Dismounting Saddles on the Likelihood Surface

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Objective

To enable parameter estimation to continue past saddle points on the -2Log Likelihood surface.

Introduction

A prominent issue with parameter estimation in nonlinear mixed-effects models is saddle points on the likelihood surface. A saddle point is characterized by at least one eigenvector along which the objective function, -2Log Likelihood, is at a maximum rather than a minimum. See figure 1 where a maximum exists along the Omega(2,2) axis. Methods that work by minimizing the gradient are unable to distinguish saddle points from minima, and may therefore produce final parameter estimates at saddle points.

Method – Proposed Algorithm

1. Estimate the maximum likelihood parameters using a gradient based algorithm.
2. Approximate the Hessian of the -2Log Likelihood (R-matrix) at the parameter values obtained in step 1.
3. Obtain the eigenvalues and eigenvectors of the R-matrix.
4. Select two sets of new parameter values along the eigenvector associated with the minimum eigenvalue obtained in step 3. One in each direction. The magnitude of the perturbation in is determined using the second-order Taylor series approximation of the OFV surface, and chosen to cause approximately 1 OFV difference from the estimated maximum likelihood in step 1.
5. Use the parameter values selected in step 4 as the initial estimate and re-estimate the maximum likelihood parameter.
6. Select the lowest OFV of the two perturbed estimations.

Method – Surface Plotting

A 3D graphical representation of the OFV surfaces around a selection of points was created to further understand features of the OFV surface. Two parameters were selected; the parameter associated with the lowest Eigen vector and one more. OFV evaluation was performed in NONMEM, using the MAXEVALS=0 setting, on all combinations of equi-spaced parameter values around the point in question.

Results – Surface Plotting

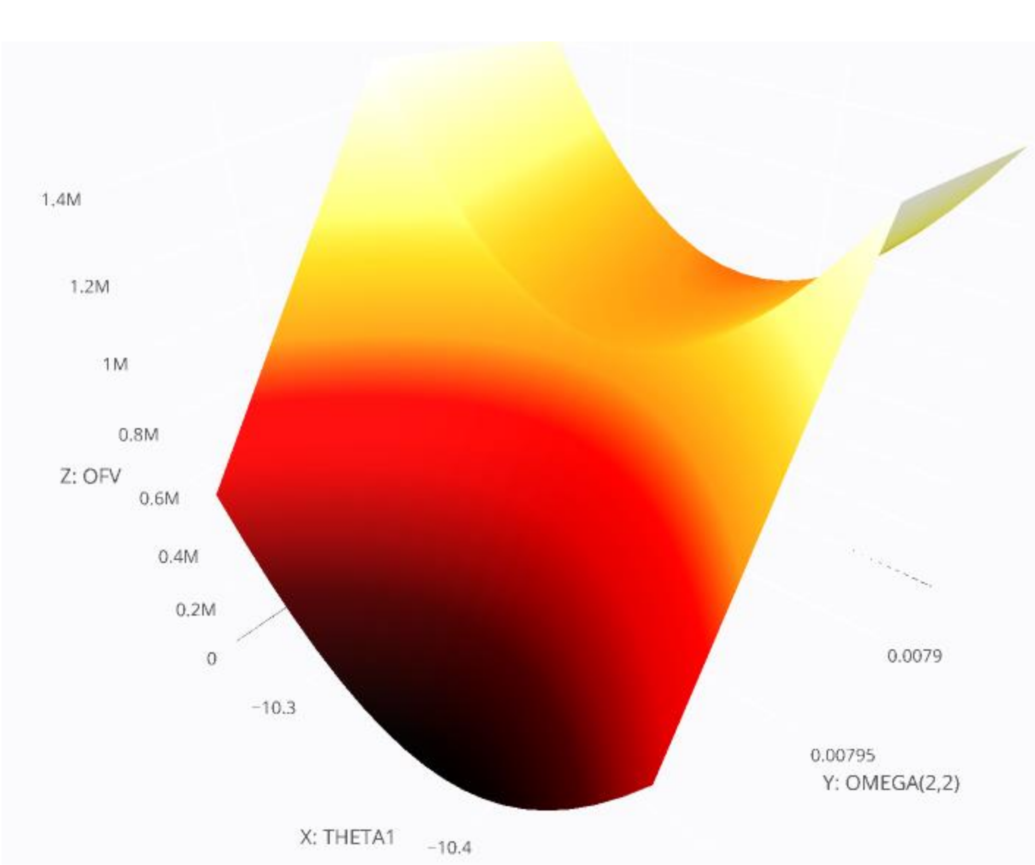

Fig 1. Example of a saddle point on the OFV surface for model 1.

Figure 1 shows a saddle point on the OFV surface where NONMEM has ended estimation with successful minimization.

In the reduced dimensions of figure 1 the maximum lies along the Omega(2,2) axis, while the point is a minimum when viewed along the Theta 1 axis.

Method – Numerical Experiment

Three PK models were examined using FOCEI parameter estimation in NONMEM[1]:

1. Jönsson et al [2]
2. Bergmann et al [3]
3. Wählby et al [4]

Estimation was performed from one thousand sets of initial parameter values for each model, randomly perturbed from the best known estimates with a degree of 0.99 (new initial value = old value * uniform random number * (+-degree * old value)).

Our proposed algorithm was applied to each of the estimations. For comparison two random perturbations were also performed using the parallel retries procedure in PsN. All estimations were categorized as having reached minimum OFV or not (OFV <= minimum OFV + 1).

Results – Numerical Experiment

The proposed method performed better than random perturbation for all three models. The improvement was most notable for model 1 where 56% more estimations were brought to minimum OFV by the proposed algorithm than with random perturbation. For models 2 and 3 the corresponding improvements were 13% and 17% respectively.

In the below figures the left side represents the original state of estimations after the initial wide perturbation, and the right is after the respective intervention. Estimations have either minimized successfully to OFV values above the minimum (red), to the minimum OFV (green). The increase in green to the right quantifies the improvement in OFV for the respective method.

Model 1

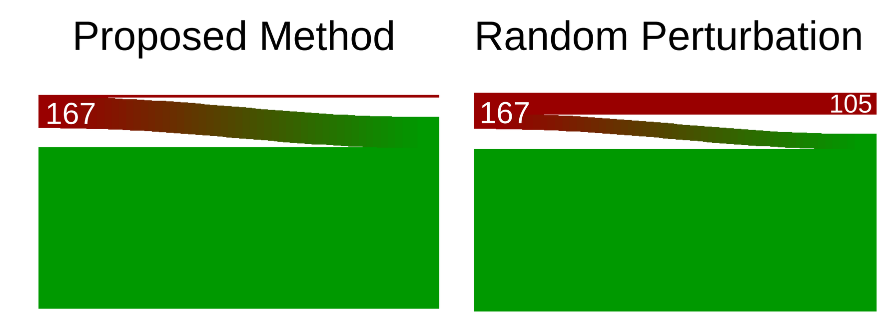

Fig 2. The proposed method left only 11 estimations in higher than minimum OFVs, while random perturbation left 105.

Model 2

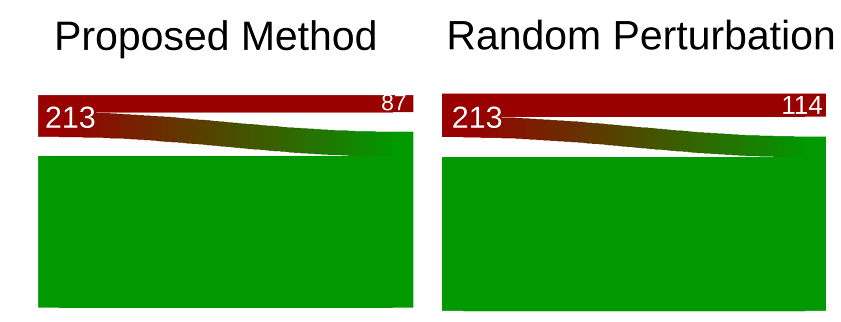

Fig 3. Improvement in estimation for model 2. Our proposed method brings 13% more estimations to min OFV.

Model 3

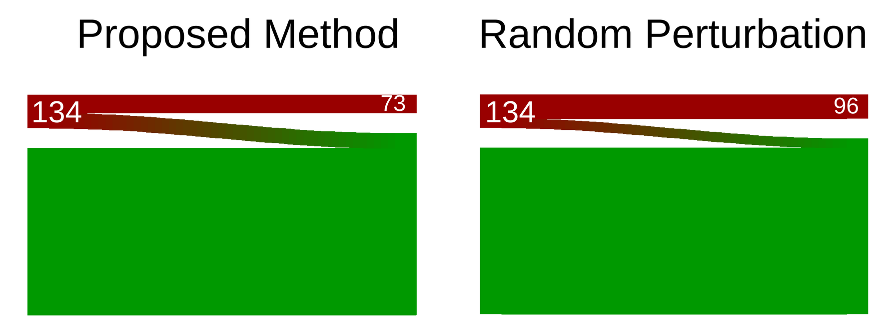

Fig 4. Improvement in estimation for model 3. Our proposed method brings 17% more estimations to minimum OFV.

The number of estimations helped by the proposed method is dependent on the model used. However, the proposed method was more efficient than random perturbation for all the models tested.

Conclusions

We have proposed a method that efficiently handles saddle points and other features on the -2Log Likelihood surface where gradient based methods reach successful minimization at above minimum OFVs.

References

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