Combination of Drugs for infectious diseases: Optimal design requires optimal doses.

Example: Antimalarial combination therapy with Artemether + Lumefantrine (ART/LUM), adult and pediatric population.

Soeny K, Bouillon T.

Basel, 11.09.2014
Acknowledgements:

- Roland Fisch: For his initial work together with Baldur Magnusson, which provided both the model structure and “proof of concept”.

- Christian Bartels and Phil Lowe, for “validating” the model code.

- Gordon Graham and the AQS management: For their graciousness to let Thomas spend 85% of his time on malaria modeling (= a humanitarian project) since the beginning of 2014.

- Barbara Bogacka and Byron Jones for their guidance and support of Kabir’s PhD work.
Outline:

- Motivation
- Model structure
- Candidate metrics for therapeutic success (optimization criteria)
- Considerations for pediatric dose finding
- Example for empirical optimization of dosing regimen
- Example for formalized optimization of dosing regimen
Motivation: Dose finding poorly formalized and in some cases quite complex.

- An optimally designed trial must either explore the dose-(exposure)-response relationship and/or confirm that a given regimen meets the clinical endpoint.

- Dose finding is a heuristic exercise using components of the dosing regimen (total amount, number of doses, dosing interval) as independent variables and balancing different safety and efficacy criteria.

- For certain indications (e.g. malaria), combination therapies across the entire population are mandatory, adding more dimensions.

- In these settings, the optimal dosing regimen is usually not identified, only approximated.

- Thomas will demonstrate the trial and error approach, Kabir will introduce a formal, model based method for optimization of a dosing regimen given multiple criteria and constraints.
Model needed for both approaches. Model Structure: Self contained blocks ("LRU’s").

- Representation of virtual pediatric population
- Pop PK model for each involved drug including size and age based scaling of parameters
- Dosing regimen for each involved drug and “bin” in population
- (Pop) PD model including disease model and drug interaction model

- N representations of individual concentration time courses across population
- N representations of individual time courses of combined PD effect(s) across population
- Evaluation criteria for treatment success

- Distribution of PK metrics/exposure by drug
- Distribution of combined PD metrics (e.g. time course of parasitemia)
- Assessment of clinical outcome for different therapeutic options
Model structure: Introduction of cumulative kill assessment (parasite numbers decrease $\geq 12$ log10 units).

- Representation of virtual pediatric population
- Pop PK model for each involved drug including size and age based scaling of parameters
- Dosing regimen for each involved drug and “bin” in population
- (Pop) PD model including disease model and drug interaction model

N representations of individual concentration time courses across population

N representations of individual max. reduction of parasite load (log10 units)

Evaluation criteria for treatment success: $\geq 12$ log unit drop of parasite load

Proportion of population achieving success

Distribution of PK metrics/exposure by drug

Histogram for high granularity comparisons

Histogram for high granularity comparisons
Semi-mechanistic accelerated kill rate model

- \( \frac{dP}{dt} \) is the rate of change of the parasite count.

- Parameters:
  - \( k_0 \) (spontaneous growth rate)
  - \( k_{\text{max}} \) (max. kill rate)
  - EC50 (plasma concentration yielding 50% of \( k_{\text{max}} \))
  - SLP (steepness of the concentration-effect curve)
  - \( P(0) \) (initial parasite count)

- For every additional drug, addl. concentration dependent \( k_{\text{max}} \) term.

- In vivo MIC, EC50 and EC90 are interrelated.

\[
EC_{50} = MIC \cdot \left( \frac{k_{\text{MAX}}}{k_0} - 1 \right)^{1/SLP}
\]

\[
EC_{90} = \left( \frac{1 - 0.90}{0.90} \right)^{(-1/SLP)} \cdot EC_{50}
\]

\[
\frac{dP}{dt} = \left( k_0 - k_{\text{MAX}} \cdot \frac{Cpl(t)}{EC_{50}^{SLP}} \right) \cdot P(t)
\]
“Cumulative Kill” (Czock 2007) from accelerated kill rate model (Hoshen 1998, Simpson 2000)

- Cumulative kill is independent of value and time of assessment of parasite counts.

- Parameters:
  - \( k_0 \) (spontaneous growth rate)
  - \( k_{max} \) (max. kill rate)
  - \( EC_{50} \) (plasma concentration yielding 50% of \( k_{max} \))
  - SLP (steepness of the concentration-effect curve)
  - \( P(0) \) (initial parasite count)

\[
\frac{dP}{dt} = \left( k_0 - k_{MAX} \cdot \left[ \frac{Cpl(t)}{EC_{50}} \right]^{SLP} \right) \cdot P(t)
\]

\[
\frac{dgrowth}{dt} = k_0 \cdot t
\]

\[
\frac{dkill}{dt} = k_{max} \cdot \left( \frac{(Cpl(t) / EC_{50})^{SLP}}{1 + (Cpl(t) / EC_{50})^{SLP}} \right) \cdot t
\]

\[
INTkill(t) = kill(t) - growth(t)
\]

max. value of INTkill: Cumulative Kill
Candidate metrics: “Posthoc empirical” and “Cumulative Kill”.

- Dosing regimen (dose fractionation).
- PK-metrics (Cmax, AUC, concentration at t=?, e.g. d7)
- Extended PK-metrics (Cmax/MIC, AUC above MIC, Time above MIC, MIC from in vitro or animal studies)
- Presentation includes the following examples for ART/LUM combination therapy:

  Cmax Artemether (first dose), AUC Lumefantrine, 168h concentration of Lumefantrine, cumulative kill.
Considerations for pediatric dose finding, extension to fixed dose combinations.

- SOP: Assume unchanged PD, adjust PK parameters for effect of age and size, match target PK metric from adults.

- For a fixed dose (ratio) combination therapy, this may not be possible (different maturation functions, idiosyncratic behavior (bioavailability) of combination partners preclude exact matching of exposure for 2 or more components).

- Ultimate goal is safe and effective therapy across all age/weight bins.

- For fixed dose combination therapies, optimization of dosing regimen therefore includes assessing clinical endpoint(s) in target populations (if possible, safety and efficacy).
Assessment of PK metrics of Artemether/Lumefantrine (1:6) across target population. Current label (>=5kg).

- Upper panel: Cmax of Artemether (geometric mean), Fraction above upper limit of 200 mcg/L. Lower panel: 168h concentration of Lumefantrine (geometric mean), Fraction above lower limit of 175 mcg/L.

<table>
<thead>
<tr>
<th>Wt [kg]</th>
<th>Age [y]</th>
<th>Fraction adult dose (Tablets)</th>
<th>LUM [mg]</th>
<th>ART [mg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=5*</td>
<td>n.a.</td>
<td>0.25 (1)</td>
<td>120</td>
<td>20</td>
</tr>
<tr>
<td>&lt;=15</td>
<td>n.a.</td>
<td>0.25 (1)</td>
<td>120</td>
<td>20</td>
</tr>
<tr>
<td>&lt;=25</td>
<td>n.a.</td>
<td>0.5 (2)</td>
<td>240</td>
<td>40</td>
</tr>
<tr>
<td>&lt;=35</td>
<td>n.a.</td>
<td>0.75 (3)</td>
<td>360</td>
<td>60</td>
</tr>
<tr>
<td>&gt;35</td>
<td>n.a.</td>
<td>1 (4)</td>
<td>480</td>
<td>80</td>
</tr>
</tbody>
</table>

* extrapolation, not approved

- Match adult cure rates (most important, but not sufficient metric).

- Fraction eradicated given typical parasite load, Fraction with cumulative kill >12 log-units.

<table>
<thead>
<tr>
<th>Wt [kg]</th>
<th>Age [y]</th>
<th>Fraction adult dose (Tablets)</th>
<th>LUM [mg]</th>
<th>ART [mg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=5*</td>
<td>n.a.</td>
<td>0.25 (1)</td>
<td>120</td>
<td>20</td>
</tr>
<tr>
<td>&lt;=15</td>
<td>n.a.</td>
<td>0.25 (1)</td>
<td>120</td>
<td>20</td>
</tr>
<tr>
<td>&lt;=25</td>
<td>n.a.</td>
<td>0.5 (2)</td>
<td>240</td>
<td>40</td>
</tr>
<tr>
<td>&lt;=35</td>
<td>n.a.</td>
<td>0.75 (3)</td>
<td>360</td>
<td>60</td>
</tr>
<tr>
<td>&gt;35</td>
<td>n.a.</td>
<td>1 (4)</td>
<td>480</td>
<td>80</td>
</tr>
</tbody>
</table>

* extrapolation, not approved
Assessment of PK metrics of Artemether/Lumefantrine (1:6) across target population. “Alternative regimen”.

- Upper panel: Cmax of Artemether (geometric mean), Fraction above upper limit of 200 mcg/L. Lower panel: 168h concentration of Lumefantrine (geometric mean), Fraction above lower limit of 175 mcg/L.

- Match adult cure rates (most important, but not sufficient metric).
- Fraction eradicated given typical parasite load, Fraction with cumulative kill >12 log-units.

<table>
<thead>
<tr>
<th>Wt [kg]</th>
<th>Age [y]</th>
<th>Fraction adult dose (Tablets)</th>
<th>LUM [mg]</th>
<th>ART [mg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>n.a.</td>
<td>&lt;0.1</td>
<td>0.083 (0.33)</td>
<td>40</td>
<td>6.6</td>
</tr>
<tr>
<td>&lt;5</td>
<td>&gt;0.1</td>
<td>0.125 (0.5)</td>
<td>60</td>
<td>10</td>
</tr>
<tr>
<td>&gt;=5</td>
<td>n.a.</td>
<td>0.25 (1)</td>
<td>120</td>
<td>20</td>
</tr>
<tr>
<td>&gt;=10</td>
<td>n.a.</td>
<td>0.5 (2)</td>
<td>240</td>
<td>40</td>
</tr>
<tr>
<td>&gt;=25</td>
<td>n.a.</td>
<td>0.75 (3)</td>
<td>360</td>
<td>60</td>
</tr>
<tr>
<td>&gt;=50</td>
<td>n.a.</td>
<td>1 (4)</td>
<td>480</td>
<td>80</td>
</tr>
</tbody>
</table>

Fraction cured vs Age [ys]

- Graph showing the relationship between fraction cured and age.
- Table showing weight and age categories with corresponding doses and medication units.

14 | Presentation Title | Presenter Name | Date | Subject | Business Use Only
Is this a good regimen? Do you have to try others?

*How would you decide?*

- Questions regarding the trial and error approach?
Dose was independent variable (input). Can we obtain a distribution of doses as output?

- Current method treats dosing regimen as independent variable.

- However, in dose optimization problems, dosing regimen is the dependent variable (as in “real life”).

- Therefore, a vector of ideal doses achieving the desired value of the optimization criterion given constraints (exposure thresholds, discrete dose sizes and (for combination products) fixed dose ratios) across the entire age-weight distribution is the desired output.

- A method to obtain this vector based on a new algorithm will be demonstrated.
The Efficient Dosing (ED) Algorithm

Explicit Optimization of the Target Criterion

- Computational algorithm to compute the optimum dose regimen to administer.

- The inputs to the algorithm are estimates of the PK parameters, dosing time points and the objective function to be optimized.

- The algorithm starts with an initial vector of doses which converges to the optimum vector in each successive iteration.

- The algorithm can also be applied to drug combinations to determine the optimal ratio and the optimal dose regimen for the combined unit.
The Efficient Dosing (ED) Algorithm

Some Notations

- \( D = (d_1, d_2, \ldots, d_n) \) denotes a vector of doses \( d_i \) that are administered at \( n \) occasions, a dose regimen.

- Let \( \mathcal{D} = [0, d_{\text{max}}]^n \) be the class of all dosing regimens \( D \), where \( d_{\text{max}} \) is the maximum dose which can be administered.

- \( C(t, d_1, \ldots, d_i) \) denotes the concentration of the drug at time \( t \) after doses \( d_1, \ldots, d_i \) are administered.

- The defined objective function is minimized by the ED algorithm to find \( D^* \) using an optimization method similar to the Line Search method.
Example Criterion 1: Target Concentration

Functions $\Delta_i : \mathbb{D} \mapsto \mathbb{R}_{\geq 0}$, $\mathbb{D} \subset \mathbb{R}_{\geq 0}^i$, $i = 1, \ldots, n$, are such that,

$$\Delta_i(d_1, \ldots, d_i) = \int_0^{\tau_i} |C(t, d_1, \ldots, d_i) - C_{tgt}| dt,$$

where $C_{tgt}$ denotes the target concentration and $\tau_i$ is the time elapsed between the $i^{th}$ and $(i + 1)^{th}$ dose.
The Efficient Dosing (ED) Algorithm

Example Criterion 2: Therapeutic Window

\[
\begin{align*}
\Delta^-_1 (d_1) &= \int_0^{T_1} \max(0, C^-_{tgt} - C(t, d_1)) dt, \\
\Delta^+_1 (d_1) &= \int_0^{T_1} \max(0, C(t, d_1) - C^+_{tgt}) dt, \\
&\vdots \quad \vdots \quad \vdots \\
\Delta^-_n (d_1, \ldots, d_n) &= \int_0^{\tau_n} \max(0, C^-_{tgt} - C(\tau_1 + \ldots + \tau_{n-1} + t, d_1) - \ldots - C(t, d_n)) dt, \\
\Delta^+_n (d_1, \ldots, d_n) &= \int_0^{\tau_n} \max(0, C(\tau_1 + \ldots + \tau_{n-1} + t, d_1) + \ldots + C(t, d_n) - C^+_{tgt}) dt.
\end{align*}
\]
The Efficient Dosing (ED) Algorithm

**Example Criterion 3: Target Reduction in Viral Load**

To find a dose regimen which:

- Causes a target reduction in viral load,
- minimizes exposure after target reduction has been achieved and,
- minimizes concentration lying outside the therapeutic window.
The Efficient Dose (ED) Algorithm

An Example:

- Consider a drug following a one compartment model with estimated parameters: \( Ka = 0.37 \, /h, \, Ke = 0.2 \, /h, \, V = 24 \, L, \, F = 0.95 \). A dose regimen is desired which maintains the concentration between 3.5 mg/L and 2.5 mg/L for \( T = 42 \, h \). Dosing time points are every 6 hours and up to 7 doses can be administered.

- \( D^* = (183.14, \, 67.71, \, 104.06, \, 91.54, \, 94.34, \, 95.06, \, 93.40) \) is the optimized dose regimen.
The algorithm permits discretization of doses. That is the optimized doses can be real numbers or multiples of whole numbers, as desired.

The algorithm can also be used in an adaptive trial setting when there is little information available on the parameters.

The basic method is to start with an initial guess of the parameters, administer the best dose regimen to a cohort of individuals based on that guess, collect blood samples at population D-optimal times and then update the estimates. This continues until a stopping rule is met.
Application of the ED Algorithm to the Problem
*Investigation of the optimal doses and ratio of Lumefantrine and Artemether*

- We define the target criterion to be the achievement of total AUC of Lumefantrine to be 400 mg/L*h.

- An upper constraint of 0.2 mg/L is strictly imposed on Artemether. If the usual 1/6\textsuperscript{th} dose of Artemether breaches this constraint, the algorithm decreases this fraction and keeps doing it until a safe dose of Artemether has been identified.

- The ratio of Artemether:Lumefantrine, along with the optimized doses are reported by the algorithm.
Application of the ED Algorithm to the Problem

**Optimal doses**

- Mode **Lumefantrine** and Artemether doses vs. Age
Application of the ED Algorithm to the Problem

Optimal doses

- Mean Lumefantrine and Artemether doses vs. Age
Mode **optimal ratio** of L:A vs. Age (note the good agreement with the 6:1 ratio in the existing formulation).
Mean optimal ratio of L:A vs. Age (note the good agreement with the 6:1 ratio in the existing formulation).
Application of the ED Algorithm to the Problem

Distribution of Optimum Doses with Age
Conclusions

*ED algorithm deserves a place in the dose finding toolbox, some caveats apply*

- “Proof of concept” of ED algorithm successful.
- “Selling point”: Multidimensional optimization, mapping the logical input (criteria) – output (dose vector) relationship.
- Could be viewed as extension of dose finding based on steady state metrics (e.g. matching AUCs), but much more powerful and flexible.
- Further extensions: Assessment of size of error for the optimal dosing regimen.
- CAVEAT: Multidimensional optimizations always include tradeoffs (weights). Quality of predictions can only be as good as choice of criteria, constraints and weights (A fool with a tool, is still a fool).