with applications in the Life Sciences are outlined. In the second section, projects focusing on one of the main research projects on campus, the COMETA project (COMETA = cocoa metabolomics) are described.
The letter code behind each project title is intended to give you a first orientation about the direction of the project:

- **B** This project requires biological background knowledge beyond high school level.
- **M** This project has a stronger mathematical component.
- **D** The focus of this project is on data mining.
- **C** In this project a computational infrastructure or 'data analysis pipeline' needs to be established.

Each of the projects described below serves as a framework for one of the following components of the Data Engineering curriculum:

MRD005-340001 Advanced Project 1
MRD006-340002 Advanced Project 2
MTMT003 Master Thesis

Even though these projects have been designed specifically for the Bioinformatics track within Data Engineering, they are accessible to students from any specialization area of Data Engineering with some interest in biological applications.
The course

MEBI001-550432 Introduction to Systems Biology

can serve as a helpful introduction to many of the questions addressed by the projects from this list.

Part I: General aspects of the Life Sciences

Construction of multi-level phylogenies to interpret microbial communities
D C

Phylogenetic trees (capturing the evolutionary relationships among species, the 'tree of life') are a highly relevant structure for the interpretation of biological data. For example, microbiome data (e.g., the composition of microbial communities in the human gut) can be interpreted by evaluating the distribution of the data on a phylogenetic tree. One technical challenge is that these trees exist on different levels of detail (called 'taxonomic ranks'). This project is about constructing a mapping between taxonomic ranks from existing databases and, based on this mapping, analyze the data distribution on multiple levels simultaneously. The potential outcome

is to detect, systematics of these data on multiple levels. Developing the computational tools for such a multi-level phylogenetic analysis will help us assess the function of a microbial community and thus will allow us to understand the role of the microbiome in human health and disease.

Further reading:

Revell, L. J. (2012). phytools: an R package for phylogenetic comparative biology (and other things). Methods in Ecology and Evolution, 3(2), 217-223.

Claussen, J. C., Skieceviciene, J., Wang, J., Rausch, P., Karlsen, T. H., Lieb, W., Baines, J. F., Franke, A., and Hütt, M.-T. (2017). Boolean analysis reveals systematic interactions among low-abundance species in the human gut microbiome. PLoS Computational Biology, 13(6):e1005361.

Constructing data analysis pipelines for GenomeSpace

C

The enormous diversity of data in biology and medicine, as well as their fragmentation into a huge number of databases and formats currently prevents us from establishing a holistic view on cellular behavior, on the response of organisms to environmental influences and on human diseases. Substantial progress towards these goals can be expected from combining multiple analysis methods to a whole data analysis pipeline, which homogenizes data formats and merges different databases. A promising framework for such projects is the recently published GenomeSpace platform. In this research project, we will focus on gene expression data (the simultaneous measurement of activies for all or many genes in a biological cell). The task is to combine two major interpretation strategies of gene expression data: (1) gene set enrichment via the Gene Ontology classification system and (2) network coherences (i.e. the clustering of gene expression data in a given biological network). These analysis methods need to be combined and integrated as a full data analysis pipeline in the GenomeSpace platform.

Further reading:

Qu, K. et al. (2016). Integrative genomic analysis by interoperation of bioinformatics tools in GenomeSpace. Nature Methods, 13(3), 245.

Gene Ontology Consortium. (2014). Gene ontology consortium: going forward. Nucleic Acids Research, 43(D1), D1049-D1056.

Knecht, C., Fretter, C., Rosenstiel, P., Krawczak, M., and Hütt, M. T. (2016). Distinct metabolic network states manifest in the gene expression profiles of pediatric inflammatory bowel disease patients and controls. Scientific Reports, 6, 32584.

A tool for merging biological interaction databases

B C

Representing large amounts of biological information as networks has become one of the main interpretation strategies of Systems Biology. Exhaustive lists of experimentally determined interactions among cellular components (e.g., genes or proteins) are the prominent data resource behind these networks. However, such interaction information is strongly diversified across a

multitude of databases and according to the specific biological type of interaction under consideration. This project sets out to merge existing interaction databases to create a unified, holistic tool, where the user can select, which databases and which types of biological interaction should be included in the network. Examples of databases to be included are: STRING, BioGrid, IntAct. This tool can then be used to analyze the topology of the full cellular-molecular interaction network, as well as for the interpretation of 'omics' data (like gene expression profiles or metabolite profiles) using this network.

Further reading:

Szklarczyk, D., Gable, A. L., Nastou, K. C., Lyon, D., Kirsch, R., Pyysalo, S., Doncheva, N. T., Legeay, M., Fang, T., Bork, P., et al. (2021). The STRING database in 2021: customizable protein-protein networks, and functional characterization of user-uploaded gene measurement sets. Nucleic acids research, 49(D1):D605ÐD612.

Oughtred, R., Stark, C., Breitkreutz, B. J., Rust, J., Boucher, L., Chang, C., ... and Tyers, M. (2019). The BioGRID interaction database: 2019 update. Nucleic acids research, 47(D1), D529-D541.

Kerrien, S., Aranda, B., Breuza, L., Bridge, A., Broackes-Carter, F., Chen, C., ... and Jandrasits, C. (2011). The IntAct molecular interaction database in 2012. Nucleic acids research, 40(D1), D841-D846.

Analysis of biological interaction data using the framework of multilayer networks

C M

Information on interactions among genes and proteins is scattered across a multitude of databases and, furthermore, organized according to different types of interactions (see previous project description). In this project, the data from several such databases, covering all types interaction, will be accumulated and the resulting interaction network will be statistically analyzed using the recently established perspecive of multilayer networks. The key questions are: Have different types of interaction 'co-evolved' to compensate each other or to enhance each other? Do different types of interaction operate on different scales (local vs. global)?

Further reading:

Szklarczyk, D., Gable, A. L., Nastou, K. C., Lyon, D., Kirsch, R., Pyysalo, S., Doncheva, N. T., Legeay, M., Fang, T., Bork, P., et al. (2021). The STRING database in 2021: customizable protein-protein networks, and functional characterization of user-uploaded gene measurement sets. Nucleic acids research, 49(D1):D605ÐD612.

Oughtred, R., Stark, C., Breitkreutz, B. J., Rust, J., Boucher, L., Chang, C., ... and Tyers, M. (2019). The BioGRID interaction database: 2019 update. Nucleic acids research, 47(D1), D529-D541.

Kerrien, S., Aranda, B., Breuza, L., Bridge, A., Broackes-Carter, F., Chen, C., ... and Jandrasits, C. (2011). The IntAct molecular interaction database in 2012. Nucleic acids research, 40(D1), D841-D846.

Kivelä, M., Arenas, A., Barthelemy, M., Gleeson, J. P., Moreno, Y., and Porter, M. A. (2014). Multilayer networks. Journal of complex networks, 2(3), 203-271.

3D predictions of bacterial chromosomes and the interpretation of gene expression profiles

D M

Understanding bacterial gene regulation is a fundamental challenge in Systems Biology. One relevant step along the way is to ask, how patterns of gene activity (gene expression profiles) come about. It has been argued that the two main contributions to gene activity are from the network of interacting genes ('digital control') and from the organization of the genome ('analog control'). Recently, new methods for predicting the 3D organization of the bacterial genome (i.e., the circular chromosome) have been published (Hacker et al. 2017). These methods can be used as a more refined model of analog control for the interpretation of gene expression profiles. This is the goal of the present project.

Further reading:

> Marr, C., Geertz, M., Hütt, M.-T., and Muskhelishvili, G. (2008). Dissecting the logical types of network control in gene expression profiles. BMC Syst Biol, 2(1):18.
>
> Hacker, W. C., Li, S., and Elcock, A. H. (2017). Features of genomic organization in a nucleotide-resolution molecular model of the Escherichia coli chromosome. Nucleic acids research, 45(13), 7541-7554.

Functional interpretation of disease-associated genes

B D

Over the last few years information on disease-associated genes has been accumulated and organized in databases. The information mainly comes from large patient cohorts and the identification of small genomic variations in these cohorts compared to reference genomes from the whole population (genome-wide association studies, GWAS). A functional interpretation of these gene lists characterizing a disease has proven to be extremely challenging. Biological networks (metabolic networks, protein-protein interaction networks, signaling networks) should provide an appropriate framework for such a functional interpretation. In this project the statistical and computational tools for analyzing the distribution of disease-associated genes in biological networks will be developed and tested.

Further reading:

> Menche, J., Sharma, A., Kitsak, M., Ghiassian, S. D., Vidal, M., Loscalzo, J., and Barabasi, A. L. (2015). Uncovering disease-disease relationships through the incomplete interactome. Science, 347(6224), 1257601.
>
> Hütt, M. T. (2014). Understanding genetic variation – the value of systems biology. British journal of clinical pharmacology, 77(4), 597-605.

Microbial interaction networks derived from the Human Microbiome Project

D

The relevance of the human microbiome (i.e., the microbial communities in the human gut, lung, mouth, etc.) for health and disease is becoming more and more apparent. Recently (Claussen et al. 2017) we published a new method for estimating a microbial interaction network from microbiome data (i.e., from a large number of microbial abundance patterns). The main goal

of the present project is apply this method to the emerging databases of microbiome compositions, the Human Microbiome Project (hmpdacc.org), set up a database of microbial interaction networks derived from the HMP database and study, how these networks differ under different conditions.

Further reading:

Human Microbiome Project Consortium (2012) A framework for human microbiome research. Nature, 486, 215-221

Claussen, J. C., Skieceviciene, J., Wang, J., Rausch, P., Karlsen, T. H., Lieb, W., Baines, J. F., Franke, A., and Hütt, M.-T. (2017). Boolean analysis reveals systematic interactions among low-abundance species in the human gut microbiome. PLoS Computational Biology, 13(6):e1005361.

The human microbiome as a metabolic meta-network

B D M

The recent publication of a large number of microbial metabolic models (Magnusdottir et al. 2017) allows us to compare microbial interaction networks (computed from microbiome data) with interaction networks predicted from considering the microbiome as a collection of interacting metabolisms (or a 'metabolic meta-network'). The goal of the project is to apply the interaction indices defined in Levy and Borenstein (2013) to the metabolic models published in Magnusdottir et al. (2017) and compare the resulting network prediction with the network computed from microbiome data via the method from Claussen et al. (2017). This comparison will provide key insights in the functional organization of the human microbiome.

Further reading:

Magnusdottir, S., Heinken, A., Kutt, L., Ravcheev, D. A., Bauer, E., Noronha, A., ... and Fleming, R. M. (2017). Generation of genome-scale metabolic reconstructions for 773 members of the human gut microbiota. Nature biotechnology, 35(1), 81.

Levy, R., and Borenstein, E. (2013). Metabolic modeling of species interaction in the human microbiome elucidates community-level assembly rules. Proceedings of the National Academy of Sciences, 110(31), 12804-12809.

Claussen, J. C., Skieceviciene, J., Wang, J., Rausch, P., Karlsen, T. H., Lieb, W., Baines, J. F., Franke, A., and Hütt, M.-T. (2017). Boolean analysis reveals systematic interactions among low-abundance species in the human gut microbiome. PLoS Computational Biology, 13(6):e1005361.

Eigenvector of gene regulatory networks and gene expression profiles

M D

One of the principal steps towards an understanding of bacterial gene regulation and therefore cellular function is to quantitatively assess, how well a given gene regulatory network 'explains'Êa given gene expression data set (i.e., the activity profile of all/many genes). An interesting mathematical approach for addressing this question is to compare spectral properties of the gene regulatory network (in particular, the eigenvectors of the graph) with the activity patterns of genes (which are vectors, where each node of the network is characterized by a

real number). This is the task of the present project. Gene expression data will be taken from the GEO database. The gene regulatory network will be downloaded from RegulonDB.

Further reading:

Clough, E., and Barrett, T. (2016). The gene expression omnibus database. Statistical Genomics: Methods and Protocols, 93-110.

Gama-Castro, S., Salgado, H., Santos-Zavaleta, A., Ledezma-Tejeida, D., Muniz-Rascado, L., Garcia-Sotelo, J. S., ... and Medina-Rivera, A. (2015). RegulonDB version 9.0: high-level integration of gene regulation, coexpression, motif clustering and beyond. Nucleic Acids Research, 44(D1), D133-D143.

An information-theoretical view on waves on graphs I: Theory

M

Self-organized excitation waves in networks have been studied in Moretti and Hütt (2020) using a simple model of excitable dynamics. Brain activity patterns are often analyzed using information theory (e.g., computing the time-delayed mutual information among cortical areas). This project is about applying information theory to the results from Moretti and Hütt (2020), in order to bridge the gap between simple simulations and brain activity patterns. An important intermediate step will be to reproduce the abstract findings within The Virtual Brain (TVB).
Further reading:

Moretti, P., and Hütt, M.-Th. (2020). Link-usage asymmetry and collective patterns emerging from rich- club organization of complex networks. PNAS, 117(31), 18332-18340.

Ritter, P., Schirner, M., McIntosh, A. R., and Jirsa, V. K. (2013). The virtual brain integrates computational modeling and multimodal neuroimaging. Brain connectivity, 3(2), 121-145.

Sanz Leon, P., Knock, S. A., Woodman, M. M., Domide, L., Mersmann, J., McIntosh, A. R., and Jirsa, V. (2013). The Virtual Brain: a simulator of primate brain network dynamics. Frontiers in Neuroinformatics, 7, 10.

An information-theoretical view on waves on graphs II: Data

B M D

Via the Human Connectome Project structural networks (derived from diffusion tensor imaging, DTI) and brain activity patterns (measured via functional magnetic resonance imaging, fMRI) are publicly available. This project is devoted to analyzing such activity patterns from the perspective of self-organized excitation waves (see Moretti and Hütt 2020; see the previous project description.
Further reading:

Bookheimer, S. Y., Salat, D. H., Terpstra, M., Ances, B. M., Barch, D. M., Buckner, R. L., ... and Yacoub, E. (2019). The lifespan human connectome project in aging: an overview. Neuroimage, 185, 335-348.

Elam, J. S., Glasser, M. F., Harms, M. P., Sotiropoulos, S. N., Andersson, J. L., Burgess, G. C., ... and Van Essen, D. C. (2021). The Human Connectome Project: A retrospective. NeuroImage, 118543.

Moretti, P., and Hütt, M.-Th. (2020). Link-usage asymmetry and collective patterns emerging from rich- club organization of complex networks. PNAS, 117(31), 18332-18340.

Part II: Research within the COMETA project

The COMETA database has been built up during more than six years within the Cocoa Metabolomics (COMETA) project, a joint research effort of Jacobs University and the company Barry Callebaut. The database is the largest collection of quantitative information on the biology and chemistry of cocoa beans. Data are spread out, broadly speaking, across three levels: space (i.e., the countries of origin of the cocoa beans), time (from the harvesting of the beans via fermentation to roasting and further industrial processes towards final chocolate products) and compounds (i.e., the biological and chemical observables a particular measurement technique provides access to: proteins, peptides, carbohydrates, polyphenols, lipids, etc.). The space and time information is present in the form of metadata about the cocoa beans (e.g., weather and geographical information), or about standard intermediary or final products of a typical cocoa processing pipeline (e.g., fermented beans, roasted nibs, liquors etc.) along with their varying chemical and physical treatment (e.g., alkalization status, roasting temperature, etc.). The compound information is available through a high throughput and untargeted metabolic profiling of cocoa beans and its associated intermediary products in the form of LC-MS fingerprinting (LC-MS = Liquid Chromatography coupled with Mass Spectrometry). The change, for example, of the chemical 'fingerprint' of cocoa over space and time is one of the overarching research questions revolving around this database. Addressing such questions requires powerful computational methods of data analysis and data interpretation.
The following topics for research projects and master theses for Data Engineering are situated in this general scenario.

Application of network inference methods to understand the change of a chemical fingerprint over time and evaluate the predictability of taste

M C

The highest level of data available is the taste profile of chocolate products. The task of this project is to statistically evaluate how much information a chemical compound (measured earlier in the timeline) provides about a component of the taste profiles.
Taste profiles are typically vectors of 10 to 20 taste components assessed by tasting panels (i.e., tastings performed by trained human experts under standardized conditions). A chemical fingerprint is a Liquid Chromatography Mass Spectrometry (LC-MS) data set containing the intensity (i.e., the concentration) of several thousands of chemical compounds.
Co-variation of both, taste components and concentration of compounds, across many samples of cocoa beans allows us to infer networks of interdependences between these levels and address the question, how far back in time can a particular taste component be predicted and by which quantities in the chemical fingerprint.
The rich inventory of (mathematical, algorithmic and computational) methods of network inference can be applied to this question.

Further reading:

Kumar, S., D'Souza, R. N., Behrends, B., Corno, M., Ullrich, M. S., Kuhnert, N., and Hütt, M. T. (2021). Cocoa origin classifiability through LC-MS data: A statistical approach for

large and long-term datasets. Food Research International, 140, 109983.

De Smet, R. and Marchal, K. (2010). Advantages and limitations of current network inference methods. Nature Reviews Microbiology, 8(10), 717.

D'Souza, R. N., Grimbs, S., Behrends, B., Bernaert, H., Ullrich, M. S. and Kuhnert, N. (2017). Origin-based polyphenolic fingerprinting of Theobroma cacao in unfermented and fermented beans. Food research international, 99, 550-559.

Ursem, R., Tikunov, Y., Bovy, A., van Berloo, R., and van Eeuwijk, F. (2008). A correlation network approach to metabolic data analysis for tomato fruits. Euphytica 161, 181.

Application of multilayer networks for understanding role of classes of chemical compounds on final sensorial profiles

D C

An LC-MS profile of cocoa derivatives may contain different classes of chemical compounds. Examples are peptides, polyphenols, lipids and carbohydrates. Due to the correlations among them, these compounds can be considered as a (correlation) network that changes in time as cocoa passes through different levels or stages in the cocoa processing pipeline (harvesting, fermentation, roasting, ...). A new approach for investigating such sequences of networks, called multilayer network, is well suited for understanding the changing profile of sub-categories of compounds, and finally relating them to the sensorial attribute of final finished products. This project aims at deciphering the role of various classes of compounds on the taste or color attributes of final products, by employing the formal concept of multilayer networks.

Further reading:

Bianconi, G. (2018). Multilayer Networks: Structure and Function. Oxford University Press.

De Domenico, M., Granell, C., Porter, M. A., and Arenas, A. (2016). The physics of spreading processes in multilayer networks. Nature Physics 12, 901.

Aleta, A., and Moreno, Y. (2019). Multilayer networks in a nutshell. Annual Review of Condensed Matter Physics, 10, 45-62.

LC-MS data preprocessing for batch analysis

B C

LC-MS (Liquid Chromatography coupled with Mass Spectrometry) is a widely used technique for analyzing chemical composition of a sample which could be, for example food, cosmetic, etc. However, there are some critical challenges involving comparative study of a bunch of LC-MS profiles. One of the prominent challenge being retention time shifts, i.e. the experiment-by-experiment variation of the time difference in detecting a peak. Inter-experiment comparisons require an alignment of retention times. Therefore, the automatization of such an alignment is under intense investigation in Bioinformatics. The COMETA database is an excellent test environment for such algorithms, because samples have been taken over many years for a comparatively well-defined biochemical system (cocoa). The aim of this project is to select the best out of the available state of the art algorithms or procedures so as to minimize external variations (instrumental or experimental condition dependent) in the LC-MS profiles of multiple

samples, and bring them to a comparable common ground for automatized batch processing.

Further reading:

Podwojski, K.; Fritsch, A.; Chamrad, D. C.; Paul, W.; Sitek, B.; Stühler, K.; Mutzel, P.; Stephan, C.; Meyer, H. E.; Urfer, W.; et al. (2009) Retention time alignment algorithms for LC/MS data must consider non-linear shifts. Bioinformatics 2009, 25 (6), 758Ð764.

Zhang, W., Lei, Z., Huhman, D., Sumner, L.W., and Zhao, P.X. (2015). MET-XAlign: A Metabolite Cross-Alignment Tool for LC/MS-Based Comparative Metabolomics. Anal. Chem. 87, 9114Ð9119.

Exploring the peptide patterns in cocoa bean samples I: Data analysis
B C

Peptides are protein fragments. In the case of cocoa, they are precursors of chemical compounds responsible for taste and flavor. At each moment in time the pattern of peptides in a cocoa bean sample can offer detailed information about the future taste attributes. At the same time, it can be expected that the peptide patterns impose tight constraints on the chemical composition (e.g., measured via LC-MS; see the project descriptions above) of the cocoa bean.
A large number of peptides are formed during the fermentation stage of cocoa. These are formed by the cleaving action of various enzymes on the main storage proteins in cocoa: Vicillin and Albumin. The resulting peptides play an important role in the Maillard reaction, which takes place during the roasting stage in a typical cocoa processing pipeline. Currently, our understanding of the formation of the peptides from the original proteins and intermediate peptides is limited. This project aims to further this understanding by developing new data analysis concepts for peptide patterns. Specifically, we wish to explore possibilities of (a) tracking fates of some proteins over the course of fermentation, and (b) defining and testing suitable metrics (distance measures) for peptide patterns motivated by the biology of the protein degradation process.

Further reading:

Kumari, N., Kofi, K. J., Grimbs, S., D'Souza, R. N., Kuhnert, N., Vrancken, G., and Ullrich, M. S. (2016). Biochemical fate of vicilin storage protein during fermentation and drying of cocoa beans. Food Research International, 90, 53-65.

Exploring the peptide patterns in cocoa bean samples II: Mathematical modeling
B M

As outlined in the project description above, peptides are protein fragments. They arise from the iterative action of protein cutting enzymes. The goal of this project is to formulate a mathematical model of protein degradation. The input to the mathematical model will be the sequence of the initial protein, the available protein-cutting enzymes (proteases), together with their cleavage (cutting) preferences. The (very few) modeling attempts of protein degradation found in the scientific literature can serve as starting points for this project.
Such a model could be instrumental in solving a long-standing puzzle in cocoa research: Can the peptides (and hence the later-stage taste and flavor components) be explained by the enzyme inventory of cocoa alone or are enzymes of the bacteria acting during fermentation

involved in the protein degradation.

Further reading:

Kumari, N., Kofi, K. J., Grimbs, S., D'Souza, R. N., Kuhnert, N., Vrancken, G., and Ullrich, M. S. (2016). Biochemical fate of vicilin storage protein during fermentation and drying of cocoa beans. Food Research International, 90, 53-65.

Luciani, F., Kesmir, C., Mishto, M., Or-Guil, M., and De Boer, R. J. (2005). A mathematical model of protein degradation by the proteasome. Biophysical journal, 88(4), 2422-2432.