Medical Informatics

Dr. P. Gautam
Guest Lecture

Medical Informatics

Dr. P. Gautam
Professor, Biotechnology &
Coordinator, Bioinformatics centre
Anna University
Chennai- 600 025
E-mail:pgautam@annauniv.edu
http://www.annauniv.edu/biotech

Medical Informatics – A Definition

Medical informatics is a developing body of knowledge and a set of techniques concerning the organizational management of information in support of medical research, education, and patient care . Medical informatics combines medical science with several technologies and disciplines in the information and computer sciences and provides methodologies by which these can contribute to better use of the medical knowledge base and ultimately to better medical care.

Association of American Medical Colleges

Medical Informatics is the rapidly developing scientific field that deals with the storage, retrieval, and optimal use of biomedical information, data, and knowledge for problem solving and decision making."

Shortliffe et.al., Medical Informatics: Computer Applications in Healthcare, Addison Wesley, 1990.

If physiology literally means 'the logic of life', and pathology is 'the logic of disease', then medical informatics is the 'logic of healthcare'.

It is the rational study of the way we think about patients, and the way that treatments are defined, selected and evolved.

It is the study of how medical knowledge is created, shaped, shared and applied.

Modern medicine has moved away from seeing disease in isolation to understanding that illness occurs at a complex system level.

Infection is not simply the result of the invasion of a pathogenic organism, but the complex interaction of an individual's immune system, nutritional status, environmental and genetic endowments.

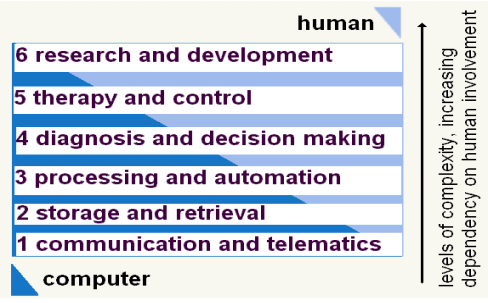
By seeing things at a system level, we come ever closer to understanding what it really means to be diseased, and how that state, however defined, can be reversed.

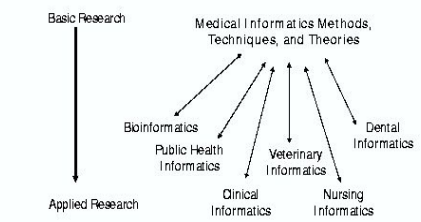
Informatics & Medicine

Informatics & Medicine

A science characterized by
complex work in ontologies of medical knowledge & problem solving methods that use them
A discipline that is unique because
of focus on complex ontological work and
issues concerned with integrating the technology into the medical milieu

- Landmark attempt at defining a theory of medical informatics
- Claimed that medicine is an epistemologically unique area of human endeavor
- Unique due to complexity and structure of knowledge
  - Medicine / Biology / Biochemistry





Potential Drug Candidate for Mycobacteium Tuberculosis – An Insilico Approach

The need for the discovery of new drug targets in *Mycobacterium tuberculosis*

Though front line TB drugs are available, prolonged treatment and non-compliance are major obstacles in effective treatment

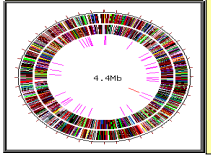
Re-emergence of TB as a global threat due to multidrug resistance strains (MDR strains)

Synergy between HIV and TB

The Mycobacterium tuberculosis genome

Deciphering the biology of Mycobacterium tuberculosis from the complete genome sequence S.T. Cole *etal* (1998) Nature 393: 537-544.

M.Tb genome approx 4000 genes



Completion of the H37Rv *M.Tb* genome has led to

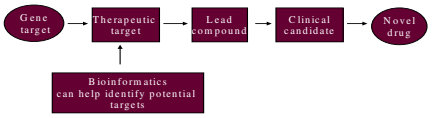
An improved understanding of genes expressed

Metabolic pathways

Virulence factors

Mycobacterial persistence

The Drug discovery pipeline



Informatics approach for identifying drug targets

Metabolic pathway information of host and pathogen are available in pathway databases like KEGG

Comparative metabolic pathway analysis of host and the pathogen

Identification of enzymes unique to the pathogen

These represent potential drug targets

Identification of Unique pathways in the pathogen

Comparison of host and pathogen pathways yields unique pathway list.

Enzymes from these pathways are bacteria specific and hence represent attractive potential drug targets.

Unique pathways identified in *Mycobacterium tuberculosis*

- Peptidoglycan biosynthesis
- Mycobactin biosynthesis
- C5 branched dibasic acid metabolism
- D-alanine metabolism
- Thiamine metabolism
- Polyketide sugar unit biosynthesis

Potential drug targets identified in *Mycobacterium tuberculosis*

Pathway	No.of targets
Cell wall biosynthesis	10
Lipid metabolism	20
Carbohydrate metabolism	40
Energy metabolism	30
Amino acid metabolism	80
Vitamin and cofactor biosynthesis	35

Two essentials for a good drug target

Should be important for the viability of the pathogen

Should not bear similarity to any host protein

Elimination of pseudo drug targets

Potential targets are screened for homologues with host.

Bioinformatics tools like BLAST help in comparing targets with all the proteins from the host.

Targets with no similarity to the host *Homo sapiens* proteins are the final candidates

Case study 1: The mycobacterial cell wall

The three components of the cell wall

Plasma membrane

Mycolic acid,
arabinogalactan
and peptidoglycan complex (MAPc)

Polysaccharide rich capsule like material.

Existing drugs isoniazid & ethambutol target cell wall biosynthesis.

Isoniazid inhibits mycolic acid biosynthesis

Ethambutol inhibits arabinan biosynthesis

Because of its complex structure, cell wall biosynthesis still remains a favourite for the discovery of new drugs

Our targets from cell wall biosynthesis: 10

Prime candidate: MurD ligase

Case study 2: Lipid metabolism

A large part of the coding region of M.Tb is devoted to the production of enzymes involved in

Lipogenesis

Lipolysis

The bacterium depends on the host cell lipids

Degradation of host cell lipids provides precursors to many of the bacterial cell processes.

Our targets from the lipid metabolism : 20

Includes virulence factors like phospholipases and lipases

Case study 3 : Iron acquisition

Mycobacterium tuberculosis inhabits one of the most hostile environments the alveolar macrophage

One of the host defensive mechanisms

Dramatic reduction of iron availability to support bacterial growth.

Bacteria have evolved sophisticated iron acquisition systems in the form of iron sequestering molecules : siderophores

M.Tb produces the mycobactin class of siderophores.

Mutant studies have shown impaired growth of the bacterium in macrophage like THP1 like cells under iron limiting conditions

Mycobactin biosynthesis is important for virulence

One of our targets is from the mycobactin biosynthetic pathway.

Case study 4: Mycobacterial persistence : Latent TB

The pathogen can survive for prolonged periods in infected individuals in a dormant form : Latent TB

Need for new drugs to combat latent forms of TB

Genes expressed during mycobacterial persistence have been identified.

Under the microaerophilic conditions of the macrophage the bacterium survives the low oxygen conditions by a metabolic downshift. It also

Switches over to anaerobic nitrate respiration

Uses glyoxylate bypass to produce carbohydrates from fatty acids

Targets from these pathways could prove useful for treatment of latent forms of TB

Once targets are discovered structure based drug design follows.....

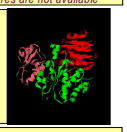
Homology modeling of one of the targets MurD ligase : A prime candidate for broad spectrum drug discovery

Why target MurD ?

Essential for cell wall biosynthesis
viability of the bacterium
Present across all eubacteria

Homology modeling
An alternative when structures are not available

M.Tb *MurD* modelled using *E.coli* MurD as a template, with **WHATIF** Molecular modeling and drug design program



What next ??

Structure based drug design
Screening of chemical libraries for ligand/drug docking
Chemoinformatics

Acknowledgement

Department of Science and Technology (DST) Govt. of India.

Council of Scientific and Industrial Research (CSIR), Govt. of India

Department of Biotechnology

Biotechnology Information Services (DBT-BTIS) Govt. of India