Comparing the Performance of Four Open-Source Methods for Multiple Parameter Estimation in a Systems Pharmacology Model

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Objective

Simultaneous estimation of identifiable parameters in systems pharmacology models can be challenging. We use a calcium/PTH/bone systems pharmacology model[1], with 44 differential equations and 171 parameters to explore:

1. the ability to use open-source methods: R (3.2.1, on Comprehensive R Archive Network (CRAN)), package *mrgsolve*[2] and optimization packages to simultaneously estimate multiple parameters within this model.

Methods

- **Simulate denosumab (DMAB) concentration time (PK) profiles[9], 100 replicates**
  - 10, 60, 210 mg doses Q6M x 4; 4 subjects per dose
  - Error was 21% CV[4]
- **Estimate DMAB PK**
  - Linear Clearance (**CL**)
  - Central distribution volume (**VC**)
  - Max nonlinear clearance (**VMAX**)
  - Peripheral distribution volume (**VP**)
- **Summarize performance**
  - Parameter estimates
  - Percent prediction error (%PE)
  - Run times
- **Optimizers tested**
  - **minqa::newuoa**
  - **stats::optim** (Nelder-Mead)
  - **DEoptim::DEoptim**
  - **MCMCpack::MCMCmetrop1R**

Summary of Optimizers Tested

Function	*Description* (unitless)	*Attributes*
minqa:: newuoa[5]	Forms a trust-region by models of interpolation and searches within this space for minimum function value	can set trust region radius but easily falls into local minimum
stats::optim (Nelder-Mead) [6]	uses simplex method that does not require gradients	gives hessian but cannot specify bounds so for difficult problem it can slip into unsolvable variable space
DEoptim[7]	A genetic algorithm which starts with a population of parameters drawn from a uniform distribution. The population is transformed and the best set of parameters is carried into the next iteration. New populations are generated & process is repeated for the specified number of iterations.	can be easily parallelized, good for stochastic, noisy functions, or those difficult to differentiate, takes boundary conditions, but slow
MCMCpack:: MCMCmetrop1R[8]	Calls stats::optim first to generate a hessian as a starting point from which to sample. Then pulls samples from a continuous distribution using a random walk Metropolis algorithm	user can supply a hessian matrix from a previous optimization step to help speed up algorithm and it is a robust method for difficult problems but slow

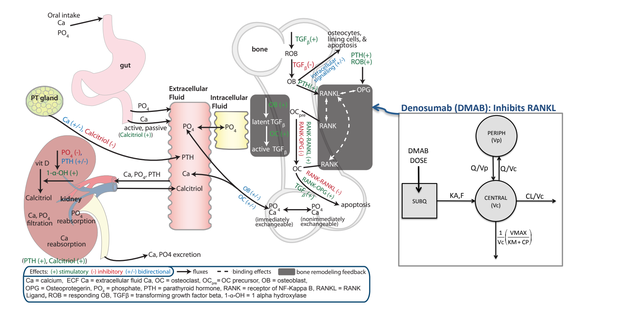

Figure 1: Model schematic: integration of pharmacokinetic model (right hand box) for denosumab (a fully human monoclonal antibody that binds to RANKL with high affinity) affects bone remodeling within this system.

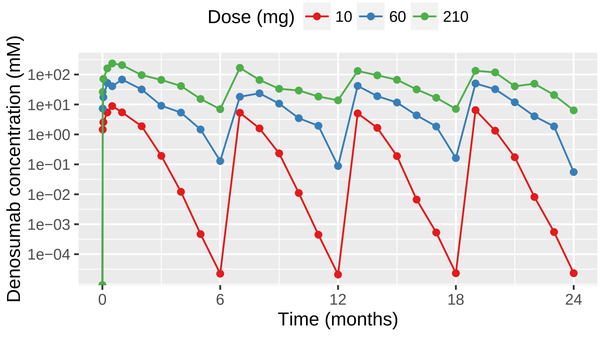

Figure 2: Simulated DMAB PK following Q6M dosing

Example Objective Function

`par: parameters, d: data set, n: parameter names`

```
ols <- function(par,d,n,pred=FALSE) {

  par <- setNames(lapply(par,exp),n)

  out<-
    mod %>%
    param(par) %>%
    data_set(d) %>%
    mrgsim(obsonly=TRUE, Req="DENCP")

  if(pred) return(out)

  log.y <- log(d$DENmMOL)

  log.yhat <- log(out[["DENCP"]])

  return(sum((log.y-log.yhat)^2))
}
```

Example Call to Optimizer

```
theta <- log(c(DENCL=3,
               DENVC=2000,
               DENVMAX=2000,
               DENVP=2000))

fit <- newuoa(par=theta,fn=ols,
              d=d,n=names(theta))
```

Results: Compare/Contrast Optimization Methods

Method	Time [min]	CL [ml/hr]	VC [ml]	VMAX [ng/hr]	VP [ml]
newuoa	11 (16)	2.803 (1.0)	2447 (3.9)	3157 (1.5)	1296 (5.2)
Nelder-Mead	7 (24)	2.804 (1.0)	2448 (3.9)	3158 (1.5)	1295 (5.3)
DEoptim	653 (3)	2.803 (1.0)	2446 (4.0)	3160 (1.6)	1296 (5.7)
MCMC	90 (11)	2.802 (1.1)	2453 (3.9)	3156 (1.5)	1293 (5.3)

Table 1: Runtimes and DMAB PK estimates as median (%CV) over 100 replicates for each estimation method. `DEoptim` was run for 500 iterations and `MCMC` was run for 1000 production iterations after 1000 burnin samples. `stats::optim` (Nelder-Mead) was called with `maxiter=1500` as a part of the `MCMC` run to generate a proposal density.

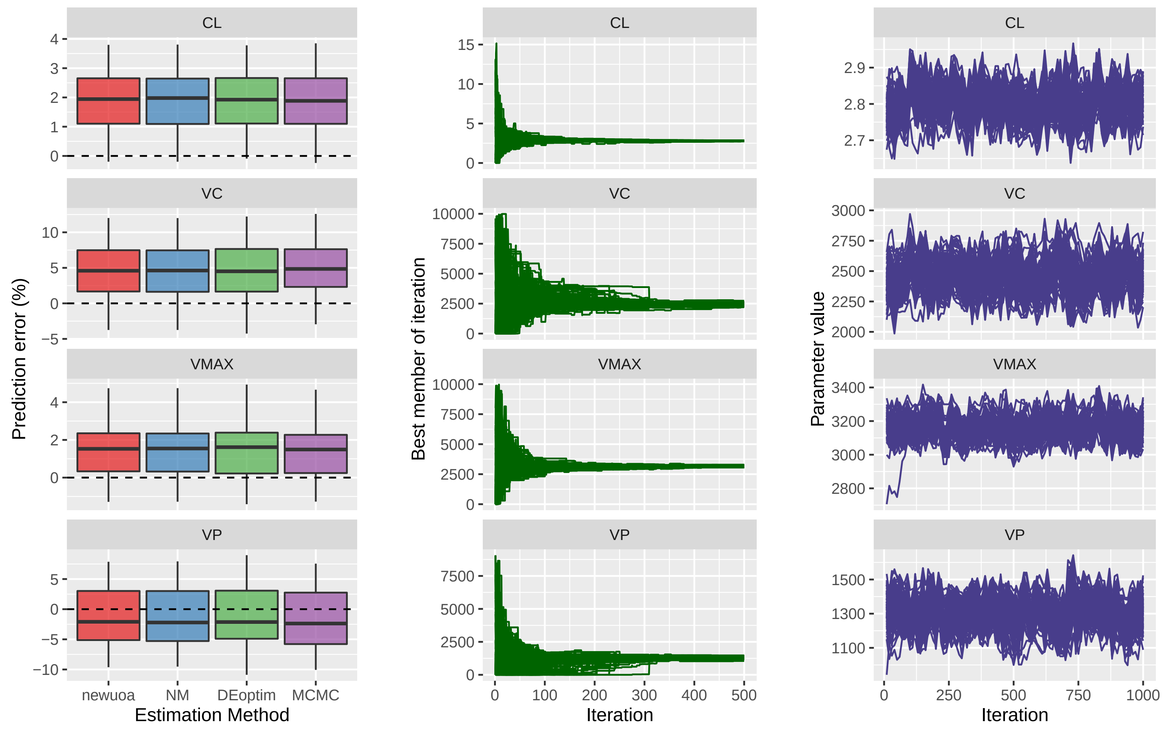

Figure 3: Parameter estimates for each optimization method (expressed as percent prediction error; **left**), parameter estimates versus iteration for the `DEoptim` optimization method (**center**), and posterior samples for the post-burnin phase for the `MCMC` optimization method (**right**).

Conclusion

All four estimation methods tested resulted in relatively efficient and precise parameter estimates for the systems pharmacology model. `DEoptim` and `MCMC` are gradient—free methods that can potentially facilitate larger numbers of simultaneous estimable parameters but took the longest runtime compared to the `newoua` and `nelder` methods for estimating the four parameters in this example. Notably, these methods are all open-source, flexible, and easily-parallelized within R and so are well-suited for additional consideration in situations of added complexity, i.e. within the context of *a priori* and *a posteriori* identifiability.

mrgsolve is free, open-source software

http://www.github.com/metrumresearchgroup/mrgsolve

https://github.com/mrgsolve/examples

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