Mathematical Modeling of Pulmonary Tuberculosis Therapy: Development of a First Prototype Model with Rifampin

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Tuberculosis Burden and Issues

- TB remains one of the biggest killers among infectious diseases: 1.8 million deaths in 2008

- Short-course chemotherapy (3-4 drugs) is effective when well conducted, but...
- TB treatment is long (min 6 months) and difficult (drug interactions, adverse effects)
- Full Patients’ compliance is hard to achieve
- Emergence of resistant *M. tuberculosis* (MDR, XDR)

Rom and Garay (Ed.). Tuberculosis 2nd ed., LWW 2004
The Need for a Shorter TB therapy

• A shorter TB therapy could greatly reduce morbidity and mortality, by reducing transmission, failure, and drug resistance

• Two ways: new TB drugs and/or optimal use of current agents

The Need for New Models

- Both drug development and optimization require predictive models
- *In vitro* models are poorly predictive of the clinical effect of anti-TB drugs
- Animal models do not fully mimic the human disease and are expensive

The objective of our study was to build a descriptive prototype mathematical model of TB treatment by rifampin

*Rom and Garay (Ed.). Tuberculosis 2nd ed., LWW 2004*
Model Structure

- Only one drug: rifampin
- Full model based on 3 submodels:
  - **PK model**: dose → pulmonary concentrations
  - **PD model**: antibacterial effect in lungs
  - **Physiological / disease model**: bacterial dynamics and immune response during TB infection
PK and PD Models

- PK data from non-infected subjects
- PK model outputs = RIF concentrations in extracellular (ELF) and intracellular (AC) lung compartments (Goutelle)

\[
\begin{align*}
\text{Plasma} & \quad \text{ELF} & \quad \text{CELL} \\
Vc & \quad Velf & \quad Vcell
\end{align*}
\]

- PD model based on the Hill equation
- PD parameter values derived from experimental data (Jayaram, Gumbo)
- PD model outputs = number of intraC (BI) and extraC (BE) bacteria in lungs

Goutelle et al. AAC 2009  
Disease Model

- Mathematical model of the human immune response and bacterial dynamics during TB infection
- Previously published by Denise Kirschner’s group (Michigan Univ)
- Lung and lymph node system
- Dynamics of cells, cytokines and two populations of bacteria (extraC and intraC)
- Can simulate *M. tuberculosis* growth in lungs from the first day of infection
- 17 ODE
Disease Model

PK Model

PD Model

Extracellular bacteria

RIF Dose

Mycobacterium tuberculosis in lungs

C_{RIF} in ELF and Cells
Full Model Building

Extracellular bacterial dynamics

\[
\frac{dB_E}{dt} = a_20 B_E (1 - \frac{B_E}{B_{E_{\text{max}}}}) (1 - \frac{C_{ELF}^{\alpha_g}}{EC_{S0_{g}}^{\alpha_g}}) - k_{k_{\max(E)}} \frac{C_{ELF}^{\alpha_k}}{EC_{S0_{k}}^{\alpha_k}} \cdot B_E
\]

\[
-k_{15} M_A B_E - k_{18} M_R B_E + k_{14} N_1 M_1 \left( \frac{T_1 / M_1}{T_1 / M_1 + c_4} \right)
\]

\[
+k_{17} N M_1 \left( \frac{B_1^m}{B_1^m + (N M_1)^m} \right) - k_2 \left( \frac{N}{2} \right) M_R \left( \frac{B_E}{B_E + c_9} \right) - d_{12} B_E IDC
\]

PK model outputs

PD model

Intracellular bacterial dynamics

\[
\frac{dB_1}{dt} = a_19 B_1 (1 - \frac{B_1^m}{B_1^m + (NB_1)^m}) (1 - \frac{C_{CELL}^{\alpha_g}}{EC_{S0_{g}}^{\alpha_g}}) - k_{k_{\max(I)}} \frac{C_{CELL}^{\alpha_k}}{EC_{S0_{k}}^{\alpha_k}} \cdot B_1
\]

\[
-k_{17} N M_1 \left( \frac{B_1^m}{B_1^m + (N M_1)^m} \right) + k_2 \left( \frac{N}{2} \right) M_R \left( \frac{B_E}{B_E + c_9} \right)
\]

\[
-k_{14} N_1 M_1 \left( \frac{T_1 / M_1}{T_1 / M_1 + c_4} \right)
\]

Immune response model
Model Features and Settings

• System of 21 ODE solved in Matlab®
• Therapeutic simulations up to 6 months
• For each simulation, 2 successive periods:
  – No drug therapy: disease model only – no variability
  – RIF therapy: individual PK parameters from the PK study – various PK/PD profiles (n=34)
• Bacterial dynamics from Day 1 of infection to the last day of RIF therapy
Analysis of the Results

• Reproduction of Kirschner’s model
• Qualitative analysis: shape of time-kill curves
• Quantitative analysis:
  – bactericidal activities (BE) simulated over the first days for various dosage regimens
  – comparison with clinical data = Early Bactericidal Activities (EBA)

\[
EBA \,(0 - 2 \, j) = \frac{\log_{10} N_{(0)} - \log_{10} N_{(2)}}{2}
\]
Simulations With No Drug

Latent TB

Active Disease

Marino et al. J Theor Biol 2004
Simulations with Rifampin

Disease model
No drug
180 days
RIF 600 mg
60 days
34 subjects

Median effect of various RIF dosage regimens
Antibacterial Effect

- Model shows a biphasic decline of $B_E$: killing slows down between days 2-10
- This result is in agreement with clinical data
- The biphasic shape of EBA has not been elucidated yet

## Antibacterial Effect

<table>
<thead>
<tr>
<th>RIF dose</th>
<th>Period</th>
<th>Bactericidal activities simulated ( \log_{10} B_E/\text{ml/j} ) Mean (SD)</th>
<th>EBA reported in literature</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean (SD)                                                             Référence</td>
<td></td>
</tr>
<tr>
<td>300 mg or 5 mg/kg</td>
<td>0-2 j</td>
<td>0.102 (0.090)                                                          0.121 (0.130)</td>
<td>Sirgel et al. (2005)</td>
</tr>
<tr>
<td></td>
<td>0-5 j</td>
<td>0.117 (0.156)                                                          0.111 (0.072)</td>
<td>Sirgel et al. (2005)</td>
</tr>
<tr>
<td></td>
<td>2-14 j</td>
<td>0.093 (0.132)                                                          0.072 (0.052)</td>
<td>Jindani et al. (1980, 2003)</td>
</tr>
<tr>
<td>600 mg or 10 mg/kg</td>
<td>0-2 j</td>
<td>0.277 (0.229)                                                          0.174 (0.228)</td>
<td>Jindani et al. (1980, 2003)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.221 (0.247)                                                          Sirget et al. (2005)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>0.29 (0.30)                                                             Chan et al. (1992)</td>
<td></td>
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<td></td>
<td></td>
<td>0.28 (0.21)                                                             Gosling et al. (2003)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-5 j</td>
<td>0.302 (0.279)                                                          0.226 (0.144)</td>
<td>Sirgel et al. (2005)</td>
</tr>
<tr>
<td></td>
<td>2-14 j</td>
<td>0.194 (0.156)                                                          0.096 (0.051)</td>
<td>Jindani et al. (1980, 2003)</td>
</tr>
<tr>
<td>1200 mg or 20 mg/kg</td>
<td>0-2 j</td>
<td>0.659 (0.512)                                                          0.383 (0.326)</td>
<td>Jindani et al. (1980, 2003)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.44 (0.24)                                                             Diacon et al. (2007)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-5 j</td>
<td>0.537 (0.372)                                                          0.30 (0.11)</td>
<td>Diacon et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>2-14 j</td>
<td>0.222 (0.142)                                                          0.154 (0.086)</td>
<td>Jindani et al. (1980, 2003)</td>
</tr>
</tbody>
</table>
Antibacterial Effect

EBA from Jindani (2003) (n=8)

Simulated Killing effect (n=34)

- The simulated antibacterial effects are in agreement with EBA data for low RIF doses (300, 600 mg)
- The model seems to overestimate the effect of high RIF doses (1200 mg)

Model Reduction

• Model reduction was explored with 2 objectives:
  – To assess the relevance of the full model
  – To analyse the factors conditionning the shape of the killing effect

• PK/PD model with no disease model

• Simulation under various assumptions:
  – Exchange or no exchange between BE and BI
  – Concentration / effect parameters identical or different between extraC and intraC compartments

\[
\frac{dB_E}{dt} = a_{20} B_E \left(1 - \frac{B_E}{B_{E_{\text{max}}}}\right) \left(1 - \frac{C_1^{\alpha_g}}{EC_{50g}^{\alpha_g} + C_1^{\alpha_g}}\right) - k_{k_{\text{max}(E)}} \frac{C_1^{\alpha_k}}{EC_{50k}^{\alpha_k} + C_1^{\alpha_k}} \cdot B_E
- k_{EI} B_E + k_{IE} B_I
\]
Insights from Model Reduction

- Intercompartment transfer rate constants KEI and KIE influence the shape of the killing effect.

- **No biphasic killing** observed when:
  - No exchange between BE and BI, $kEI = kIE = 0$, (blue curve)
  - Similar PD effect of RIF in extraC and intraC compartment, $K_{k_{\text{max}}(E)} = K_{k_{\text{max}}(I)}$, (black curve)
  - Fast transfer from intraC to extraC compartment (high values of KIE)
A New Hypothesis

• 2 hypothesis have been proposed to explain the slow down of the antibacterial effect and the requirement for long therapy \textit{in vivo}
  – Persistent subpopulations of bacilli
  – Genetically resistant subpopulations
• No such special populations included in the model
• A new hypothesis: role of a protected / reservoir compartment of intracellular bacteria (Antia 1996)
• In the simulations, this reservoir appears to be due to:
  – Reciprocal transfer between BE and BI
  – Slow transfer from intraC to extraC compartment
  – Drug less effective in intraC conditions (PD parameters)

\textit{Antia Proc R Soc Lob B 1996}
Conclusion and Perspective

• A very preliminary effort towards a complete mathematical description
• Many limits / assumptions:
  – Only one anti-TB drug
  – PD data from in vitro / animal studies
  – No PD variability
  – No drug resistant subpopulation
  – No post antibiotic effect
  – No autoinduction

• The model is able to reproduce some qualitative and quantitative properties of the effect of RIF observed in human TB patients
• A descriptive tool to study, analyse and explore complex drug-pathogen-host interactions during TB infection