Swiss Institute of Bioinformatics

netherlands bioinformatics centre

International Winterschool 2013 NBIC/SIB
In the intersection of bioinformatics and medicine

Bioinformatics has an essential place in the interplay of genomics, drug discovery and clinical diagnostics, and can thus bring new insights to the physicians' daily work. Bioinformatics is needed, for instance, in massive genome data analysis, data integration, clever data mining, clinical expert systems, variant databases, from protein domain knowledge to phenotype, among many options.

Recognising the importance of bioinformatics in medicine, the SIB and NBIC have joined forces to organise a joint Winter School focusing in the intersection of bioinformatics and medicine. The topics that will be covered by leading scientists in the field include: cancer genomics and treatments, GWAS studies, analysis of medical records and ontologies, drug testing and design.

Venue: Kandersteg, Hotel Alpha Soleil http://www.alfasoleil.ch/
Dates: 10-15 March 2013
Target audience: PhD students and researchers in bioinformatics and computational biology and related disciplines.
Maximum number of participants: 30
Format: Lectures, scientific papers' discussion and practical/hands-on with computers.
Note: Participants will bring laptops (with preinstalled software). Wireless connection will be available in the classroom.
NBIC website: http://www.nbic.nl/education/nbic-phd-school/winterschool-2013/
SIB website: http://www.isb-sib.ch/education/sib-phd-training-network/phd-winter-school-2013.html

General program

Day 0: Mar 10 Arrival and welcome dinner

Day 1: Mar 11 – Cancer genomics and treatments
- Niko Beerenwinkel (BSSE, ETHZ, and SIB, CH)
- Florian Markowetz (Cancer Research, UK)

Day 2: Mar 12 – Drug testing and design
- Tina Ritschel (Centre Molecular Life Sciences, Radboud Univ. Nijmegen Medical Centre, NL)
- Christian Lemmen (BioSolveIT, D)

Day 3: Mar 13: Dedicated to social and networking activities, skiing or any other suitable alternatives.

Day 4: Mar 14 – GWAS studies
- Sven Bergmann (University of Lausanne and SIB, CH)
- Han Brunner (Radboud University Nijmegen Medical Centre, and NBIC, NL)

Day 5: Mar 15 - Analysis of medical records and ontologies
- Frank van Harmelen (VU University, Amsterdam, NL)
- Janna Hastings (EBI, UK and SIB, CH)

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Abstracts

Cancer genomics and treatments

Niko Beerenwinkel (BSSE, ETHZ, and SIB, CH) and **Florian Markowetz** (Cancer Research, UK)
Abstract: Cancer is a highly diverse disease caused by genetic alterations in the genome that impair signalling pathways of the cell. Depending on the cell of origin and the tissue environment, tumors can develop very differently among patients. In addition, considerable genetic diversity is present within tumors as a result of ongoing somatic evolution of cancer cells. Tumors have traditionally been treated with cytotoxic drugs, but new so-called targeted therapies are nowadays available that interfere with specific dysregulated pathways and make precision medicine possible. However, inter- and intra-tumor genetic diversity challenge this approach and drug resistance development is a common problem. In this session, we will discuss computational methods for translational cancer genomics. We present methods for analyzing data obtained from tumor biopsies, including next-generation sequencing of DNA and RNA, and we introduce basic mathematical models of tumor progression and therapy optimization. In several case studies, we will highlight the opportunities and challenges for computational methods as a tool enabling and improving individualized cancer treatment.

Drug testing and design

Tina Ritschel (Centre Molecular Life Sciences, Radboud Univ. Nijmegen Medical Centre, NL)
Computer-Assisted Drug Design
Abstract: Different aspects of computer-assisted drug design (CADD) will be presented during the lecture. Both ligand-based as structure-based design techniques will be discussed, with a strong emphasis on the difference between the two approaches, both in methodology as applicability. The two structure-based methods molecular doing and structure-based pharmacophores will be explained in more detail, including latest method developments and cross-discipline application fields. Several examples and case studies will be presented of the introduced techniques as applied in modern pharmaceutical research.

Christian Lemmen (BioSolveIT, D)
Docking & Scoring: The Optimization Perspective
Abstract: Docking is a very important and much used computer simulation in the drug discovery process. It answers two questions: a) What is the likely position of a candidate molecule in a cavity, and b) how happy is the molecule in that cavity, i.e., what is its binding affinity, its 'score'? Both questions can be seen in the light of "optimization": We try to "optimize" a (ligand) position in a cavity, and we aim at b) optimizing the respective energy function, hoping to find a minimum reflecting the bioactive conformation. Since optimization processes are of crucial importance not only in docking and scoring, the lecture will give a brief introduction into mathematical concepts and general optimization strategies - exemplified using the docking and scoring facilities in BioSolveIT's LeadIT2 program.

GWAS studies

Sven Bergmann (University of Lausanne and SIB, CH) and **Han Brunner** (Radboud University Nijmegen Medical Centre, and NBIC, NL)
Analysis of sequence information for a better understanding of disease: From cohort-based genome-wide association studies to genome-sequencing of patients with rare diseases

Lecturers: Han G. Brunner and Sven Bergmann (UNIL, SIB). HGB studied medicine at the University of Groningen, the Netherlands, and then obtained his Ph.D. and specialized in clinical genetics at the Radboud University Nijmegen Medical Centre, where he is now chair of the Department of Human Genetics. His interests range from the genetic causes of malformations to those of intellectual disability and behaviour. He is particularly fascinated by the potential for translating new genomic knowledge into effective medical care. SB received his PhD in elementary particle physics at the Weizmann Institute of Science (Israel) where subsequently joined the group of Prof. Naama Barkai for his postdoctoral studies in Systems Biology. His work in the field of computational biology includes designing and applying novel algorithms for the analysis of large-scale biological and medical data, as well as modeling of genetic networks pertaining to developmental processes.

Abstract: We will provide an overview on Genome-wide Association Studies (GWAS), explaining the basic methodology, reporting our own experience in various projects and discussing critically limitations and challenges in this field of research, most prominently the failure to explain a sizable portion of the heritable variance of most complex traits. We will then transition from the study of common variants in large populations to very rare variants or de-novo mutations that give rise to genetic diseases. The latter are now routinely identified by whole-genome or whole-exome sequencing approaches. We will discuss recent findings suggesting that de novo mutations play a prominent part in rare and common forms of neurodevelopmental diseases, including intellectual disability, autism and schizophrenia. De novo mutations provide a mechanism by which early-onset reproductively lethal diseases remain frequent in the population. These mutations, although individually rare, may capture a significant part of the heritability for complex genetic diseases that is not detectable by GWAS.

Reading Material:
1. “The case of the missing heritability” (NATURE, Vol 456, 18-21)
2. “De novo mutations in human genetic disease” (Nature Reviews Genetics 13, 565-575)

Analysis of medical records and ontologies

Frank van Harmelen (VU University, Amsterdam, NL)

Janna Hastings (EBI, UK and SIB, CH)
Harnessing the knowledge encoded in bio-ontologies for interdisciplinary analysis and translation
Abstract: Bio-ontologies encode knowledge in various biological and medical domains that can be used to drive sophisticated computational analyses of large-scale data. I will present one such method, namely ontology-based enrichment analysis, in the context of several different domains, from functional genomics through chemical biology to comparative phenomics. I will then show how

bio-ontologies are becoming increasingly interconnected with knowledge-based bridges between different domains, and I will discuss how these interconnections enable translation of basic biological research into the medical domain, in the context of an application being developed for behavioural disorders.