Implementing research in personalized medicine

Niko Beerenwinkel

Department of Biosystems Science and Engineering, ETH Zurich
SIB Swiss Institute of Bioinformatics
Competence Center Personalized Medicine UZH/ETHZ
The future of health care – 15 years ago

- Genome
- Decision support systems
- Genotype
- Molecular profile
- Patient history
- Knowledge base
- Drugs
- Diagnostics
- Prognostics

Sander 2000
Outline

- Case study: Optimizing antiretroviral therapy
- Some (computational) challenges in Personalized Medicine
- Competence Center Personalized Medicine UZH/ETHZ
Optimizing antiretroviral therapy
HIV drug resistance
HIV drug resistance – challenges

Large genetic diversity

Many drug combinations
Given many short error-prone reads from a mixed virus population, reconstruct all haplotype sequences and estimate their frequencies.
Challenges

1. Alignment uncertainty
2. Several confounding sources of variation
3. Short read length
Beerenwinkel et al 2012
Viral quasispecies assembly

Haplotype 1, strain A
Haplotype 2, strain B
Haplotype 3, strain B with deletion
Reference genome
Read alignment

Read alignment graph
Max-cliques

Töpfer et al 2014
Most drug combinations are rare
Predicting HIV phenotypic drug resistance

Is the present virus resistant to drugs?  How likely is it to evolve resistance?

Statistical learning  Evolutionary modeling
A model of drug resistance development
The individualized genetic barrier

What is the probability of a susceptible virus to become resistant?
Predicting treatment response

New predictor based on genomic data and evolutionary model
Comparative performance

computational model

human expert panels

Altmann et al 2009
Clinical decision support

ranked treatment options
Genomic medicine in action

McCarthy et al. 2013
Goals of genome-based personalized medicine

- Improved, individualized
  - **diagnostics** and **prognostics**: earlier, more precise, broad molecular profiling

- **treatments**: targeting specific disease markers, higher likelihood of response, enhanced drug safety, optimized dosing

McCarthy et al. 2013
Some challenges in Personalized Medicine
Cost per genome

Moore’s Law
High throughput due to parallelization

Applications of next-generation sequencing

Shendure et al. 2012
The real cost of sequencing

Sboner et al. 2011
Exome sequencing data analysis pipeline

- Fastq Files
  - Clipping, Trimming
    - Trimmomatic
  - Alignment
    - Bowtie2
  - Sort
  - Filter
  - Merge
  - Remove duplicates
  - Index
  - SNV calling
    - Pindel
    - Dindel
    - CONTRA
    - ADTEx
  - Annotation, Filtering, ...
  - Overlap
  - Overlap
Five common SNV callers on a cancer exome

top 10% calls
Challenges

- Data management
  - secure, reliable, cost- and time-efficient
- Data analysis
  - statistically sound
  - computationally efficient
  - robust
  - reproducible
  - traceable
  - transparent
  - auditable
Developing open-source software for PM

SOUND
Statistical Multi-Omics Understanding

Statistical Algorithms
WP 1 - 4

Methodological and Computational Integration
WP 8 - 12

Bioinformatic Tools for R&D in Personalized Medicine

Clinician Scientists

Statistical Omics Community

Multi-Omic Patient Studies
WP 2, 5 - 7
Most PM projects require customized analyses

- Good pipelines alone will not suffice
- Need for service and consulting
Competence Center Personalized Medicine UZH/ETHZ (CC-PM)
Competence Center Personalized Medicine (CC-PM)

- 25 PIs from USZ/UZH and ETHZ
- PhD program Molecular and Translational Biomedicine (~50 students)
CC-PM flagship projects

- *Towards individualized prevention and therapy in hereditary cancer diseases*
- *Brown fat tissue – personalized strategies to achieve weight loss*
- *Metastatic ccRCC 1 – Personalising prognosis and therapy of metastatic renal carcinoma*
- *Digital biobanking*
- *The intra-tumor heterogeneity census project – decoding mechanisms of intra-tumor heterogeneity for precision medicine*

http://www.cc-pm.uzh.ch/flagships_en.html
Technology for personalized medicine research

- Molecular and clinical data management, analysis, and integration
- Lab automation and robotics tools and advanced cell systems
- Tissue and serum biobanking

PM-ICT
Theragnostics Discovery
Biobank
Hochschulmedizin Zurich

Competence Center Personalized Medicine (CC-PM)

joint PM research projects

PM-ICT Unit
TD Unit
Biobanking (UZH/USZ)

nexus (ETHZ)
- Bioinformatics and statistics services
  - genome analysis (WGS, WES, targeted sequencing)
  - transcriptome analysis (RNA-seq)
  - proteome analysis
  - association studies
  - image analysis for digital pathology
  - ...

- Consulting

- Education: courses, internships, etc.
Acknowledgements

CGB, D-BSSE, ETH Zurich
- Simona Constantinescu
- Madeline Diekmann
- Christos Dimitrakopoulos
- Monica Golumbeanu
- Ariane Hofmann
- Katharina Jahn
- Vinay Jethava
- Jack Kuipers
- Hesam Montazeri
- Caroline Perraudin
- Susana Posada Cespedes
- Hans-Joachim Ruscheweyh
- Fabian Schmich
- David Seifert
- Jochen Singer
- Ewa Szczurek

Collaborators
- Huldrych Günthard, USZ
- Willy Krek, ETH Zurich, NEXUS
- Holger Moch, USZ, CC-PM
- Daniel Stekhoven, NEXUS

Funding: ETH Zurich, SNSF, Swiss HIV Cohort Study, SystemsX.ch, ERASysAPP, Swiss Cancer League, EU H2020, ERC Synergy

www.cbg.ethz.ch