A Multistate Model for Cure and Death

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antimicrobial resistance is a growing problem worldwide

evaluated to the top three threats identified by the WHO – estimated 25,000 deaths and €1,5 Billion per year in Europe

urgent need for new medicines

to tackle antimicrobial resistance, the Innovative Medicines Initiative (IMI) set up the New Drugs for Bad Bugs Programme (ND4BB) with several calls for different (sub-)topics including Combatting Bacterial Resistance in Europe (COMBACTE)
COMBACTE includes several networks, e.g. STAT-Net (research platform)

motivation of STAT-Net: evaluate novel clinical trial design strategies based on modern biostatistical and epidemiological concepts to increase efficiency and success rates of clinical trials

clinical trials with patients that suffer from severe diseases and an additional resistant infection

in this population, a mortality rate of about 10% up to 30% can be assumed within 30 days
▶ the new treatment should improve the **cure** rates (clinical cure or microbiological cure – difficult to define)

▶ we have to understand the etiological process how the new treatment influences the **cure process** ⇒ **multistate model**

▶ following step: two-armed clinical trial design
  → new treatment should be superior regarding cure and non-inferior regarding death
  → develop a test technique for the **combination of non-inferiority and superiority**

▶ **aim:** provide an analysis strategy that is preconditioned for planning such a trial
Mathematical Background

- simplest multistate model: transition from initial state 0 (e.g. alive) to absorbing state 1 (e.g. dead) at some random failure time $T$ (survival time)

- hazard rate $\lambda(t) = \lim_{h \to 0} \frac{P(t < T \leq t + h | T > t)}{h}$
  instantaneous probability per time unit of going from state 0 to state 1 (transition intensity)

- survival function
  $$S(t) = P(T > t) = 1 - P(T \leq t) = 1 - F(t) = \exp \left( - \int_0^t \lambda(u) du \right)$$
  $S(t)$ = probability of being in state 0 at time $t$
  $F(t)$ = probability of being in state 1 at time $t$
  or transition probability from state 0 to state 1 for $[0, t]$
Competing Risks

**competing risks model** (multiple absorbing endpoints)

- **event-specific hazard rate**
  \[ \lambda_{0i}(t) = \lim_{h \to 0} \frac{P(t < T \leq t + h; \text{cause } i | T > t)}{h} \]

- **cumulative incidence function**
  \[ P_{0i}(0, t) = \int_0^t P_{00}(0, u) \lambda_{0i}(u) du \]
  depends on **all** event specific hazards!

**illness-death-model without recovery**

- **transition probability**
  \[ P_{01}(0, t) = \int_0^t P_{00}(0, u) \lambda_{01}(u) \underbrace{P_{11}(u, t)}_{= \exp(-\int_0^t \lambda_{12}(v) dv)} du \]
  \[ P_{02}(0, t) = 1 - (P_{00}(0, t) + P_{01}(0, t)) \]
“Although many experts believe that mortality is the ultimate patient-centered outcome for critically ill patients, others have called for greater use of nonmortal clinical endpoints [...]. Unfortunately, nonmortal endpoints face [...] the limits of commonly used statistical methods for addressing the competing risks and informative dropout attributable to high ICU mortality rates.”

Harhay et al., Am J Respir Crit Care Med, 2014
Analogies in Oncology

- originally, these kind of models are used in cancer studies
- death or progression are competing events for the tumour response (e.g. tumour shrinking by 50 per cent)
- naive analysis of time to response would ignore competing risks
- caution: So-called “cure-models” in oncology are different! They consider cure not as outcome but as a state that prevents an observation of the outcome (e.g. recurrence or death).
OUTCOMEREA Data

- French multicenter study – includes 32 hospitals with a total of 6238 patients

- use **observational data** to examine the underlying death hazard rate of patients **with** infection, here: pneumonia, (0.0212) and **without** infection (0.0186)

- death rate after being cured in cure-death model should be similar to the mortality rate for non-infected patients, at least for early deaths
With these rates, several simulation scenarios are examined:

- **scenario 1**: $\lambda_0(t) = 0.02$
- **scenario 2**: $\lambda_0(t) = 0.04$
- **scenario 3**: $\lambda_0(t) = 0.06$
- **scenario 4**: $\lambda_0(t) = 0.08$
- **scenario 5**: $\lambda_0(t) = 0.1$
- **scenario 6**: $\lambda_0(t) = 0.12$
Simulation

Let us now set the rate from cure to death to 0.005:

\[ \lambda_{01}(t) = 0.02 \]

scenario 1: \( \lambda_{01}(t) = 0.02 \)

scenario 2: \( \lambda_{01}(t) = 0.04 \)

scenario 3: \( \lambda_{01}(t) = 0.06 \)

scenario 4: \( \lambda_{01}(t) = 0.08 \)

scenario 5: \( \lambda_{01}(t) = 0.1 \)

scenario 6: \( \lambda_{01}(t) = 0.12 \)
• estimation of baseline hazard functions shows that hazards are not constant over time

• OUTCOMEREA data contains ICU mortality, in the cure-death-model all-cause mortality will be considered
Harhay et al. point out that nonmortal endpoints (here: cure) as well as mortality are important for studies including critically ill patients. \textit{cure-death-model} provides suitable conditions, handles competing risks.

\textbf{Simulation:}

French OUTCOMEREA data provided a possibility to examine realistic death rates for first simulations (hazards are not constant over time). Simulate \textit{time-dependent hazards}.

\textbf{Application:}

Up to now, application was not possible because of unsuitable data examples (too old, incomplete follow-up). A suitable study to test this model, which provides a complete follow-up (up to 30 days), is the recent published ceftobiprole trial by Basilea. Currently, the data transfer with Freiburg team is prepared.
Discussion and Future Work II

Still, an agreement for the **cure definition** has to be made
→ a delphi technique with a panel of intensivists is planned

**following step**: two-armed clinical trial design
→ new treatment should be superior regarding cure and non-inferior regarding death
→ develop a test technique for the **combination of non-inferiority and superiority** and for the **difference of two transition probabilities**

include frailty term to adjust for **heterogeneity** between different intensive care units

**aim**: provide an analysis strategy that is preconditioned for a trial design
References


Back-Up: Hazard Rate and Survival Function

\[
\lambda(t) = \lim_{h \to 0} \frac{P(t < T \leq t + h \mid T > t)}{h} \\
= \lim_{h \to 0} \frac{P(t < T \leq t + h)}{h} \frac{1}{P(T > t)} \\
= \lim_{h \to 0} \frac{P(T \leq t + h) - P(T \leq t)}{h} \frac{1}{P(T > t)} \\
= \lim_{h \to 0} \frac{F(t + h) - F(t)}{h} \frac{1}{S(t)} \\
= \frac{F'(t)}{S(t)} = -\frac{S'(t)}{S(t)} = -\frac{\partial}{\partial t} \log S(t) \\
\Rightarrow S(t) = \exp \left( -\int_{0}^{t} \lambda(u)du \right)
\]
Back-Up: Competing Risks

\[
P_{01}(0, t) = \int_{0}^{t} P_{00}(0, u) \lambda_{01}(u) du
\]

\[
= \int_{0}^{t} \exp \left( - \int_{0}^{u} \left( \lambda_{01}(v) + \lambda_{02}(v) \right) dv \right) \lambda_{01}(u) du
\]

\[
= \lambda_{01} \int_{0}^{t} \exp \left( - (\lambda_{01} + \lambda_{02}) u \right) du
\]

\[
= \lambda_{01} \left[ - \frac{1}{\lambda_{01} + \lambda_{02}} \exp \left( - (\lambda_{01} + \lambda_{02}) u \right) \right]_{0}^{t}
\]

\[
= \frac{\lambda_{01}}{\lambda_{01} + \lambda_{02}} (1 - \exp(- (\lambda_{01} + \lambda_{02}) t))
\]

\[
P_{02}(0, t) = \frac{\lambda_{02}}{\lambda_{01} + \lambda_{02}} (1 - \exp(- (\lambda_{01} + \lambda_{02}) t))
\]
Back-Up: Meropenem Trial

- Sep 1991 – Jan 1993 by AstraZeneca
- for the treatment of patients with febrile neutropenia compare **Meropenem** (carbapenem antibiotic by AZ) with **Ceftazidime** (third-generation cephalosporin β-lactam antibiotic)
- prospective, randomized and double-blind
- multi-centre (North-America and Netherlands)
- $N = 411$ cancer patients with 471 episodes of fever
- event of interest: successful **clinical cure** at the end of treatment

“Patient deaths were recorded for the treatment period and the 7-day follow-up period.”

too short observation time ⇒ deaths not reported
Back-Up: Meropenem Trial

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- too short observation time ⇒ deaths not reported

![Graph showing individuals over time from randomisation](image)