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

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

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Basel, 11.09.2014

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Acknowledgements:

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- 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.

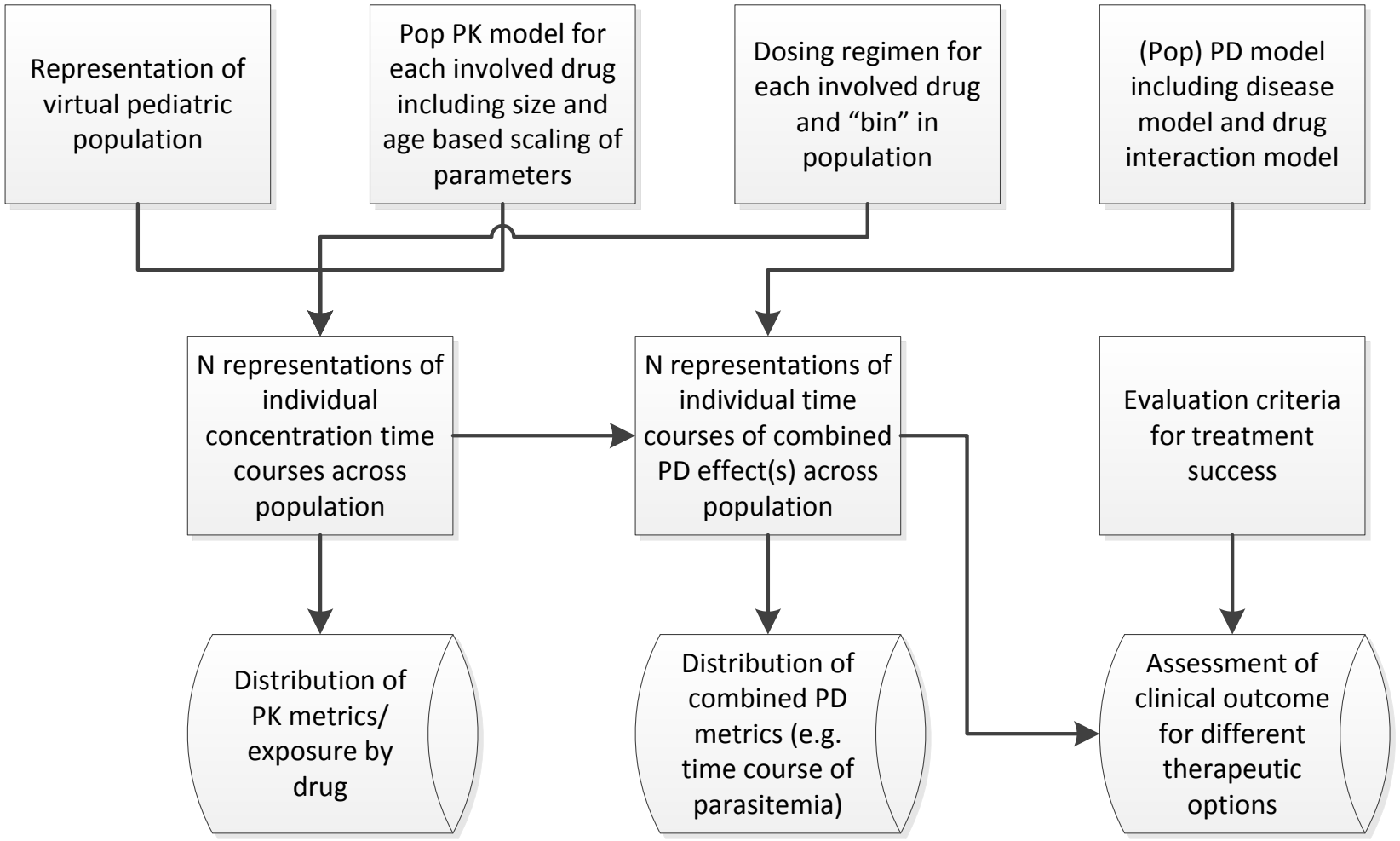
Outline:

- 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”).



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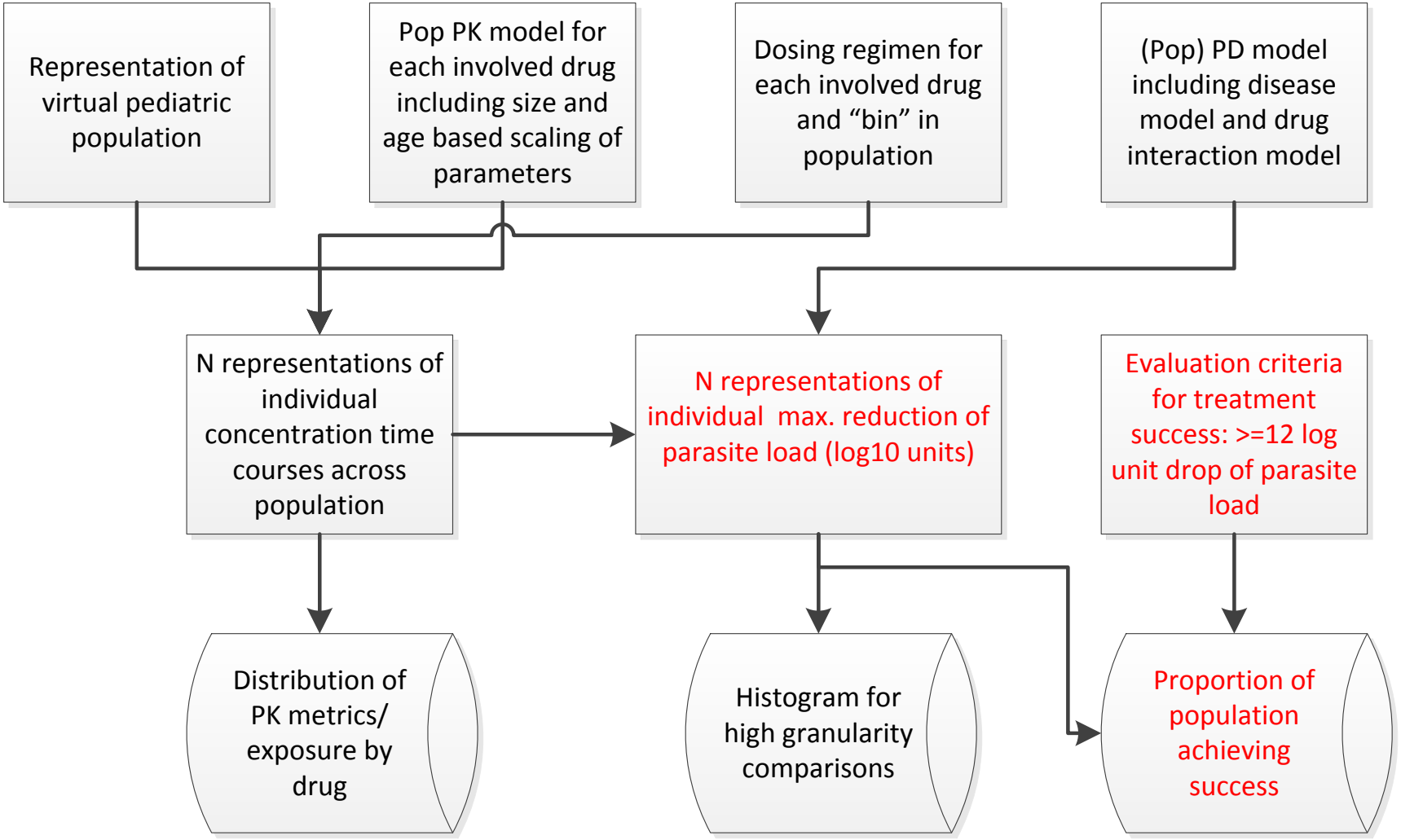
Model structure: Introduction of cumulative kill assessment (parasite numbers decrease>=12 log10 units).



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Semi-mechanistic accelerated kill rate model

- dP/dt is the rate of change of the parasite count.
- Parameters:
  - k0 (spontaneous growth rate)
  - kmax (max. kill rate)
  - EC50 (plasma concentration yielding 50% of kmax)
  - SLP (steepness of the concentration-effect curve
  - P(0) (initial parasite count)
- For every additional drug, addl. concentration dependent kmax term.
- In VIVO MIC, EC50 and EC90 are interrelated.

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

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

$$\frac{dP}{dt} = \left(k_0 - k_{MAX} \cdot \frac{\left(\frac{Cpl(t)}{EC_{50}} \right)^{SLP}}{\left[1 + \left(\frac{Cpl(t)}{EC_{50}} \right)^{SLP} \right]} \right) \cdot P(t)$$

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“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:
  - k0 (spontaneous growth rate)
  - kmax (max. kill rate)
  - EC50 (plasma concentration yielding 50% of kmax)
  - SLP (steepness of the concentration-effect curve
  - P(0) (initial parasite count)

$$\frac{dP}{dt} = \left(k_0 - k_{MAX} \cdot \frac{\left(\frac{Cpl(t)}{EC_{50}} \right)^{SLP}}{\left[1 + \left(\frac{Cpl(t)}{EC_{50}} \right)^{SLP} \right]} \right) \cdot P(t)$$

$$\frac{dgrowth}{dt} = k_0 \cdot t$$

$$\frac{dkill}{dt} = k_{\max} \cdot \left(\frac{(Cpl(t)/EC50)^{SLP}}{1 + (Cpl(t)/EC50)^{SLP}} \right) \cdot t$$

$$INTkill(t) = kill(t) - growth(t)$$

max. value of INTkill: Cumulative Kill

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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,

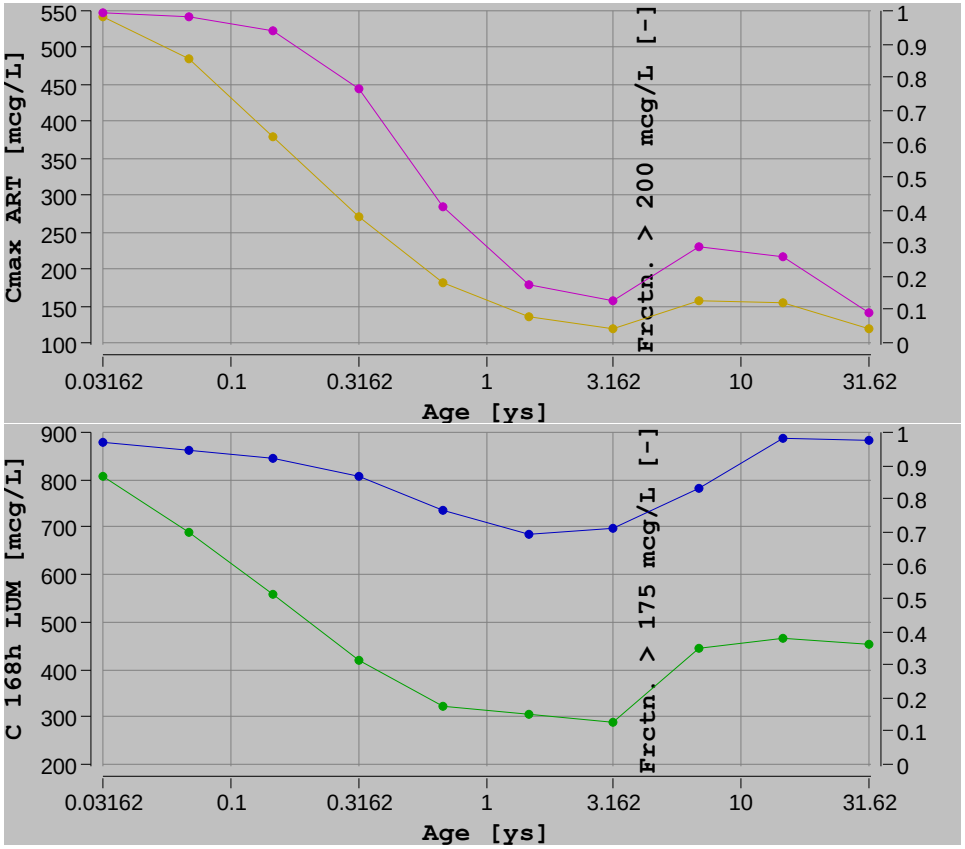
168h concentration of Lumefantrine, cumulative kill.

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).



Wt [kg]	Age [y]	Fraction adult dose (Tablets)	LUM [mg]	ART [mg]
<=5*	n.a	0.25 (1)	120	20
<=15	n.a.	0.25 (1)	120	20
<=25	n.a.	0.5 (2)	240	40
<=35	n.a.	0.75 (3)	360	60
>35	n.a.	1 (4)	480	80

* extrapolation, not approved

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“Efficacy” assessment of Artemether/Lumefantrine (1:6) across target population. Current label (>=5kg).

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

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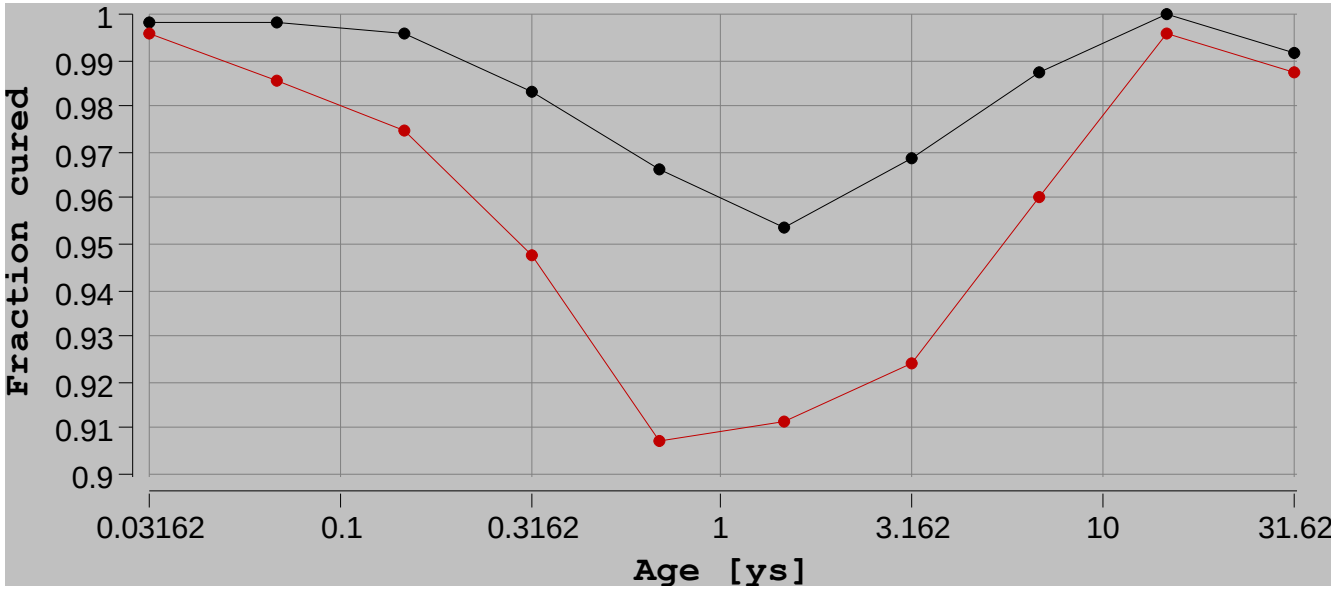

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Assessment of PK metrics of Artemether/Lumefantrine (1:6) across target population. “Alternative regimen”.

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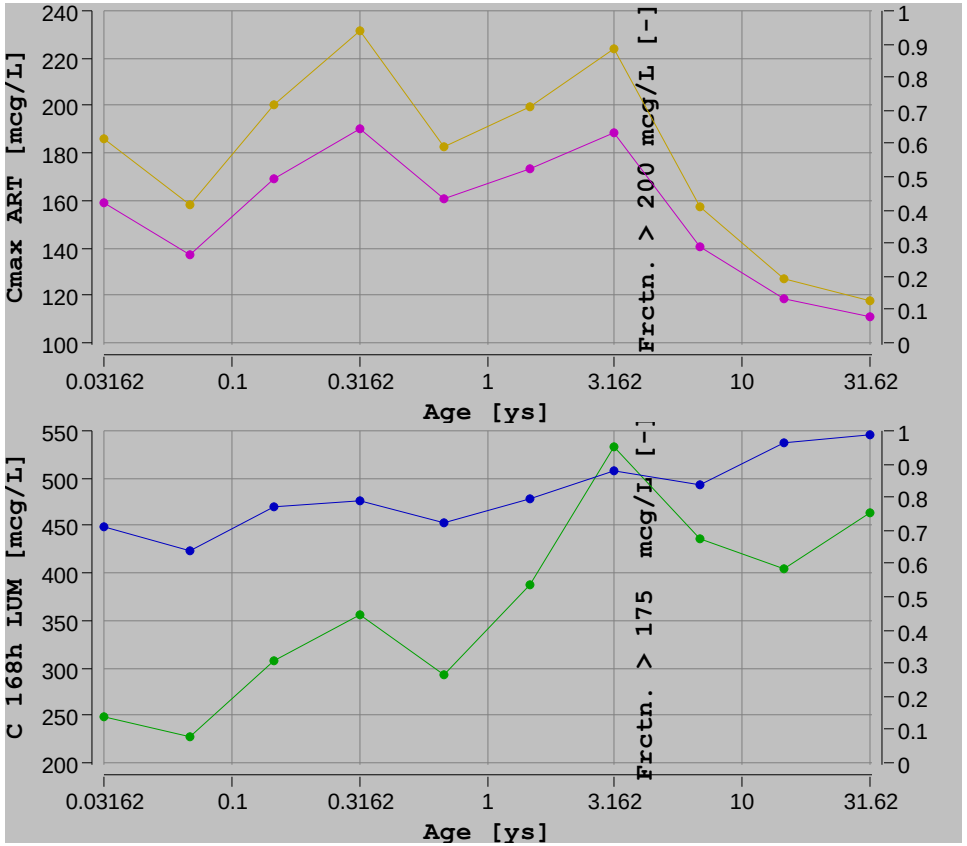

Wt [kg]	Age [y]	Fraction adult dose (Tablets)	LUM [mg]	ART [mg]
n.a.	<0.1	0.083 (0.33)	40	6.6
<5	>0.1	0.125 (0.5)	60	10
>=5	n.a	0.25 (1)	120	20
>=10	n.a.	0.5 (2)	240	40
>=25	n.a.	0.75 (3)	360	60
>=50	n.a.	1 (4)	480	80

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“Efficacy” assessment of Artemether/Lumefantrine (1:6) across target population. “Alternative regimen”.

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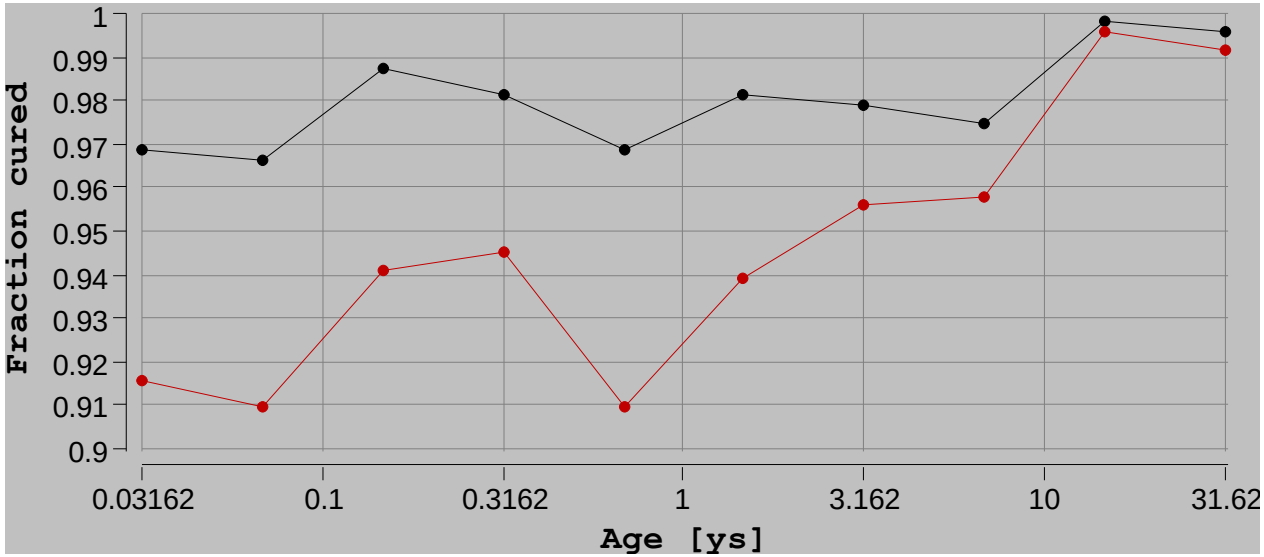

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Is this a good regimen? Do you have to try others?

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

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

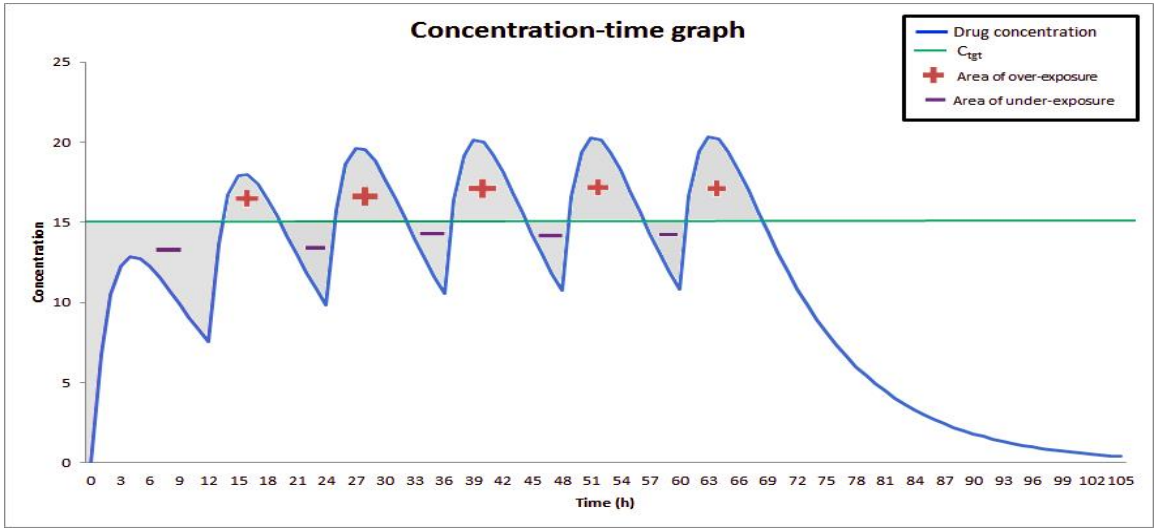
- Let $\mathfrak{D} = [0, d_{max}]^n$ be the class of all dosing regimens $\boldsymbol{D}$, where d_{max} is the maximum dose which can be administered.

- $C(t, d_1, \ldots, d_i)$ 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.

The Efficient Dosing (ED) Algorithm

Example Criterion 1: Target Concentration



Functions $\Delta_i : \mathfrak{D} \mapsto \mathbb{R}_{\geq 0}, \quad \mathfrak{D} \subset \mathbb{R}^i_{\geq 0}, \; i = 1, \ldots, n$, 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 τ_i is the time elapsed between the i^{th} and $(i+1)^{th}$ dose.

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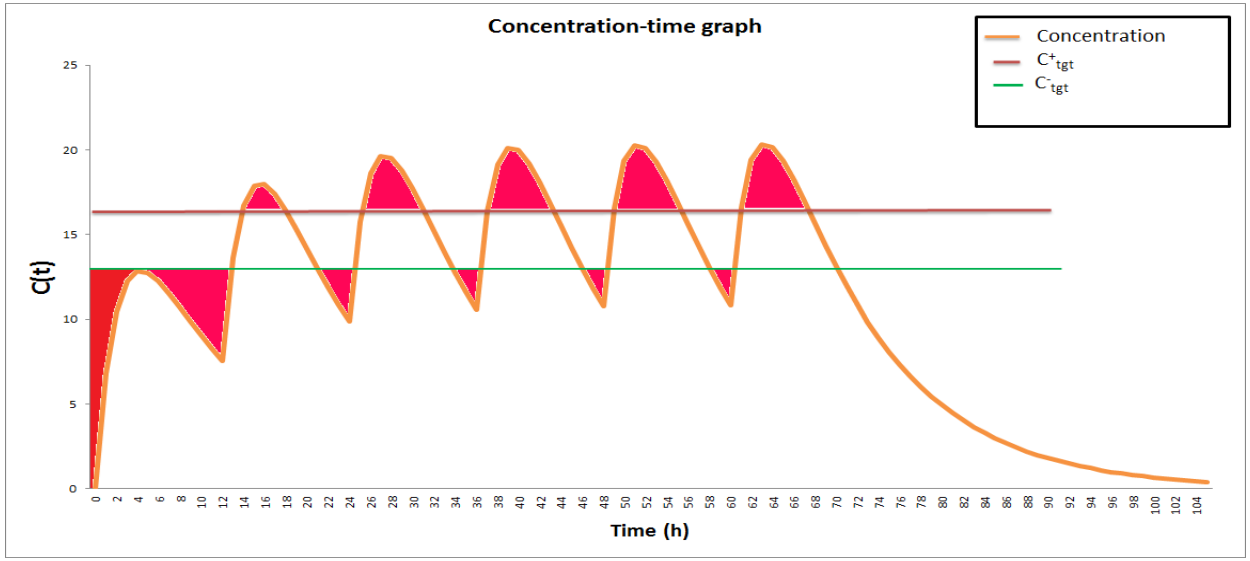
The Efficient Dosing (ED) Algorithm

Example Criterion 2: Therapeutic Window



$$\Delta_1^-(d_1) = \int_0^{\tau_1} \max(0, C_{tgt}^- - C(t, d_1))dt,$$

$$\Delta_1^+(d_1) = \int_0^{\tau_1} \max(0, C(t, d_1) - C_{tgt}^+)dt,$$

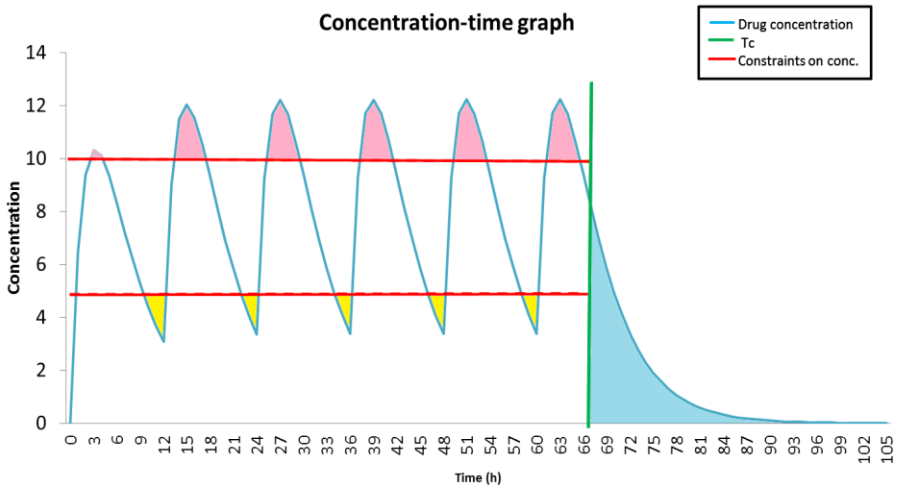
$$\vdots \qquad \vdots \qquad \vdots$$

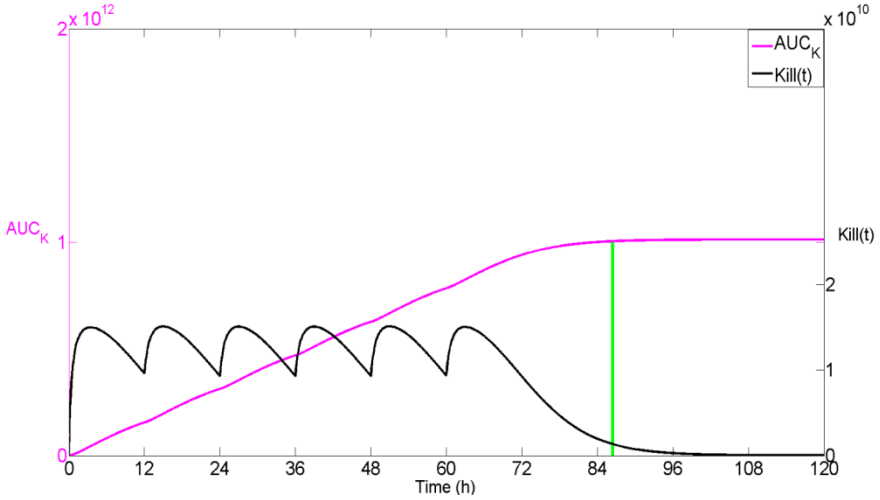
$$\Delta_n^-(d_1, ..., d_n) = \int_0^{\tau_n} \max(0, C_{tgt}^- - C(\tau_1 + ... + \tau_{n-1} + t, d_1) - ... - C(t, d_n))dt,$$

$$\Delta_n^+(d_1, ..., d_n) = \int_0^{\tau_n} \max(0, C(\tau_1 + ... + \tau_{n-1} + t, d_1) + ... + C(t, d_n) - C_{tgt}^+)dt.$$

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.

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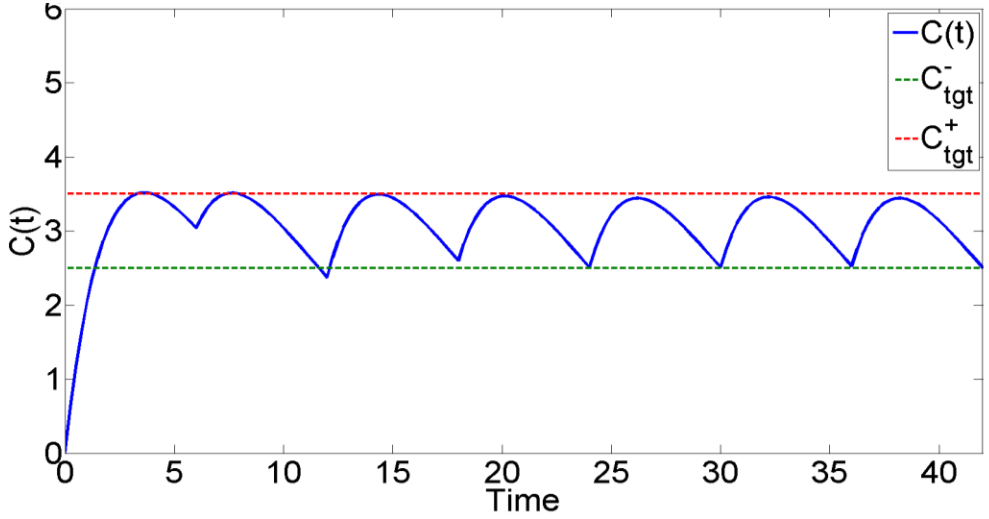
The Efficient Dose (ED) Algorithm

An Example:



- Consider a drug following a one compartment model with estimated parameters: Ka = .37 /h, Ke = 0.2 /h, V = 24 L, F = .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.

- $\boldsymbol{D}^{*} = (183.14,\ 67.71,\ 104.06,\ 91.54,\ 94.34,\ 95.06,\ 93.40)$ is the optimized dose regimen.

The Efficient Dose (ED) Algorithm

Other Features of the Algorithm

- 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.

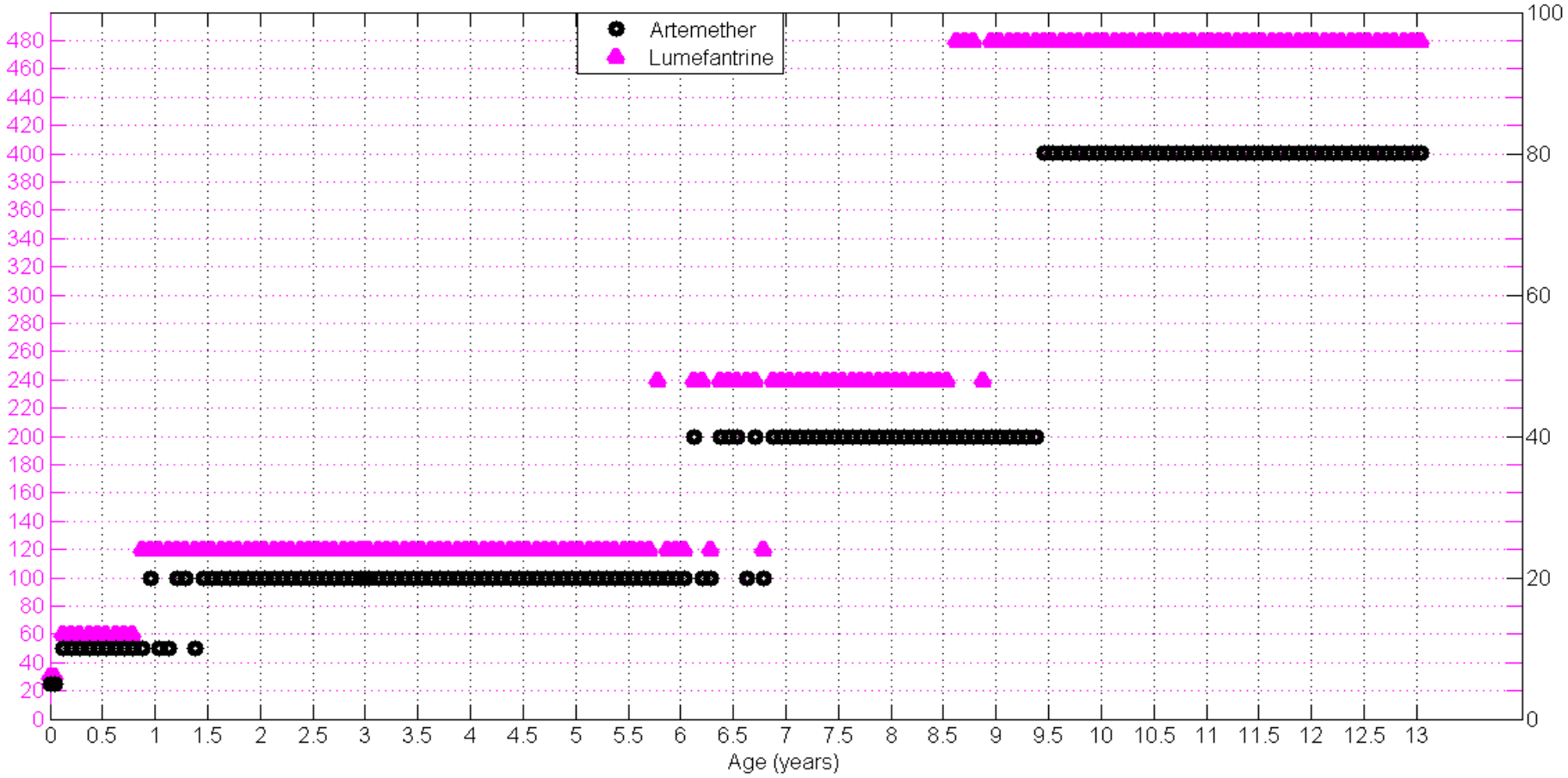
Application of the ED Algorithm to the Problem

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 $1/6^{th}$ 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

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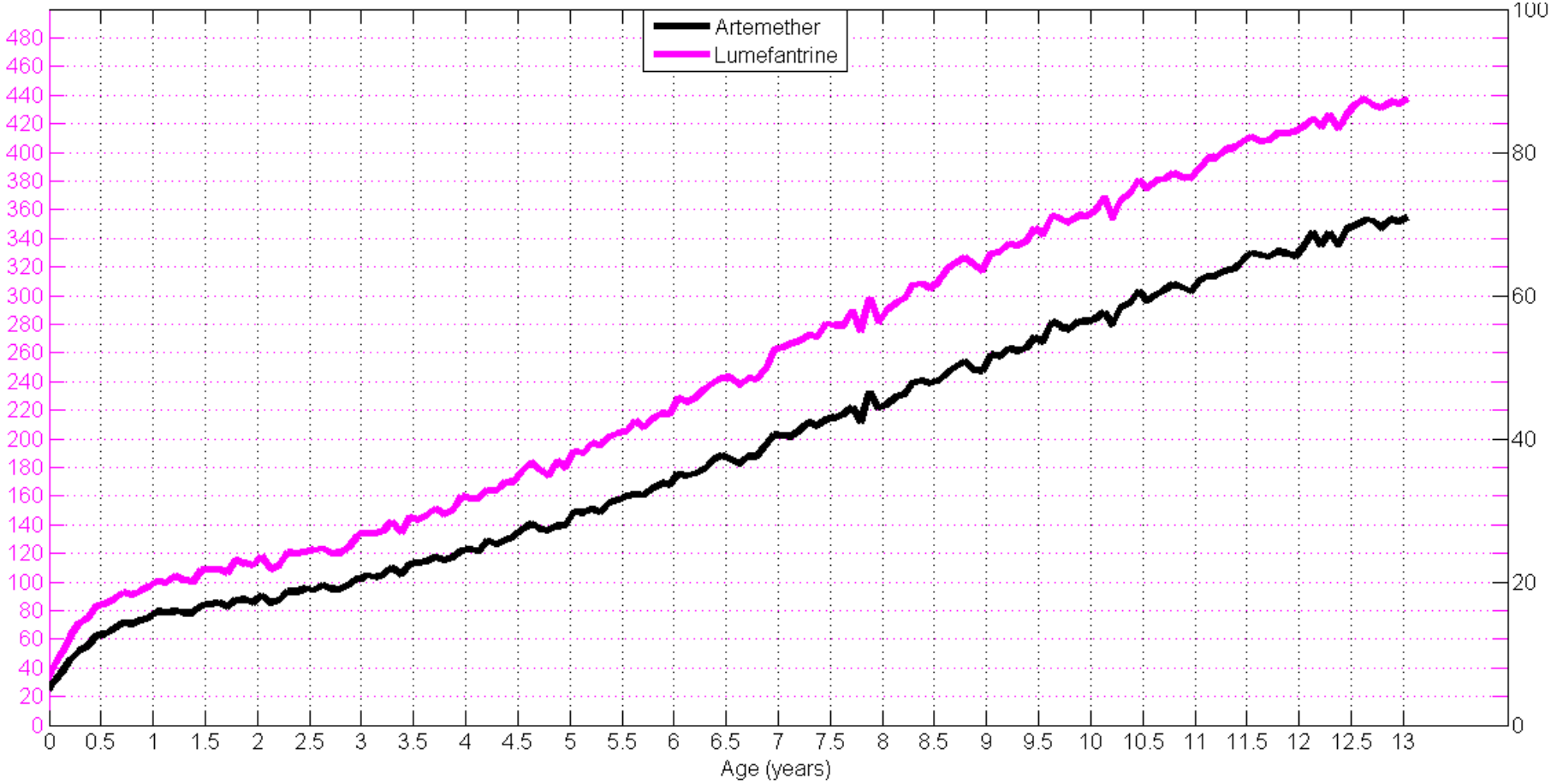
Application of the ED Algorithm to the Problem

Optimal doses



- Mean Lumefantrine and Artemether doses vs. Age

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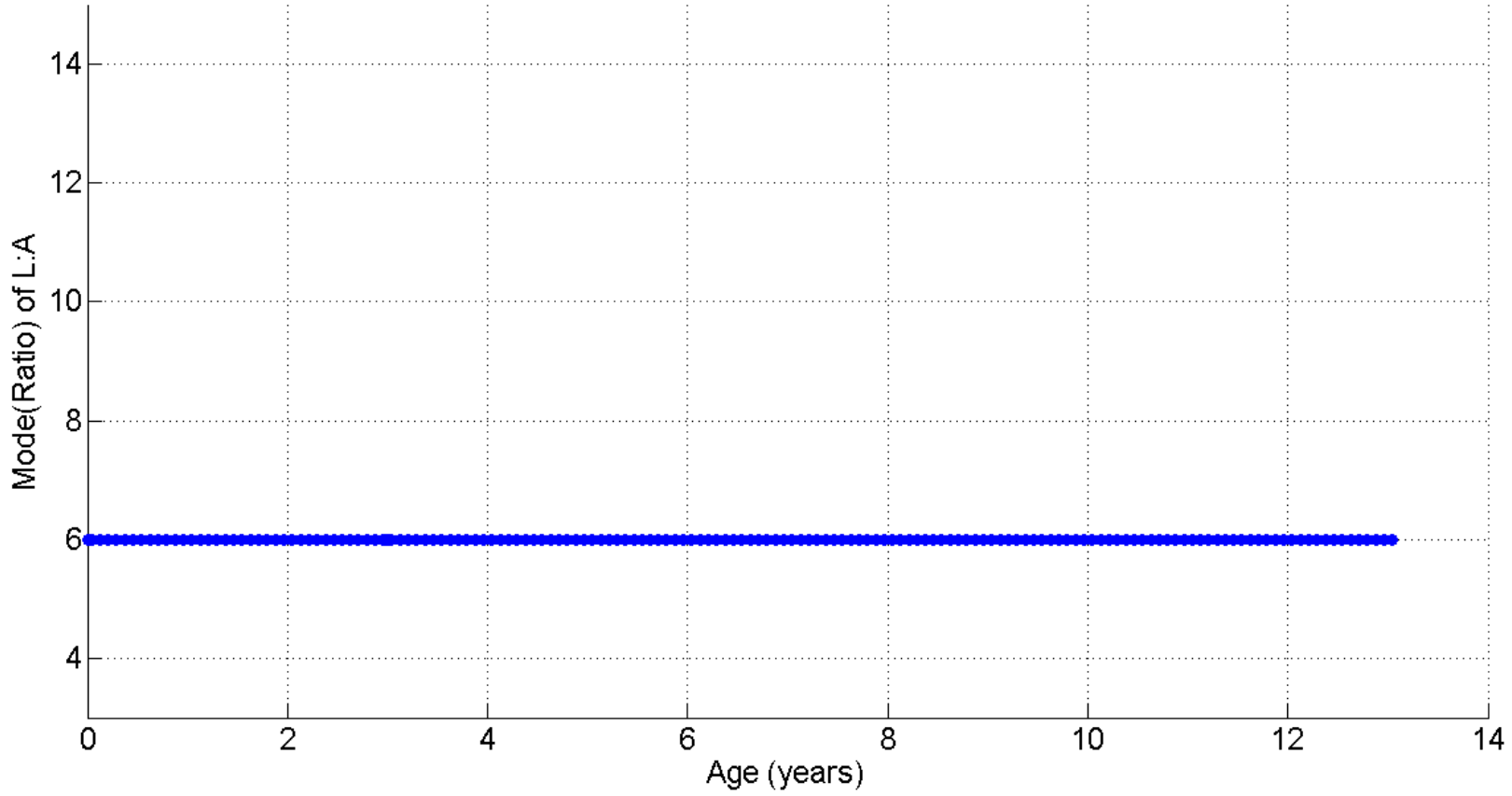
Application of the ED Algorithm to the Problem

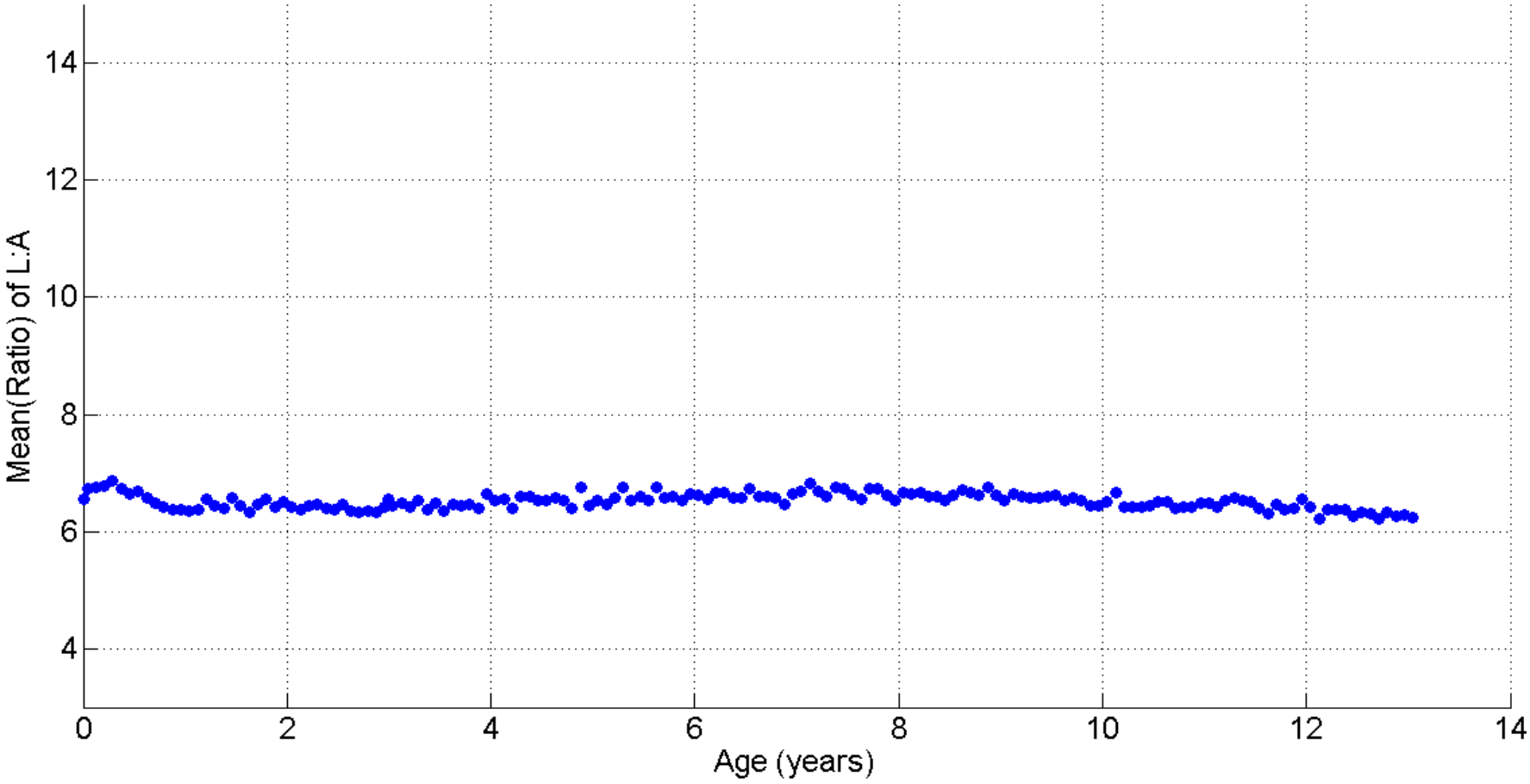
Optimal ratio



Mode 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

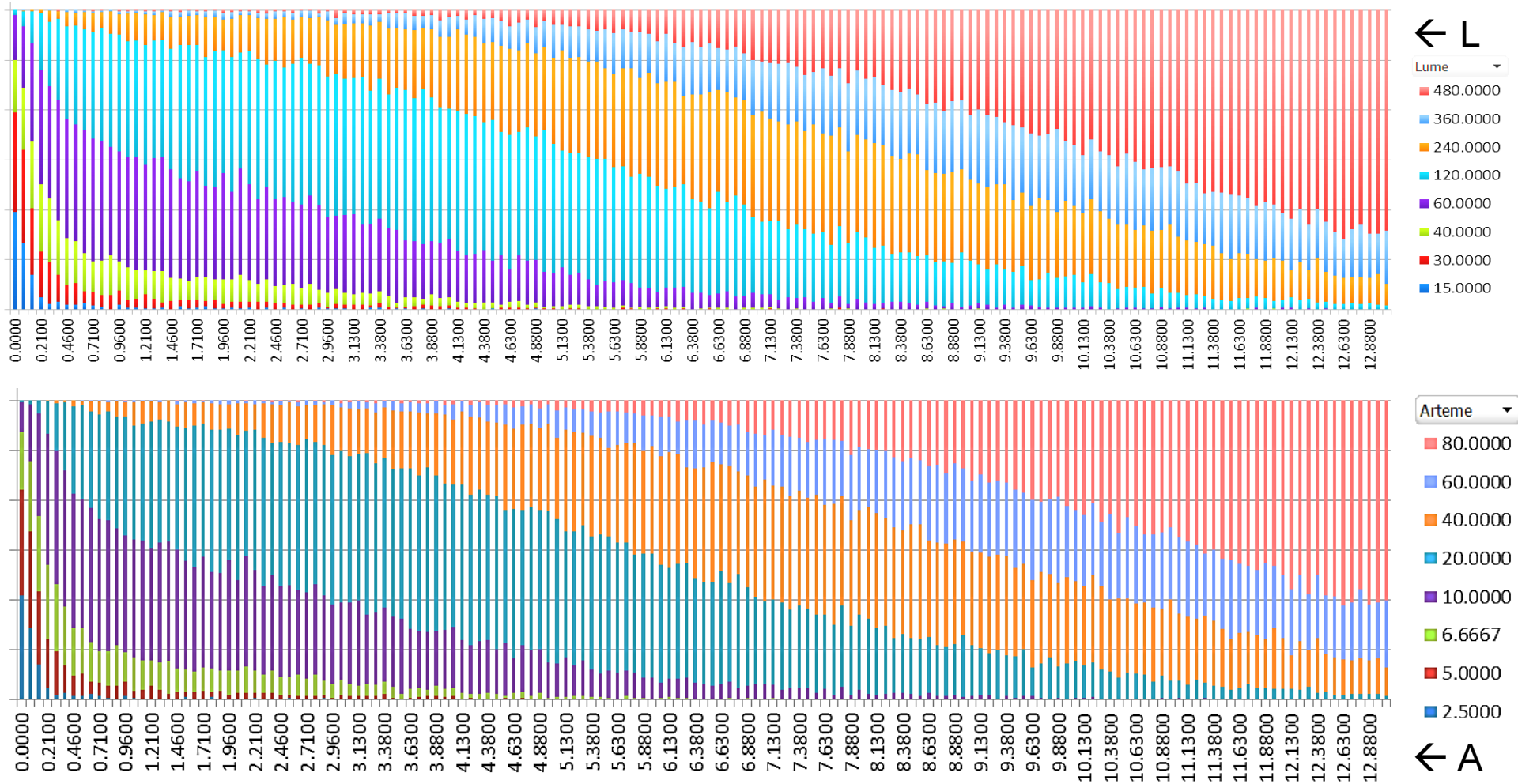
Optimal ratio



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



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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).