SADDLE_RESET

more robust parameter estimation with a check for local practical identifiability

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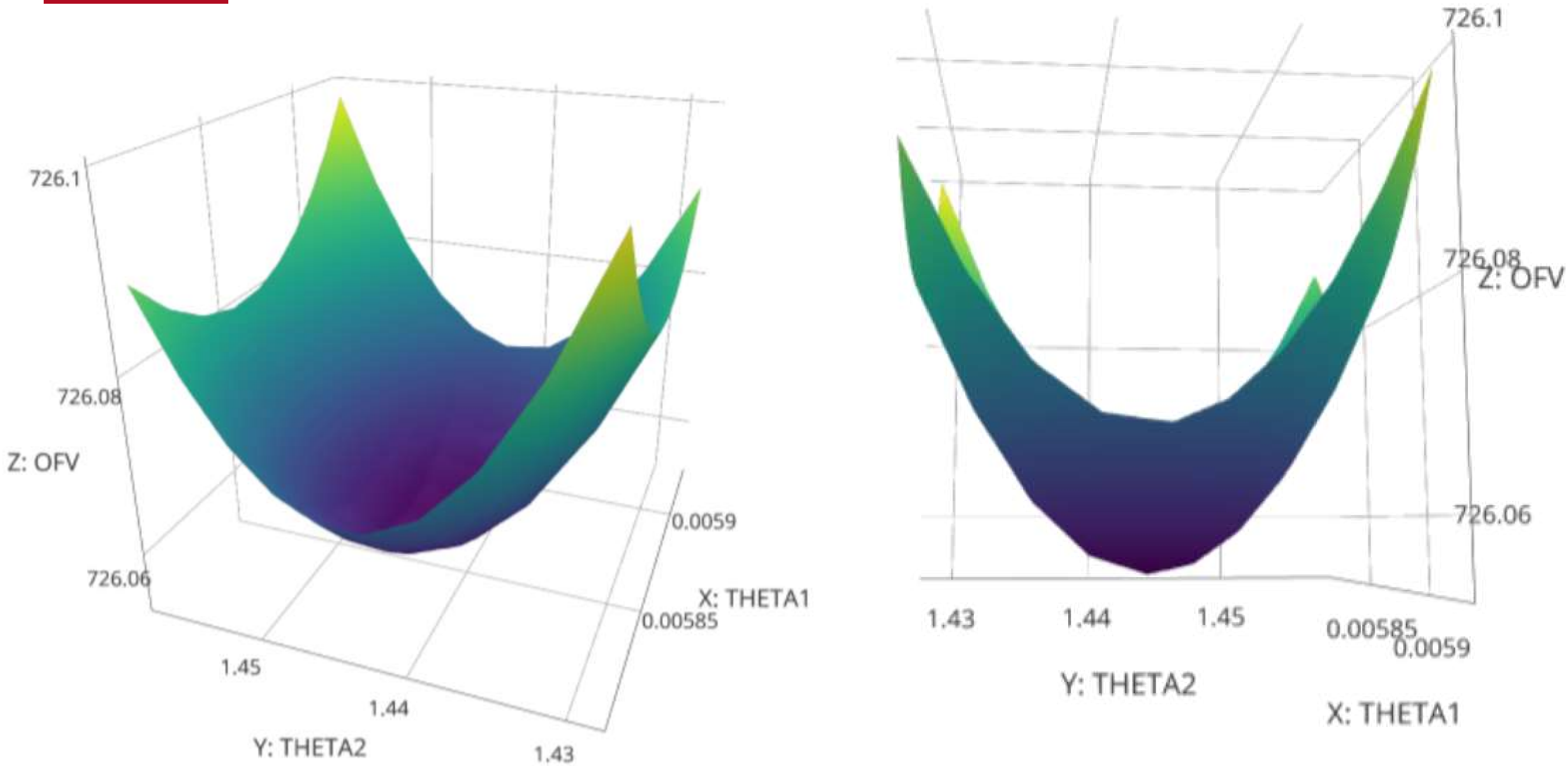
Introduction

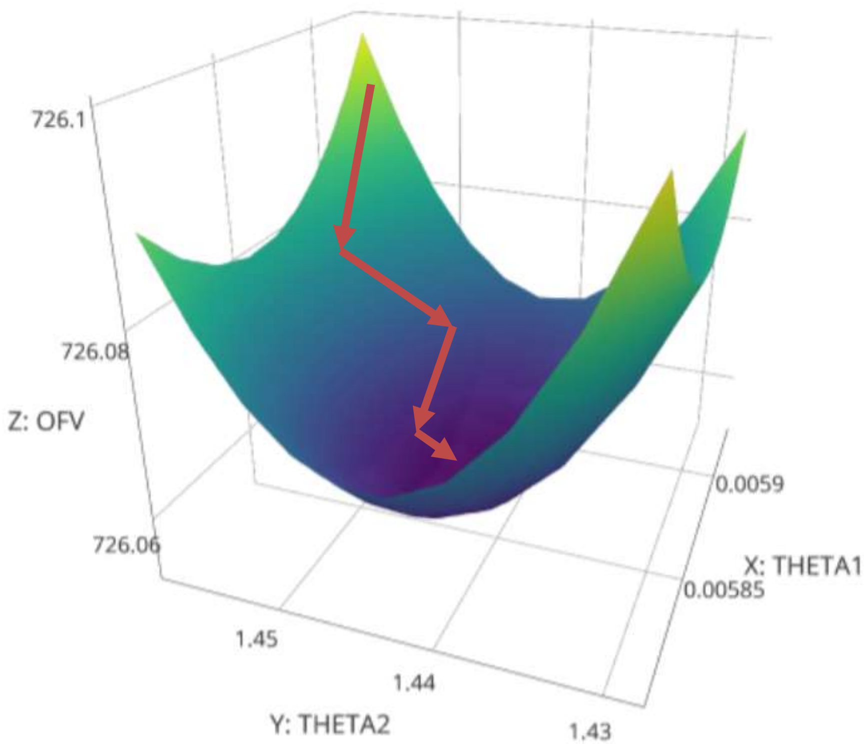


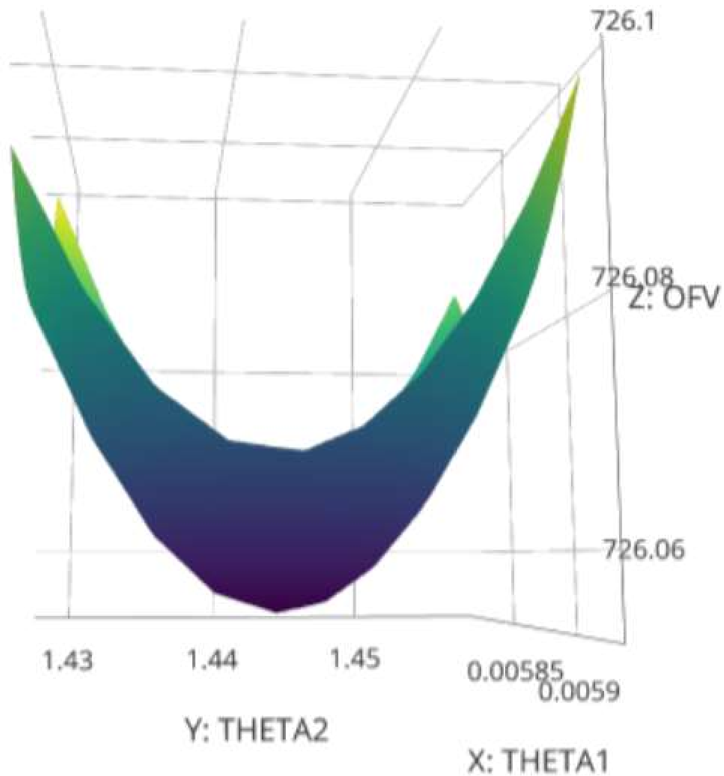
Introduction

Efficient and accurate parameter estimation is crucial to Pharmacometrics

Methods that minimize gradients have become ubiquitous to our field

Introduction





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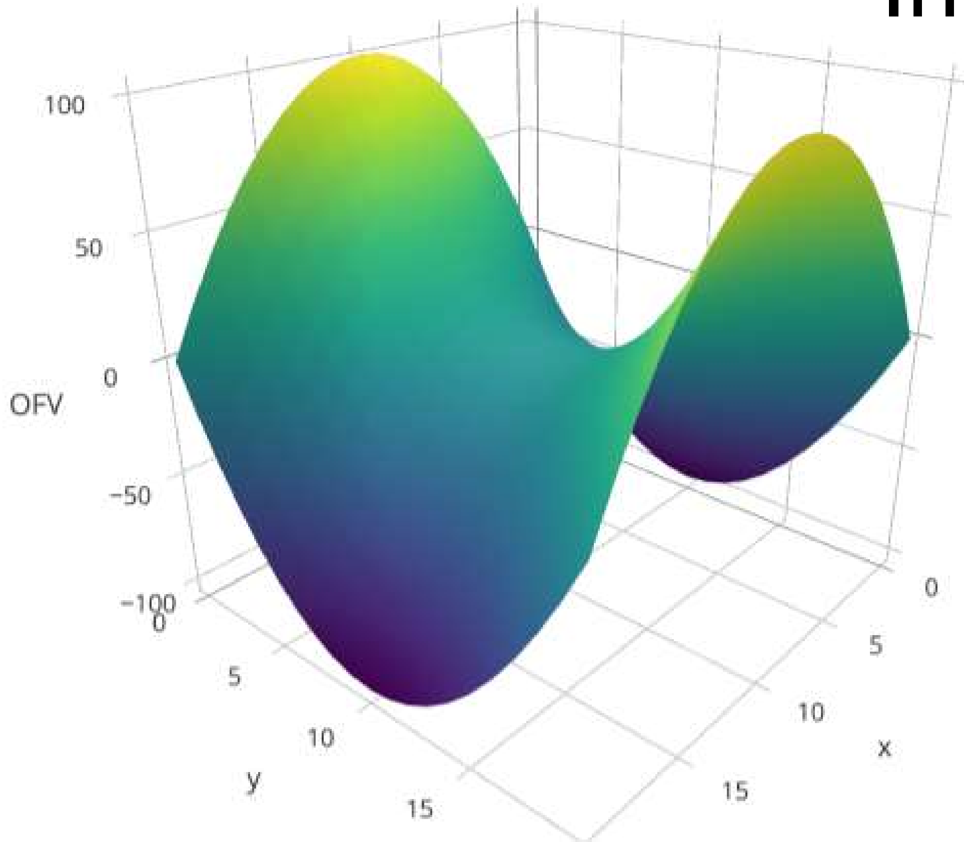

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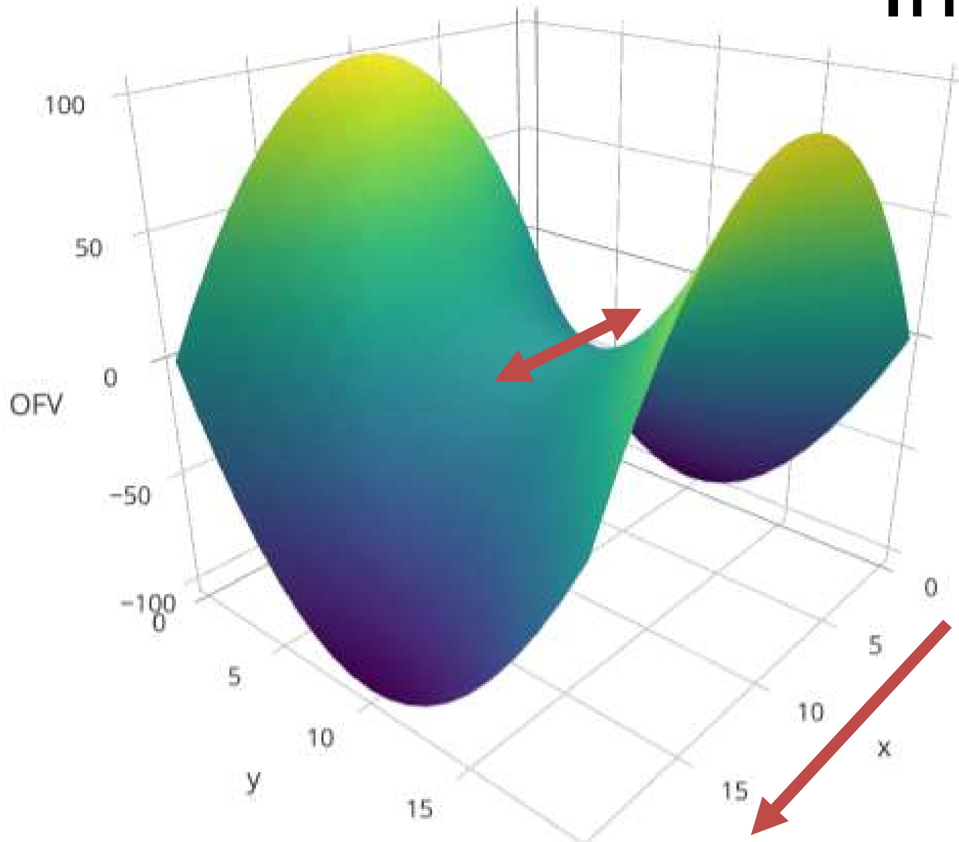

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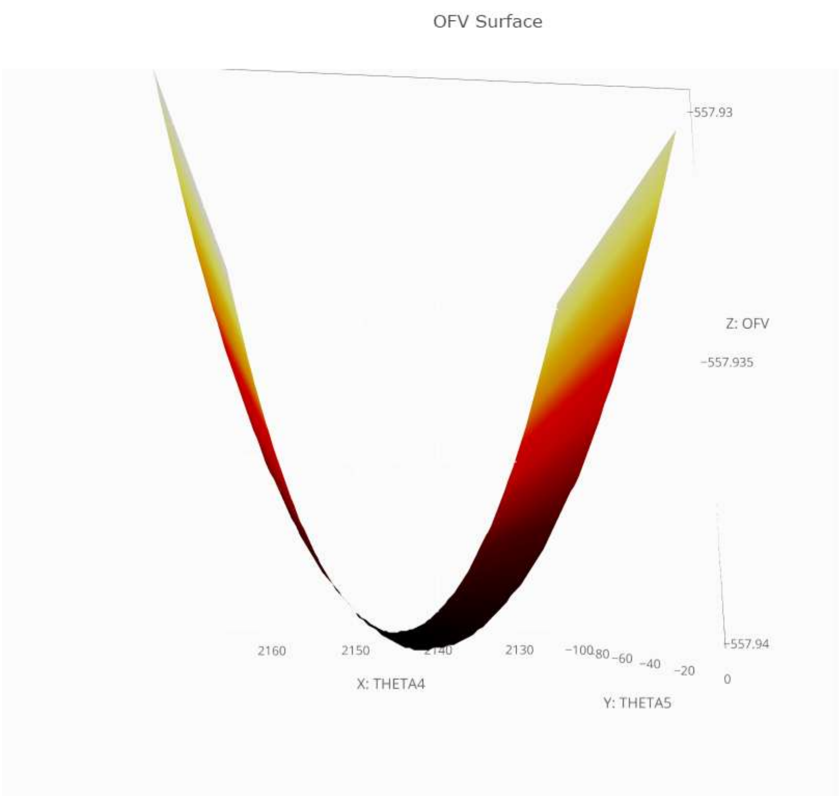

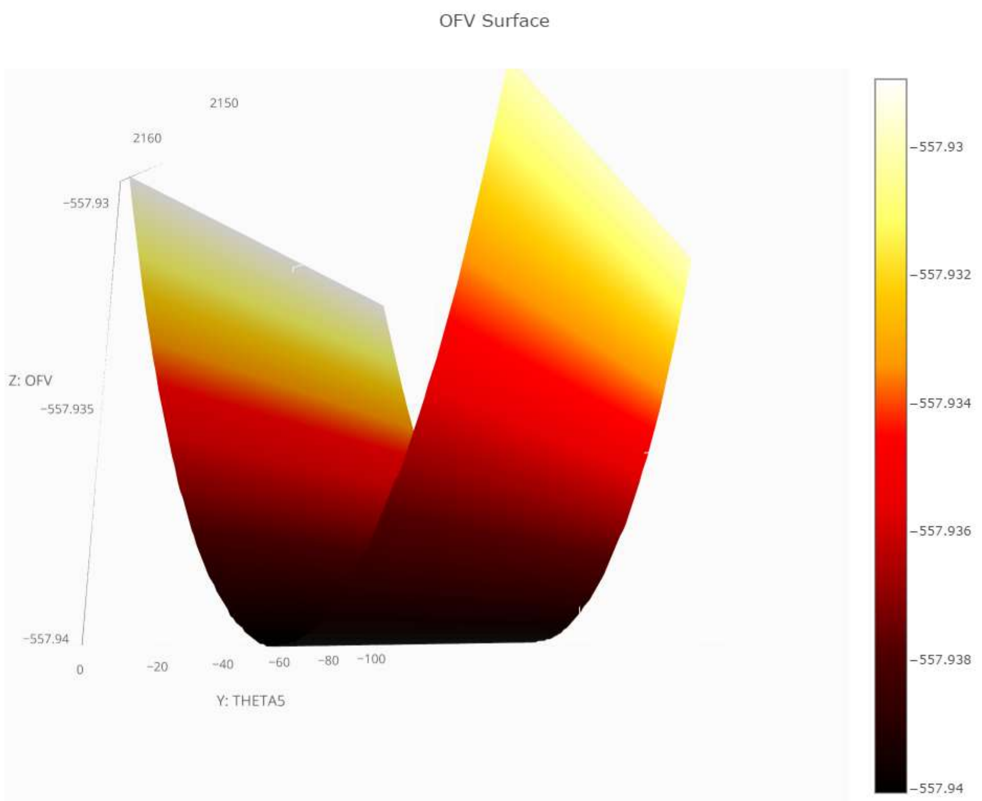

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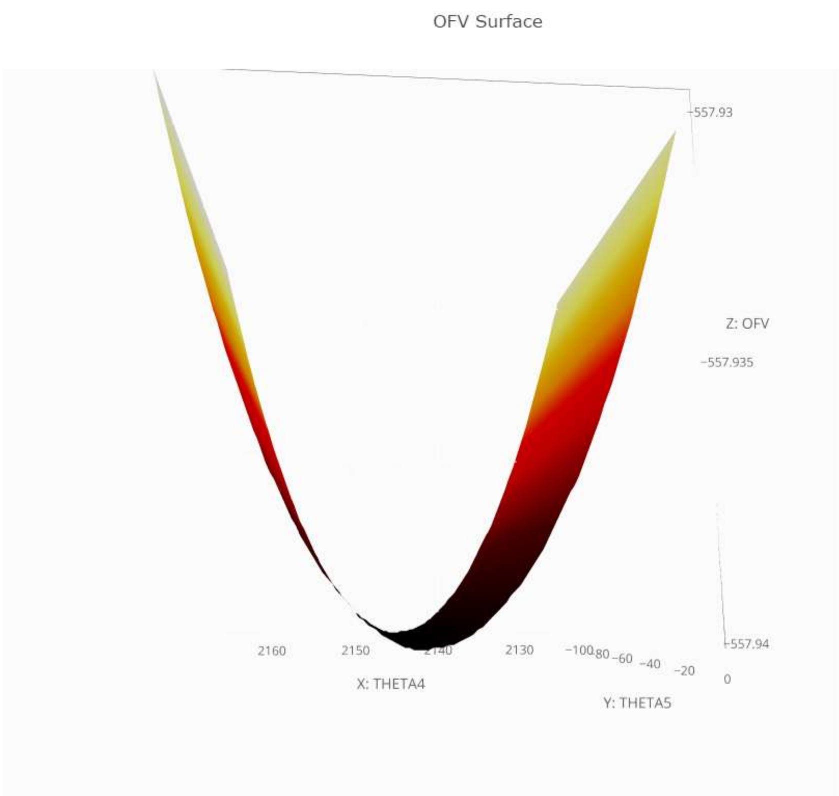

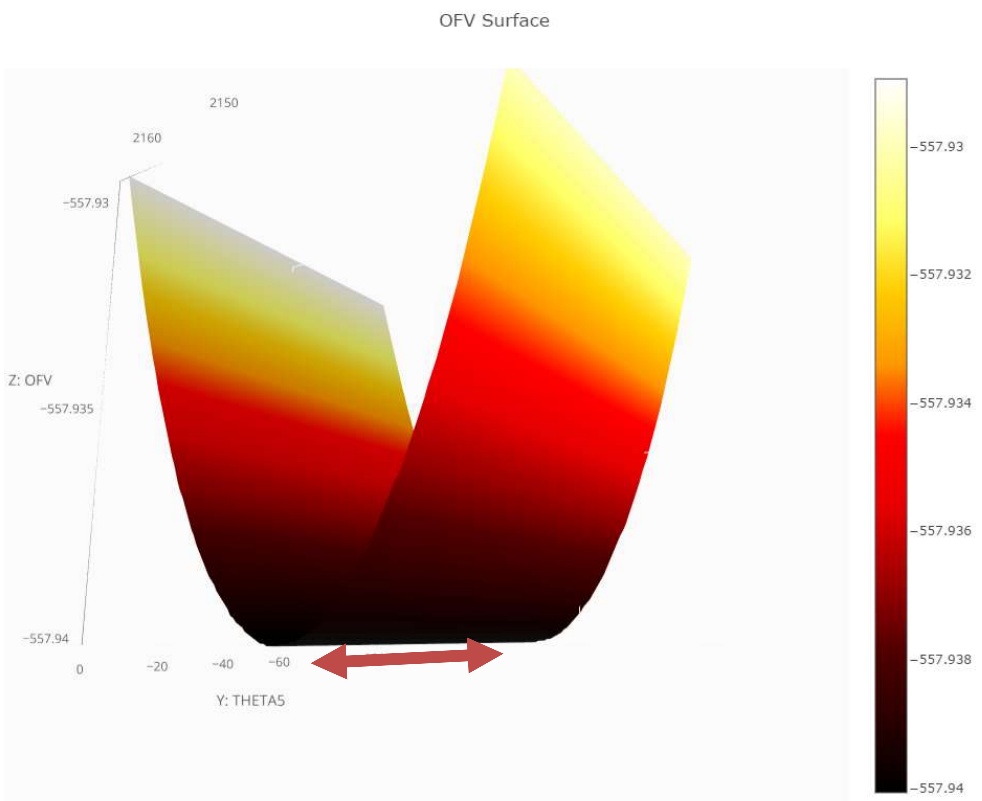

Introduction

After estimation we know little about the likelihood around our point

– We may not be in a minimum, but a saddle point

– We may have parameters that are non-identifiable (non-estimable)

Introduction

Local:

– Our algorithm is only concerned with the immediate surroundings around the final estimate point on the

  - 2log(likelihood) surface

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  - 2log(likelihood) surface

Practical:

- Our algorithm considers the model-data combination

- Structural identifiability is evaluated assuming infinite data

Brief Technical Description

1. Gradient minimization based estimation is performed as normal

2. The result is checked for zero gradients

    - If zero gradients are found, the associated parameters are reset to initial values and estimation is resumed

    - If none are found move to the next step

Brief Technical Description

3. The Hessian of the likelihood (the R-matrix) is eigendecomposed and the minimum curvature (including negative curvature) of the -2log(likelihood) is identified

3. Parameters are changed along the minimum curvature

    - Step length calculated from curvature to give ΔOFV ≈ 1

4. Estimation is resumed from this new point

Brief Technical Description

Implemented in NONMEM 7.4

```
$ESTIMATION
      MAXEVAL=9999
      NSIG=4
      METHOD=COND INTERACTION
      SADDLE_RESET=1
      PRINT=5
```

Brief Technical Description

The BFGS approximation of the Hessian is used by default

- Constrained to be positive-definite
- As efficient as the true Hessian in our experiments

With option SADDLE_HESS=1 the true second derivative Hessian is used

- Computationally expensive (same as covariance step)

Brief Technical Description

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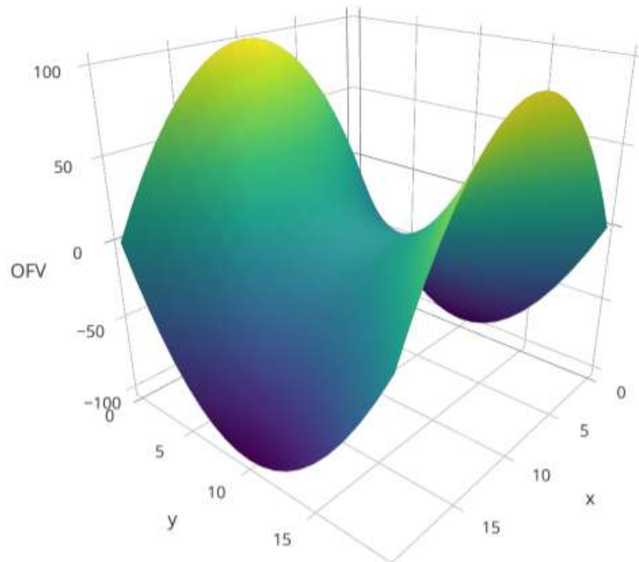
Numerical Experiment 1

SADDLE_RESET can help us avoid saddle points



Numerical Experiment 1 - Models

Four published, fully identifiable models:

Model	Type	No Parameters	No IDs	No Samples	Solution
A	PK	9	177	1196	Closed Form
B	PK	13	93	274	Closed Form
C	PKPD	11	47	530	Diff. Eq.
D	PK	6	59	155	Closed Form

A. Jönsson et al, Clinical Pharmakocinetics (2005), 44(8):863-78
B. Bergmann et al, The Pharmacogenomics Journal (2011) 11, 113–120
C. Wählby et al, Br J Clin Pharmacol. (2004) 58:367– 77.
D. Grasela Donn, Dev. Pharmacol. Ther. (1985) 8: 374-383

Numerical Experiment 1 - Method

Wide random perturbation around best parameter estimates

1,000 NONMEM estimations for each model

Successful estimation measured as OFV < (best known OFV + 1)

Some estimations will complete to saddle points and local minima

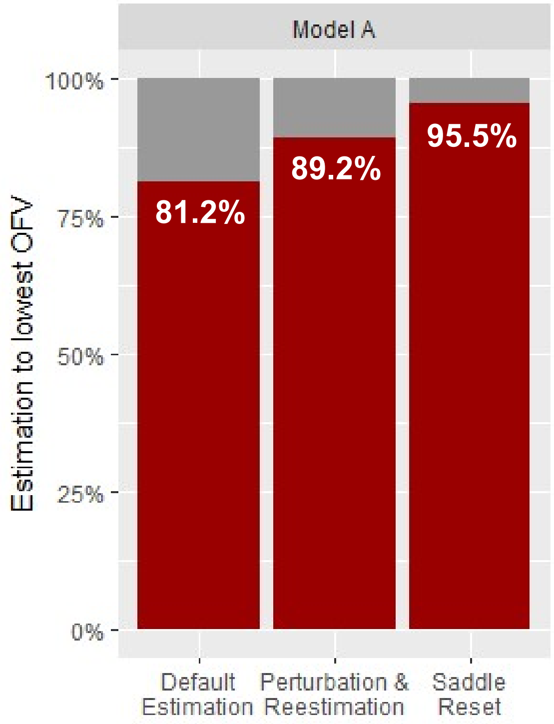
Numerical Experiment 1 - Method

Comparison to perturbation of parameter values within 10%

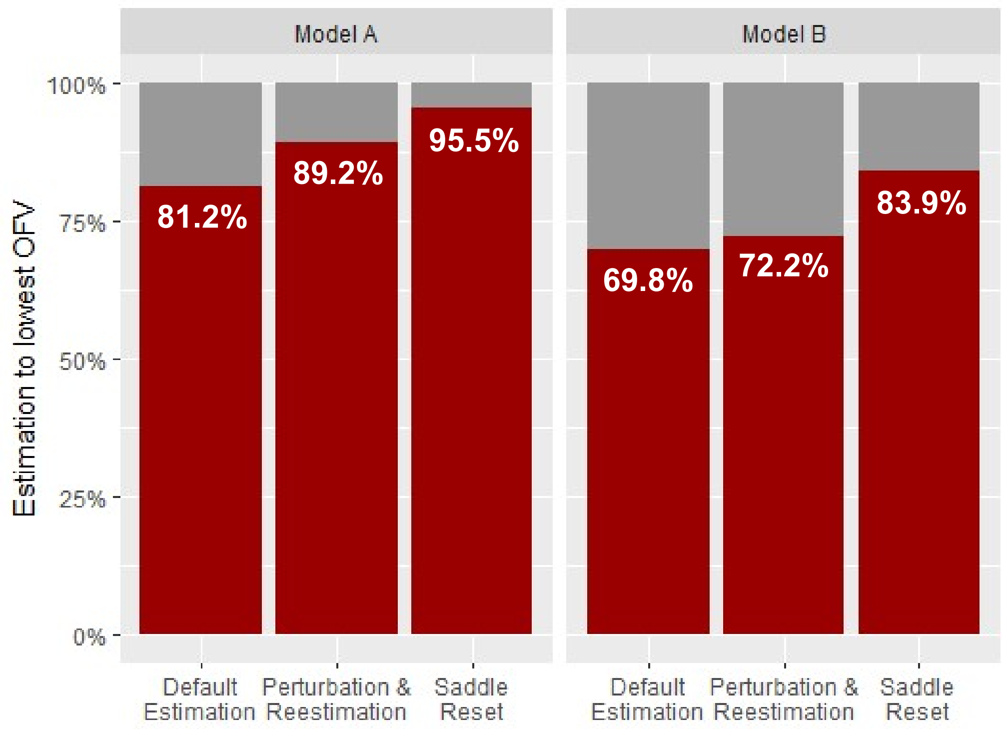
Two estimations per model

- One from randomly perturbed estimates
- One from final estimates of previous estimation

Numerical Experiment 1 - Results



Numerical Experiment 1 - Results



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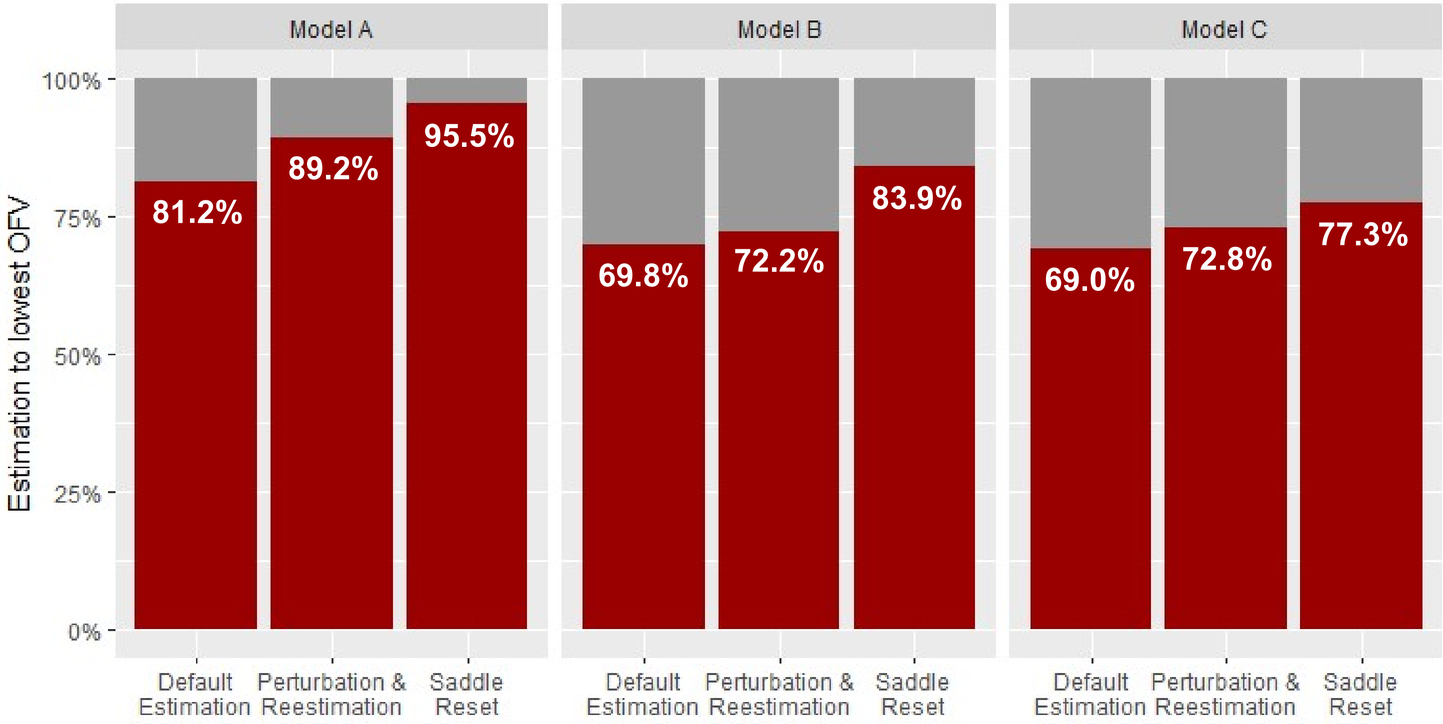

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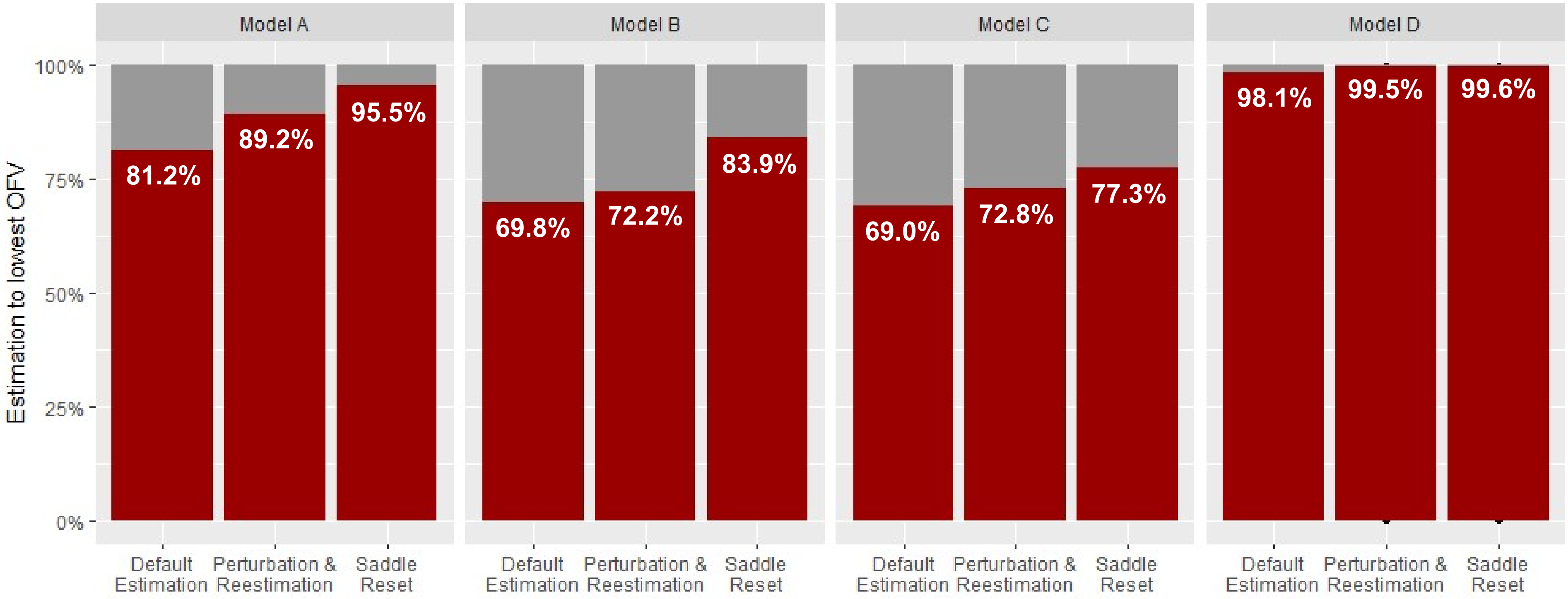


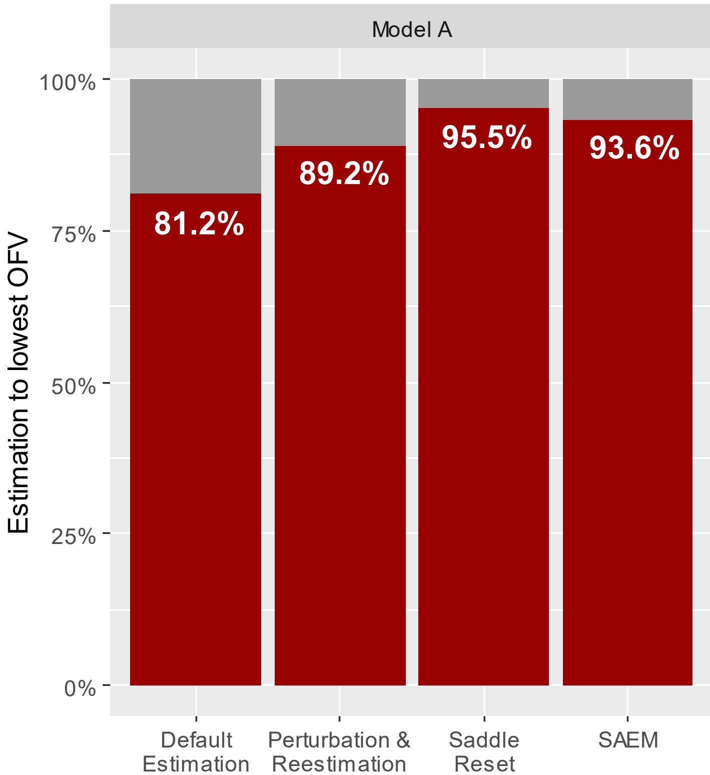
Numerical Experiment 1 - Results

Does it matter if we end up in a saddle?

Three saddles and the lowest known minimum for Model A

OFV	Prop Err	V1	Q	V2	CL	CLCR-CL	WT-V1	IIV CL	IIV V1
-2029.10	0.222	10.360	4.280	5.616	2.893	0.019	0.014	0.055	0.008
-2233.49	0.169	7.744	13.909	7.391	1.928	0.050	0.021	0.079	0.174
-2339.87	0.166	6.770	18.959	8.354	2.882	0.019	0.027	0.053	0.239
-2346.79	0.165	7.913	13.122	7.170	2.914	0.019	0.019	0.054	0.162

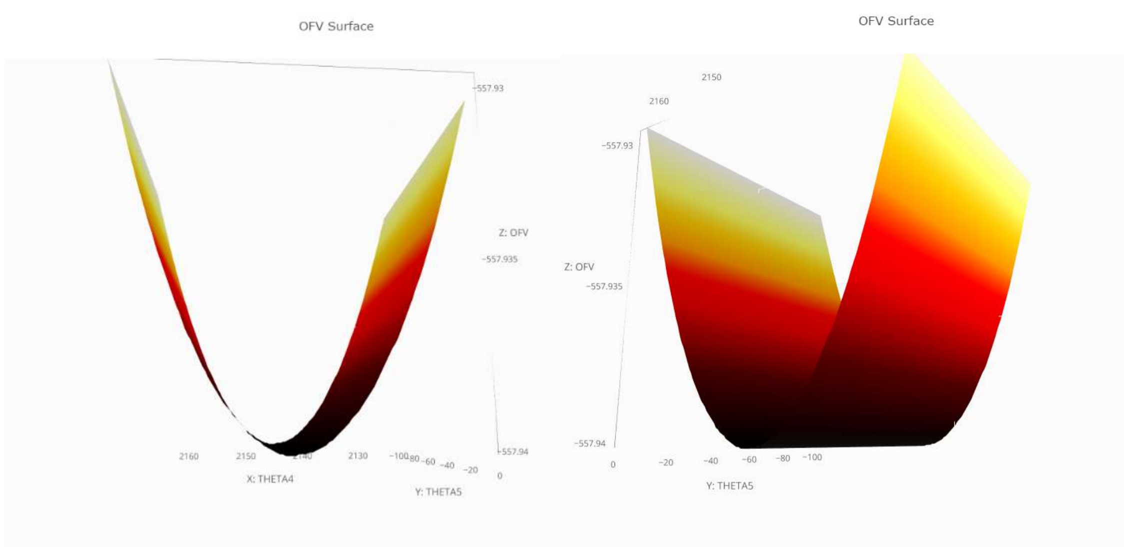
SAEM Comparison



- Saddle Reset has a success rate comparable to a Monte-Carlo method such as SAEM

Numerical Experiment 2

SADDLE_RESET can help us discover local practical non-identifiability



Numerical Experiment 2 - Models

Two models representing two identifiability issues

E. Practically non-identifiable Emax model-data combination
F. Structurally non-identifiable model

Numerical Experiment 2

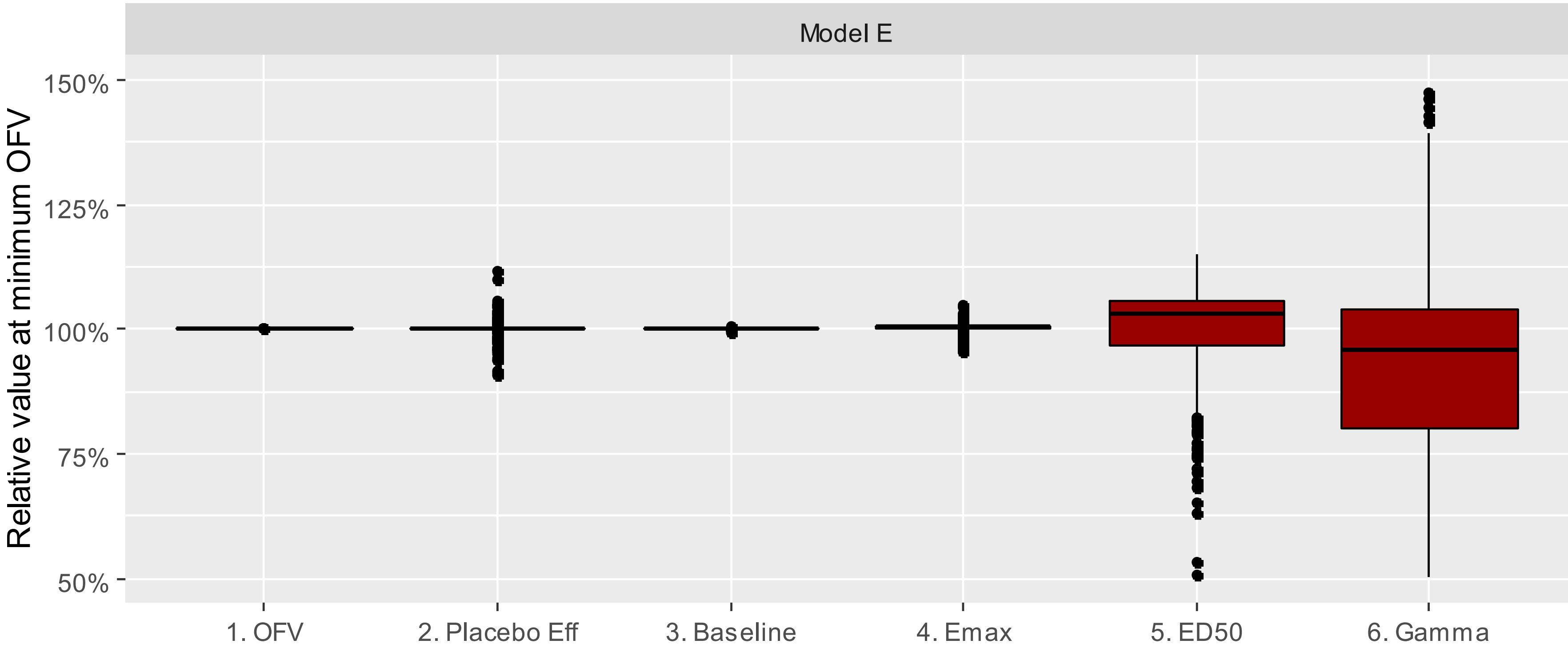
Model E – Multiple parameter values with same OFV

OFV	Placebo Eff.	Baseline	Emax	ED50	Gamma
-2710.52	0.13338	2.5084	0.30203	39.1895	104.173
-2710.52	0.13339	2.5083	0.30229	33.5416	12.1728
-2710.52	0.13348	2.5083	0.30228	29.8024	7.17949

Numerical Experiment 2 - Results

SADDLE_RESET found alternative parameter values with the same OFV in 96% and 95% of 1,000 cases for models E and F respectively

Numerical Experiment 2 - Results



SADDLE_RESET Benefits

Improves confidence in parameter estimates

- Expose local practical non-identifiability
- Avoid saddle points

I hope you will add this to your smorgasbord of methods

Thank you!

NONMEM 7.4

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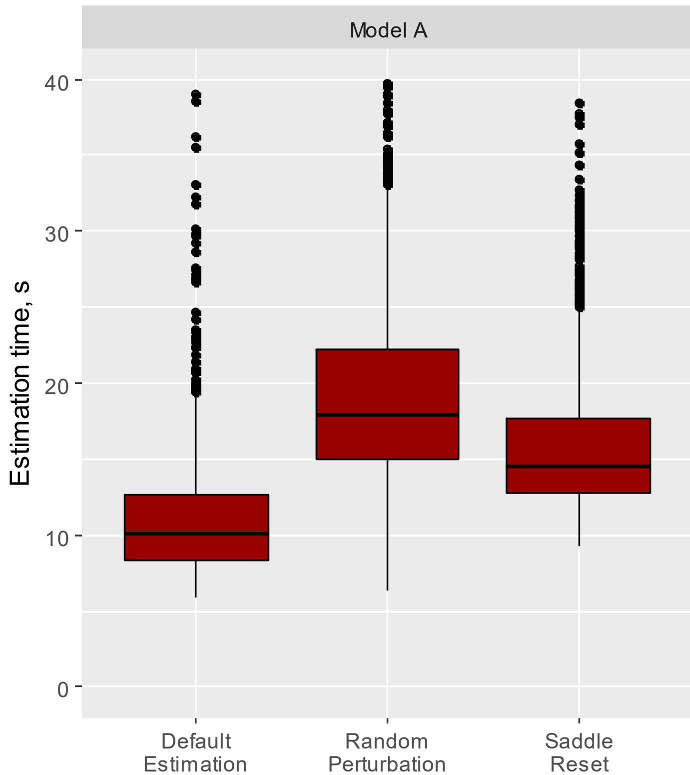
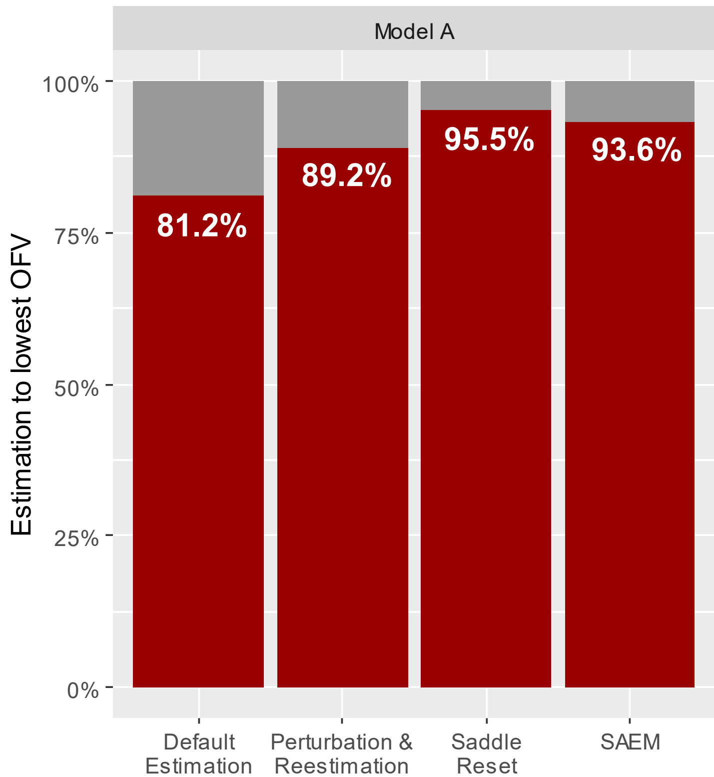
Extra Materials

Runtime



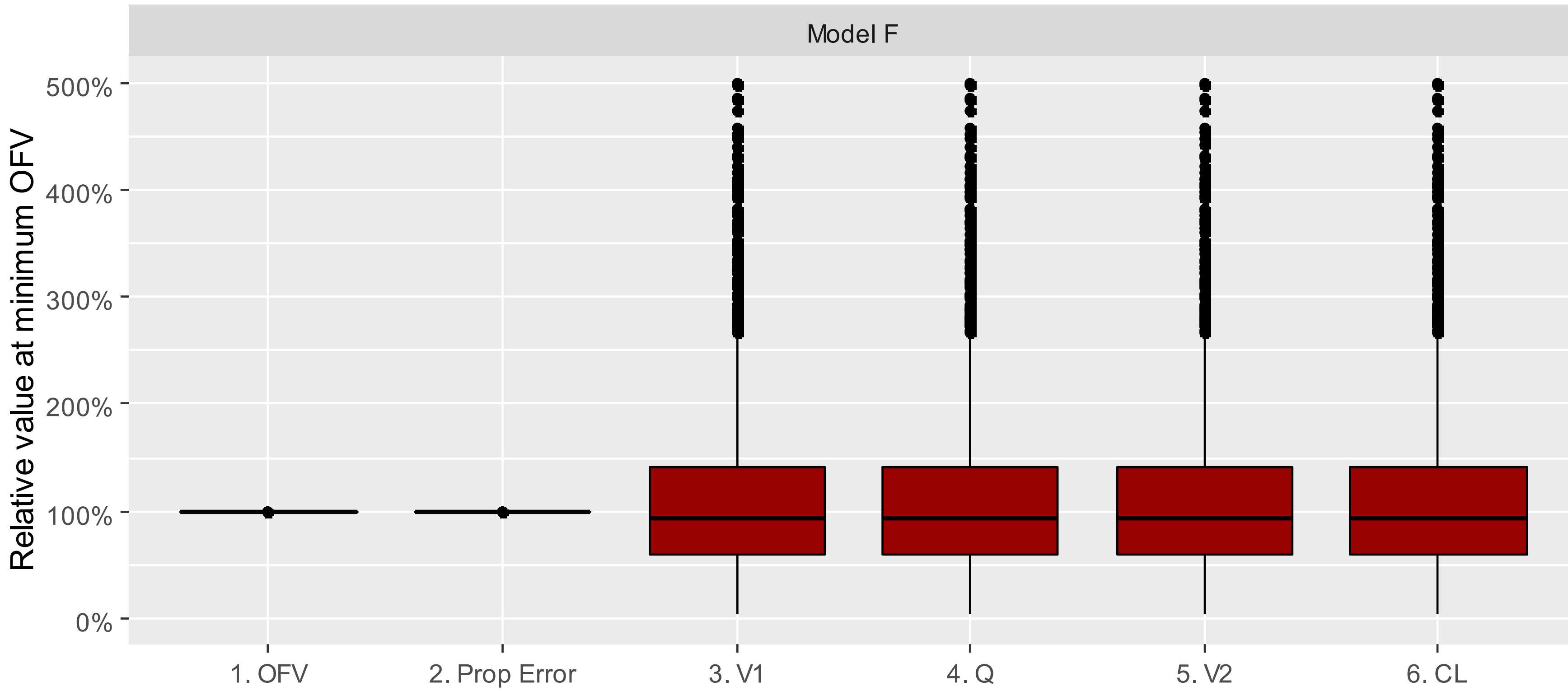
- Not a rigorous runtime experiment
- Not same execution environment
- 1,000 samples

SAEM



- Comparable success rate as a Monte-Carlo method such as SAEM

Structurally Non-Identifiable Case



Saddle Examples

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