2010-CNB-IMS
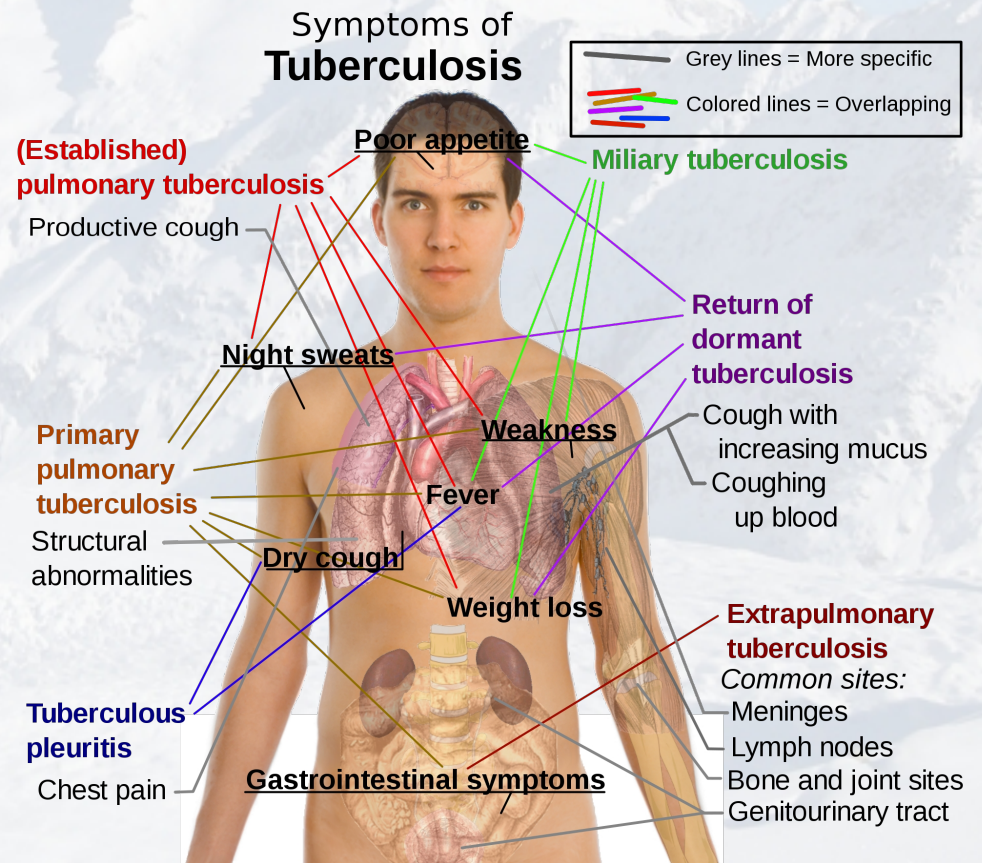
Introduction

José R. Valverde
EMBnet/CNB

Summary

- Target description

- Goals

- Introduce molecular simulations

Target

- References:
  - http://en.wikipedia.org/wiki/Tuberculosis
  - http://en.wikipedia.org/wiki/Multi-drug-resistant_tuberculosis

- The suspect
  - TBC is a major neglected disease
  - Prevalence is raising
 - MDR-TB becoming more frequent

Effects

- TBC is a systemic disease
- Can simulate many other diseases
- Often misdiagnosed
- Deadly in late stages

Symptoms of **Tuberculosis**

Grey lines = More specific
Colored lines = Overlapping

(Established) pulmonary tuberculosis
Productive cough

Miliary tuberculosis

Poor appetite

Return of dormant tuberculosis
Cough with increasing mucus
Coughing up blood

Night sweats

Primary pulmonary tuberculosis
Structural abnormalities

Weakness

Fever

Dry cough

Weight loss

Extrapulmonary tuberculosis
Common sites:
Meninges
Lymph nodes
Bone and joint sites
Genitourinary tract

Tuberculous pleuritis
Chest pain

Gastrointestinal symptoms

Epidemiology

- ~1/3 of the world population has been infected

- 1 new infection per second

- Resurgence

- MDR-TB emergence
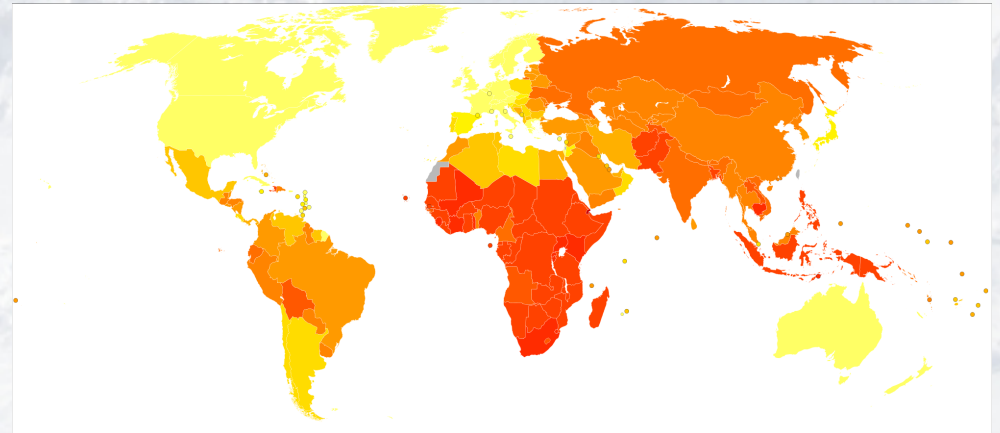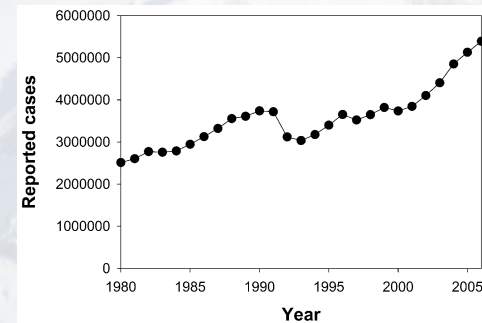
Age-standardized death from tuberculosis per 100,000 inhabitants in 2004
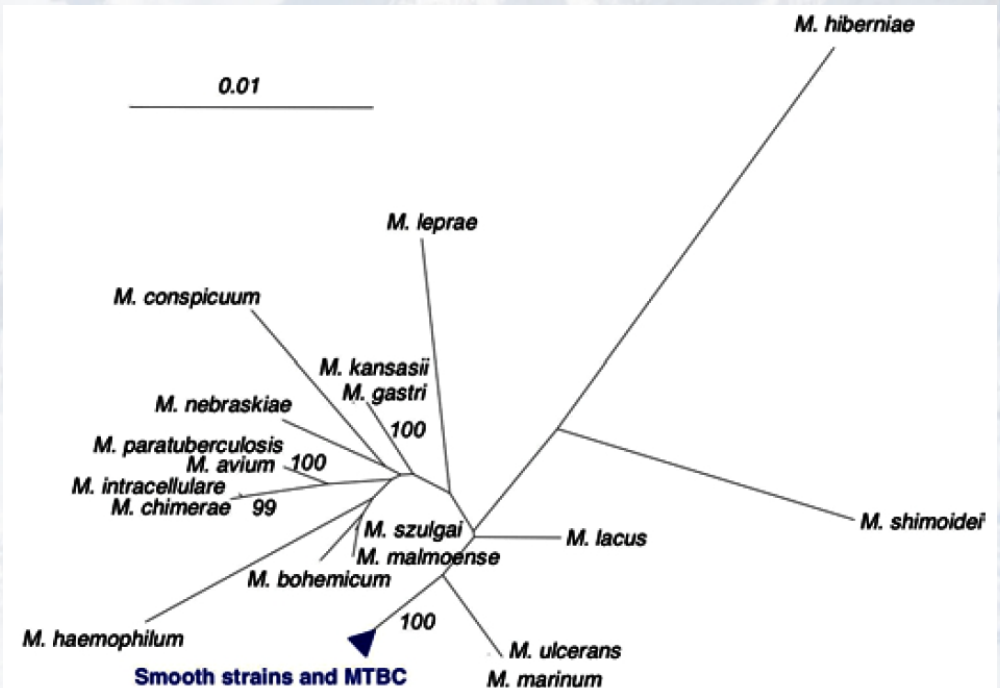
The culprit

- Mycobacterium tuberculosis
  - Aerobic bacillum
  - Slow growth
  - Genetically diverse
  - Undigestible by macrophages

The convict's family

- ## Genome of H37Rv

  - Bison 18K years BC

  - Neolithic men (7K BC)

  - Mummies (3K BC)

  - Not descended from M. bovis

MDR-TB / XDR-TB

- ## First line therapy

  - Ethambutol (EMB, E), Isoniazid (INH, H), Pyrazinamide (PZA, Z), Rifampicin (RMP, R), Streptomycin (STM, S)

  - 2HREZ/4HR$_3$ (2 months HREZ daily, followed by 4 months HR three times a week)

- ## Multi-drug resistant tuberculosis

  - Develops in the course of treatment
  - Less fit, less transmissible
  - SHREZ+MXF(Moxyfloxacin)+Cycloserine

KatG

- Responsible for resistance to INH

- Well known

  Most mutations are found between codons 138 and 328 with the most commonly observed gene alteration being at codon 315 of the katG gene (Slayden and Barry, III, 2000). The Ser315Thr substitution is estimated to occur in 30–60% of INH resistant isolates (Ramaswamy and Musser, 1998; Musser et al., 1996; Slayden and Barry, III, 2000). The katG 463 (CGG-CTG) (Arg-Leu) amino acid substitution is the most common polymorphism found in the katG gene and is not associated with INH resistance.

KatG S94A

- Build mutant
  - From wild type
  - InsightII Biopolymer
- Molecular docking
  - Refine INH using MOPAC
  - AutoDock/AutoGrid
- Molecular Dynamics simulation
  - Amber8 using AMBER2003 FF

KatG S315T

- Build mutant
    - MODELLER
- Dock INH
    - Autodock/AutoGrid
- MD
    - TINKER, GROMACS
- QM
    - MOPAC