From biomedical informatics to translational research

Olivier Bodenreider
Lister Hill National Center for Biomedical Communications
Bethesda, Maryland - USA
Outline

- Translational research
- Enabling translational research
- Anatomy of a translational research experiment
- Promising results
- Challenging issues
Translational research

(Translational medicine)
Translational medicine/research

◆ Definition
- Effective transformation of information gained from biomedical research into knowledge that can improve the state of human health and disease

◆ Goals
- Turn basic discoveries into clinical applications more rapidly ("bench to bedside")
- Provide clinical feedback to basic researchers

[Butte, JAMIA 2008]
Combining clinical informatics and bioinformatics

◆ Associates
  ● Clinical informatics
    ■ Electronic medical records
    ■ Clinical knowledge bases
  ● Common computational resources
    ■ Biomedical natural language processing
    ■ Biomedical knowledge engineering
  ● Bioinformatics
    ■ Sequence databases
    ■ Gene expression
    ■ Model organism databases
Translational bioinformatics

“… the development of storage, analytic, and interpretive methods to optimize the transformation of increasingly voluminous biomedical data into proactive, predictive, preventative, and participatory health.

Translational bioinformatics includes research on the development of novel techniques for the integration of biological and clinical data and the evolution of clinical informatics methodology to encompass biological observations.

The end product of translational bioinformatics is newly found knowledge from these integrative efforts that can be disseminated to a variety of stakeholders, including biomedical scientists, clinicians, and patients.”

AMIA strategic plan
http://www.amia.org/inside/stratplan
Aspects of translational research

- Huge volumes of data
- Publicly available repositories
- Publicly available tools
- Data-driven research
Huge volumes of data

- Affordable, high-throughput technologies
  - DNA sequencing
    - Whole genomes
    - Multiple genomes
  - Single nucleotide polymorphism (SNPs) genotyping
    - Millions of allelic variants between individuals
  - Gene expression data from micro-array experiments
  - Text mining
    - Full-text articles
    - Whole MEDLINE
  - Electronic medical records
  - Genome-wide association studies
Publicly available repositories

- DNA sequences
  - GenBank / EMBL / DDBJ
- Gene Expression data
  - GEO, ArrayExpress
- Biomedical literature
  - MEDLINE, PubMedCentral
- Biomedical knowledge
  - OBO ontologies
- Clinical data (genotype and phenotype)
  - dbGaP
Publicly available tools

- **DNA sequences**
  - BLAST

- **Gene Expression data**
  - GenePattern, …

- **Biomedical literature**
  - Entrez, MetaMap

- **Biomedical knowledge**
  - Protégé

Culture of sharing encouraged by the funding agencies
- Grants for tools and resource development
- Mandatory sharing plan in large NIH grants
- Mandatory sharing of manuscripts in PMC for NIH-funded research
Data-driven research

◆ Paradigm shift

● Hypothesis-driven
  - Start from hypothesis
  - Run a specific experiment
  - Collect and analyze data
  - Validate hypothesis (or not)

● Data-driven
  - Integrate large amounts of data
  - Identify patterns
  - Generate hypothesis
  - Validate hypothesis (or not) through specific experiments

Biomedical informatics as a supporting discipline for biology and clinical medicine

Biomedical informatics as a discipline in its own right, addressing important questions in medicine
“The availability of substantial public data enables bioinformaticians’ roles to change. Instead of just facilitating the questions of biologists, the bioinformatician, adequately prepared in both clinical science and bioinformatics, can ask new and interesting questions that could never have been asked before.

[...] There is a role for the translational bioinformatician as question-asker, not just as infrastructure-builder or assistant to a biologist.”

[Butte, JAMIA 2008]
Enabling translational research

Clinical Translational Research Awards (CTSA)
Re-engineering the Clinical Research Enterprise

TRANSLATIONAL RESEARCH

OVERVIEW

To improve human health, scientific discoveries must be translated into practical applications. Such discoveries typically begin at "the bench" with basic research — in which scientists study disease at a molecular or cellular level — then progress to the clinical level, or the patient’s "bedside."

Scientists are increasingly aware that this bench-to-bedside approach to translational research is really a two-way street. Basic scientists provide clinicians with new tools for use in patients and for assessment of their impact, and clinical researchers make novel observations about the nature and progression of disease that often stimulate basic investigations.
Clinical and Translational Science Awards

The purpose of the CTSA Program is to assist institutions to forge a uniquely transformative, novel, and integrative academic home for Clinical and Translational Science that has the consolidated resources to:

- 1) captivate, advance, and nurture a cadre of well-trained multi- and inter-disciplinary investigators and research teams;
- 2) create an incubator for innovative research tools and information technologies; and
- 3) synergize multi-disciplinary and inter-disciplinary clinical and translational research and researchers to catalyze the application of new knowledge and techniques to clinical practice at the front lines of patient care.

http://nihroadmap.nih.gov/
CTSA program (NCRR)

- 38 academic health centers in 23 states
  - 14 centers added in 2008
  - 60 centers upon completion
- Funding provided for 5 years
- Total annual cost: $500 M
- Annual funding per center: $4-23 M
  - Depending on previous funding

http://www.ncrr.nih.gov/clinical_research_resources/clinical_and_translational_science_awards/
Clinical and Translational Science Awards

http://www.ctsaweb.org/
Other related programs

- **National Centers for Biomedical Computing**

  "networked national effort to build the computational infrastructure for biomedical computing in the nation"

http://www.ncbcs.org/
Other related programs

◆ Cancer Biomedical Informatics Grid (caBIG)

“an information network enabling all constituencies in the cancer community – researchers, physicians, and patients – to share data and knowledge.”

- Key elements
  - Bioinformatics and Biomedical Informatics
  - Community
  - Standards for Semantic Interoperability
  - Grid Computing
- 1000 participants from 200 organizations
- Funding: $60 M in the first 3 years (pilot)

https://cabig.nci.nih.gov/
Translational research and data integration
Genotype and phenotype

b  Disease Gene Network

[Goh, PNAS 2007]
Genotype and phenotype

- Publicly available data
  - OMIM
    - 1284 disorders
    - 1777 genes
- No ontology
  - Manual classification of the diseases into 22 classes based on physiological systems
- Analyses supported
  - Genes associated with the same disorders share the same functional annotations

[Image: Disease Gene Network]

[Source: Goh, PNAS 2007]
Genes and environmental factors

• MEDLINE (MeSH index terms)
• Genetic Association Database

[Li, BMC Bioinf. 2008]
Genes and environmental factors

- Publicly available data
  - MEDLINE
    - 3342 environmental factors
    - 3159 diseases
  - Genetic Association Database
    - 1100 genes
    - 1034 complex diseases
  - 863 diseases with both
    - Genetic factors
    - Environmental factors

- Analyses supported
  - Proof-of-concept study

[Liu, BMC Bioinf. 2008]
Integrating drugs and targets

(Yildirim, Nature Biot. 2007)
Genes and environmental factors

- Publicly available data
  - DrugBank
    - 4252 drugs
    - 808 experimental drugs associated with at least one protein target
  - ATC
    - Aggregate drugs into classes
  - Gene ontology
    - Aggregate gene products by functional annotations
  - OMIM
    - Gene-disease associations
  - ...

- Analyses supported
  - Industry trends
  - Properties of drug targets in the context of cellular networks
  - Relations between drug targets and disease-gene products

[Yildirim, Nature Biot. 2007]
Anatomy of a translational research experiment
Integrating genomic and clinical data

- No genomic data available for most patients
- No precise clinical data available associated with most genomic data (GWAS excepted)
Integrating genomic and clinical data

**Dataset Description**

- **Accession:** GDS2639
- **Title:** Aging and cognitive impairment: hippocampus
- **DataSet type:** gene expression array-based (RNA / in situ oligonucleotide)
- **Summary:** Analysis of hippocampi from aged learning-impaired animals on the last day of training in the Morris water maze (MWZ) or 21 days post-training. The MWZ task is a dorsal hippocampal-dependent task. Results provide insight into the molecular basis of aging-related cognitive impairment.
- **Platform:** GPL341: Affymetrix GeneChip Rat Expression Set 230 Array RAE230A

**Sample organism:** Rattus norvegicus
**Feature count:** 16923
**Series:** GSE5666
**Last GDS update:** 04/27/2007

**MeSH Terms:**

- Age Factors
- Animals
- Cognition Disorders genetics
Integrating genomic and clinical data

Genomic data

Upregulated genes

Diseases
(extracted from text + MeSH terms)
Integrating genomic and clinical data

Genomic data

Clinical data

Upregulated genes

Diseases (extracted from text + MeSH terms)

Coded discharge summaries

Laboratory data
The Butte approach  Methods

Data integration overview

- Gene Expression data (GDS)
- Gene Expression Omnibus (GEO)
- UMLS CUI
- SNOMED CT
- ICD9 CM
- Patient biomarker data
- Unified Medical Language System (UMLS)
- Lucile Packard Children’s Hospital (STRIDE)

Courtesy of David Chen, Butte Lab
The Butte approach Results

- 737 GEO Data Sets that were related to human disease
- 238 disease concepts were associated with GDS subsets
- 29,541 microarray samples were coded with SNOMED CT identifiers
- Note, we only included GDS that compared disease state to normal state
- 13,452 patients (of 49,414) mapped to 211 (of 238) of the disease concepts
The Butte approach

◆ Extremely rough methods
  ● No pairing between genomic and clinical data
  ● Text mining
  ● Mapping between SNOMED CT and ICD 9-CM through UMLS
  ● Reuse of ICD 9-CM codes assigned for billing purposes

◆ Extremely preliminary results
  ● Rediscovery more than discovery

◆ Extremely promising nonetheless
The Butte approach References


Promising results
Pharmacogenomics of warfarin

- Narrow therapeutic range
- Large interindividual variations in dose requirements
- Polymorphism involving two genes
  - CYP2C9
  - VKORC1
- Genetic test available
- Development of models integrating variants of CYP2C9 and VKORC1 for predicting initial dose requirements (ongoing RCTs)
- Step towards personalized medicine
Integration of existing studies/datasets

- 49 experiments in the domain of obesity
  - Rediscovery of known genes
  - Identification of potential new genes

- Analysis of genes potentially associated with nicotine dependence
  - Rediscovery of known findings

- Identification of networks of genes associated with type II diabetes mellitus

[English, Bioinformatics 2007]
[Sahoo, JBI 2008]
[Liu, PLoS 2007; Rasche, MBC Gen. 2008]
Challenging issues
Challenging issues

- Datasets
- Ontologies
- Tools
- Other issues
Challenging issues Datasets

- **Lack of annotated datasets**
  - Largely text-based (need for text mining)

- **Limited availability of clinical data (EHRs, PHRs)**
  - Need for deidentification
  - Largely text-based (need for text mining)

- **Heterogeneous formats**
  - Need for conversion

- **Lack of metadata**
  - Limited discoverability, limited reuse
Challenging issues  Ontologies

- Lack of universal identifiers for biomedical entities
  - Need for normalization through terminology integration systems (e.g., UMLS)

- Lack of standard for identifiers
  - Need for bridging across formats

- Lack of universal formalism
  - Need for conversion between formalisms

- Limited availability of some ontologies

- Delay in adopting standards
  - e.g., SNOMED CT
Challenging issues  Tools

- Lack of semantic interoperability
  - Difficult to combine tools/services
- Limited scalability of automatic reasoners
  - Difficult to process large datasets
Other challenging issues

- Limited number of researchers “adequately prepared in both clinical science and bioinformatics”
- Need for validation of potential in silico discoveries through specific experiments
  - Collaboration with (wet lab) biologists
  - Must be factored in in grants
Conclusions
Conclusions

◆ Translational medicine is an emerging discipline
  ● We live in partially unchartered territory
◆ Biomedical informatics is at the core of translational medicine
  ● Strong informatics component to translational medicine

◆ We live in exciting times
  ● New possibilities for biomedical informaticians
  ● From service providers…
    …to biomedical researchers
Medical Ontology Research

Contact: olivier@nlm.nih.gov
Web: mor.nlm.nih.gov

Olivier Bodenreider
Lister Hill National Center for Biomedical Communications
Bethesda, Maryland - USA