Designing Longitudinal Studies with Repeated Measures: the Case of Salivary Cortisol in the Multi-Ethnic Study of Atherosclerosis

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Presenter Disclosures

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MESA Stress & Salivary Cortisol

- MESA Stress is a large scale epidemiology study which explores the association between stress and cardiovascular disease.
- Incoporate salivary cortisol as an objective and field-friendly measure for stress.

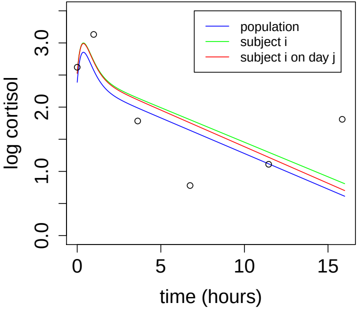


Figure: Cortisol Profile

- Multi-level variability and sampling of nonlinear response.

Models for the Cortisol Profile

For subject i on day j, we measure the salivary cortisol

$$y_{ijk} = f(t_k, \theta_{ij}) + \epsilon_{ijk}$$

- $\epsilon_{ijk} \sim N(0, \sigma^2)$: independent measurement error
- $\theta_{ij} | \theta_i \overset{iid}{\sim} MVN(\theta_i, \Sigma^d)$: parameter specific to subject i on day j
- $\theta_i \overset{iid}{\sim} MVN(\theta, \Sigma^s)$: parameter specific to subject i
- Piecewise Linear Model (Hajat et al., 2010):

$$f(t;\theta) = \theta_0 + \theta_1 t + \theta_2 (t - 0.5h)_+ + \theta_3 (t - 2h)_+$$

- Nonlinear Model (Stroud et al., 2004):

$$f(t;\theta) = \theta_0 + \theta_1 t + \theta_2 t \exp(-\theta_3 t)$$

Cortisol Features

Features	G	References
Baseline	$f(0, \theta)$	Kumari et al. (2009)
Cortisol Awakening Response	$f(0.5, \theta) - f(0, \theta)$	Pruessner et al. (1997)
Evening Decline	$\frac{1}{16-10}(f(16, \theta) - f(10, \theta)dt$	Adam (2006)
Area Under the Curve	$\int_0^{16} f(t, \theta)dt$	Badrick et al. (2007)
Prediction	$f(t, \theta)$	Powell et al. (2002)

Table: Cortisol Features

Optimal Design to Estimate Cortisol Features

Identify the optimal design (n, m, d, T) that minimizes

- the variance of a single cortisol feature
- the weighted sum of variances of several cortisol features

Components of the optimal design (n, m, d, T):

- n: the total number of subjects
- m: the number of days for sampling
- d: the number of samples per day
- $T = (t_1, \ldots, t_d)$: the daily sampling schedule

Existing Approaches

There have been some research on the optimal schedule in the context of PD/PK:

Retout et al. (2002)

- Maximizes the determinant of the information matrix of the parameters
- It is the reciprocal of the size of the confidence region.

Stroud et al. (2001)

- Minimizes the pre-posterior prediction error
- Employs a Bayesian adaptive strategy for the sampling schedule given previous data.

We will take a different perspective:

- Focus on the variance of estimating the cortisol features.
- Analyze the implication of between-subject and between-day variability on multi-level sampling.

Computing the Variance of Cortisol Feature G

Denote the MLE of G by $\hat{G}$ and the information matrix by $I(\theta)$

- $\sqrt{n}(\hat{G} - G) \rightarrow N(0, \nabla G' I^{-1}(\theta) \nabla G)$ by the delta method
- We can show that under some conditions

$$I(\theta) = \nabla f(T,\theta)' \Sigma \nabla f(T,\theta)$$

where

$$\Sigma = \begin{pmatrix} \Sigma^s + \Sigma^d & \Sigma^s & \cdots & \Sigma^s \\ \Sigma^s & \Sigma^s + \Sigma^d & \ddots & \vdots \\ \vdots & \ddots & \ddots & \Sigma^s \\ \Sigma^s & \cdots & \Sigma^s & \Sigma^s + \Sigma^d \end{pmatrix}$$

- Roy et al. (2007) shows that

$$I(\theta)^{-1} = \Sigma^s + \frac{1}{m}(\Sigma^d + \sigma^2 (X'(T)X(T))^{-1})$$

Computing the Variance of Cortisol Feature G

$$Var(\hat{G}) = \frac{1}{n}\nabla G' I(\theta) \nabla G$$

$$= \underbrace{\frac{\nabla G' \Sigma^s \nabla G}{n}}_{\text{subject}} + \underbrace{\frac{\nabla G' \Sigma^d \nabla G}{nm}}_{\text{day}} + \underbrace{\frac{\sigma^2 \nabla G'(X'(T)X(T))^{-1} \nabla G'}{nm}}_{\text{schedule within day}}$$

Clear Interpretation for each component

- $\nabla G' \Sigma^s \nabla G$: the between subject variability for G
- $\nabla G' \Sigma^d \nabla G$: the between day variability for G
- $\sigma^2 \nabla G'(X'(T)X(T))^{-1} \nabla G'$: the estimation variance assuming no between-subject / between-day variability

Properties of Optimal Design

Optimal schedule, T

- minimizes $\nabla G'(X'(T)X(T))^{-1}\nabla G'$
- No knowledge of the variability components is required.

Optimal number of days, m

- When total number of samples is fixed, more subjects (fewer days) is almost always more efficient.

$$Var(\hat{G}(\alpha n, m, d, T)) \leq Var(\hat{G}(n, \alpha m, d, T)) \quad " = " \text{ if } \nabla G' \Sigma^s \nabla G = 0$$

- When the total cost is fixed, the optimal m depends on the cost ratio and within-between variability ratio.

Bayesian Design

- The optimal design depends on unknown parameters.
- Incorporate the uncertainty by considering expected variance (Atkinson et al., 2007)
- Assuming θ and $\Sigma^s, \Sigma^d, \sigma^2$ are independent

$$
\begin{aligned}
E(Var(\hat{G})) &= \int Var(\hat{G}) dp(\theta, \Sigma^s, \Sigma^d, \sigma^2) \\
&= \text{tr}(E(\nabla G' \nabla G)(\frac{E(\Sigma^s)}{n} + \frac{E(\Sigma^d)}{n \cdot m})) \\
&\quad + \frac{E(\sigma^2)}{n \cdot m} E(\nabla G'(X'(T)X(T))^{-1} \nabla G)
\end{aligned}
$$

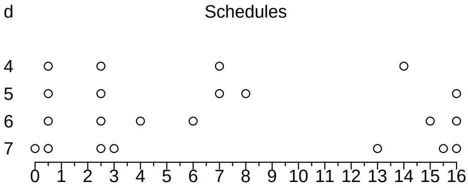
- Simple to compute
- Results on the previous slide still hold
- Only the mean, not the full distribution of $\Sigma^s, \Sigma^d, \sigma^2$ is required.

Application to MESA Stress Study

Context: Determine the optimal design for 2nd-stage data collection.

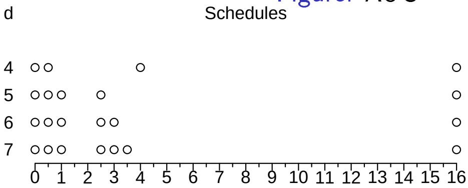
- The estimates and prior distributions are generated from the existing MESA data.
- # of samples per day: $d = 4..7$
- # of days: $m = 1..5$
- Times points of the daily schedule T are chosen from $\{0, 0.5, \ldots, 16\}$

Optimal Design



	Variance				
d	1 Day	2 Day	3 Day	4 Day	5 Day
4	82.7	67.6	62.6	60	58.6
5	76.6	64.6	60.6	58.6	57.4
6	73.4	63	59.5	57.8	56.7
7	71.4	62	58.8	57.2	56.3

Figure: AUC



	Variance				
d	1 Day	2 Day	3 Day	4 Day	5 Day
4	0.562	0.281	0.188	0.141	0.113
5	0.419	0.212	0.140	0.106	0.0854
6	0.369	0.183	0.122	0.0935	0.0738
7	0.333	0.169	0.112	0.0847	0.0676

Figure: CAR

- $\nabla G' \Sigma^s \nabla G = 0.00033 \approx 0$ for CAR
- Expanding the days of sampling is almost as good as expanding subject.

Optimal m for a Fixed Total Cost

- Depends on the cost ratio $\frac{\text{Initial}}{\text{Day}}$ and variability ratio $\frac{\text{Day}}{\text{Subject}}$.

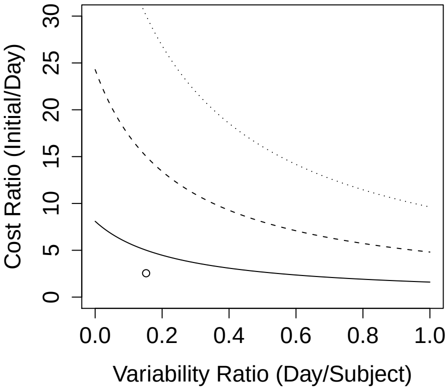


Figure: AUC

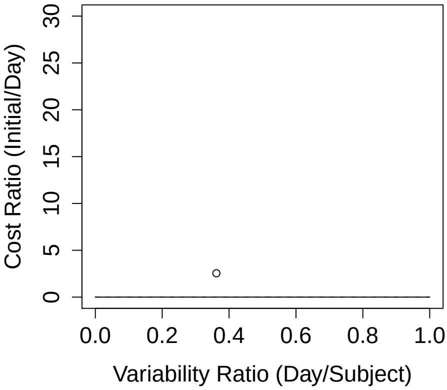
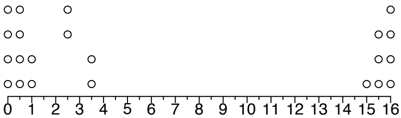


Figure: CAR

Compound Objective

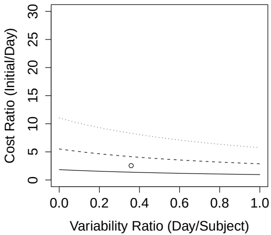
- Minimize the weighted average of variance of Baseline, CAR, Evening Decline and AUC

Schedules



Variance 10^–3

d	1 Day	2 Day	3 Day	4 Day	5 Day
4	3.94	2.62	2.18	1.96	1.83
5	3.45	2.38	2.02	1.84	1.73
6	3.18	2.24	1.93	1.77	1.68
7	3.01	2.15	1.87	1.73	1.64



Summary and Future Work

Summary

- We discussed the properties of the optimal design for longitudinal study.
- The key is the closed form solution of $Var(\hat{G})$.
- We applied these results to MESA Stress Study.
- The results also hold for arbitrary levels of variabilities.

Future Work

- More flexible ways to model variabilities.
- Optimal designs for joint modeling of salivary cortisol and CVD outcome.

Thank you!

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