Application of a Bayesian Markov chain Monte Carlo approach for modelling the dynamics of *Plasmodium falciparum* parasitaemia in severe malaria patients

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Biometrics by the Harbour 2015

Severe malaria

- Four different types of malaria parasites: *falciparum*, *vivax*, *malariae*, *ovale*
- *falciparum* most dangerous (responsible for 198 million clinical cases and approximately 584,000 deaths worldwide in 2013*)
- *falciparum* malaria can progress from uncomplicated (mild) to severe in a few hours
- Symptoms of severe malaria: very large parasite burden and major organ dysfunction

* WHO (2014). World Malaria Report 2014 summary.

Treatment of severe malaria

- WHO recommends intra-venous artesunate (IV-ARS) as the first line treatment for adults and children with severe malaria*
- WHO treatment guidelines for severe malaria revised in 2015

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ORIGINAL ARTICLE

Population Pharmacokinetics of Intravenous Artesunate: A Pooled Analysis of Individual Data From Patients With Severe Malaria

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- Smaller children (body weight < 20kg) need a higher dose of IV-ARS to achieve drug exposures similar to children and adults with higher body weights

* WHO (2015). Guidelines for the treatment of malaria (Third edition).

Project aims

- A mathematical model of how drug (IV-ARS) clears parasites from the patient has been developed*
- ***AIM*:** To fit this model to parasite counts measured over time in severe malaria patients treated with IV-ARS and examine the following:
  - Does this mechanistic model "fit/reproduce" the observed data?
  - Estimates of parameters governing *in vivo* drug action, e.g. fold reduction in parasite burden per hour of treatment

* Saralamba S *et al.* (2011) PNAS, 108(1):397-402; Zaloumis S *et al.* (2012) Malaria Journal, 11:303

Data description

Study descriptions

Study	Site	Population	Design	No. patients
1	Malawi	Children	RCT	157
2	Ghana	Children	Cross-over	29
3	Gabon	Children	Cross-over	9
4	Bangladesh	Adults	Clinical study	17
5	Thailand	Adults	Cross-over	48
6	Vietnam	Adults	RCT	6
Total	–	–	–	265*

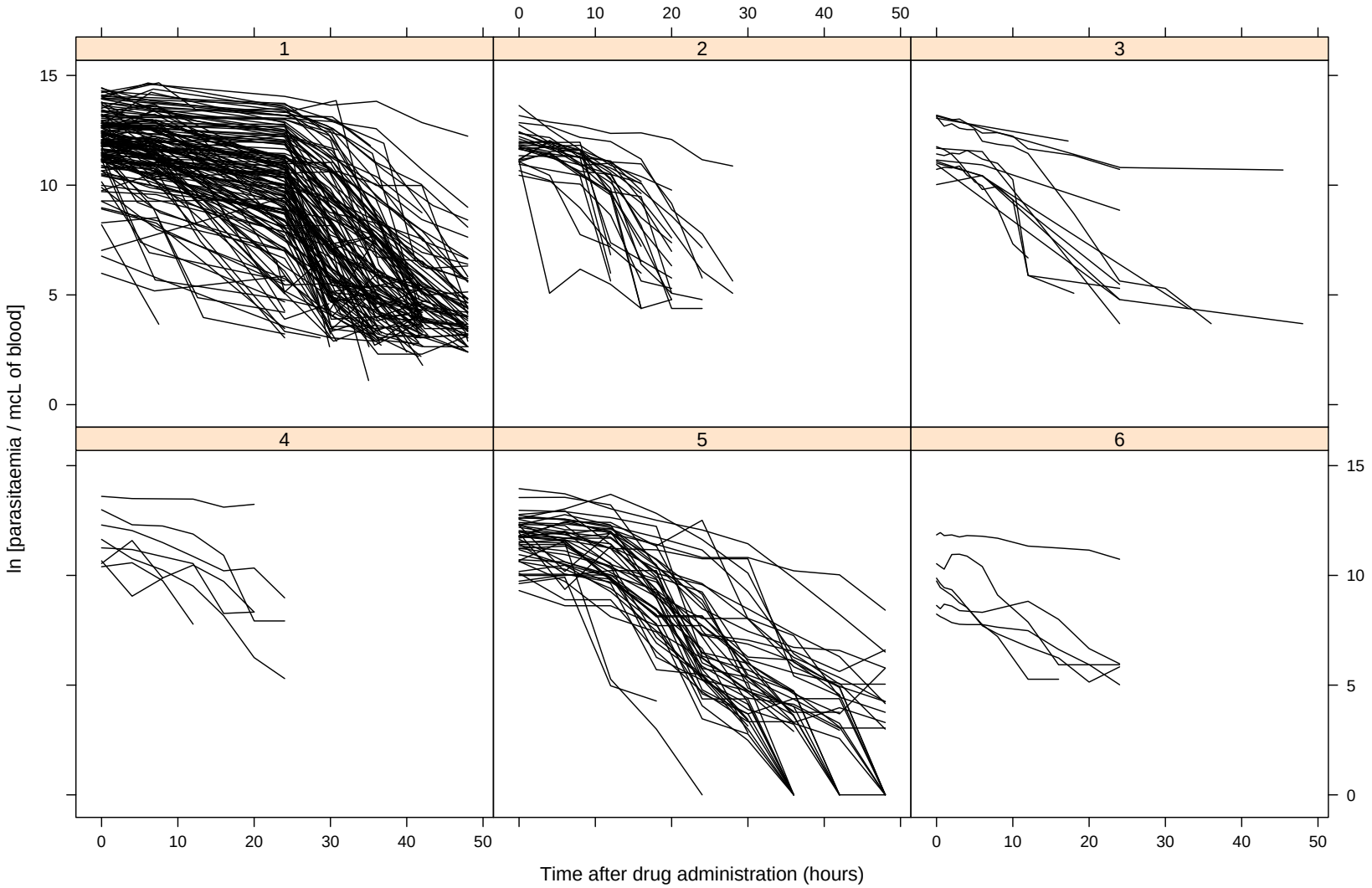
*Children: 195; Adults: 70

Parasitaemia sampling

- parasitaemia – no. parasites / μL of blood

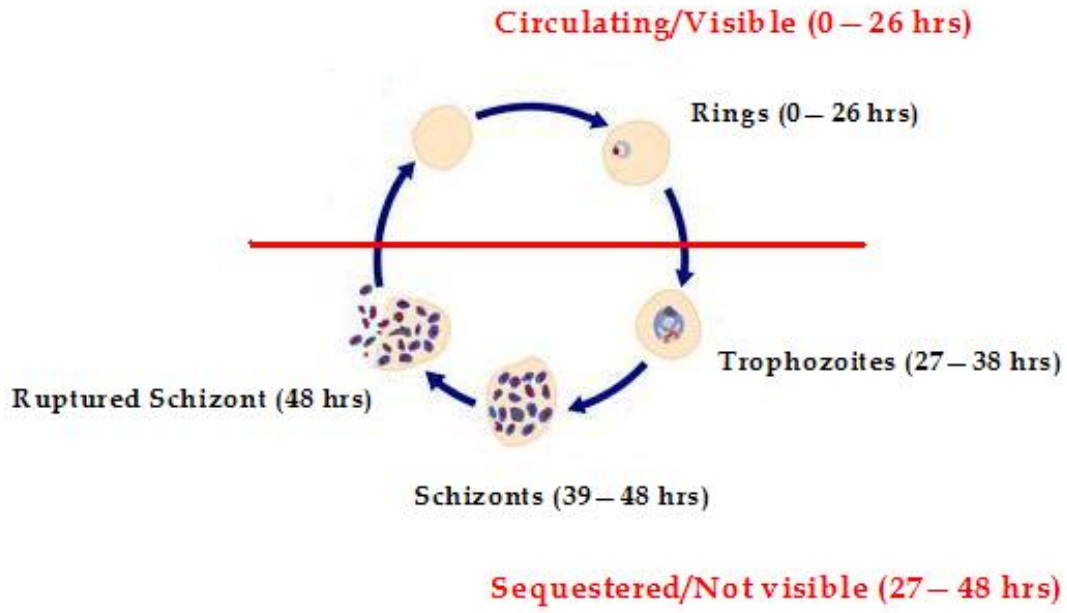
Study	No. samples	Median (Min, Max) /patient	% < LoD (No.)
1	869	6 (1, 8)	13 (113)
2	167	6 (4, 8)	0 (0)
3	45	5 (1, 7)	0 (0)
4	84	3 (1, 14)	4 (3)
5	377	8 (4, 9)	16 (59)
6	69	12 (10, 12)	0 (0)
Total	1611	–	

Data description (cont.)

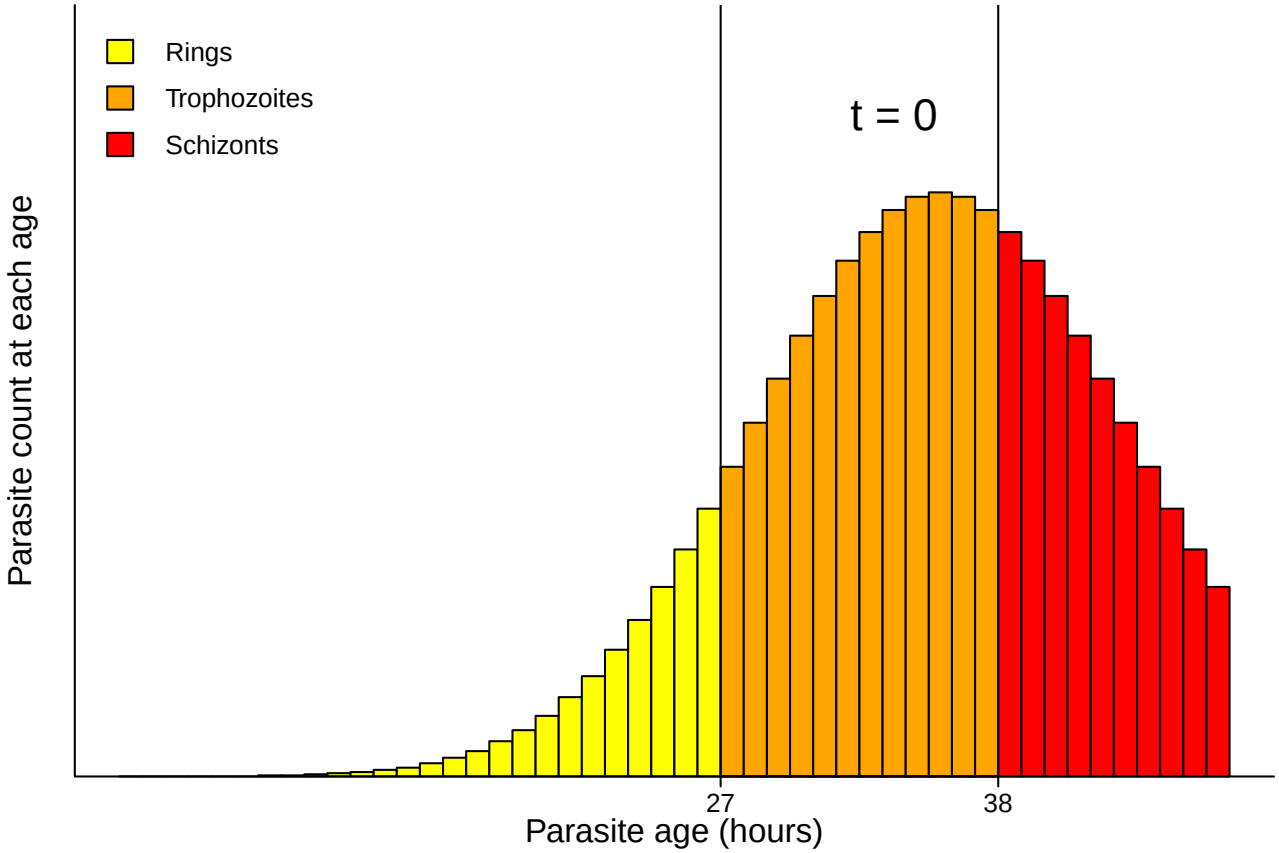


Asexual life cycle of *falciparum* within human RBCs

- The life cycle lasts for 48 hrs on average



Age distribution of initial parasite load

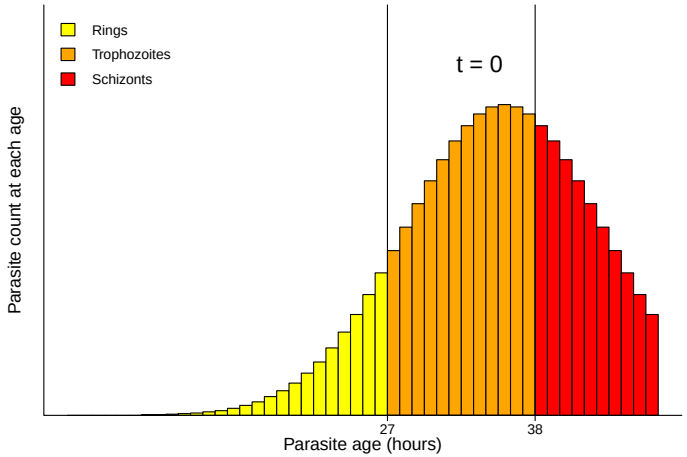


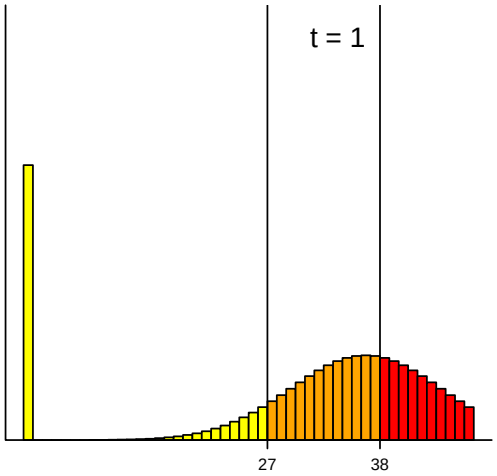
Initial parasite load harboured by a patient on admission to a clinic (i.e., t = 0).

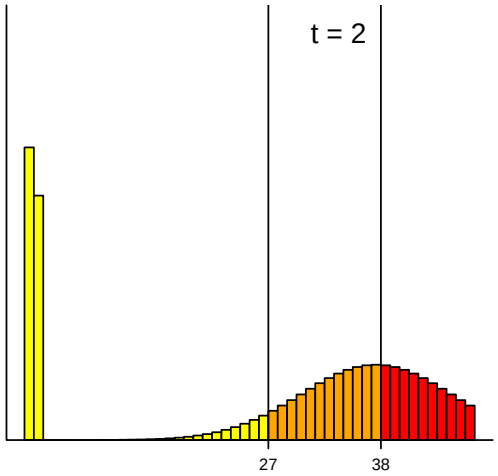
Model of parasite dynamics (growth)

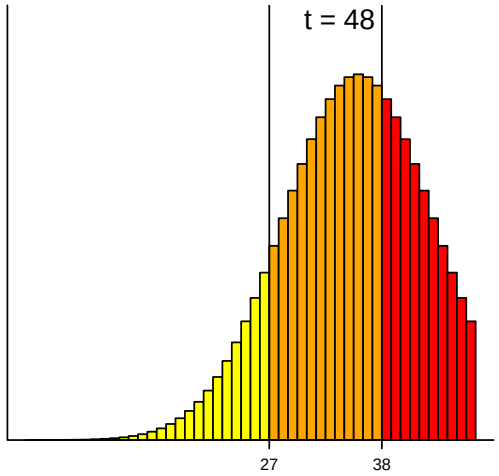
$$N_{ki}(1, t+1) = PMF_{ki} \times N_{ki}(48, t)$$
$$N_{ki}(2, t+1) = N_{ki}(1, t)$$
$$\vdots$$
$$N_{ki}(48, t+1) = N_{ki}(47, t)$$

- $N_{ki}(a, t+1)$ = the number of parasites aged a at time-point $t+1$
- PMF = number of merozoites released by a ruptured schizont that successfully infect other RBCs







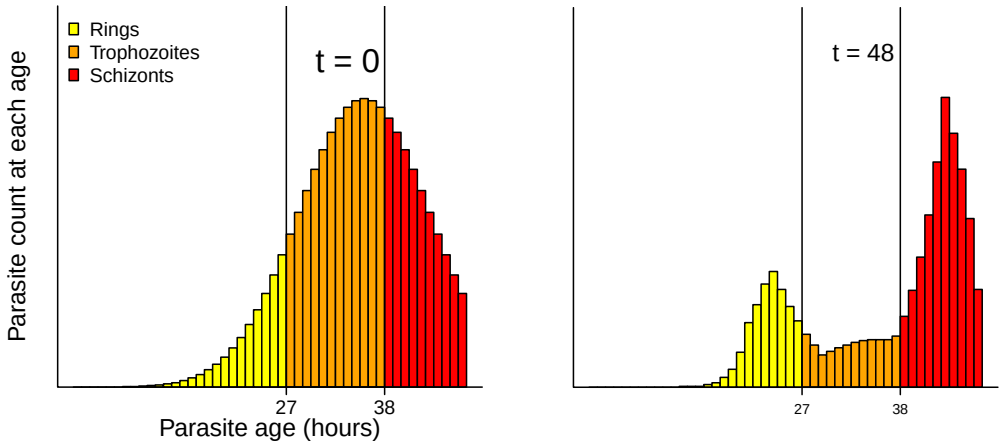


Model of parasite dynamics in presence of treatment

$$N_{ki}(1, t+1) = PMF_{ki} \times N_{ki}(48, t) \times s_i(t)$$
$$N_{ki}(2, t+1) = N_{ki}(1, t) \times s_i(t)$$
$$\vdots$$
$$N_{ki}(48, t+1) = N_{ki}(47, t) \times s_i(t)$$

Ages (hrs)	Survival Function
1–5	$s_0(t) = 1$
6–44	$s_1(t) = \exp\{-k_{DHA}(t)\}$
45–48	$s_2(t) = 1$

- $s_i(t)$ = proportion of parasites that survive an hourly interval when the drug is active
- i = indexes the age intervals when DHA is either active or inactive

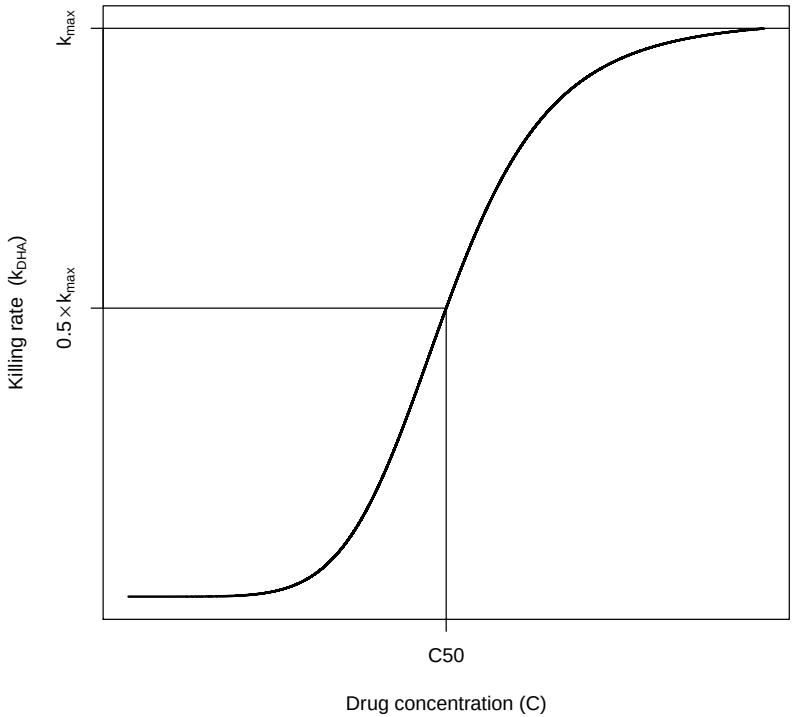


Relationship between drug concentration & effect

Killing constant

$$k_{DHA} = k_{max} \frac{C^{\gamma}}{C^{\gamma} + C50^{\gamma}}$$

Parameter	Description
k_{DHA}	Fold reduction in parasites killed / hour
C	Drug concentration at sampling time (predicted from population PK model)
k_{max}	Maximal killing constant of the drug (/h)
$C50$	Drug concentration at which parasite killing is 50% of maximum k_{max}
γ	Slope of the concentration -effect curve



- Sigmoid relationship — based on results from *in vitro* assays on malaria cultures

Nonlinear mixed effects model

Within-subject: $\ln y_{ij} \sim N(\ln f(x_{ij}; \theta_i), \sigma^2)$

- y_{ij} — j^{th} **observed parasitaemia** measurement for the i^{th} individual
- $f(x_{ij}; \theta_i)$ — **predicted parasitaemia** measurement
- $x_{ij} = (t_{ij}, C_{ij})$ are **design variables** (t_{ij} — sampling time; C_{ij} — predicted drug concentration)
- $\theta_i = [IPL_i, \mu_{IPL,i}, \sigma_{IPL,i}, PMF_i, k_{max,i}, \gamma_i, C50_i]'$ — **individual parameters** constrained to be within biological plausible ranges
- σ^2 — residual error/**within-subject variability**

Parameter	Range
IPL	3.97×10^9, 1.87×10^{13}
μ_{IPL} (h)	4, 28
σ_{IPL} (h)	2, 14
PMF	4, 20
k_{max} (/h)	0.26, 0.6
γ	1, 13
$C50$ (ng/mL)	1, 533

Zaloumis *et al.* (2012) [12]

Between-subject: $h(\theta_i) \sim MVN(h(\theta), \Sigma)$

- $\theta = [IPL, \mu_{IPL}, \sigma_{IPL}, PMF, k_{max}, \gamma, C50]'$ — **population parameters**
- $h(u) = \log((u - A)/(B - u))$ maps $u \in (A, B)$ to $\mathbb{R}$
- $\Sigma = \text{diag}(\sigma^2_{h(IPL)}, \sigma^2_{h(\mu_{IPL})}, \sigma^2_{h(\sigma_{IPL})}, \sigma^2_{h(PMF)}, \sigma^2_{h(k_{max})}, \sigma^2_{h(\gamma)}, \sigma^2_{h(C50)})$ — **between-subject variability** on the transformed scale

Bayesian Inference

Posterior Distribution

$$\pi(h(\theta_1), \ldots, h(\theta_N), \ln\sigma, h(\theta), \ln\Sigma | \ln y)$$
$$\propto \underbrace{\pi(\ln y | h(\theta_1), \ldots, h(\theta_N), \ln\sigma)}_{\text{Likelihood}} \times \underbrace{\pi(h(\theta_1), \ldots, h(\theta_N) | h(\theta), \ln\Sigma)}_{\text{Prior}} \times \underbrace{\pi(h(\theta), \ln\Sigma, \ln\sigma)}_{\text{Hyperprior}}$$

Likelihood

$$\ln y_{ij} \sim N(\ln f_{ij}, \sigma^2)$$

Prior

$$h(\theta_i) \sim MVN(h(\theta), \Sigma)$$

Hyperprior

$$\pi(h(\theta)) \propto 1$$
$$\pi(\ln\Sigma) \propto 1$$
$$\pi(\ln\sigma) \propto 1$$

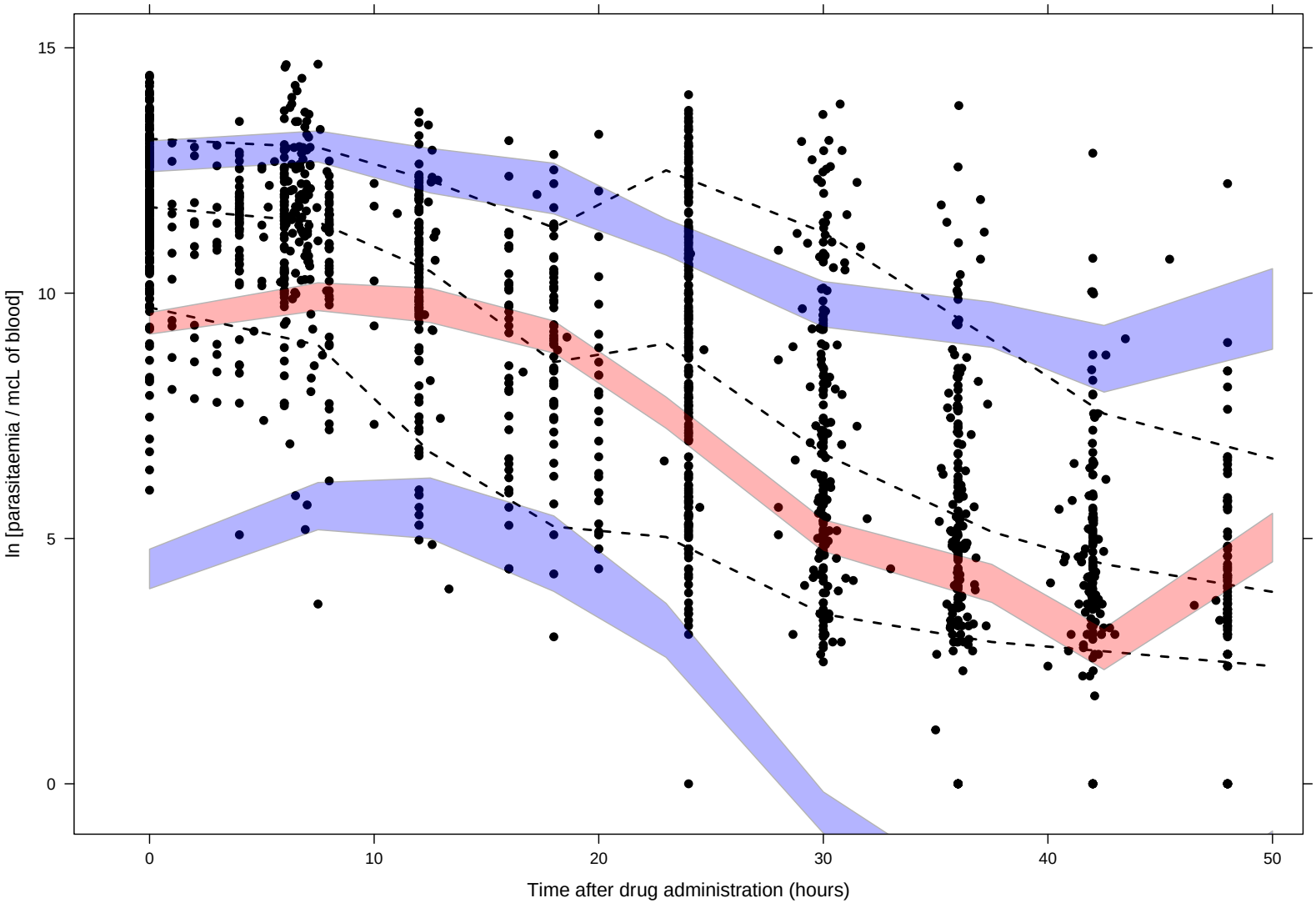
Posterior simulation

- Gibbs sampler (with Metropolis steps) coded in R
- Parallel tempering used to improve performance of sampler for high-dimensional posterior distributions
  - Used R code from "R-bloggers, Parallel Tempering in R with R mpi" (`http://www.r-bloggers.com/parallel-tempering-in-r-with-rmpi/`)
- 3 chains for 25 000 iterations each (10 000 discarded as burn-in)
- Single iteration 17.4 seconds (1 chain for 25 000 iterations $\sim$ 7375.43 mins (5.12 days))

Preliminary results

Parameter	Posterior Median (95% Credible Interval)
Population parameters	
IPL	3.71×10^{12} (5.0×10^{12}, 1.09×10^{12})
μ_{IPL}	31.41 (22.13, 37.83)
σ_{IPL}	10.24 (7.60, 12.09)
PMF	7.40 (6.20, 8.01)
k_{max} (/h)	
Rings (0-26 h)	0.47 (0.38, 0.52)
Trophozoites (27-38 h)	0.45 (0.40, 0.50)
Schizonts (39-48 h)	0.45 (0.37, 0.51)
γ	3.09 (1.85, 3.89)
$C50$ (ng/mL)	97.94 (15.59, 502.54)

Posterior predictive check



Conclusions

- Evidence that the model may under-predict parasitaemia after treatment with IV-ARS
- Sampling unconstrained parameters from the posterior could be causing slow exploration of the parameter space
- Data limited, e.g. only circulating parasitaemia observed and age specific parasitaemia measurements are not available

Future work

- Implement the Metropolis algorithm and sample parameters on the original scale
- Include steps to adapt the scale (Robbins-Munro step scaler) and variance parameters of the proposal distributions
- Improve efficiency of code by allowing the likelihood contribution for each subject can be computed in parallel

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