METAHEURISTICS FOR FINDING EFFICIENT LONGITUDINAL DESIGNS FOR BIPOLAR PATIENTS WITH AND WITHOUT A GENETIC COVARIATE TREATED WITH SUSTAINED RELEASE LITHIUM

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1. MOTIVATION

Bipolar disorder is the 17th leading cause of disability in the world[1]. Although used for treatment since the 1960's, lithium is poorly tolerated and not well studied. We provide optimal designs to estimate model parameters more accurately with a focus on better monitoring early responders to sustained release lithium. We incorporate a genetic covariate at the design stage for comparison purposes.

2. PHARMACOKINETIC MODEL OF SUSTAINED RELEASE LITHIUM

$$f(\theta,d,t) = d \times \frac{k_a}{V_S}\Big(\frac{k_{SE}-k_a}{((B+A)/2-k_a)\times((B-A)/2-k_a)} \times \frac{\exp(-k_a\times t)}{1-\exp(-k_a\times\tau)} + \frac{k_{SE}-(B+A)/2}{(k_a-(B+A)/2)\times((B-A)/2-(B+A)/2)} \times \frac{\exp(-(B+A)/2\times t)}{1-\exp(-(B+A)/2\times\tau)} + \frac{k_{SE}-(B-A)/2}{(k_a-(B-A)/2)\times((B+A)/2-(B-A)/2)} \times \frac{\exp(-(B-A)/2\times t)}{1-\exp(-(B-A)/2\times\tau)}\Big), \quad (12)$$

with $k_{SE} = CL_{SE}/V_S$, $k = CL \times \exp(\beta_{CL}\times 1_G)/V_S$, $k_{SE} = CL_{ES}/57.5$, $B = k + k_{SE} + k_{ES}$ and $A = \sqrt{B^2 - 4\times k\times k_{SE}}$.

Notational Interpretation for the above Two-Compartment Exponential Nonlinear Mixed Effects Model

- K_a = absorption constant
- V_s = Distribution volume in serum
- CL = Clearance in urine
- CL_{se} = Clearance from serum to erythrocyte
- CL_{es} = Clearance from erythrocyte to serum
- G = Genetic covariate effects
- σ^2 = Error parameter

Nominal Values	K_a	V_s	CL	CL_{se}	CL_{es}	G
Fixed Effects	0.93	22.3	1.24	4.15	11.1	0.32
Log-normally distributed variance components	0.72	0.3	0.2		0.27	

3. OBJECTIVE

Find a locally optimal design to estimate all parameters in the model to sample observations in the first 8 hours after lithium administration. Clinicians apriori limit the number of blood draws to 5 draws.

Graphically assess a dual-objective design primarily estimating the fixed and random effects of "Clearance in urine" and the genetic covariate effect, G.

4. ISSUES AND SOLUTIONS

1. No analytical form of Fisher Information Matrix (FIM) for NLMEM. Multidimensional integration is challenging in this 11-parameter model.
2. Pharmaceutical software, PFIM 4.0,[3] applies a first-order linearization around a nominal value of the fixed effects.
3. Standard methods (Simplex) are prone to local optima and early convergence.
4. Metaheuristics[4] are high-level algorithmic frameworks used often in engineering and avoid local optimas.

5. DUAL-OBJECTIVE OPTIMIZATION

Let D_{s3} , D^*_{s3} and D_{s8} , D^*_{s8} be the D_s-optimal values using design found for estimating the 3 (8 remaining) parameters. Cook and Wong (1994)[4] proposed optimizing the below ϕ to graphically determine a compromised design (via the weight λ), i.e.

$$\phi = \lambda * \frac{D_{s3}}{D^*_{s3}} + (1-\lambda) * \frac{D_{s8}}{D^*_{s8}}$$

6. METAHEURISTIC ALGORITHMS

Often inspired by nature

Discover good solutions in little time

Non-derivative methods

Flexible to multiple types of problems.

We tried many metaheuristic algorithms, and the 4 below gave consistent results.[6]

Particle Swarm Optimization (PSO)

Grey Wolf Optimization (GWO)

Moth-flame Optimizer (MFO)

Whale Optimization Algorithm (WOA)

8. CONCLUSION

More effective algorithmic tools for finding optimal designs with more accurate estimates will result in better understanding of the pharmacokinetics and pharmacodynamics of lithium and hence its tolerance and interaction of the genetic marker effects, which can lead to an improved treatment strategy.

7. RESULTS

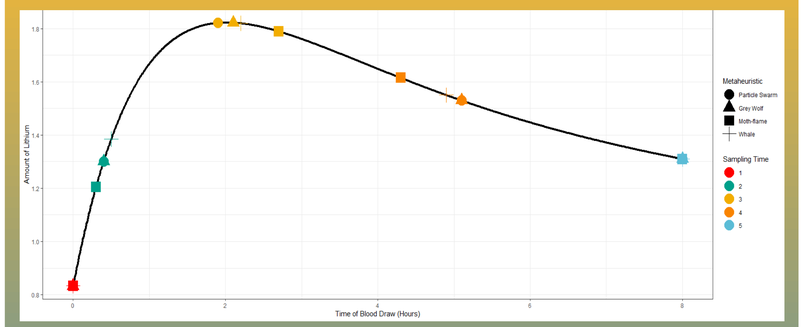

Figure 1: Example design results for the first 8 hours of lithium administration from the Simplex (traditional) and 4 metaheuristic algorithms

Algorithm	Without Gene	With Gene
Simplex	(0,0.4,2.3,4.9,8) 30.48	(0,0.4,2.3,4.9,8) 34.46
PSO	(0,0.4,2.1,5.1,8) 30.64	(0,0.4,2.1,5.1,8) 34.61
GWO	(0,0.4,2.1,5.1,8) 30.64	(0,0.4,2.1,5.0,8) 34.60
MFO	(0,0.4,2.1,5.1,8) 30.64	(0,0.4,2.1,5.1,8) 34.61
WOA	(0,0.4,2.1,5.0,8) 30.64	(0,0.4,2.1,5.1,8) 34.61

Table 1: Designs found from the Simplex (traditional) and 4 metaheuristic algorithms and their criterion values w/ or w/o the genetic covariate

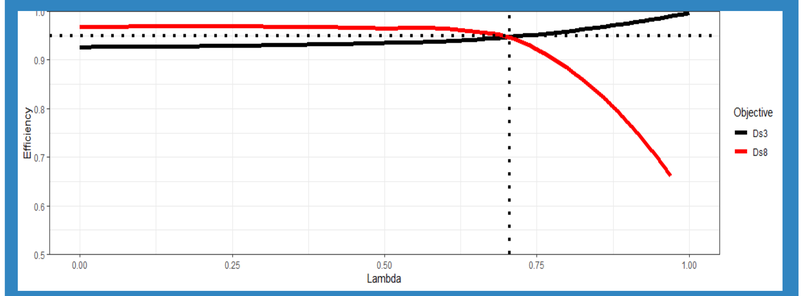

Figure 2: Multi-objective efficiency plot for estimating parameters of interest vs remaining parameters

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