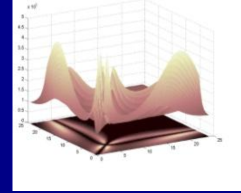


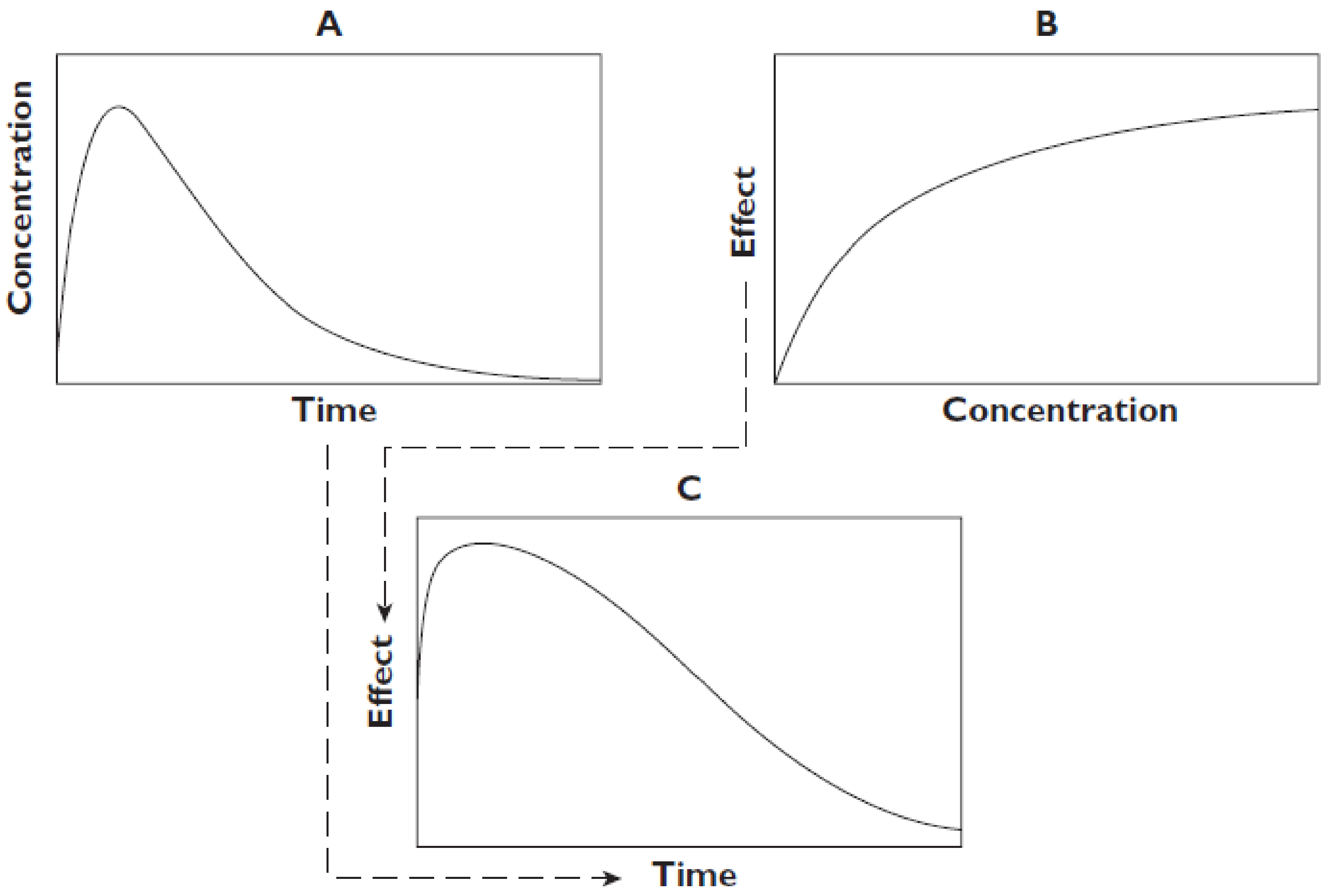
A General Method to Determine Sampling Windows for Nonlinear Mixed Effects Models

Stephen Duffull

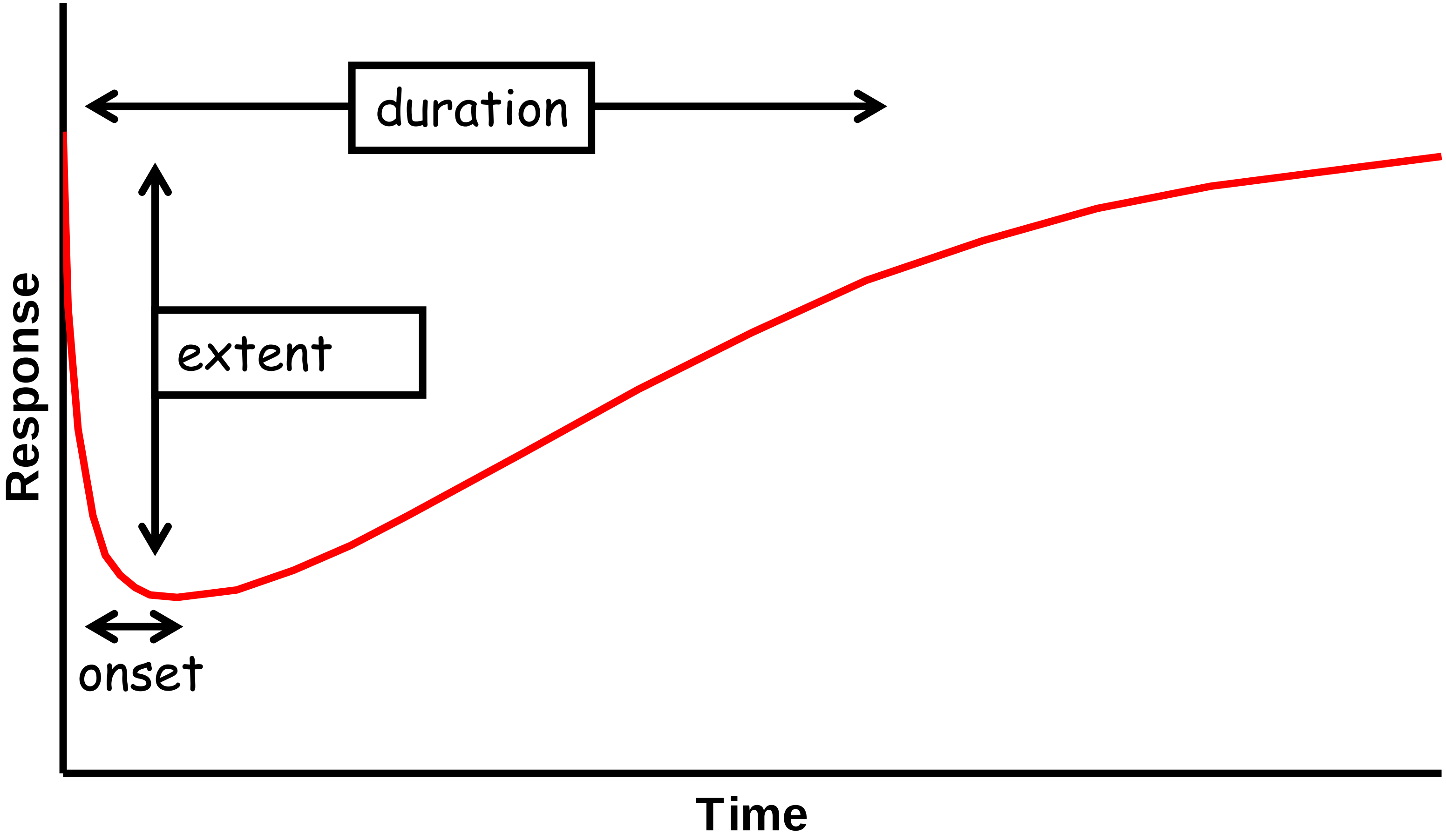
School of Pharmacy
University of Otago
New Zealand

The context:
Clinical Pharmacology Studies

- Clinical pharmacology studies provide a framework to describe the time course of drug effects
  - How quickly do drugs work?
  - What is the expected magnitude of effect?
  - How long will the actions last?
- Models of the time course of drug effects are generally constructed to be biologically plausible and are:
  - Nonlinear in the parameters
  - Have medium dimensionality (5-20 parameters)
  - Contain many random effects for patient heterogeneity


A
Concentration
Time
B
Effect
Concentration
C
Effect
Time

The time course of medicine response



Nonlinear Mixed Effects Model

- Can be specified as a two stage hierarchical model
- Stage 1: Data model $y_{ij} = f\left(t_{ij}, \theta_i\right) + \varepsilon_{ij}$

  y_{ij} : j^{th} measurement of i^{th} individual

  f : a parametric function of the structural model

  θ_i : model parameters of the i^{th} individual

  t_{ij} : design variables

  ε_{ij} : residual error, $\varepsilon_{ij} \sim N\left(0, \sigma^2\right)$

- Stage 2: Heterogeneity model $\theta_i = \mu + \eta_i$

  μ : population mean

  η_i : between subject variability, $\eta_i \sim N(0, \Omega)$

Designs for nonlinear mixed effects models

- The Fisher information matrix was described for nonlinear mixed effects models in 1997 (Mentré et al)
- Various extensions to this work followed in the next 2-5 years.
- Various methods have been proposed to accommodate the dependence of the design on the prior estimates of the parameter values
  - ED, EID, API, HClnD
- Most work in pharmacology has concentrated on the determinant and related criteria

D-optimal Design

- Given by $$\xi_D = \underset{\xi \in \Xi}{\arg\max}\left(\left|\mathrm{M}(\xi, \boldsymbol{\theta})\right|\right)$$
- Population clinical pharmacology studies
  - Design variable: e.g. blood sampling time
  - Software: PFIM, POPT/WinPOPT, PopED, PopDes, ….
- Uncontrolled clinical environment
  - Out patient
  - Emergency room
- Impossible for designs to be conducted exactly per protocol
  - This leads to unplanned suboptimality in which the clinical setting dictates the informativeness of the design

Sampling Windows
(planned suboptimality)

- A time window of opportunity where nearly optimal samples can be taken

$$\Psi(\xi) = \left(\frac{\left| \mathrm{M}(\xi, \boldsymbol{\theta}) \right|}{\left| \mathrm{M}(\xi_D, \boldsymbol{\theta}) \right|} \right)^{1/p}, \mathrm{p} = \mathrm{number\ of\ parameters}$$

- We pre-specify an efficiency $\nabla (= 0.9)$ for the i^{th} window to take a blood sample $[a_i, b_i]$

$$\forall \xi_i \in [a_i, b_i] \Rightarrow \Psi(\xi_i) \geq \nabla, i = 1 \ldots n$$

and where $b_i > a_i$, $a_i > b_{i\text{-}1}$

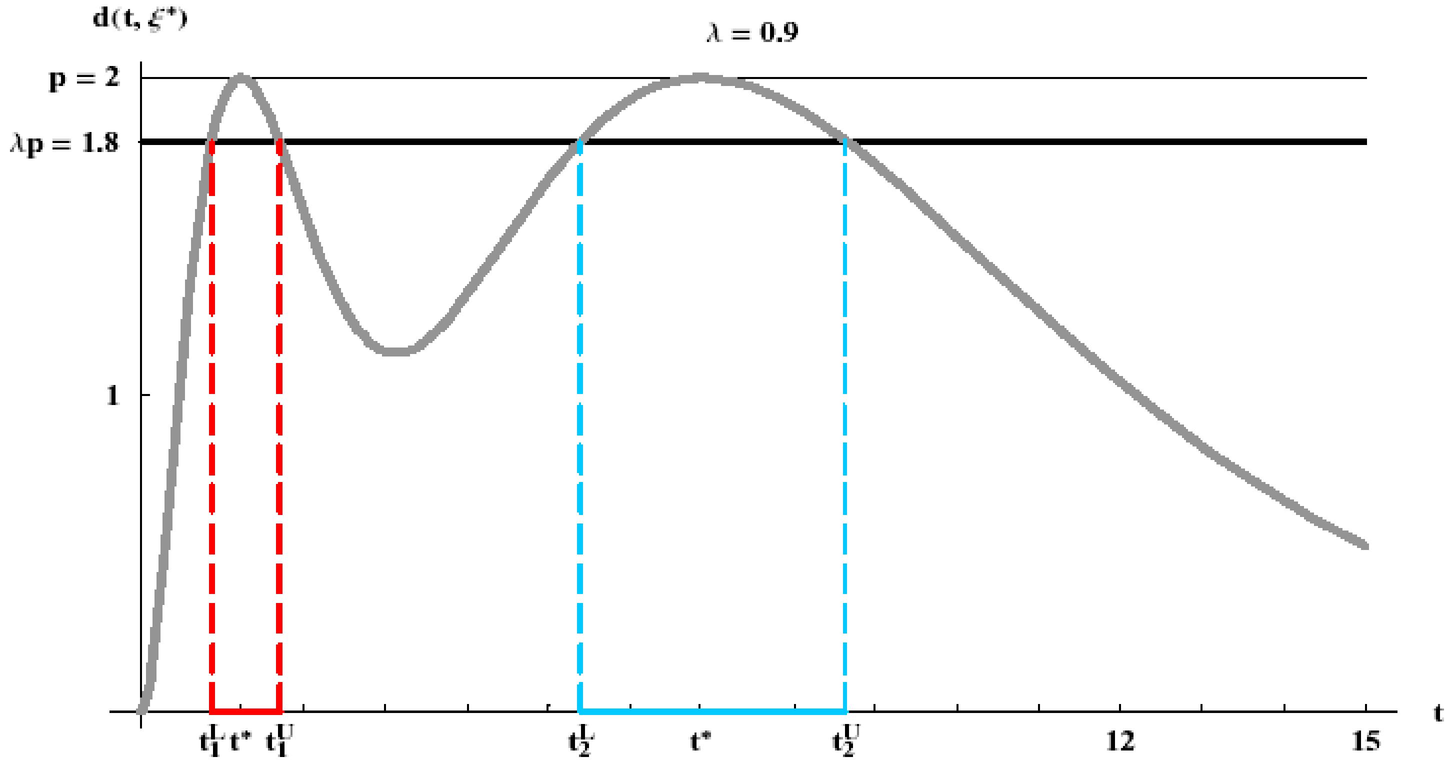
The issue

- No analytical solution is available for sampling windows for nonlinear mixed effects models

Three techniques for defining sampling windows

- Based on the standardised variance
- Optimised windows
- POSTHOC windows
  - Marginal
  - Joint
- Adaptive sampling windows

The Surface of the Standardised Variance



This method does not currently link the loss λ to a specific loss of efficiency – but this is not problematic

Requires assumption of independence.

Bogacka et al. ICODOE, Memphis, 2005

Optimized Sampling Windows

- Two basic approaches have been proposed for this problem:
  - Optimize the length of a fixed set of sampling windows assuming the windows are symmetric ($\pm\delta^{W}$) around the optimal sampling times [1]
    - Later work relaxed the assumption of symmetry to allow symmetry on either the real or log domain.
  - Construct a finite set of potential sampling windows and then search over the sampling window space to see which sampling windows appear to perform best [2].
- Assumptions of symmetry/prior set of windows contain a set of acceptable values…

[1] Graham and Aarons Stat Med 2006; 25: 4004-4019
[2] Ogungbenro and Aarons. J Biopharm Stat 2009

POSTHOC Windows - Marginal

- This method is similar in spirit to a profile likelihood method for determining a confidence interval on a parameter (for estimation)
- The process takes the following steps
  - The optimal sampling schedule for the population study is located
  - One time allowed to vary until the loss in efficiency achieves some predefined level
  - This is repeated for all sampling times
- Very fast but anti-conservative

Duffull et al. Pharm Res 2001;18:83-89
Green and Duffull, JPKPD 2003;30:145-161

Adaptive Sampling Windows

- A Bayesian method has been proposed for solving for sampling windows in a sequential manner for a fixed effects model
- Theory:
  - If the first sampling time were known then the next sampling window could be estimated that fulfilled an pre-specified efficiency criteria
- The method provides estimates of the windows – not the optimal sampling times

Duffull et al J Biopharm Stat (2010)

Aim

- To develop and assess a method for determining sampling windows that can be applied to population pharmacokinetic studies

Sampling windows - theory

- An exact solution for sampling windows exists for a case where there is only a single sample
  - i.e. for any given single sample design the window providing a 90% efficiency can be computed analytically

- A simple solution (therefore) is to recast the problem into one in which the window for any given time point is considered as if the other time points were already known

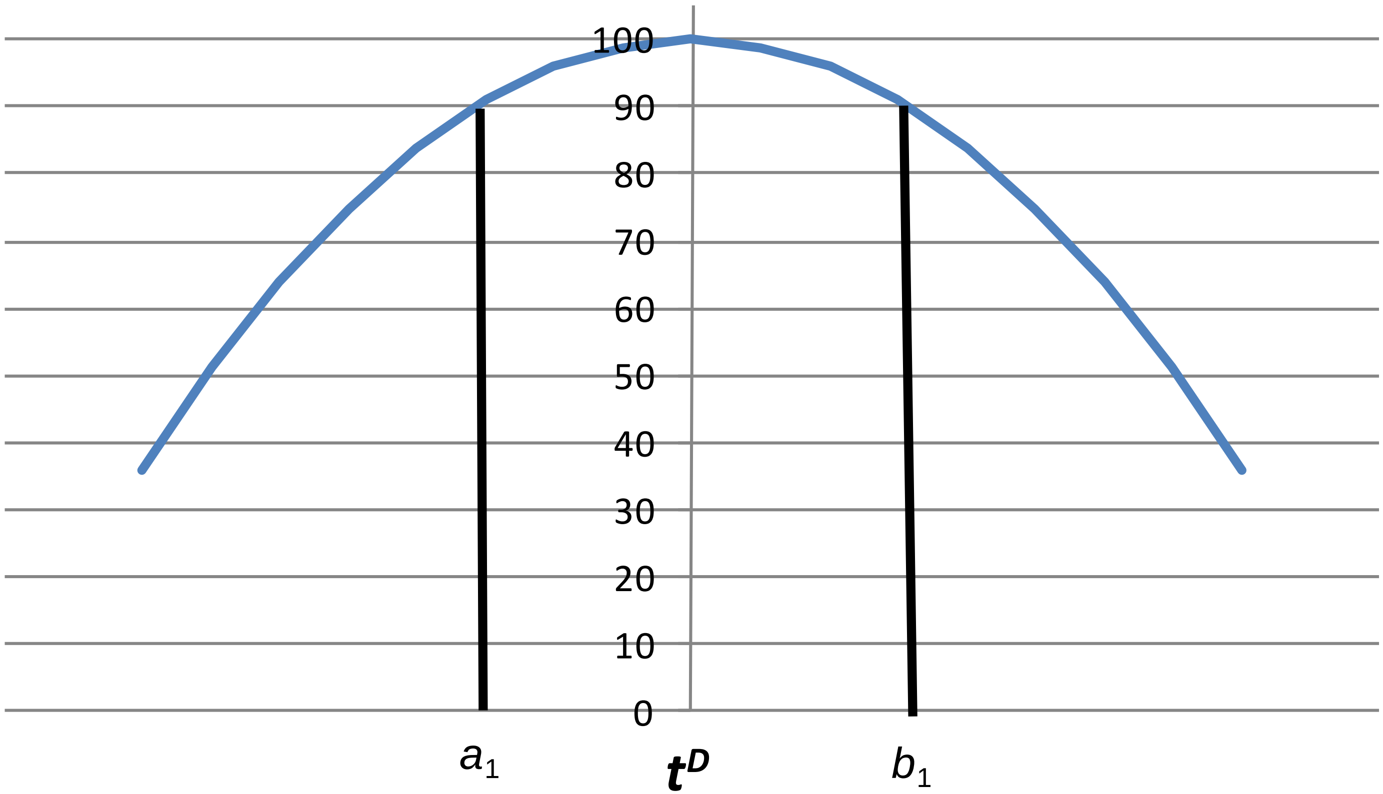
The approach – the first sampling time

- Given a design range $[t_L, t_H]$
- Given a D-optimal design $\xi_D = \left(t_1^D, t_2^D, \ldots, t_k^D\right)$
- Determine sampling window for t_1 with ∇ efficiency
- The first sampling window SW_1 can be calculated analytically by setting the subsequent sampling times as if they were taken at the D-optimal design points

$$SW_1 = [a_1, b_1] = [\min(t_1), \max(t_1)] \Rightarrow \Psi(\xi) \geq \nabla$$

$$\xi = \left(t_1, t_2^D, \ldots, t_k^D\right) \quad ; \quad t_1 \in [t_L, t_H]$$

Calculation of SW



The second sampling time…

- Generate $\tilde{t}_1 \sim [a_1, b_1]$ as a pseudo-sample
- Given a design $\xi = \left(\tilde{t}_1, t_2, t_3^D \ldots, t_k^D\right)$
- The second sampling window SW_2 is obtained by conditioning on the pseudo-sample and the remaining D-optimal samples

$$SW_2 = [a_2, b_2] = [\min(t_2), \max(t_2)] \Rightarrow \Psi(\xi) \geq \nabla$$

Recursive Random Sampling

Given $\xi^{(n)} = (t_1^{(n)}, t_2^{(n)}, \ldots, t_k^{(n)})$

and $SW^{(n)} = (SW_1^{(n)}, SW_2^{(n)}, \ldots, SW_k^{(n)})$

$= ([a_1^{(n)}, b_1^{(n)}], [a_2^{(n)}, b_2^{(n)}], \ldots, [a_k^{(n)}, b_k^{(n)}])$

1) $t_1^{(n+1)} \sim p_1(SW_1^{(n+1)} \mid t_2^{(n)}, t_3^{(n)}, \ldots, t_k^{(n)})$

2) $t_2^{(n+1)} \sim p_2(SW_2^{(n+1)} \mid t_1^{(n+1)}, t_3^{(n)}, \ldots, t_k^{(n)})$

$\vdots$

k) $t_k^{(n+1)} \sim p_k(SW_k^{(n+1)} \mid t_1^{(n+1)}, t_2^{(n+1)}, \ldots, t_{k-1}^{(n+1)})$

3-parameter bi-exponential model

$$C_{ij} = Dose_i \frac{ka_i}{V_i(ka_i - k_i)}\left[\exp(-k_i t_{ij}) - \exp(-ka_i t_{ij})\right]\varepsilon_{p_{ij}} + \varepsilon_{a_{ij}}$$

$$\ln\begin{pmatrix} CL \\ V \\ ka \end{pmatrix} \sim \mathrm{N}_p(\boldsymbol{\mu}, \boldsymbol{\Omega})$$

$$\boldsymbol{\mu} = \begin{pmatrix} \ln(4) \\ \ln(20) \\ \ln(1) \end{pmatrix} \quad \boldsymbol{\Omega} = \begin{bmatrix} 0.1 & 0 & 0 \\ 0 & 0.1 & 0 \\ 0 & 0 & 0.1 \end{bmatrix} \qquad \varepsilon_p \sim N(0, 0.1) \qquad \varepsilon_a \sim N(0, 0.05)$$

$0 \le t \le 24$ Dose = 100 $Ns = 100$

Application

- Initial samples: $\xi^{(0)} = (0.59, 3.46, 12.63)$
- Iteration 1:

1) $SW_1^{(1)} = [a_1^{(1)}, b_1^{(1)}] = [\min t_1, \max t_1]$ for $\Psi(\xi) \geq \nabla$

$\xi = (t_1, 3.46, 12.63)$ $\quad$ $t_1 \in [0, 24]$

generate $t_1^{(1)} \sim U(a_1^{(1)}, b_1^{(1)})$

Application

- Initial samples: $\xi^{(0)} = (0.59, 3.46, 12.63)$
- Iteration 1:

1) $SW_1^{(1)} = [a_1^{(1)}, b_1^{(1)}] = [\min t_1, \max t_1]$ for $\Psi(\xi) \geq \nabla$

$\xi = (t_1, 3.46, 12.63)$ $\qquad t_1 \in [0, 24]$

generate $t_1^{(1)} \sim U(a_1^{(1)}, b_1^{(1)})$

2) $SW_2^{(1)} = [a_2^{(1)}, b_2^{(1)}] = [\min t_2, \max t_2]$ for $\Psi(\xi) \geq \nabla$

$\xi = (t_1^{(1)}, t_2, 12.63)$ $\qquad t_2 \in [b_1^{(1)}, 24]$

generate $t_2^{(1)} \sim U(a_2^{(1)}, b_2^{(1)})$

Application

- Initial samples: $\xi^{(0)} = (0.59, 3.46, 12.63)$
- Iteration 1:

1) $SW_1^{(1)} = [a_1^{(1)}, b_1^{(1)}] = [\min t_1, \max t_1]$ for $\Psi(\xi) \geq \nabla$

$\xi = (t_1, 3.46, 12.63)$ $\quad t_1 \in [0, 24]$

generate $t_1^{(1)} \sim U(a_1^{(1)}, b_1^{(1)})$

2) $SW_2^{(1)} = [a_2^{(1)}, b_2^{(1)}] = [\min t_2, \max t_2]$ for $\Psi(\xi) \geq \nabla$

$\xi = (t_1^{(1)}, t_2^{(1)}, 12.63)$ $\quad t_2 \in [b_1^{(1)}, 24]$

generate $t_2^{(1)} \sim U(a_2^{(1)}, b_2^{(1)})$

3) $SW_3^{(1)} = [a_3^{(1)}, b_3^{(1)}] = [\min t_3, \max t_3]$ for $\Psi(\xi) \geq \nabla$

$\xi = (t_1^{(1)}, t_2^{(1)}, t_3)$ $\quad t_3 \in [b_2^{(1)}, 24]$

generate $t_3^{(1)} \sim U(a_3^{(1)}, b_3^{(1)})$

Computing pre-posterior mean of sampling windows

- Iteration 1:

  $SW^{(1)} = ([a_1^{(1)}, b_1^{(1)}], [a_2^{(1)}, b_2^{(1)}], [a_3^{(1)}, b_3^{(1)}])$

- Repeat for 2000 iterations

- Calculate the pre-posterior mean for the boundaries of the sampling windows

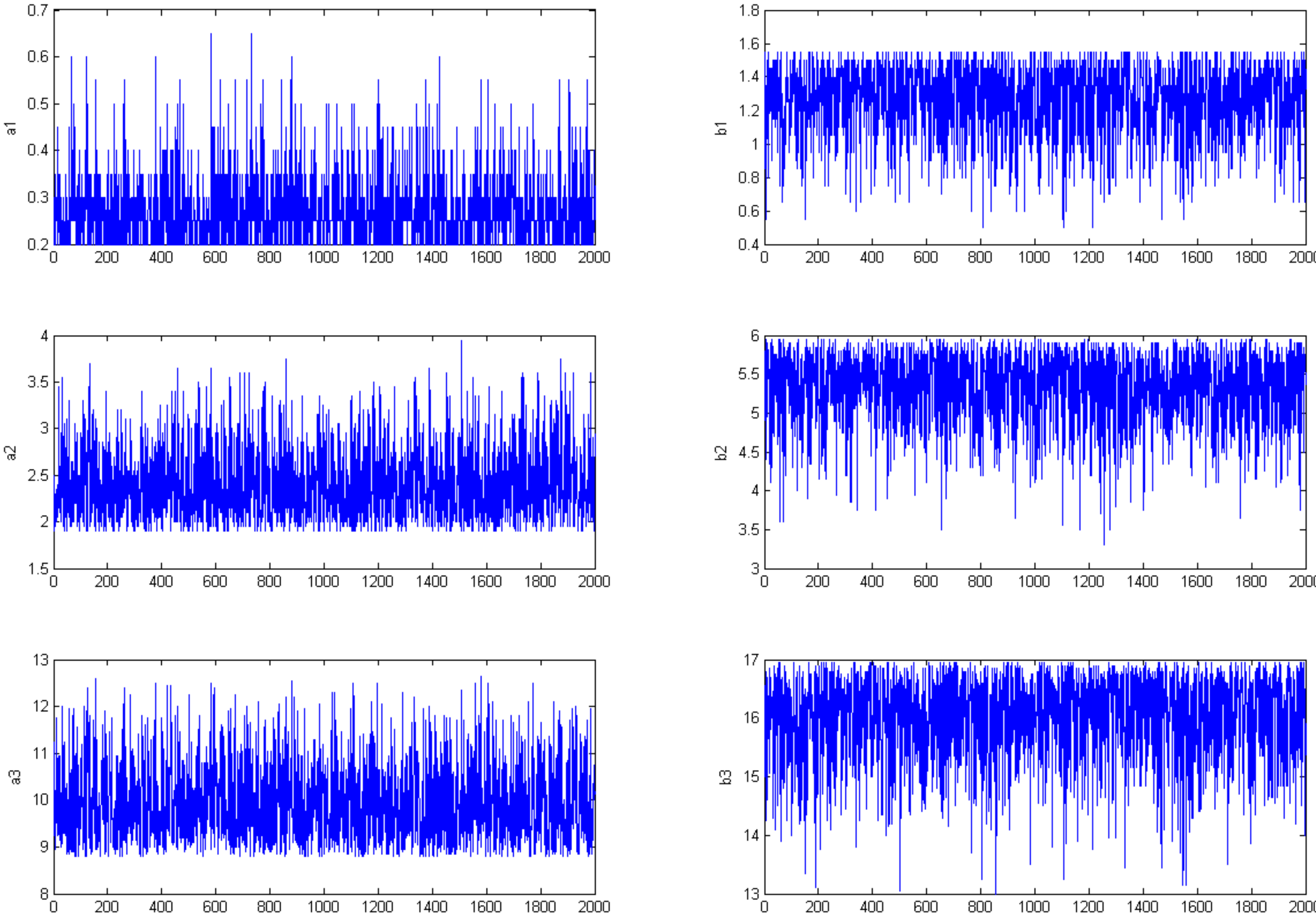
  $a_1 = \text{mean}\ (a_1^{(1)}, a_1^{(2)}, \ldots, a_1^{(2000)})$

  $b_1 = \text{mean}\ (b_1^{(1)}, b_1^{(2)}, \ldots, b_1^{(2000)})$

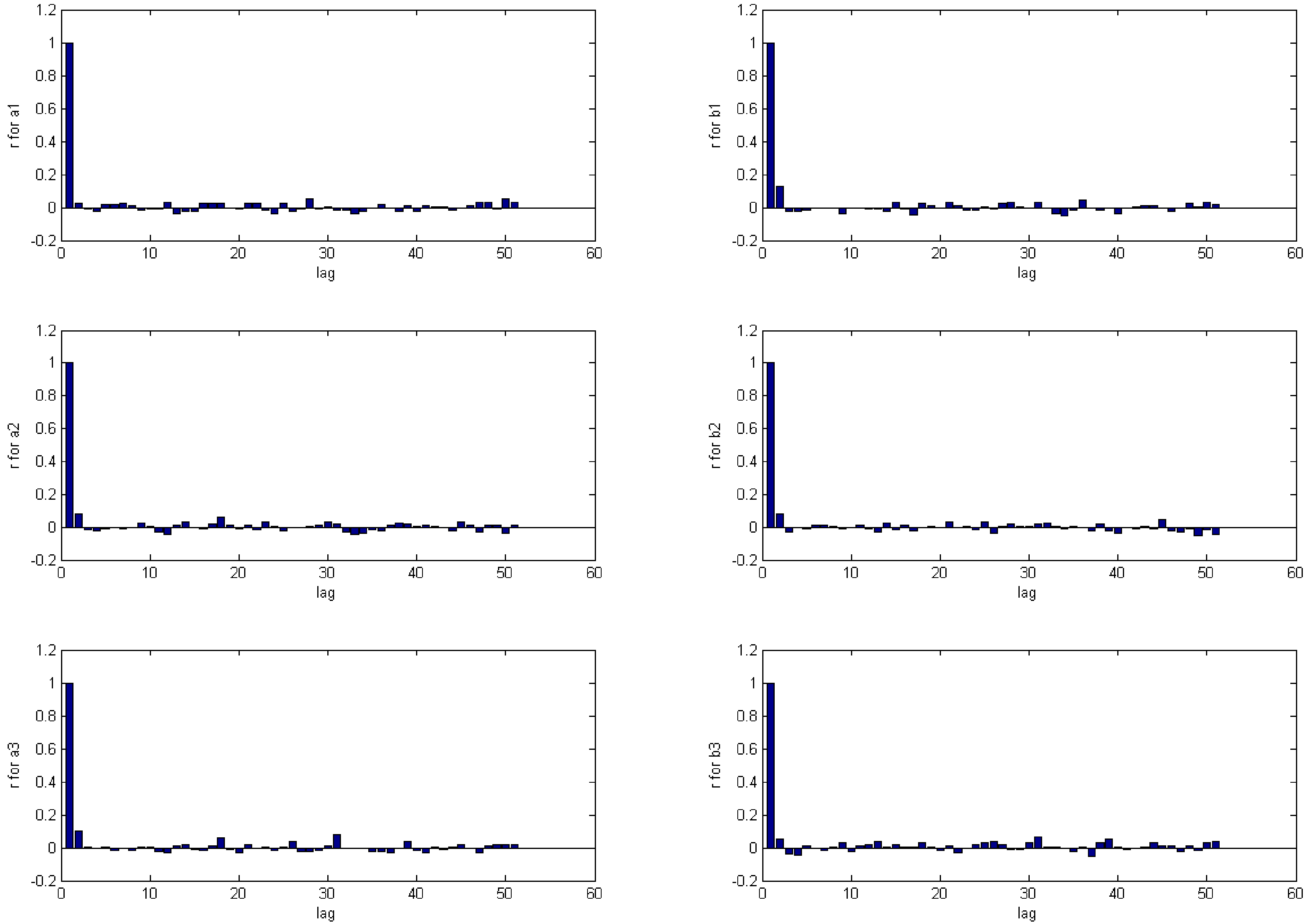
  $\vdots$

  $b_3 = \text{mean}\ (b_3^{(1)}, b_3^{(2)}, \ldots, b_3^{(2000)})$

Trace Plot


a1
0.7
0.6
0.5
0.4
0.3
0.2
0 200 400 600 800 1000 1200 1400 1600 1800 2000
b1
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0 200 400 600 800 1000 1200 1400 1600 1800 2000
a2
4
3.5
3
2.5
2
1.5
0 200 400 600 800 1000 1200 1400 1600 1800 2000
b2
6
5.5
5
4.5
4
3.5
3
0 200 400 600 800 1000 1200 1400 1600 1800 2000
a3
13
12
11
10
9
8
0 200 400 600 800 1000 1200 1400 1600 1800 2000
b3
17
16
15
14
13
0 200 400 600 800 1000 1200 1400 1600 1800 2000

Auto Correlation Plot



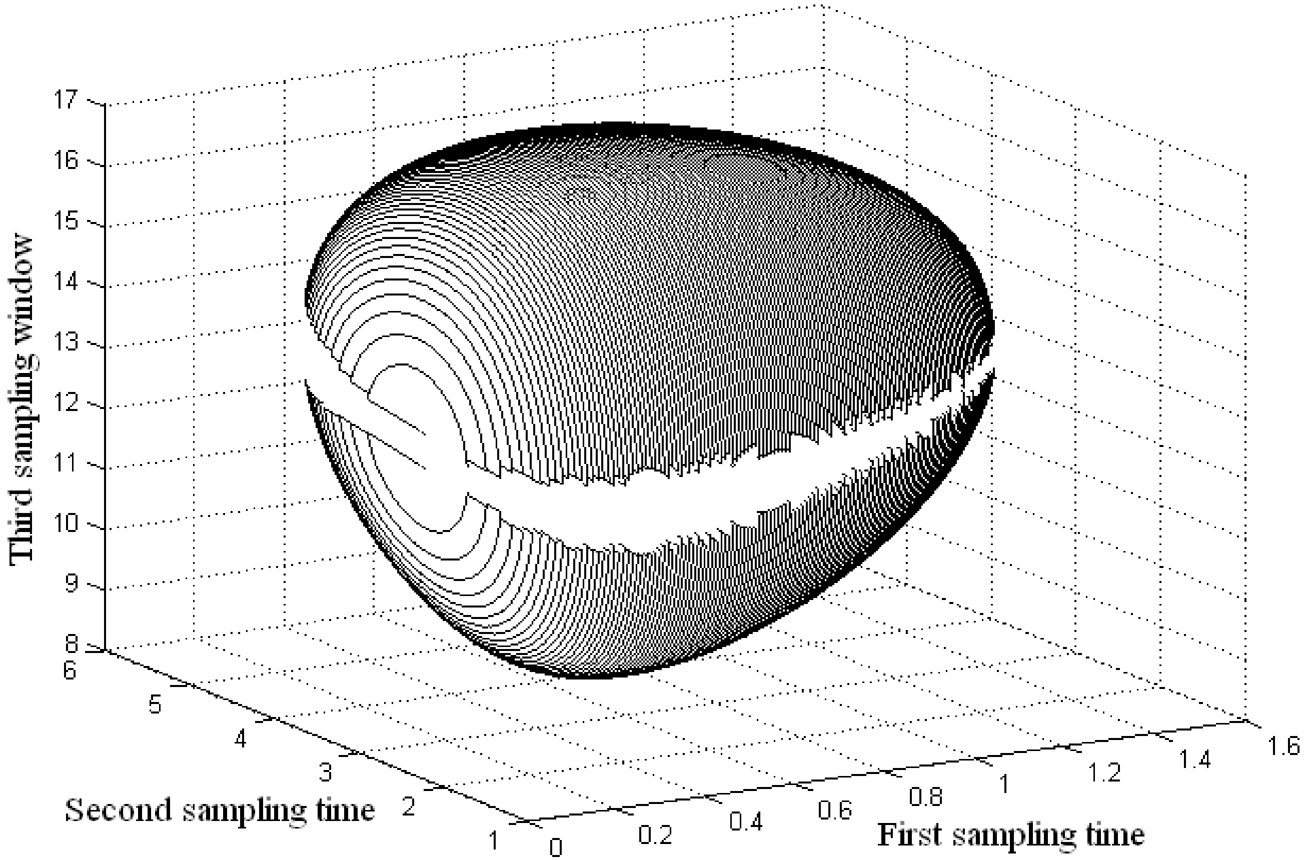
Sampling windows

- 90% efficiency sampling windows:
  - Pre-posterior mean of the boundaries

    (0.28, 1.25), (2.40, 5.31), (9.94, 15.99)
- The D-optimal time points were

  (0.59, 3.46, 12.63)

A representation of the conditional sampling windows



Checking for convergence

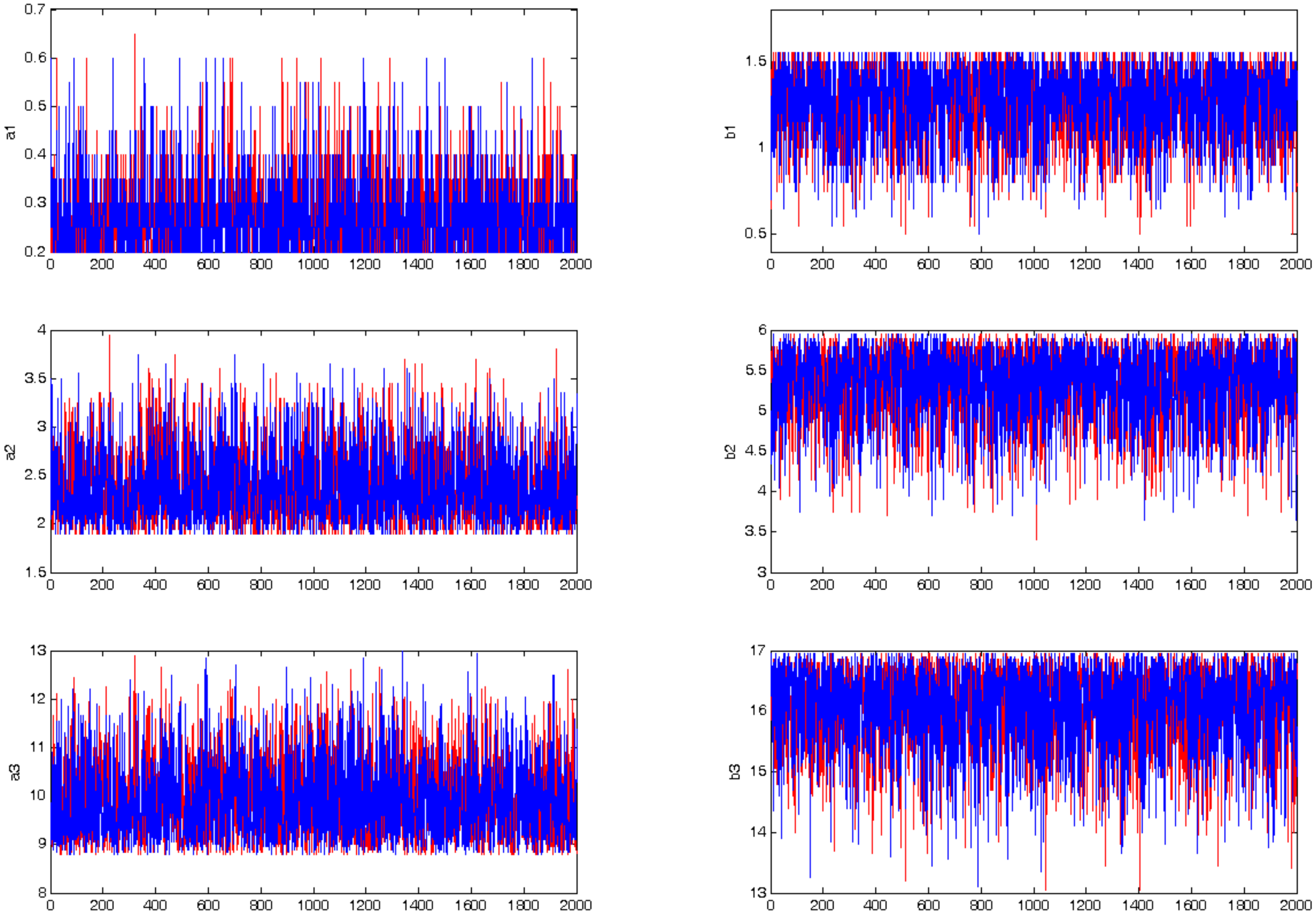
- 2 chains with over-dispersed starting points

$$\tau^{(0),\#1} = (0.59, 2.46, 10.13)$$

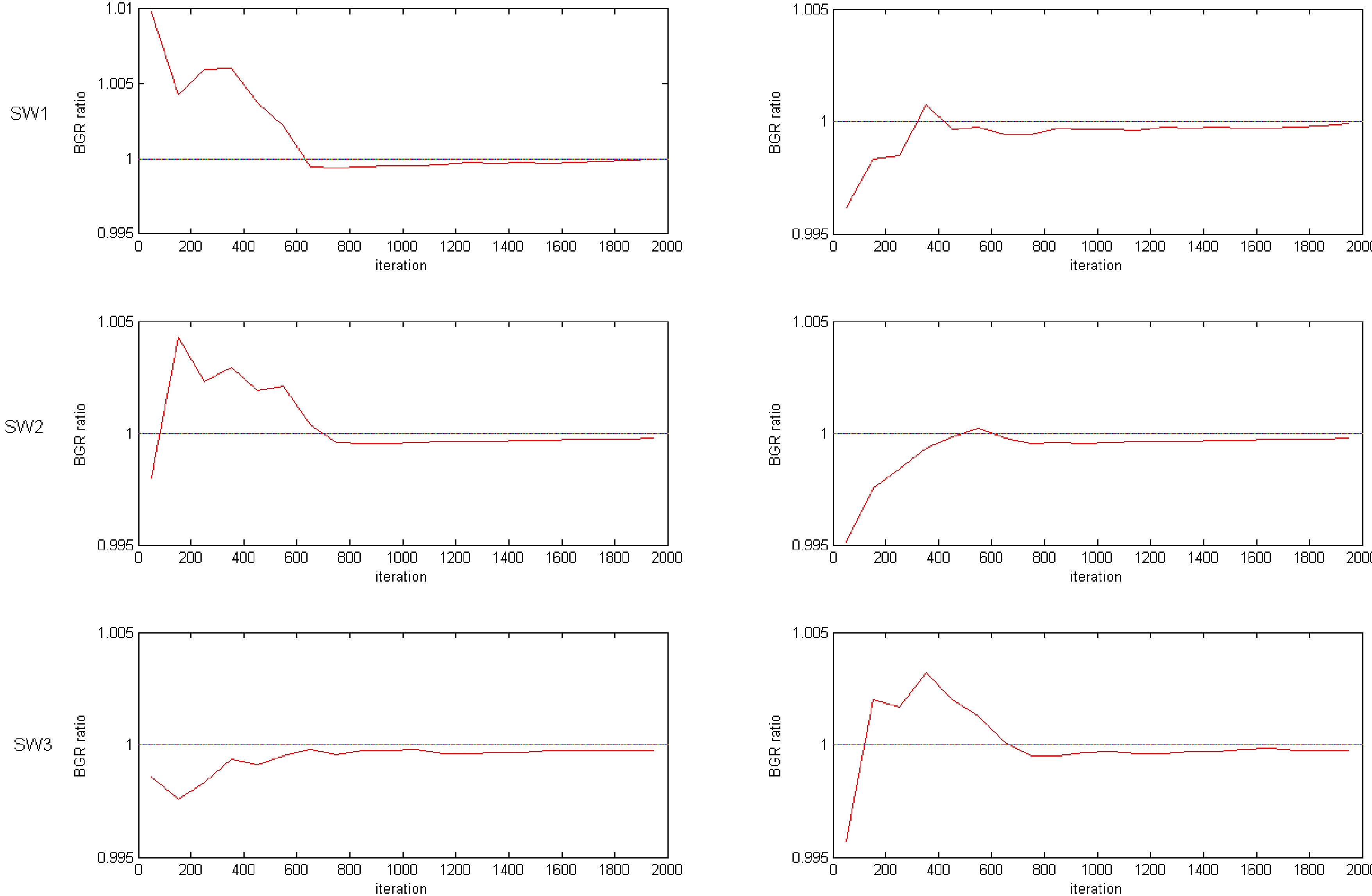
$$\tau^{(0),\#2} = (0.59, 4.46, 15.13)$$

- 2000 iterations

Trace Plot for Two Chains



BGR Ratio Plot

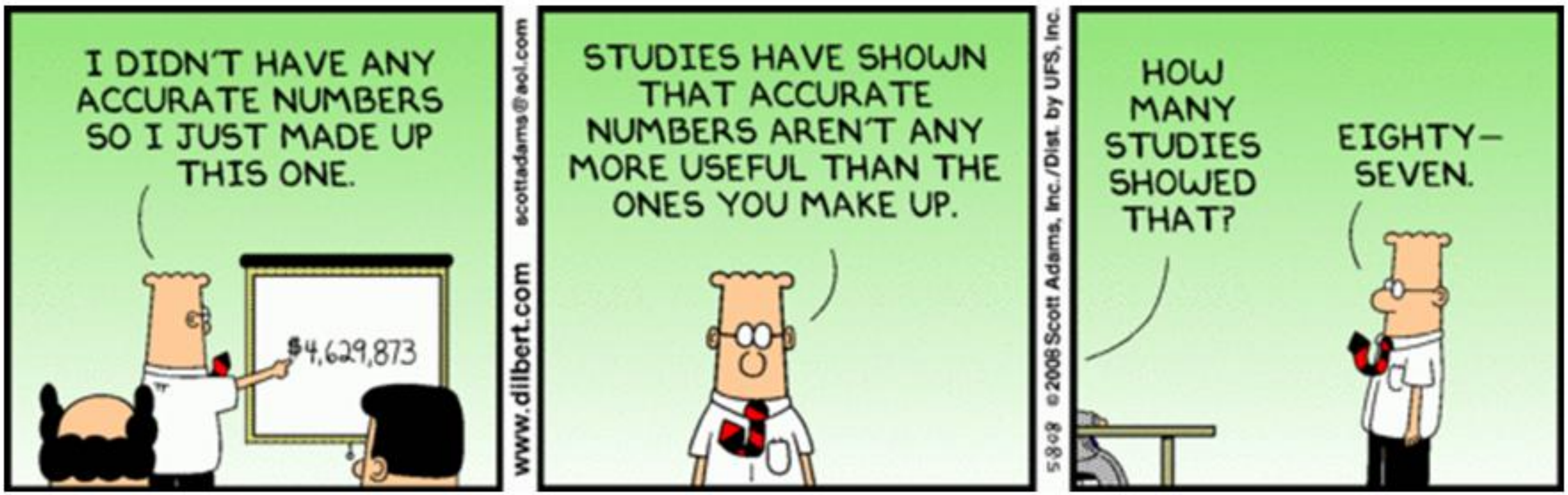


Discussion

- A method was proposed to determine sampling windows for nonlinear mixed effects models
- The method uses a MCMC style recursive sampling approach
- At each iteration the windows are computed exactly
- It was not necessary to condition the search such that the windows did not overlap
- The method converged rapidly and remained stable over subsequent iterations.

Acknowledgements

- Lee-Kien Foo
- James McGree
- John Eccleston


I DIDN'T HAVE ANY ACCURATE NUMBERS SO I JUST MADE UP THIS ONE.
$4,629,873
www.dilbert.com
scottadams@aol.com
STUDIES HAVE SHOWN THAT ACCURATE NUMBERS AREN'T ANY MORE USEFUL THAN THE ONES YOU MAKE UP.
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HOW MANY STUDIES SHOWED THAT?
EIGHTY-SEVEN.