Sparse Grids-Particle Swarm Optimization for finding Bayesian Optimal Designs

Yu Shi, Zizhao Zhang, Weng Kee Wong

Department of Biostatistics
University of California Los Angeles

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Outline

Background

- Bayesian non-linear mixed effects models are widely used to analyze longitudinal data.
- Designs to estimate parameters in such models are often of interest but challenging.
- Such models are often employed to study HIV dynamics over time.

Bayesian Non-linear Mixed Effects Models

- A general set up of Non-linear Mixed Effects Model:

$$Y_i(\xi) = \eta(\xi; \beta_i) + \epsilon, \quad \epsilon \sim N(0, \sigma^2 I_n)$$

where $\beta_i = \beta + b_i$ and $b_i \sim N(0, D)$. Then an n-run exact experiment ξ takes observations at $t_1, ..., t_n$ results in a Fisher information for β_i as

$$M(\beta_i; \xi) = \frac{1}{\sigma^2} \sum_{j}^{n} \nabla\eta(t_j; \beta_i) \nabla\eta(t_j; \beta_i)^T$$

Bayesian Optimal Design

- A Bayesian D-optimal design η maximizes the criterion function wrt a prior parameter distribution $\pi(\beta_i)$ as:

$$\xi_{BayesD} = \underbrace{\underset{\xi}{\text{argmax}} \underbrace{\int \{\log(\det[M(\xi, \beta_i)])\}\pi(\beta_i)\, d\beta_i}_{\text{Integration}}}_{\text{Optimization}}$$

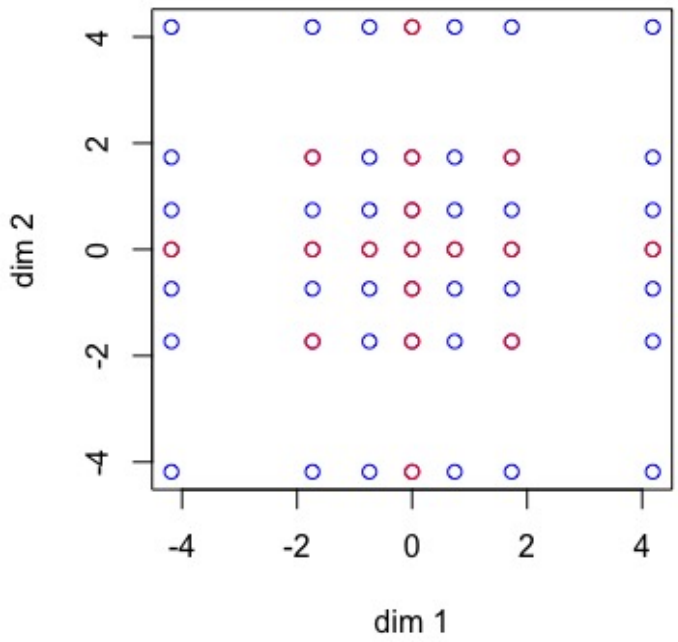
  where $M(\xi, \beta_i)$ is the information matrix.

- Numerical (multi-dimensional) integration results evaluated by optimization process.

Numerical Integration

- Monte Carlo: $\sim$100,000 samples (Nyberg, Karlsson, Hooker, 2009).
- MCMC: $\sim$10,000 iterations (Wakefield, 1996; Huang and Wu, 2008).
- Adaptive Gaussian quadrature (Ueckert and Mentre, 2016); Hamiltonian Monte Carlo (Riviere, Ueckert, and Mentre, 2016).
- Sparse Grids (Smolyak, 1963): the computational costs to achieve a negligible approximation error are considerably lower than with simulation techniques like pseudo-random Monte Carlo and quasi-random Monte Carlo (Heiss et. al., 2008). It has been used various fields like engineering and econometrics, and also used in computer experiment design (Plumlee, 2014).

Sparse Grids Method



- - Complexity: $O(N(logN)^{D-1})$ instead of $O(N^D)$
  - Error bound: $O(N^{-2}(logN)^{D-1})$ instead of $O(N^{-2})$.
  - Deterministic.

Brief Intro to Sparse Grids

- Define the difference of the approximation when increasing the accuracy level from $i-1$ to i as

$$\Delta_i[g] = V_i[g] - V_{i-1}[g] \quad \forall i \in \mathbb{N}$$

with $i = [i_1, ..., i_D]$. For any non negative integer q, define non empty set

$$\mathbb{N}_q^D = \{i \in \mathbb{N}^D : \sum_d^D i_d = D + q\}$$

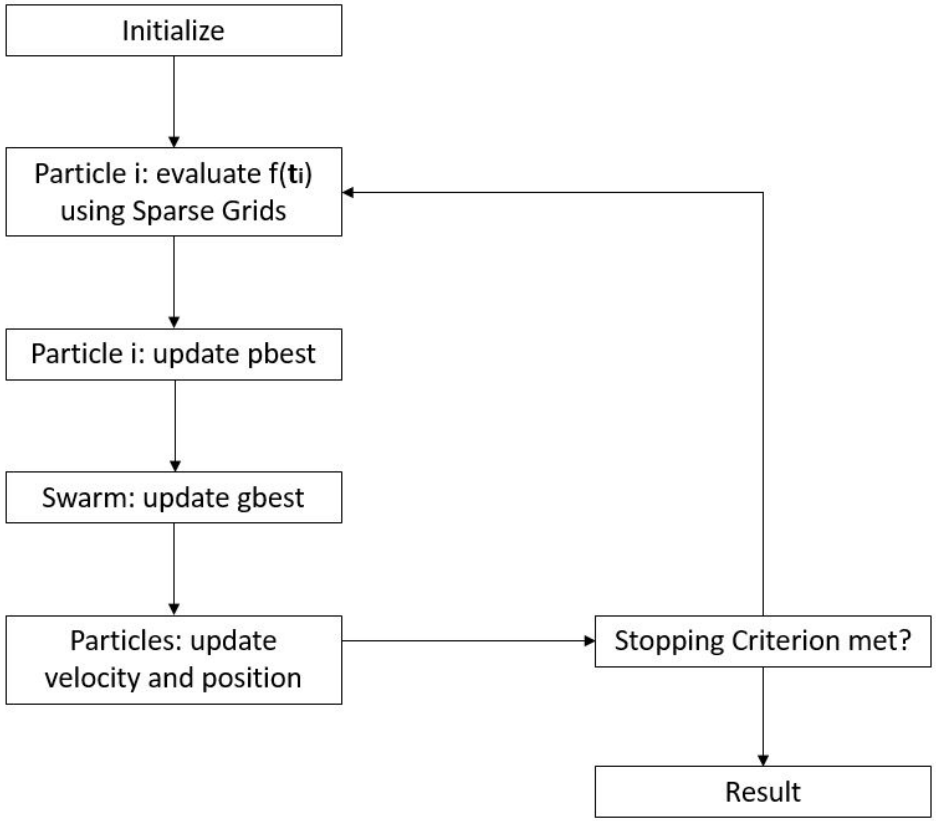
For instance, $\mathbb{N}_2^2 = \{[1,3],[2,2],[3,1]\}$. Then the sparse grids quadrature rule for D-dimensional integration at accuracy level k is defined as

$$A_{D,k}[g] = \sum_{q=0}^{k-1} \sum_{i \in \mathbb{N}_q^D} (\Delta_{i_1} \otimes ... \otimes \Delta_{i_D})[g]$$

Optimization

- Compare a small number of candidate designs (Huang and Wu, 2008).
- Fedorov algorithm (Fedorov, 1972; Retout, Mentre, Bruno, 2002).
- Coordinate exchange algorithm (Meyer and Nachtsheim, 1995; Gotwalt, Jones, Steinberg, 2009).
- Particle Swarm Optimization (Eberhart and Kennedy, 1995; Wong et al., 2015; Chen et al., 2015; Phoa et al., 2016. Kim and Wong, 2017).

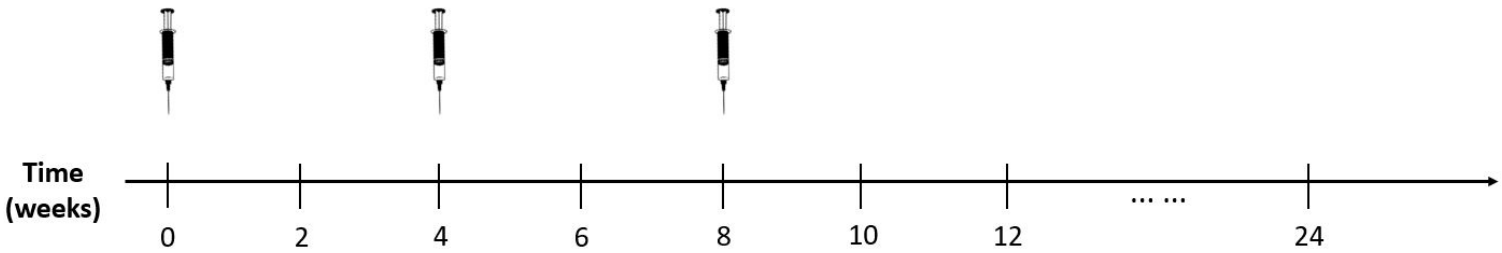
SG-PSO for Finding Bayesian Optimal Designs



$f(t_i) = \int_\beta log(det[M(\xi, \beta_i)])\pi(\beta_i)d\beta_i$ evaluated at SG samples. PSO parameters: 1000 iter, 40 particles, inertia $\frac{1}{2ln\ 2}$, $c_1 = c_2 = 0.5 + ln\ 2$.

Application in HIV Studies

- HIV experiments often requires to get plasma samples from patients to quantify viral load at specific time points. The longitudinal change is important to study the pathological process involved in HIV dynamics.



- In this work we focus on deciding the best sampling schedule.

Application in HIV Studies I

- Model Structure (Hu and Ding, 1999): the log-transformation of the total viral load for the i-th subject at j-th time point is modeled as

$$y_{ij} = log(V(t_{ij}, \beta_i)) + e_{ij} = log(e^{\theta_i - \delta_i t_j} + e^{\tau_i - \lambda_i t_j}) + e_{ij}$$

  assume isotropic errors across time and subjects $e_{ij}|\beta_i \sim N(0, \sigma^2)$, $\beta_i = (\theta_i, \tau_i, \delta_i, \lambda_i)' = (\theta, \tau, \delta, \lambda)' + (b_{1i} + b_{2i} + b_{3i} + b_{4i})' = \beta + b_i$; $b_i \sim N(\underline{0}, D)$. θ, τ represent initial viral production rate and δ, λ represent exponential decay rate of virus in compartments.

- Prior Distribution: estimates from 46 patients' data: $\hat{\beta} = (12.142, 7.624, 0.442, 0.032)'$, $\hat{\sigma}^2 = 0.267^2$, $\hat{D} = diag(1.397^2, 1.545^2, 0.137^2, 0.015^2)$.

Application in HIV Studies I

- Want to find an exact design $\xi = (t_1, ..., t_n)$ that gives best parameter estimations in response curve.

- Design Space and Number of Support Points:

  - Schedule 1 (9 points in [0, 168]); ACTG Protocol A5055: 0, 7, 14, 28, 56, 84, 112, 140, 168.

  - Schedule 2 (8 points in [2, 84]); ACTG Protocol 315: 2, 7, 12, 13, 21, 27, 55, 84.

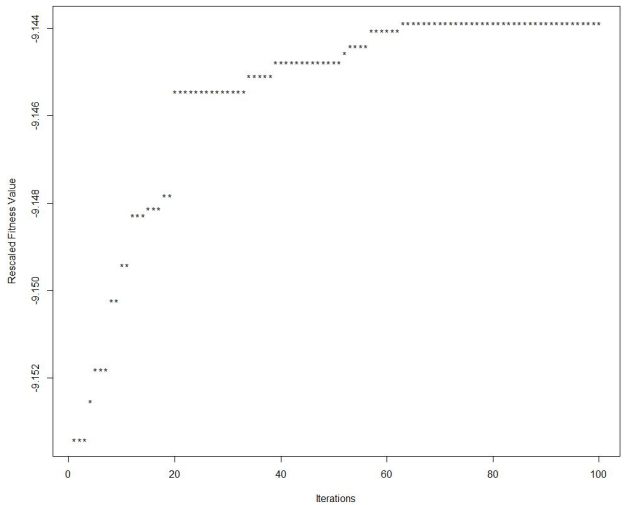
  - Schedule 3 (6 points in [0, 168]); Standard sampling schedule currently used in many AIDS clinical trials: 0, 28, 56, 84, 112, 168.

Results from SGPSO

	logdet $M(\xi)$	SGPSO Design	logdet $M(\xi^{SGPSO})$	RE	time[1]
1	14.83	0, 0, 4.7, 8.2, 15.0, 27.0, 45.5, 168, 168	15.80	78.5%	18.9
2	12.27	2, 2, 6.1, 10.9, 20.3, 34.7, 84, 84	12.73	88.9%	15.6
3	2.46	0, 4.7, 10.2, 21.6, 43.0, 168	14.01	5.6%	10.9

Relative Efficiency:

$$\left(\frac{|M(\xi, \beta_i)|}{|M(\xi^{SGPSO}, \beta_i)|}\right)^{1/4}$$



[1]CPU time. Computer configuration: x86_64−win64 (64 bit) 3.6GHz, 16GB RAM, Intel i7−4790 CPU on Windows 10 Enterprise OS. R version: 3.3.0.

Application in HIV Studies I: Other criteria

Another criterion is to maximize the determinant of FIM whose (k, l) term is denoted as (Riviere, Ueckert, Mentre, 2016)

$$M(\beta,\xi)_{k,l} = E_y[\frac{\partial log(L(y|\beta))}{\partial \beta_k}\frac{\partial log(L(y|\beta))}{\partial \beta_l})]$$

$$= E_y[E_{b|y}(\frac{\partial log(p(y|b,\beta)p(b))}{\partial \beta_k})E_{b|y}(\frac{\partial log(p(y|b,\beta)p(b))}{\partial \beta_l})]$$

	logdet $M(\xi)$	SGPSO Design	logdet $M(\xi^{SGPSO})$	RE	time
1	37.32	0, 8.6, 14.3, 18.9, 30.3, 157.9, 164.5, 167.8, 168	46.46	10.17%	1983
2	37.96	2, 2.3, 15.8, 16.2, 34.1, 37.7, 65.1, 83.0	40.84	48.6%	1847
3	36.67	0, 29.3, 29.4, 32.3, 168, 168	44.62	13.7%	1688

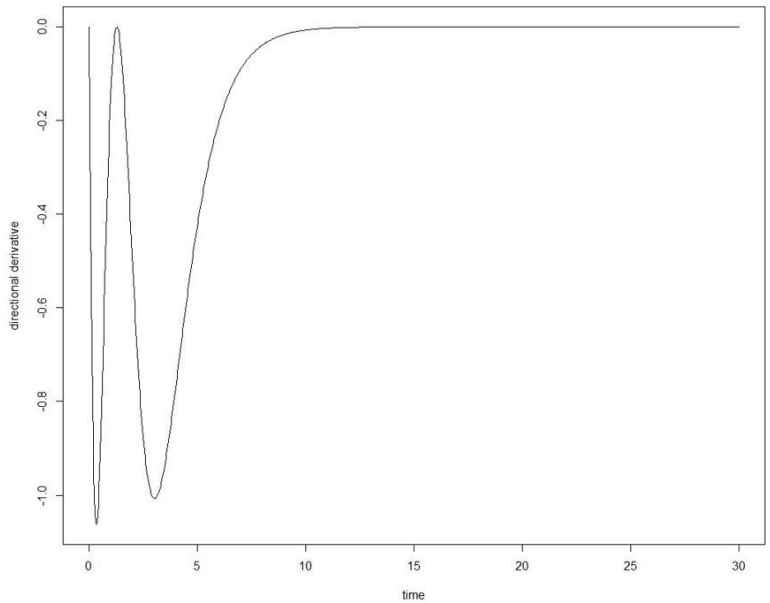
Application in HIV Studies II: Approximate Design

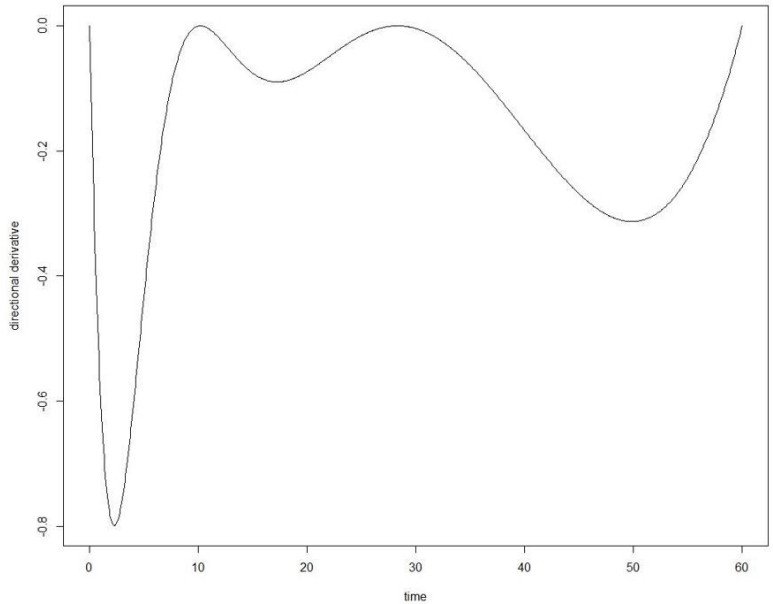
- An exponential model which describes the trajectory of plasma HIV RNA level under antiviral treatment (Han and Chaloner, 2003)

$$Y_j = log(P_0 + P_1 e^{-\delta t_j}) + \epsilon_j$$

where $\epsilon_j \overset{iid}{\sim} N(0, \sigma^2)$, $t_j \in [0, 60]$, P_0, $P_1 \sim$ unif(0.5, 1.5).

- $\delta \sim$u(0.9, 1.1): $\begin{pmatrix} 0 & 1.27 & 14 \\ 1/3 & 1/3 & 1/3 \end{pmatrix}$; $\delta \sim$u(0, 0.2): $\begin{pmatrix} 0 & 10.17 & 28.30 & 60 \\ 0.32 & 0.28 & 0.10 & 0.30 \end{pmatrix}$





(Preliminary) Conclusion

- The proposed SGPSO algorithm is promising for finding Bayesian optimal designs with mixed effects models.
- Fast and convenient: softwares and packages widely available.
- Flexible: deals with different priors, design space constrains, number of support points with minimal adjustment; good for practical use.
- Works for approximate designs, also seems to work for exact designs.
- Deals with various criteria.

Advanced Topics: Hybrid Algorithm

- Advanced versions: Quantum PSO (Sun et. al, 2004), Competitive Swarm Optimizer (Cheng and Jin, 2015), Galactic Swarm Optimization (Muthiah-Nakarajan and Noel, 2016), etc.

Algorithm 1 Hybrid Swarm Optimization (Zhang et al., 2017+)

Lower Level Initialization: $\mathbf{x}$, $\mathbf{v}_L$.
Upper Level Initialization: $\mathbf{v}_U$.
for EP in 1 to EP_{max} **do**
    for subswarm 1 to M **do**
        CSO m_1 iterations by updating $\mathbf{x}$, $\mathbf{v}_L$;
        Pick k_1 winner particles;
    end for
    do CSO among winners by updating $\mathbf{x}$, $\mathbf{v}_U$;
end for

Advanced Topics: Hybrid Algorithm

- The hybrid swarm optimization algorithm has been tested for finding locally optimal design for a logistic model with 4 factors with all pairwise interaction terms (80-dimensional). Ten different sets of coefficients have been tested and the average efficiency lower bound obtained from 20 experiments show as follows:

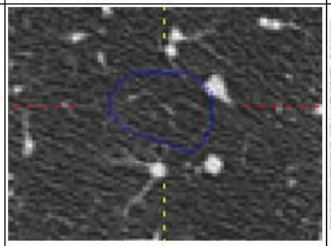
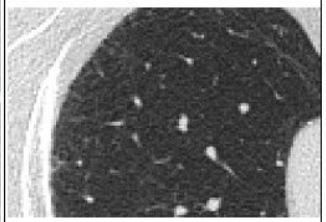
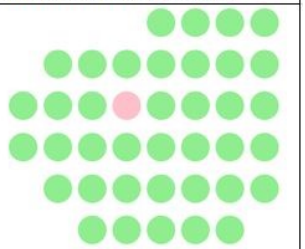
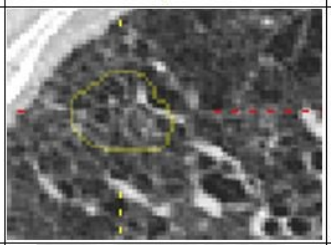
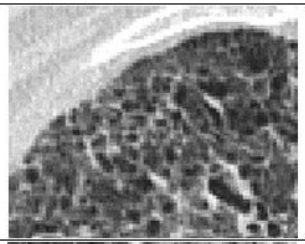
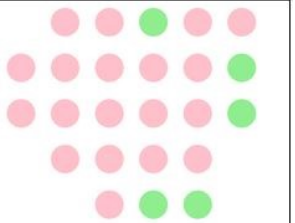
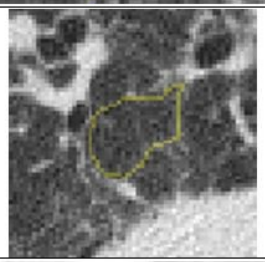
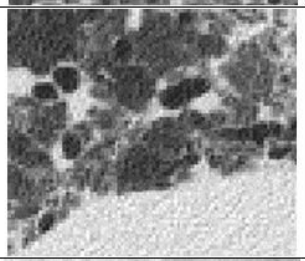
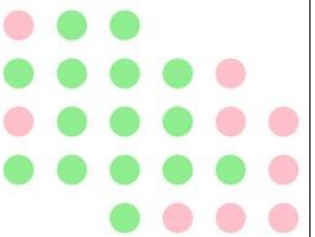
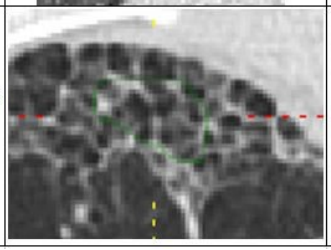
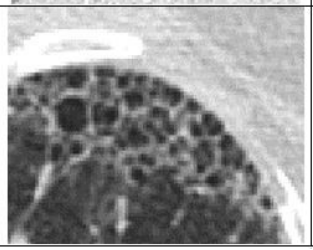
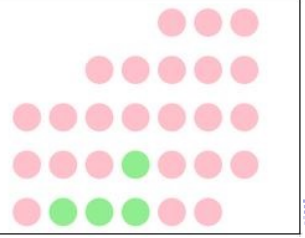
	HSO	CSO	GSO	PSO
Average ELB	81.2%	43.4%	14.56%	6.7%

Advanced Topics: Application in Other Fields

- Biomedical imaging study: using QPSO to maximize the lung cancer status prediction.
- Idiopathic Pulmonary Fibrosis (IPF) is a rare and ultimately fatal lung disease of unknown cause with a median survival of 2$\sim$5 years. The disease natural history is unpredictable at the time of diagnosis; as a result, some patients miss the best time to receive transplant. We want to predict the progression status so that the timely treatment can be delivered to increase patients' survival.

Advanced Topics: Application in Other Fields

- LASSO: sensitivity 63.04%, specificity 75.18%, accuracy 73.04% (51 features). QPSO: 77.27% sensitivity, 85.15% specificity, 83.74% accuracy (19 features).

Case	Classfication type	ROI on CT-baseline	ROI on CT-followup	classification at voxel level
1	non-progression ROI classified as non-progression			
2	progression ROI classified as progression			
3	progression ROI classified as non-progression			
4	non-progression ROI classified as progression			

Remarks and Future Work

- Sparse Grid rule usually works better for normal priors.
- No free lunch theorem (Wolpert and Macready, 1997).
- Future work:
  - Explore advanced swarm algorithms; hybridized algorithms.
  - Apply the SGPSO algorithm to other design criteria for non-linear mixed effect models and some other models.
  - ...etc.

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