Optimum Dosing Regimen Selection For a Target Drug Concentration

Kabir Soeny, Barbara Bogacka
Queen Mary, University of London

Byron Jones, Thomas Bouillon
Novartis Pharma AG

Introduction

Introduction

- Following the correct selection of a therapy based on the indication, an optimal dosing regimen is the most important determinant of therapeutic success of a medical therapy.

Introduction

- Following the correct selection of a therapy based on the indication, an optimal dosing regimen is the most important determinant of therapeutic success of a medical therapy.
- Most physicians rely on the prescription information for choosing dosing regimens, so the ethical responsibility for supplying an optimal dosing regimen remains largely with pharmaceutical companies.

Introduction

- Following the correct selection of a therapy based on the indication, an optimal dosing regimen is the most important determinant of therapeutic success of a medical therapy.
- Most physicians rely on the prescription information for choosing dosing regimens, so the ethical responsibility for supplying an optimal dosing regimen remains largely with pharmaceutical companies.
- In the past, the pharmaceutical industry was predominantly interested in achieving approval based on differentiation of the drug against placebo or an active comparator, neglecting the optimization of dosing regimens.

Introduction

- The maximal safe dose was often chosen for confirmatory phase III trials and initially approved/administered to the general patient population.

Introduction

- The maximal safe dose was often chosen for confirmatory phase III trials and initially approved/administered to the general patient population.
- In several cases, this initial dose had to be lowered after marketing of the drug, in some cases, the entire program was stopped after unacceptable adverse effects within the high dose range occurred.

Introduction

- The maximal safe dose was often chosen for confirmatory phase III trials and initially approved/administered to the general patient population.
- In several cases, this initial dose had to be lowered after marketing of the drug, in some cases, the entire program was stopped after unacceptable adverse effects within the high dose range occurred.
- Provision of the minimal clinical effective dose, the maximum safe dose and the optimal dose by indication not only improves the chances of a successful approval, but can cure the disease more effectively.

Introduction

- Here we present an algorithm for optimization of loading and maintenance doses
  - of single drugs
  - and two combined drugs, where the combination ratio is also optimized.

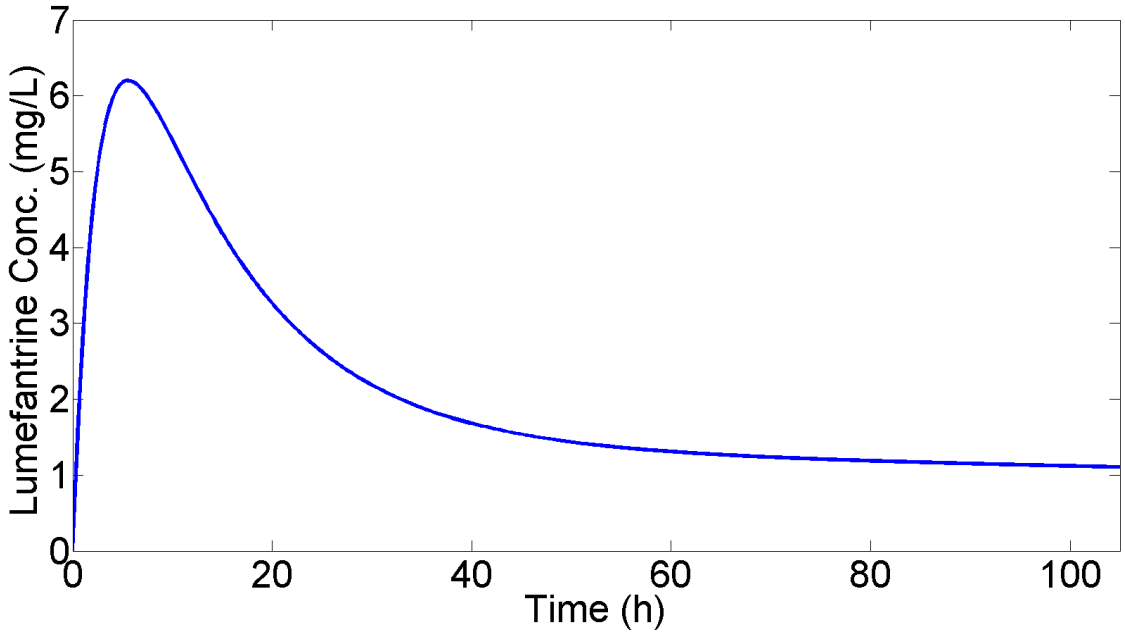
Introduction

- Here we present an algorithm for optimization of loading and maintenance doses
  - of single drugs
  - and two combined drugs, where the combination ratio is also optimized.
- This is achieved based on a target concentration or a therapeutic concentration window.

Introduction

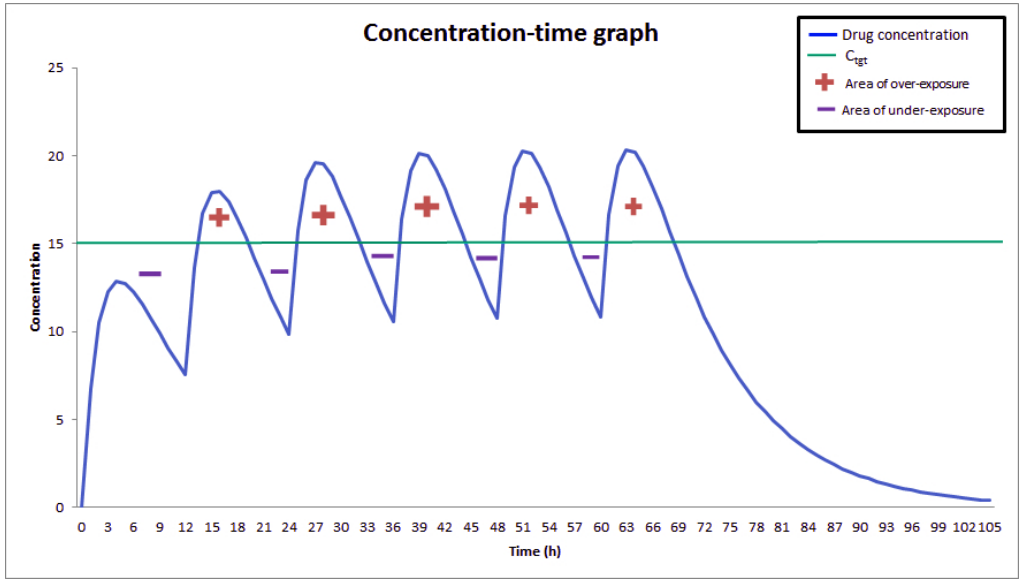
- Here we present an algorithm for optimization of loading and maintenance doses
  - of single drugs
  - and two combined drugs, where the combination ratio is also optimized.
- This is achieved based on a target concentration or a therapeutic concentration window.
- We also present a design for an adaptive clinical trial and some simulation studies.

Introduction



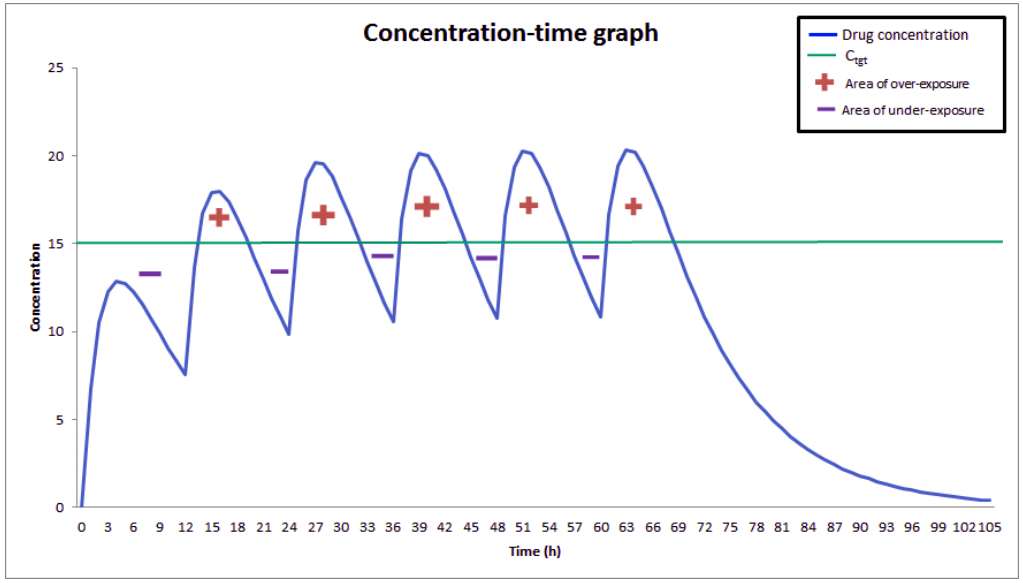
Concentration of a drug in blood after administering a single dose.

Introduction



The concentration of a drug with multiple dosing.

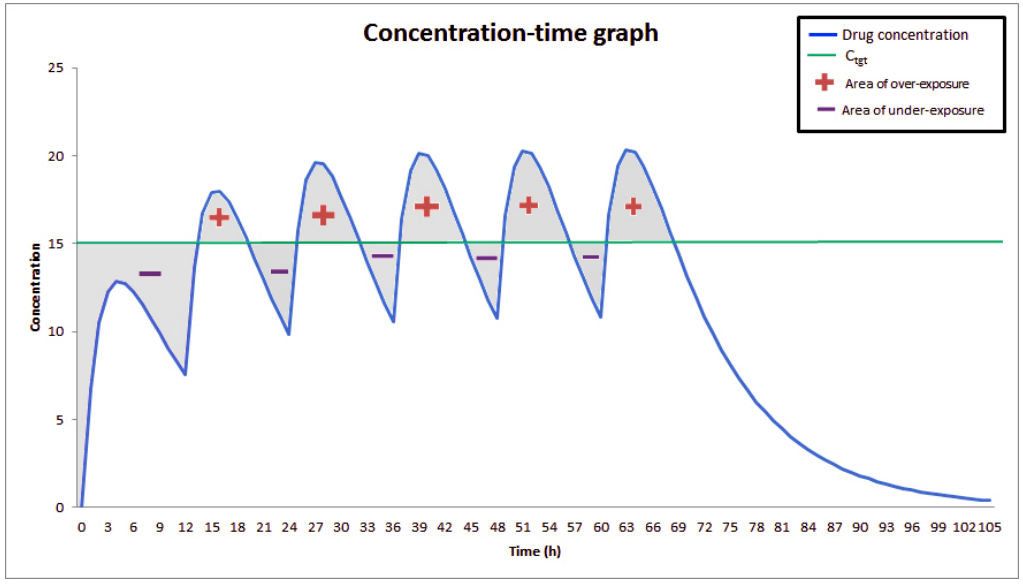
Introduction



The concentration of a drug with multiple dosing.

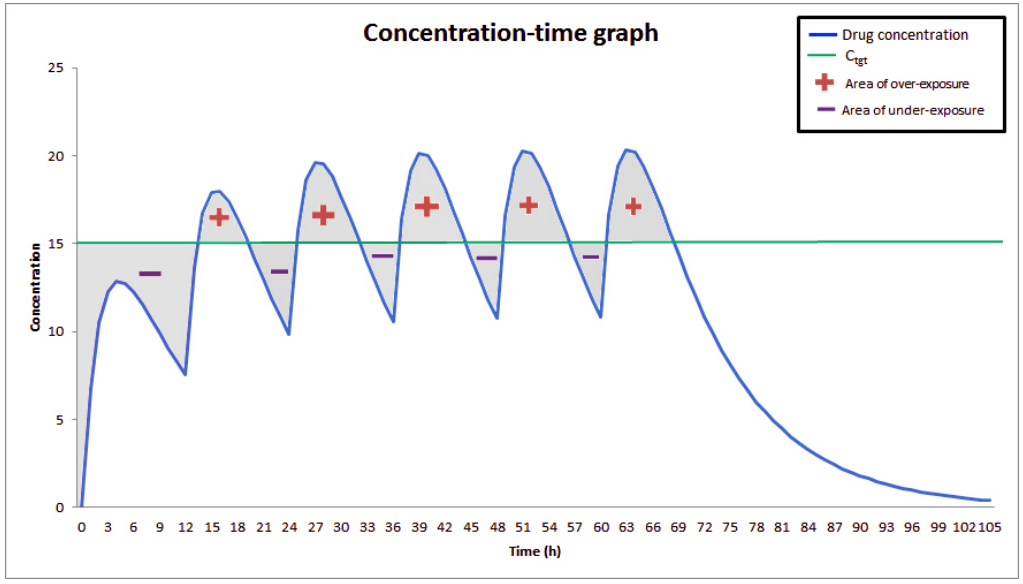
The areas of under-exposure are marked with '-' sign and over-exposure are marked with '+' sign. The green line represents the target concentration of the drug that is desired to be maintained.

Introduction



The areas of under- and over-exposure are to be minimized by an optimum choice of dose levels.

Introduction



The areas of under- and over-exposure are to be minimized by an optimum choice of dose levels.

We start assuming that the PK model is known and that we know the estimates of the model parameters.

Efficient Dosing Regimens

Notation

Efficient Dosing Regimens

Notation

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

Efficient Dosing Regimens

Notation

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

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

Efficient Dosing Regimens

Notation

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

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

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,

$$\Delta_i(d_1, \ldots, d_i) = \int_{t_{i-1}}^{t_i} |C(t, d_1, \ldots, d_i) - C_{tgt}| dt,$$

where C_{tgt} denotes the target concentration.

Efficient Dosing Regimens

Notation

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

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

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

$$\Delta_i(d_1, \ldots, d_i) = \int_{t_{i-1}}^{t_i} |C(t, d_1, \ldots, d_i) - C_{tgt}| dt,$$

where C_{tgt} denotes the target concentration.

The Δ-functions measure the areas of under- and over-exposure around the target concentration.

Efficient Dosing Regimens

Notation

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

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

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

$$\Delta_i(d_1, \ldots, d_i) = \int_{t_{i-1}}^{t_i} |C(t, d_1, \ldots, d_i) - C_{tgt}| dt,$$

where C_{tgt} denotes the target concentration.

The Δ-functions measure the areas of under- and over-exposure around the target concentration.

We denote by $\boldsymbol{\Delta} = (\Delta_1,\ \Delta_2,\ \ldots,\ \Delta_n)$ the vector of Δ-functions.

Efficient Dosing Regimens

Criteria of Efficiency

Efficient Dosing Regimens

Criteria of Efficiency

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.

Efficient Dosing Regimens

Criteria of Efficiency

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.

Definition (φ_A-efficiency)

A regimen $\boldsymbol{D}^\star = (d_1^*, \ldots, d_n^*) \in \mathfrak{D}$ is called φ_A-efficient if the function

$$\varphi_A(\boldsymbol{\Delta}) = \frac{1}{n} \sum_{i=1}^{n} \Delta_i$$

is minimized by $\boldsymbol{D}^\star$ or equivalently

$$\sum_{i=1}^{n} \Delta_i^* \leq \sum_{i=1}^{n} \Delta_i$$

for all $\boldsymbol{D} \in \mathfrak{D}$, where $\Delta_i^* = \Delta_i(d_1^*, ..., d_i^*)$, $i = 1, ..., n$.

Efficient Dosing Algorithm

Efficient Dosing Algorithm

Let

$$\boldsymbol{L}_i^k = \{d_{i1}^k, d_{i2}^k, d_{i3}^k\}$$

be the set of 3 possible doses (*dose sets*) that can be administered at the ith occasion, $i = 1, ..., n$, and k-th iteration, $k = 1, 2, ..., w$.

Efficient Dosing Algorithm

Let

$$\boldsymbol{L}_i^k = \{d_{i1}^k, d_{i2}^k, d_{i3}^k\}$$

be the set of 3 possible doses (*dose sets*) that can be administered at the ith occasion, $i = 1, ..., n$, and k-th iteration, $k = 1, 2, ..., w$.

Thus, the number of possible dosing regimens in this case is 3^n.

Efficient Dosing Algorithm

Let

$$\boldsymbol{L}_i^k = \{d_{i1}^k, d_{i2}^k, d_{i3}^k\}$$

be the set of 3 possible doses (*dose sets*) that can be administered at the ith occasion, $i = 1, ..., n$, and k-th iteration, $k = 1, 2, ..., w$.

Thus, the number of possible dosing regimens in this case is 3^n.

Iteration No. 1

Efficient Dosing Algorithm

Let

$$\boldsymbol{L}_i^k = \{d_{i1}^k,\, d_{i2}^k,\, d_{i3}^k\}$$

be the set of 3 possible doses (*dose sets*) that can be administered at the ith occasion, $i = 1, ..., n$, and k-th iteration, $k = 1, 2, ..., w$.

Thus, the number of possible dosing regimens in this case is 3^n.

Iteration No. 1

Set

$$\boldsymbol{L}_i^1 = \{10\% \text{ of } d_{max},\ 50\% \text{ of } d_{max},\ d_{max}\}$$

for all $i = 1, \ldots, n$.

Efficient Dosing Algorithm

Let

$$\boldsymbol{L}_i^k = \{d_{i1}^k,\, d_{i2}^k,\, d_{i3}^k\}$$

be the set of 3 possible doses (*dose sets*) that can be administered at the ith occasion, $i = 1, ..., n$, and k-th iteration, $k = 1, 2, ..., w$.

Thus, the number of possible dosing regimens in this case is 3^n.

Iteration No. 1

Set

$$\boldsymbol{L}_i^1 = \{10\% \text{ of } d_{max},\ 50\% \text{ of } d_{max},\ d_{max}\}$$

for all $i = 1, \ldots, n$.

For each of the 3^n dosing regimens, we compute $\varphi(\boldsymbol{\Delta})$.

Efficient Dosing Algorithm

Let

$$\boldsymbol{L}_i^k = \{d_{i1}^k,\, d_{i2}^k,\, d_{i3}^k\}$$

be the set of 3 possible doses (*dose sets*) that can be administered at the ith occasion, $i = 1, ..., n$, and k-th iteration, $k = 1, 2, ..., w$.

Thus, the number of possible dosing regimens in this case is 3^n.

Iteration No. 1

Set

$$\boldsymbol{L}_i^1 = \{10\% \text{ of } d_{max},\ 50\% \text{ of } d_{max},\ d_{max}\}$$

for all $i = 1, \ldots, n$.

For each of the 3^n dosing regimens, we compute $\varphi(\boldsymbol{\Delta})$.

$\boldsymbol{D}^1$ is the dosing regimen which minimizes $\varphi(\boldsymbol{\Delta})$.

Efficient Dosing Algorithm

Iteration No. k

Efficient Dosing Algorithm

Iteration No. k

The dose sets $\boldsymbol{L}_i^k$ are reconstituted based on the doses in $\boldsymbol{D}^{k-1}$.

Efficient Dosing Algorithm

Iteration No. k

The dose sets $\boldsymbol{L}_i^k$ are reconstituted based on the doses in $\boldsymbol{D}^{k-1}$.

For example, if d_{i3}^{k-1} was selected for i-th occasion in iteration $k-1$, the new dose set will be:

$$\boldsymbol{L}_i^k = \left\{ \epsilon \times d_{i3}^{k-1},\ d_{i3}^{k-1},\ \min\left(\frac{d_{i3}^{k-1}}{\epsilon}, d_{max} \right) \right\}.$$

where $\epsilon \in (0, 1)$ is a fixed constant, called the *resolution*.

Efficient Dosing Algorithm

Iteration No. k

The dose sets $\boldsymbol{L}_i^k$ are reconstituted based on the doses in $\boldsymbol{D}^{k-1}$.

For example, if d_{i3}^{k-1} was selected for i-th occasion in iteration $k-1$, the new dose set will be:

$$\boldsymbol{L}_i^k = \left\{ \epsilon \times d_{i3}^{k-1},\ d_{i3}^{k-1},\ \min\left(\frac{d_{i3}^{k-1}}{\epsilon}, d_{max} \right) \right\}.$$

where $\epsilon \in (0,1)$ is a fixed constant, called the *resolution*.

For each of the 3^n dosing regimens, we compute $\varphi(\boldsymbol{\Delta})$.

Efficient Dosing Algorithm

Iteration No. k

The dose sets $\boldsymbol{L}_i^k$ are reconstituted based on the doses in $\boldsymbol{D}^{k-1}$.

For example, if d_{i3}^{k-1} was selected for i-th occasion in iteration $k-1$, the new dose set will be:

$$\boldsymbol{L}_i^k = \left\{ \epsilon \times d_{i3}^{k-1},\ d_{i3}^{k-1},\ \min\left(\frac{d_{i3}^{k-1}}{\epsilon}, d_{max} \right) \right\}.$$

where $\epsilon \in (0, 1)$ is a fixed constant, called the *resolution*.

For each of the 3^n dosing regimens, we compute $\varphi(\boldsymbol{\Delta})$.

$\boldsymbol{D}^k$ is the dosing regimen which minimizes $\varphi(\boldsymbol{\Delta})$.

Efficient Dosing Algorithm

Terminal Iteration No. w

Efficient Dosing Algorithm

Terminal Iteration No. w

The algorithm is terminated at w^{th} iteration if

$$d_i^w = d_i^{w-1} \ \forall \ i = 1, \ldots, n,$$

where d_i^k denotes the optimal dose to be administered at the i^{th} occasion, at the k^{th} iteration.

Efficient Dosing Algorithm

Terminal Iteration No. w

The algorithm is terminated at w^{th} iteration if

$$d_i^w = d_i^{w-1} \ \forall \ i = 1, \ldots, n,$$

where d_i^k denotes the optimal dose to be administered at the i^{th} occasion, at the k^{th} iteration.

Thus, the algorithm terminates when for the given resolution, no further improvement is possible.

Efficient Dosing Algorithm

Terminal Iteration No. w

The algorithm is terminated at w^{th} iteration if

$$d_i^w = d_i^{w-1} \ \forall \ i = 1, \ldots, n,$$

where d_i^k denotes the optimal dose to be administered at the i^{th} occasion, at the k^{th} iteration.

Thus, the algorithm terminates when for the given resolution, no further improvement is possible.

By choosing appropriate resolution, $\boldsymbol{D}^w$ can be driven as close as required to the most efficient dosing regimen $\boldsymbol{D}^\star$.

Efficient Dosing Algorithm

Properties

Theorem

The ED Algorithm converges to the true unknown φ-efficient dosing regimen $\boldsymbol{D}^{\star}$ when the resolution tends to 1, that is

$$\epsilon \to 1 \;\; \Rightarrow \boldsymbol{D}^{w} \to \boldsymbol{D}^{\star}.$$

Efficient Dosing Algorithm

Properties

Theorem

The ED Algorithm converges to the true unknown φ-efficient dosing regimen $\boldsymbol{D}^{\star}$ when the resolution tends to 1, that is

$$\epsilon \to 1 \;\; \Rightarrow \boldsymbol{D}^{w} \to \boldsymbol{D}^{\star}.$$

The major argument in the proof is that the unknown true optimal doses d_i^* lie in the respective intervals, that is

$$d_i^{\star} \in \left(\epsilon d_i^{w}, \min \left\{ \frac{d_i^{w}}{\epsilon}, d_{max} \right\} \right).$$

Efficient Dosing Algorithm

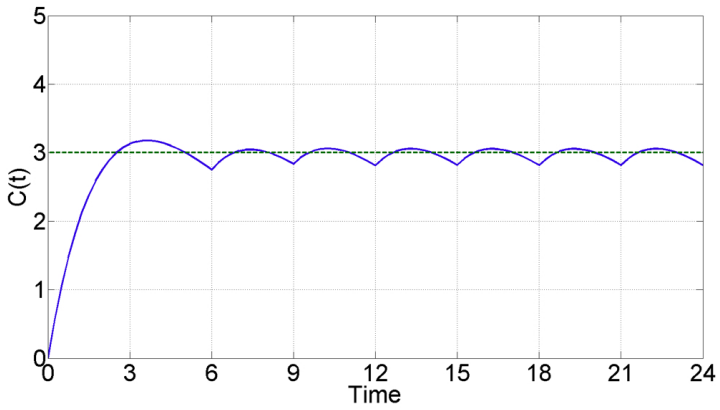
Properties

We can decrease the under- and over-exposure by planning more frequent dosing.

Efficient Dosing Algorithm

Properties

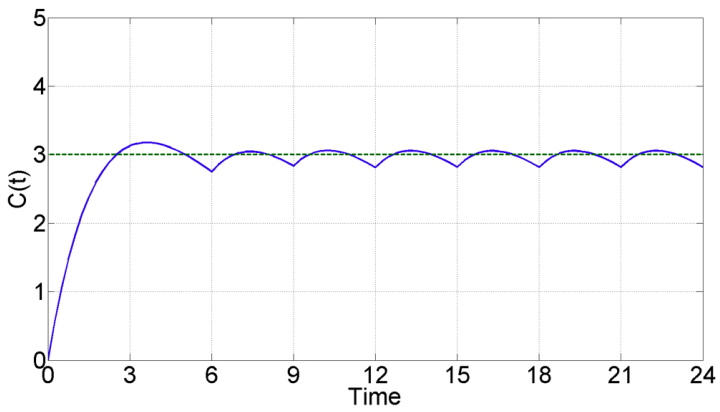
We can decrease the under- and over-exposure by planning more frequent dosing.

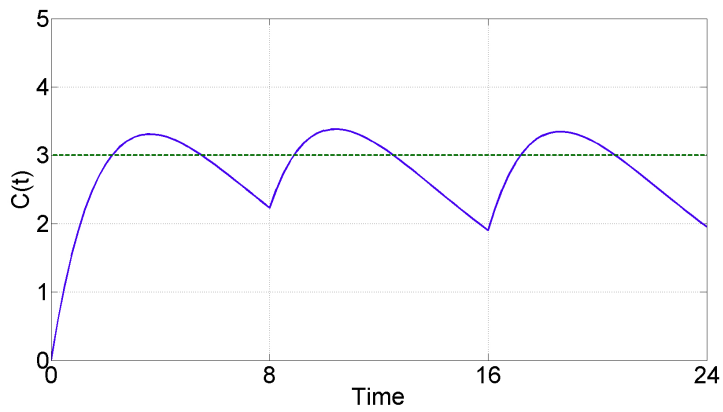


Efficient Dosing Algorithm

Properties

We can decrease the under- and over-exposure by planning more frequent dosing.

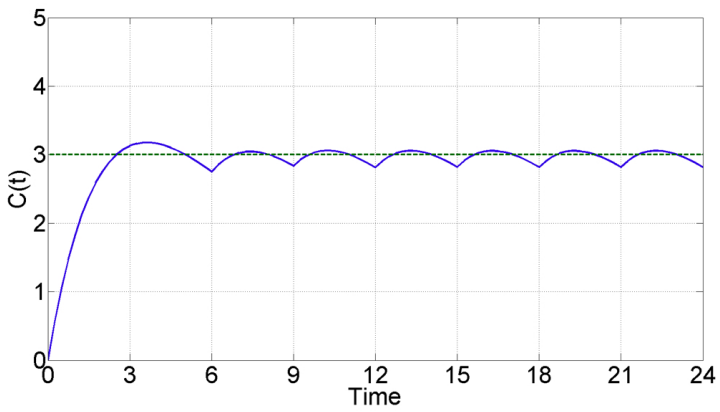




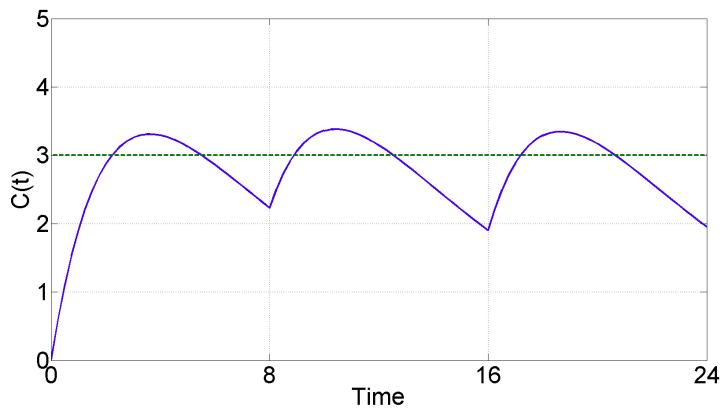
Efficient Dosing Algorithm

Properties

We can decrease the under- and over-exposure by planning more frequent dosing.



$C(t)$ when $\tau = 3$h.

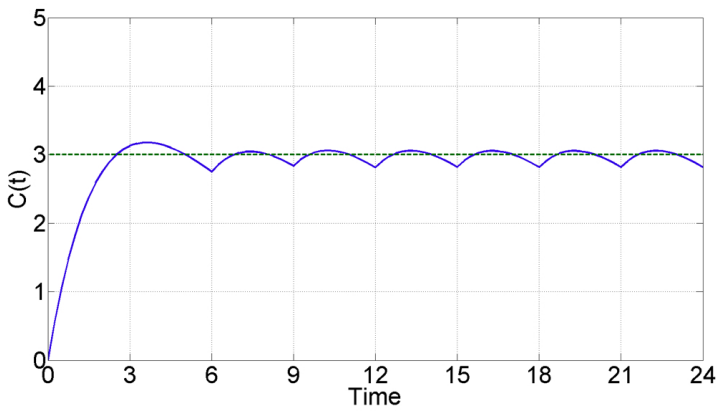


$C(t)$ when $\tau = 8$h.

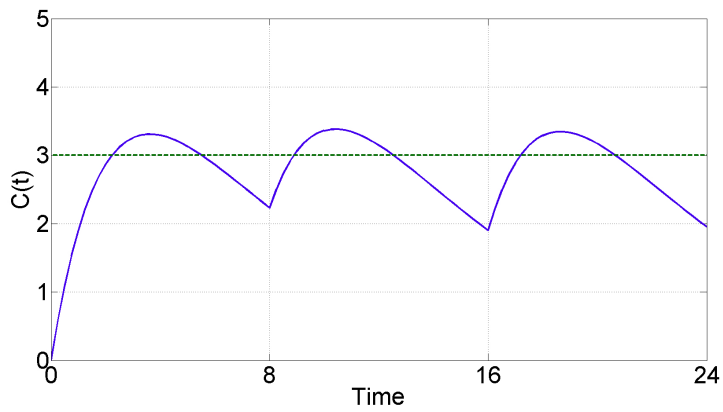
Efficient Dosing Algorithm

Properties

We can decrease the under- and over-exposure by planning more frequent dosing.



$C(t)$ when $\tau = 3$h.
$\varphi_A(\boldsymbol{\Delta}^*|.99) = 0.5284.$



$C(t)$ when $\tau = 8$h.
$\varphi_A(\boldsymbol{\Delta}^*|.99) = 3.4515.$

Efficient Dosing Algorithm

Example: one-compartment model

Efficient Dosing Algorithm

Example: one-compartment model

$$C(t,d) = \frac{FdK_a}{V(K_a - K_e)}\left(e^{-K_e t} - e^{-K_a t}\right),$$

where
K_a and K_e denote the absorption and elimination rate constants,
V is the volume of distribution,
F is the bio-availability.

Efficient Dosing Algorithm

Example: one-compartment model

$$C(t,d) = \frac{FdK_a}{V(K_a - K_e)}\left(e^{-K_e t} - e^{-K_a t}\right),$$

where
K_a and K_e denote the absorption and elimination rate constants,
V is the volume of distribution,
F is the bio-availability.

For the calculations we take the following estimates of the parameters

$$(\hat{K}_a,\ \hat{K}_e,\ \hat{V},\ \hat{F}) = (0.37\,h^{-1},\ 0.2\,h^{-1},\ 24\,L,\ 0.95).$$

Efficient Dosing Algorithm

Example: one-compartment model

$$C(t,d) = \frac{FdK_a}{V(K_a - K_e)}\left(e^{-K_e t} - e^{-K_a t}\right),$$

where
K_a and K_e denote the absorption and elimination rate constants,
V is the volume of distribution,
F is the bio-availability.

For the calculations we take the following estimates of the parameters

$$(\hat{K}_a,\ \hat{K}_e,\ \hat{V},\ \hat{F}) = (0.37\,h^{-1},\ 0.2\,h^{-1},\ 24\,L,\ 0.95).$$

Also, $C_{tgt} = 3mg\,L^{-1}$ and $d_{max} = 250\,mg$ and we consider $n = 7$ occasions to administer the drug with $\tau_j = 6h$, $j = 1, \ldots, 7$ so that $T = 42$.

Efficient Dosing Algorithm

Example: one-compartment model

At resolution of $\epsilon = 0.99$, φ_A-efficient dosing regimen is

$$\boldsymbol{D} = (163.87,\ 69.04,\ 92.12,\ 87.00,\ 87.88,\ 88.49,\ 87.88)\,.$$

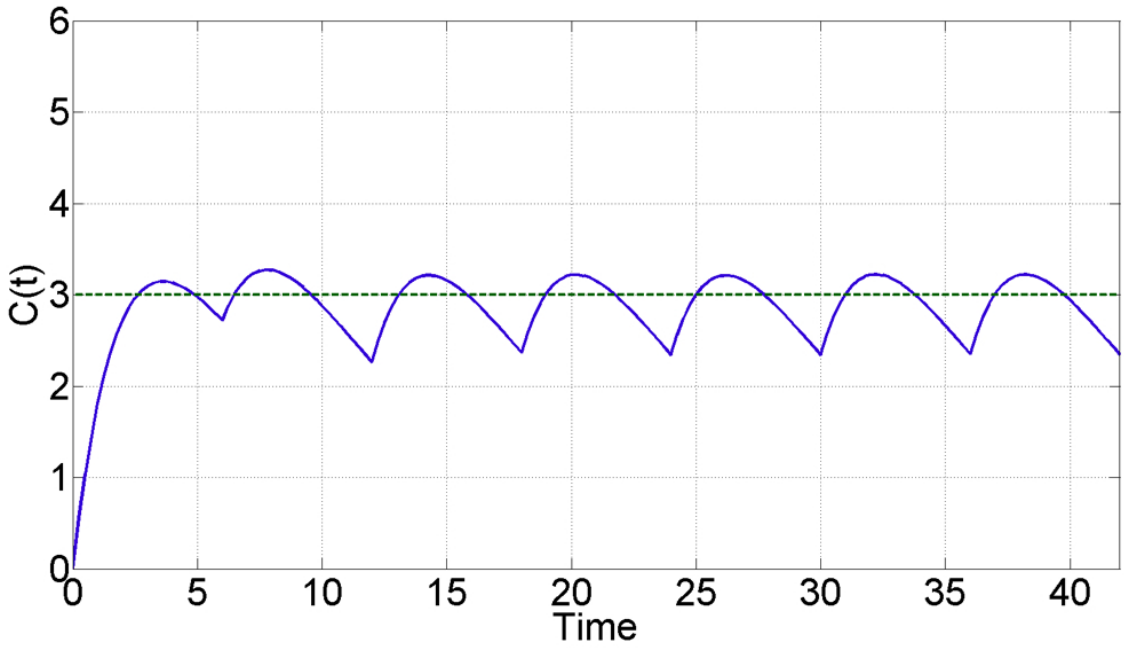
Efficient Dosing Algorithm

Example: one-compartment model

At resolution of $\epsilon = 0.99$, φ_A-efficient dosing regimen is

$$\boldsymbol{D} = (163.87,\ 69.04,\ 92.12,\ 87.00,\ 87.88,\ 88.49,\ 87.88)\,.$$

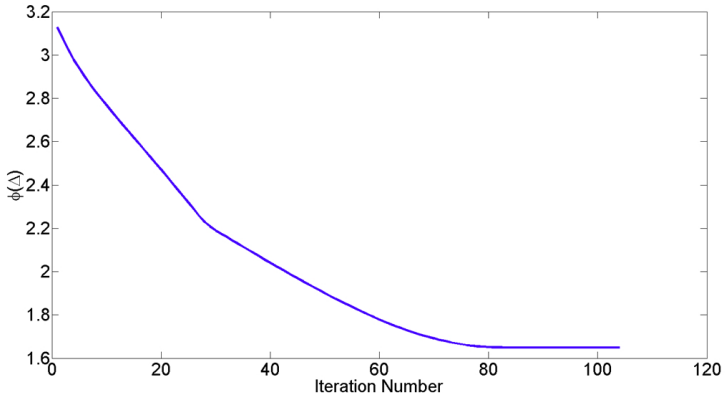
The concentration profile is shown below.



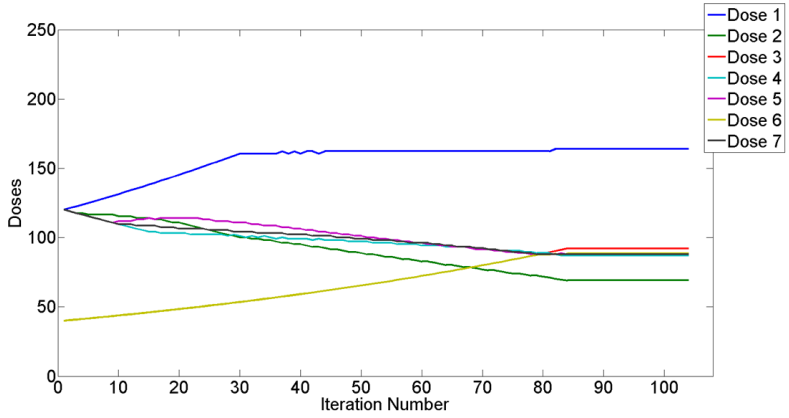
Efficient Dosing Algorithm

Example: one-compartment model

The algorithm converged in 84 iterations ($\epsilon = 0.99$).



Convergence of $\phi_A(\boldsymbol{\Delta})$.



Convergence of $\boldsymbol{D} = (d_1, \ldots, d_7)$.

Extension: Combination of two drugs

Extension: Combination of two drugs

Let the ratio of drug A to drug B in the tablet be $1 : \theta$.

Extension: Combination of two drugs

Let the ratio of drug A to drug B in the tablet be $1 : \theta$.

The problem then is two-fold:

Extension: Combination of two drugs

Let the ratio of drug A to drug B in the tablet be $1 : \theta$.

The problem then is two-fold:

Find the optimal ratio θ^* in which the drugs should be combined and find the most efficient dosing regimen $\boldsymbol{D}^\star$ for the tablet.

Extension: Combination of two drugs

Let the ratio of drug A to drug B in the tablet be $1 : \theta$.

The problem then is two-fold:

Find the optimal ratio θ^* in which the drugs should be combined and find the most efficient dosing regimen $\boldsymbol{D}^\star$ for the tablet.

- We have two target concentrations C^A_{tgt} and C^B_{tgt}.

Extension: Combination of two drugs

Let the ratio of drug A to drug B in the tablet be $1 : \theta$.

The problem then is two-fold:

Find the optimal ratio θ^* in which the drugs should be combined and find the most efficient dosing regimen $\boldsymbol{D}^\star$ for the tablet.

- We have two target concentrations C^A_{tgt} and C^B_{tgt}.
- The dosing regimen for the tablet will be

$$\boldsymbol{D}^A + \boldsymbol{D}^B = \boldsymbol{D}^A(1 + \theta)$$

Extension: Combination of two drugs

Let the ratio of drug A to drug B in the tablet be $1 : \theta$.

The problem then is two-fold:

Find the optimal ratio θ^* in which the drugs should be combined and find the most efficient dosing regimen $\boldsymbol{D}^\star$ for the tablet.

- We have two target concentrations C^A_{tgt} and C^B_{tgt}.
- The dosing regimen for the tablet will be

$$\boldsymbol{D}^A + \boldsymbol{D}^B = \boldsymbol{D}^A(1+\theta)$$

- We minimize

$$\varphi^C(\boldsymbol{\Delta}) = \omega\varphi^A_A(\boldsymbol{\Delta}) + (1-\omega)\varphi^B_A(\boldsymbol{\Delta})$$

where ω is a weighting constant.

Extension: Combination of two drugs

Example: Coartem®

Extension: Combination of two drugs

Example: Coartem®

This is a combination of two drugs:

1. Arthemether (A)
2. Lumefantrine (B)

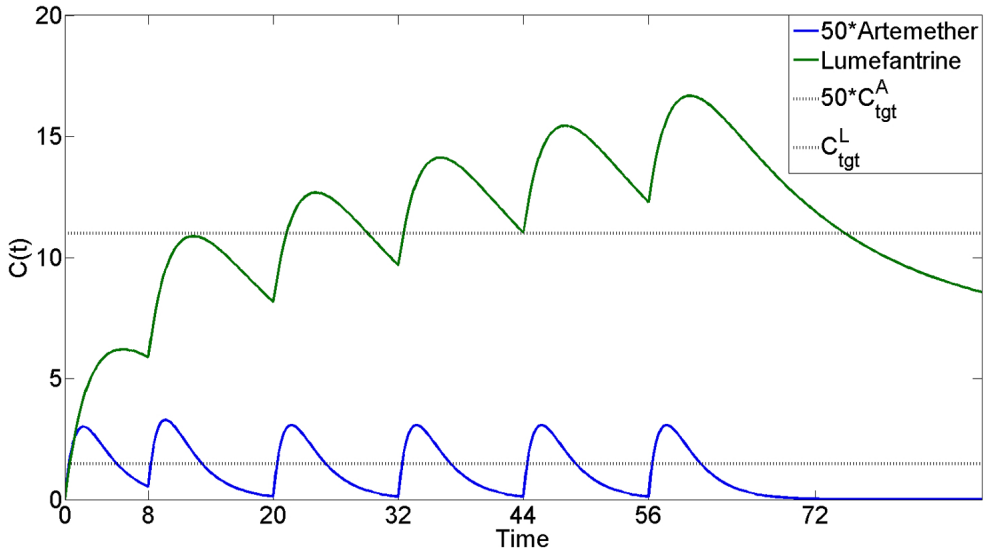
Extension: Combination of two drugs

Example: Coartem®

This is a combination of two drugs:

1. Arthemether (A)
2. Lumefantrine (B)

The current dosing regimen with the ration of $\theta = 6$ over three days gives a typical concentration profile as shown in the figure below.



Extension: Combination of two drugs

Example: Coartem®

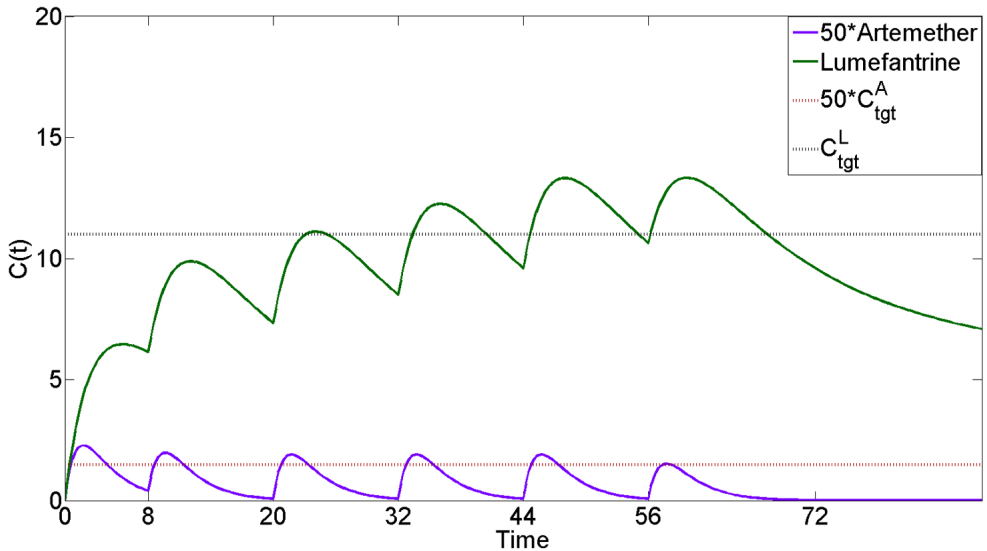
Alternative Regimen I The *Efficient Dosing Algorithm* is applied keeping the same times of dosing and the same number of doses.

Extension: Combination of two drugs

Example: Coartem®

Alternative Regimen I The *Efficient Dosing Algorithm* is applied keeping the same times of dosing and the same number of doses.

The Figure below shows the concentration profile of the two drugs for the optimum regimen $\boldsymbol{D}_I^\star$, with $\theta^\star = 8.24$.



Extension: Combination of two drugs

Example: Coartem®

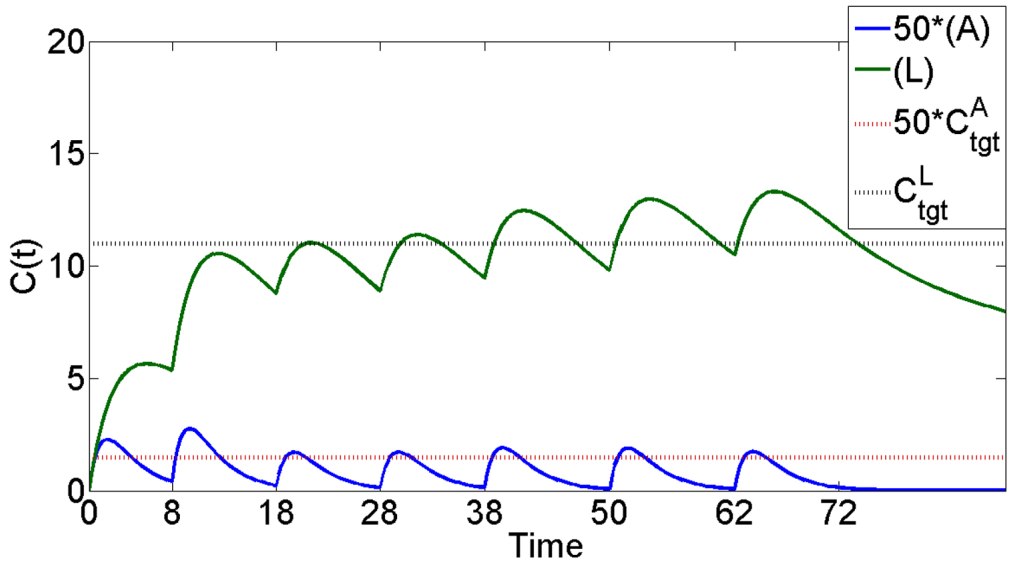
Alternative Regimen II The *Efficient Dosing Algorithm* is applied with a different dosing schedule, 7 doses instead of 6 over the period of three days.

Extension: Combination of two drugs

Example: Coartem®

Alternative Regimen II The *Efficient Dosing Algorithm* is applied with a different dosing schedule, 7 doses instead of 6 over the period of three days.

The Figure below shows the concentration profile of the two drugs for the optimum regimen $\boldsymbol{D}_{II}^{\star}$, with $\theta^{\star} = 7.21$.



Extension: Combination of two drugs

Example: Coartem®

Comparison of the dosing regimens and the combination ratios.

Dosing Regimen	θ^*	ϕ^C
$\boldsymbol{D}^A = (80.0, 80.0, 80.0, 80.0, 80.0, 80.0)$ $\boldsymbol{D}^B = (480.0, 480.0, 480.0, 480.0, 480.0, 480.0)$	6.00	135.2
$\boldsymbol{D}_I^{A^*} = (60.6, 46.7, 49.6, 49.6, 49.4, 39.3)$ $\boldsymbol{D}_I^{B^*} = (499.7, 384.8, 408.7, 408.7, 407.3, 324.4)$	8.24	106.8
$\boldsymbol{D}_{II}^{A^*} = (60.6, 67.7, 42.2, 43.8, 48.9, 49.4, 45.1)$ $\boldsymbol{D}_{II}^{B^*} = (437.2, 488.3, 304.5, 315.9, 352.8, 356.4, 325.6)$	7.21	80.7

Population Optimum Dose Regimen

Population PK Model

Population Optimum Dose Regimen

Population PK Model

We consider the compartment model:

$$C(t, d, \boldsymbol{\beta}) = \frac{dK_a}{V(K_a - K_e)}(e^{-K_e t} - e^{-K_a t}),$$

where $\boldsymbol{\beta} = (K_a, K_e, V)$ are unknown parameters,
K_a is the absorption rate constant,
K_e is the elimination rate constant,
V is the volume of distribution.

Population Optimum Dose Regimen

Population PK Model

We consider the compartment model:

$$C(t, d, \beta) = \frac{dK_a}{V(K_a - K_e)}(e^{-K_e t} - e^{-K_a t}),$$

where $\beta = (K_a, K_e, V)$ are unknown parameters,
K_a is the absorption rate constant,
K_e is the elimination rate constant,
V is the volume of distribution.

The aim is to maintain a target concentration,

$$C_{tgt} = 5mg/L \quad \text{for} \quad T = 40h$$

by administering $n = 5$ doses at $t_k^* = 0, 8, 16, 24, 32$ h.

Population Optimum Dose Regimen

Population PK model

We take the stage 1 model as

$$y_{ij} = C(t_{ij}, \boldsymbol{d}_i, \boldsymbol{\beta}_j) \exp\{e_{ij}\}, \qquad \boldsymbol{d}_i = (d_1, \ldots, d_i),\ \boldsymbol{\beta}_j = (K_{aj}, K_{ej}, V_j)$$

Population Optimum Dose Regimen

Population PK model

We take the stage 1 model as

$$y_{ij} = C(t_{ij}, \boldsymbol{d}_i, \boldsymbol{\beta}_j)\exp\{e_{ij}\}, \qquad \boldsymbol{d}_i = (d_1, \ldots, d_i),\ \boldsymbol{\beta}_j = (K_{aj}, K_{ej}, V_j)$$

and the stage 2 model as

$$\begin{pmatrix} K_{aj} \\ K_{ej} \\ V_j \end{pmatrix} = \begin{pmatrix} K_a \exp\{b_{K_{aj}}\} \\ K_e \exp\{b_{K_{ej}}\} \\ V \exp\{b_{V_j}\} \end{pmatrix},$$

Population Optimum Dose Regimen

Population PK model

We take the stage 1 model as

$$y_{ij} = C(t_{ij}, \boldsymbol{d}_i, \boldsymbol{\beta}_j)\exp\{e_{ij}\}, \qquad \boldsymbol{d}_i = (d_1, \ldots, d_i),\ \boldsymbol{\beta}_j = (K_{aj}, K_{ej}, V_j)$$

and the stage 2 model as

$$\begin{pmatrix} K_{aj} \\ K_{ej} \\ V_j \end{pmatrix} = \begin{pmatrix} K_a \exp\{b_{K_{aj}}\} \\ K_e \exp\{b_{K_{ej}}\} \\ V \exp\{b_{V_j}\} \end{pmatrix},$$

where

$$e_{ij} \sim \mathcal{N}(0, \sigma^2), \qquad \boldsymbol{b}_j = \begin{pmatrix} b_{K_{aj}} \\ b_{K_{ej}} \\ b_{V_j} \end{pmatrix} \sim \mathcal{N}_3(\boldsymbol{0}, \boldsymbol{\Omega})$$

and e_{ij} are independent from $\boldsymbol{b}_j$.

Population Optimum Dose Regimen

Adaptive Clinical Trial

Population Optimum Dose Regimen

Adaptive Clinical Trial

At stage k of the Trial:

Population Optimum Dose Regimen

Adaptive Clinical Trial

At stage k of the Trial:

Step 1 Apply the ED algorithm to determine the efficient dosing regimen $\boldsymbol{D}_k$ for given $\hat{\boldsymbol{\beta}}^{k-1}$.

Population Optimum Dose Regimen

Adaptive Clinical Trial

At stage k of the Trial:

- Step 1 Apply the ED algorithm to determine the efficient dosing regimen $\boldsymbol{D}_k$ for given $\hat{\boldsymbol{\beta}}^{k-1}$.
- Step 2 Administer the dosing regimen $\boldsymbol{D}_k$ to the k^{th} cohort.

Population Optimum Dose Regimen

Adaptive Clinical Trial

At stage k of the Trial:

- Step 1 Apply the ED algorithm to determine the efficient dosing regimen $\boldsymbol{D}_k$ for given $\hat{\boldsymbol{\beta}}^{k-1}$.
- Step 2 Administer the dosing regimen $\boldsymbol{D}_k$ to the k^{th} cohort.
- Step 3 Obtain the PK responses at the respective D-optimal sampling time points.

Population Optimum Dose Regimen

Adaptive Clinical Trial

At stage k of the Trial:

- Step 1 Apply the ED algorithm to determine the efficient dosing regimen $\boldsymbol{D}_k$ for given $\hat{\boldsymbol{\beta}}^{k-1}$.
- Step 2 Administer the dosing regimen $\boldsymbol{D}_k$ to the k^{th} cohort.
- Step 3 Obtain the PK responses at the respective D-optimal sampling time points.
- Step 4 Obtain the estimates of the PK parameters as $\hat{\boldsymbol{\beta}}^{k}$.

Population Optimum Dose Regimen

Adaptive Clinical Trial

At stage k of the Trial:

- Step 1 Apply the ED algorithm to determine the efficient dosing regimen $\boldsymbol{D}_k$ for given $\hat{\boldsymbol{\beta}}^{k-1}$.
- Step 2 Administer the dosing regimen $\boldsymbol{D}_k$ to the k^{th} cohort.
- Step 3 Obtain the PK responses at the respective D-optimal sampling time points.
- Step 4 Obtain the estimates of the PK parameters as $\hat{\boldsymbol{\beta}}^{k}$.
- Step 5 Stop the trial if the stopping rule is met, otherwise set k = k + 1 and repeat steps 1-4.

Population Optimum Dose Regimen

Adaptive Clinical Trial

At stage k of the Trial:

- Step 1 Apply the ED algorithm to determine the efficient dosing regimen $\boldsymbol{D}_k$ for given $\hat{\boldsymbol{\beta}}^{k-1}$.
- Step 2 Administer the dosing regimen $\boldsymbol{D}_k$ to the k^{th} cohort.
- Step 3 Obtain the PK responses at the respective D-optimal sampling time points.
- Step 4 Obtain the estimates of the PK parameters as $\hat{\boldsymbol{\beta}}^{k}$.
- Step 5 Stop the trial if the stopping rule is met, otherwise set k = k + 1 and repeat steps 1-4.
- Step 6 Analyze the gathered data to recommend the best possible dosing regimen.

Population Optimum Dose Regimen

Adaptive Clinical Trial: Simulation Study

For the simulation we assume the true population parameters be $\boldsymbol{\beta} = (K_a, K_e, V) = (.85,\ .15,\ 17)$, $\sigma^2 = .01$ and

$$\boldsymbol{\Omega} = \begin{pmatrix} .015 & 0 & 0 \\ 0 & .015 & .005 \\ 0 & .005 & .005 \end{pmatrix}.$$

Population Optimum Dose Regimen

Adaptive Clinical Trial: Simulation Study

For the simulation we assume the true population parameters be $\boldsymbol{\beta} = (K_a, K_e, V) = (.85,\ .15,\ 17)$, $\sigma^2 = .01$ and

$$\boldsymbol{\Omega} = \begin{pmatrix} .015 & 0 & 0 \\ 0 & .015 & .005 \\ 0 & .005 & .005 \end{pmatrix}.$$

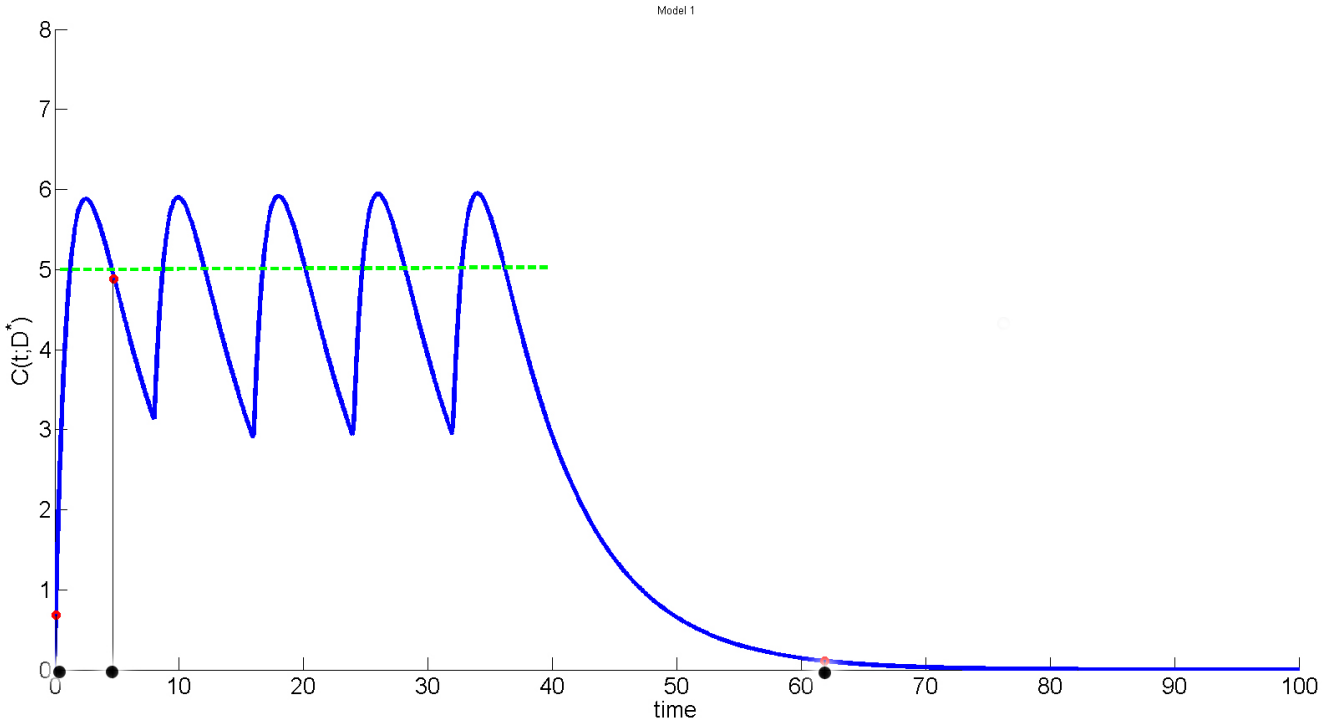
Based on these parameters, the efficient dose regimen is:

$$\boldsymbol{D}^* = (145,\ 90,\ 95,\ 95,\ 95)$$

with $\varphi(\boldsymbol{\Delta}_5^*) = 7.13$.

Population Optimum Dose Regimen

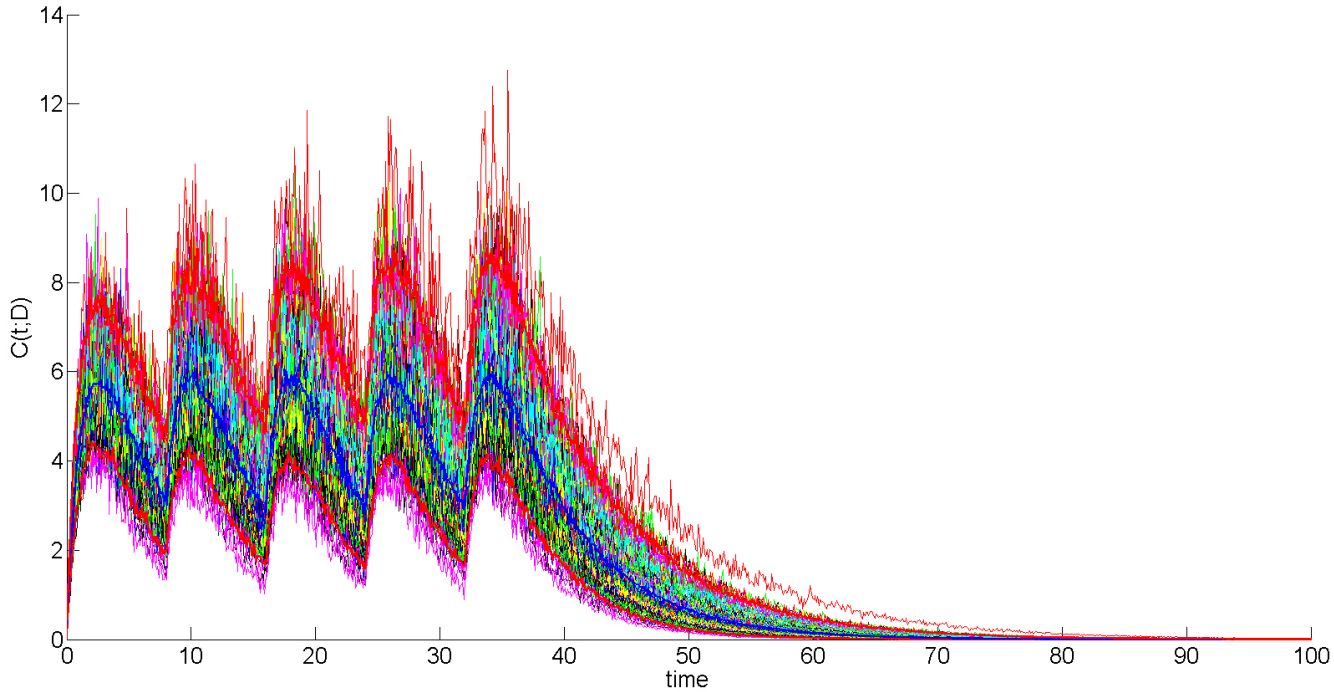
Adaptive Clinical Trial: Simulation Study



The dosing regimen for the true model parameters and the D-optimum sampling times $\xi^{\star} = \{0.10,\ 4.77,\ 61.88\}$

Population Optimum Dose Regimen

Population Variability



Simulated profiles of concentration of a 100 patients

Population Optimum Dose Regimen

Adaptive Clinical Trial: Simulation Study

We assume that some prior knowledge about the PK parameters and population variability is available from previous studies.

Population Optimum Dose Regimen

Adaptive Clinical Trial: Simulation Study

We assume that some prior knowledge about the PK parameters and population variability is available from previous studies.

Here we have $\beta_0 = (1.5,\ .25,\ 13)^T$, $\sigma_0^2 = .5$ and

$$\Omega_0 = \begin{pmatrix} .3 & 0 & 0 \\ 0 & .4 & .6 \\ 0 & .6 & .5 \end{pmatrix}.$$

Population Optimum Dose Regimen

Adaptive Clinical Trial: Simulation Study

We assume that some prior knowledge about the PK parameters and population variability is available from previous studies.

Here we have $\boldsymbol{\beta}_0 = (1.5,\ .25,\ 13)^T$, $\sigma_0^2 = .5$ and

$$\boldsymbol{\Omega}_0 = \begin{pmatrix} .3 & 0 & 0 \\ 0 & .4 & .6 \\ 0 & .6 & .5 \end{pmatrix}.$$

The parameters to be estimated are

$$\boldsymbol{\Psi}_k = \left(\boldsymbol{\beta}_k, \boldsymbol{\omega}_k, \sigma_k^2\right)$$

where $\boldsymbol{\omega}_k = (\omega_{11_k},\ \omega_{22_k},\ \omega_{33_k},\ \omega_{23_k})$.

Population Optimum Dose Regimen

Adaptive Clinical Trial: Stopping Rules

Population Optimum Dose Regimen

Adaptive Clinical Trial: Stopping Rules

Stopping Rules

1. The trial is terminated when the same dose regimen gets administered to two successive cohorts.

Population Optimum Dose Regimen

Adaptive Clinical Trial: Stopping Rules

Stopping Rules

1. The trial is terminated when the same dose regimen gets administered to two successive cohorts.
2. The trial is terminated at the k^{th} iteration when the dose regimen for the next cohort coincides with $\boldsymbol{D}^*$.

Population Optimum Dose Regimen

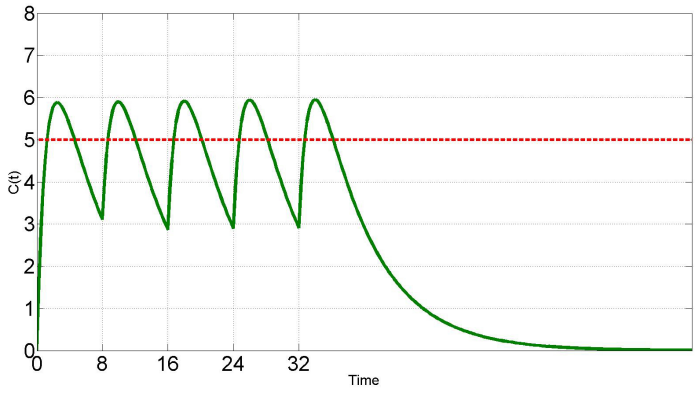
Adaptive Clinical Trial: Stopping Rules

Stopping Rules

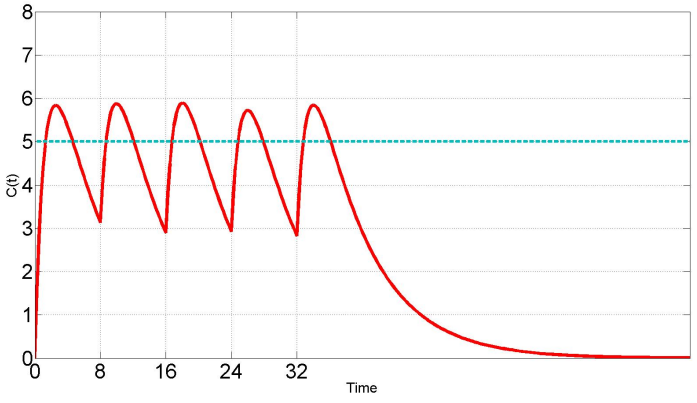
1. The trial is terminated when the same dose regimen gets administered to two successive cohorts.
2. The trial is terminated at the k^{th} iteration when the dose regimen for the next cohort coincides with $\boldsymbol{D}^*$.
3. The trial is terminated at the k^{th} iteration if all the elements of $\boldsymbol{\Psi}_k$ are within 10% of the true parameters.

Population Optimum Dose Regimen

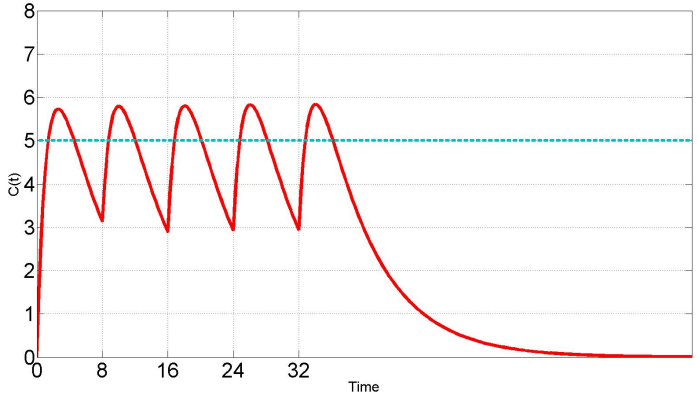
Results of the Simulated Adaptive Clinical Trial



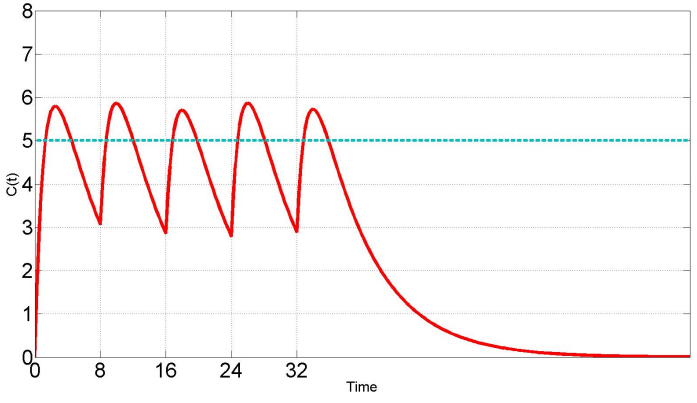
For true parameters: $\boldsymbol{D} = (145,\ 90,\ 95,\ 95,\ 95)^T$



Stopping Rule 1: $\boldsymbol{D}_8 = (145,\ 90,\ 95,\ 90,\ 95)^T$



Stopping Rule 2: $\boldsymbol{D}_5 = (145,\ 90,\ 95,\ 95,\ 95)^T$



Stopping Rule 3: $\boldsymbol{D}_{12} = (135,\ 85,\ 85,\ 90,\ 85)^T$

Population Optimum Dose Regimen

Software used

- RELME algorithm in MatLab is used for estimation of PK parameters at each stage of the trial,
- D-optimality criterion is used to determine the optimal blood sampling times, using the software PopED.

Conclusions

Conclusions

- This is work in progress.

Conclusions

- This is work in progress.
- The method can be applied for other criteria and other models.

Conclusions

- This is work in progress.
- The method can be applied for other criteria and other models.
- Continuous or discrete set of dose levels can be used.

Conclusions

- This is work in progress.
- The method can be applied for other criteria and other models.
- Continuous or discrete set of dose levels can be used.
- Combining population D-optimum design for blood sampling with the ϕ_A-optimum dose regimen selection in an adaptive trial gives good results.

Conclusions

- This is work in progress.
- The method can be applied for other criteria and other models.
- Continuous or discrete set of dose levels can be used.
- Combining population D-optimum design for blood sampling with the ϕ_A-optimum dose regimen selection in an adaptive trial gives good results.
- Farther work includes incorporation of covariates to make the dose regimen more suitable for a stratified population.

Conclusions

Paracelsus

All things are poison, and nothing is without poison; only the dose permits something not to be poisonous.

Conclusions

Paracelsus

All things are poison, and nothing is without poison; only the dose permits something not to be poisonous.

Paracelsus (Philippus Aureolus Theophrastus Bombastus von Hohenheim, 1493-1541) was a Swiss German Renaissance physician, botanist, alchemist, astrologer,
and general occultist.

WIKIPEDIA

THANK YOU