Parameter estimation in nonlinear fixed-effects QSP models: benchmark of optimization methods

Sergei Vavilov[1], Victor Sokolov[1], Kirill Zhudenkov[1], Leonid Stolbov[1], Kirill Peskov[1,2]
([1] M&S Decisions LLC, Moscow, Russia, [2] Sechenov University, Moscow, Russia)
Contact at: sergei.vavilov@msdecisions.ru

Abstract

The objective of this work is to compare selected software solutions that provide parameter estimates in nonlinear fixed-effects (NLFE) models. Nelder-Mead, variants of L-BFGS (Broyden–Fletcher–Goldfarb–Shanno), BOBYQA (Bound Optimization by Quadratic Approximation) and MMA (method of moving asymptotes) all converged to the same optimum, as well as provided similar confidence intervals, and showed the same performance. As expected, global optimization algorithms only managed to converge to the same optimum after a larger number of objective function evaluations.

Introduction

Robust and efficient parameter estimation is one of the key steps in quantitative systems pharmacology (QSP) model development. The problem of parameter estimation is solved by maximizing an objective function that describes the likelihood of predicting the observed data, given a suggested set of parameters [1]. Therefore, parameter estimation in QSP models requires an informed choice of a suitable numerical optimization algorithm. This algorithm should provide point estimates and respective confidence intervals based on aggregated experimental data and a likelihood function, given a calibrated ODE-based model.

Methods

A previously published semi-mechanistic QSP model [2] that describes the effect of exenatide, a GLP-1 receptor agonist, on food retention was used to assess the performance of selected optimization methods. The model incorporates 11 ODEs, 2 estimated parameters, and a single observed variable. A set of R-based packages and standalone software were tested to provide parameter estimates for this model.

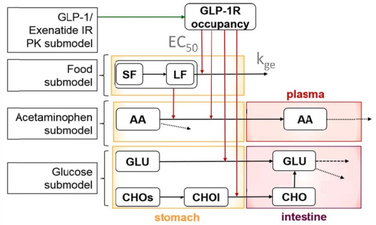

Figure 1. A scheme of the QSP food retention model used to benchmark the optimization algorithms. Adopted from [2]. The food retention depends on two estimated parameters, k_{ge} (food retention rate) and EC_{50} (half-max concentration).

Results

Running time

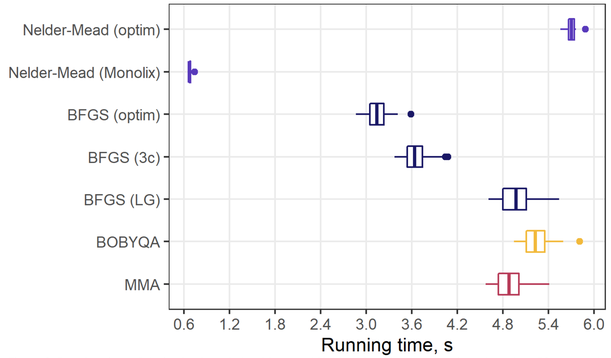

Figure 2. Running time of derivative-based algorithms and Nelder-Mead implementations, based on 50 repeated evaluations. Timing for stochastic algorithms not shown here.

Variations of the BFGS algorithm, BOBYQA and MMA perform similarly fast, while a standalone Monolix implementation of the Nelder-Mead algorithm allows to reach a speed improvement, and an R-based Nelder-Mead implementation takes most time. Despite this, the point estimates and confidence intervals given by all methods remain consistent.

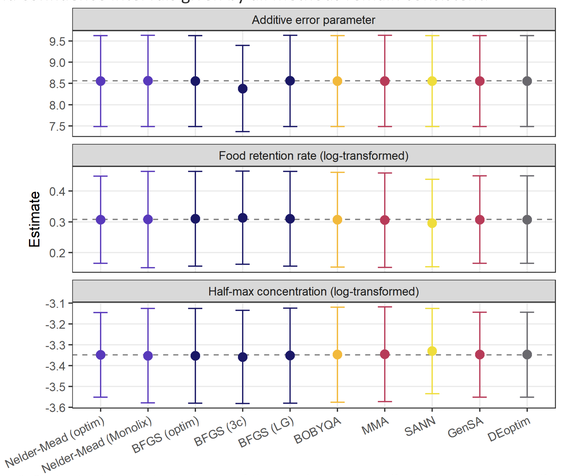

Figure 3. Point estimates and standard errors of three model parameters (food retention rate k_{ge}, half-max concentration EC_{50} [2] and an additive error parameter) estimated by optimization routines. True parameter values are shown with the dashed line.

Derivative-based methods

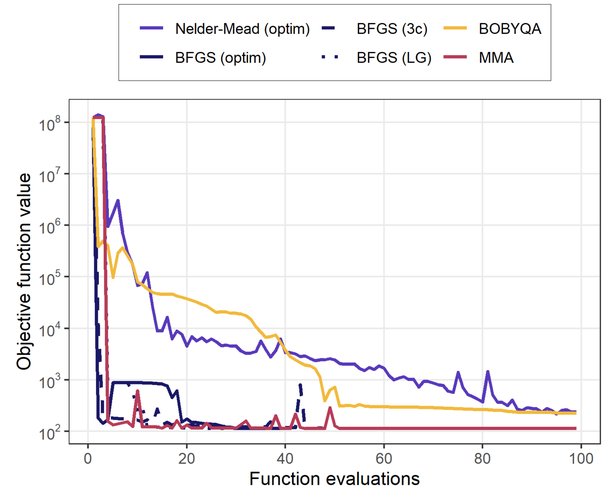

Figure 4. Objective function value for first 100 iterations of derivative-based methods. Nelder-Mead curve is added as a reference. After > 1000 evaluations, all methods converge to the same objective function value.

Global stochastic methods

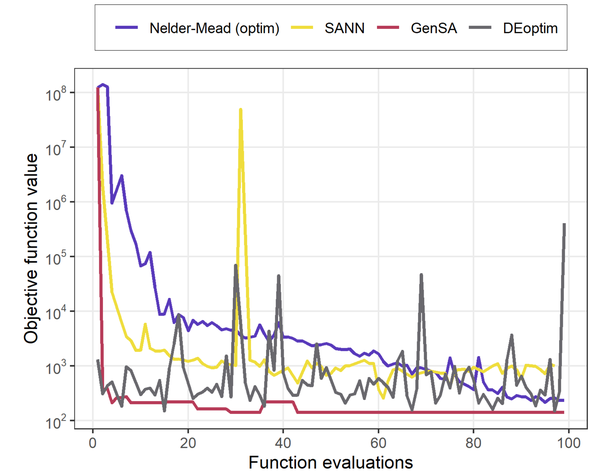

Figure 5. Objective function value for first 80 evaluations of global stochastic methods. Nelder-Mead curve is added as a reference. DEoptim: differential evolution optimization; GenSA: generalized simulated annealing; SANN: simulated annealing. DEoptim does not require a starting parameter guess. After > 1000 iterations, all methods converge to the same objective function value.

Derivative-free optimization methods are suitable when calculation of the gradient and the Hessian of the likelihood function is numerically costly or unreliable, such as in the case of ODEs with discontinuous explicit functions or stiff ODEs. These methods include the Nelder-Mead simplex method and a class of *global stochastic methods*: simulated annealing, differential evolution optimization. In contrast, *derivative-based* methods such as BFGS, trust-region and quadratic approximation methods use projected gradient norm or trust region radius as their convergence and termination criteria.

Among selected algorithms, Nelder-Mead, BOBYQA and MMA took more than 50 iterations to converge to a target objective function value and a target point in parameter space, while BFGS-based methods needed less than 50 iterations to converge and terminate. As expected, global optimization algorithms only managed to converge to the same optimum after a larger number of objective function evaluations (upwards of 300 evaluations). The exact number of evaluations needed to reach a target objective value was stochastic, which translated to an unpredictable solution time limited by the pre-set maximum evaluations count.

Conclusions

Local methods such as Nelder-Mead or L-BFGS-B serve as a good start for estimating parameters in NLFE problems. Depending on the constraints in the parameter space, smoothness of the likelihood function, or the number of local minima, a derivative-free local algorithm (BOBYQA or MMA) or a derivative-free global algorithm (generalized simulated annealing or differential evolution) can perform equally well or better. Further benchmarking of optimization algorithms could involve more advanced QSP models with a larger parameter space and multiple observed variables.

References

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[2] Veronika Voronova, Kirill Zhudenkov, Robert C. Penland, David W. Boulton, Gabriel Helmlinger, Kirill Peskov. Exenatide effects on gastric emptying and oral glucose appearance in plasma: A quantitative assessment using an integrative systems pharmacology model, ACoP9, October 2018.

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