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Malaria PKPD model library

Method documentation

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Table of contents

# GR models

## Linear growth

## Cure threshold

#### Model with sigmoidal term to swith off growth rate at low parasite concentrations

#### Model implementing immunity at low parasite concentrations.

This model was inspired by Martin Bergstrand. A term is added to the parasite level ODE representing the body´s ability to clear completely parasites at low parasite concentrations.

The choice of PMAX is to large extent arbitrary if not leading to numerical issues. However, it needs to be higher than the growth rate. One potential choice is to set it to a value 20% higher than the growth rate:

In its original implementation there is no cure threshold in the enumerator and the rate of elimination by the body´s immune system is approaching . Thus, it is dependent on two parameters that should be adjusted to eachother to avoid inappropriate values.

# PK models

## Monotherapy

## Combination therapy

# PD models

## Monotherapy

## Combination therapy

### Additive drug effect model

#### Parasitemia ODE

#### GPDI model: Interaction terms for mutual impact on PD parameters

### Bliss independence model

Bliss independence model describes the combined drug effect of two drugs with different and independent mode of action. Combination of drugs fulfilling this criterion have an effect according to . The effects of the two drug need to be normalized by the maximum effect of the more effective drug, e.g., ( is normalized to the interval (0,1) and to (0,). The total effect is then scaled by the larger maximum effect. The resulting ODE for logtransformed parasite levels is

with > and

.

#### Empirical Bliss independence

with indicating Bliss independence, < for synergism and > for antagonism.

#### GPDI Bliss independence model

ODE is unchanged, but the EC50 values might be changed by other drug

.

#### Combination of clearance model with other models

Assume that is larger than and that the PD of drug 1 is described by a clearance model and the PD of drug 2 by a Emax model.

According to the Bliss model, the total kill is:

For combining the clearance model (drug 1) with an Emax model (drug 2), the total kill is distributed between "being killed and immediately cleared" (drug 2) and "being killed, but persisting in the circulation as dead parasites until cleared" (drug 2).

One solution is to attribute the pure monodrug kill terms () to the respective kill and distribute the interaction term () based on the fraction of the monodrug kill and the total additive effect.