1. (a)
$$y_{ij} \mid \alpha_i \text{ ind. } N(\mu + \alpha_i + \beta_j, \sigma^2), \quad \lambda = 1, \dots, m$$

$$\alpha_i \text{ ind } N(0, \sigma_a^2)$$

$$N = mn.$$

where $a_{i} \stackrel{\text{iid}}{\sim} N(0, \sigma_{i}^{2})$ $\mathcal{E}_{ij} \stackrel{\text{iid}}{\sim} N(0, \sigma^{2})$

Z

$$Cov(y_{ij}, y_{i'j'}) = \{ \sigma_a^2, \lambda = \lambda', j \neq j' \}$$

$$Var(\underline{Y}) = diag\{\Sigma_1, \Sigma_2, \dots, \Sigma_n\}, \Sigma_m\}$$

where $\Sigma_n = \sigma_n^2 J + \sigma^2 I$

(b)
$$\forall ij \mid ai, bj \quad indep \quad N(\mu + ai + bj, \sigma^2)$$

$$a_i \quad iid \quad N(o, \sigma_a^2) \quad \text{indep}.$$

$$b_j \quad iid \quad N(o, \sigma_b^2) \quad \text{indep}.$$

$$\Rightarrow \forall ij = M + a_i + b_j + \epsilon_{ij}$$
where $a_i \stackrel{\text{iid}}{\text{od}} N(0, \sigma_a^2)$

$$b_j \stackrel{\text{iid}}{\text{od}} N(0, \sigma_b^2) \quad \text{indep}.$$

$$\epsilon_{ij} \stackrel{\text{iid}}{\text{od}} N(0, \sigma^2).$$

$$\frac{1}{3} \frac{1}{3} \frac{1$$

where
$$Z_1 = \underline{I}_m \otimes \underline{I}_n$$
, $Z_2 = \underline{I}_m \otimes \underline{I}_n$, $\underline{d}_1 = (a_1, \dots, a_m)^T$

$$\underline{d}_1 = (b_1, \dots, b_n)^T$$

$$\begin{aligned}
Z_{1}Z_{1}^{T} &= (\underline{I}_{m} \otimes \underline{I}_{n}) (\underline{I}_{m} \otimes \underline{I}_{n})^{T} &= (\underline{I}_{m} \otimes \underline{I}_{n}) (\underline{I}_{m}^{T} \otimes \underline{I}_{n}^{T}) \\
&= (\underline{I}_{m} \otimes \underline{I}_{n} \underline{I}_{n}^{T}) \\
&= \underline{I}_{m} \otimes \underline{I}_{n} (\underline{I}_{m} \otimes \underline{I}_{n})^{T} &= (\underline{I}_{m} \otimes \underline{I}_{n}) (\underline{I}_{m}^{T} \otimes \underline{I}_{n}^{T}) \\
&= \underline{I}_{m} \underline{I}_{m}^{T} \otimes \underline{I}_{n} \underline{I}_{n}^{T} \\
&= \underline{I}_{m} \underline{I}_{m}^{T} \otimes \underline{I}_{n} \underline{I}_{n}^{T}
\end{aligned}$$

$$= \sigma_a^2 \left(I_m \otimes J_n \right) + \sigma_b^2 \left(J_m \otimes I_n \right) + \sigma^2 I_N$$

(c)
$$y_{ijk} \mid \alpha_i, \beta_{ij} \stackrel{indep}{\longrightarrow} N(M + \alpha_i + \beta_j + \beta_{ij}, \sigma^2)$$

$$\alpha_i \stackrel{iid}{\longrightarrow} N(0, \sigma_a^2) \longrightarrow mdep.$$

$$g_{ij} \stackrel{iid}{\longrightarrow} N(0, \sigma_g^2)$$

for i=1, ..., m; j=1, ..., n; k=1, ..., r

where
$$X = (\frac{1}{2}N, \frac{1}{2}m\otimes (\frac{1}{2}n\otimes \frac{1}{2}n))$$

$$A = (\frac{1}{2}N, \frac{1}{2}m\otimes (\frac{1}{2}n\otimes \frac{1}{2}n))$$

$$A = (\frac{1}{2}N, \frac{1}{2}N\otimes \frac{1}{2}n)$$

$$A = (\frac{1}{2}N\otimes \frac{1}{2}N\otimes \frac{1}{2}n)$$

$$A = (\frac{1}{2}N\otimes \frac{1}{2}N\otimes \frac{1}{2}N\otimes \frac{1}{2}n)$$

$$A = (\frac{1}{2}N\otimes \frac{1}{2}N\otimes \frac{1}{2}N\otimes \frac{1}{2}N\otimes \frac{1}{2}n)$$

$$A = (\frac{1}{2}N\otimes \frac{1}{2}N\otimes \frac$$

$$b = (b_1, b_2)^T, b_1 = (a_1, -a_1, a_m)^T, b_2 = (a_1, a_2, a_m)^T$$

$$Z = (z_1, z_2)$$

$$Z = (z_1, z_2)$$

$$Z_1 = I_m \otimes 1_m$$
, $Z_2 = I_{mn} \otimes 1_r$

$$Var(\frac{1}{2}) = \sigma_{\alpha}^{2} Z_{1} Z_{1}^{T} + \sigma_{\alpha}^{2} Z_{2} Z_{3}^{T} + \sigma^{2} I_{N}$$

$$Z_{1} Z_{1}^{T} = (I_{m} \otimes 1_{nr}) (I_{m}^{T} \otimes 1_{nr})$$

$$= (I_{m} \otimes 1_{nr} 1_{nr})$$

$$= I_{m} \otimes J_{nr}$$

$$Z_{2} Z_{3}^{T} = (I_{mn} \otimes 1_{r}) (I_{mn}^{T} \otimes 1_{r})$$

$$= I_{mn} \otimes 1_{r} 1_{r}^{T}$$

$$= I_{mn} \otimes J_{r}$$

 $E(Y) = XB \quad (E(Y) = \mu)$

2. (a) First consider $\operatorname{var}(Y_{ij})$. If we write the first stage model as $Y_{ij} = (\beta_0 + \beta_1 t_{ij}) + b_{0i} + b_{1i} t_{ij} + e_{ij}$, because the term in parentheses is a constant, we only need find $\operatorname{var}\{(b_{0i} + b_{1i}t_{ij}) + e_{ij}\}$. This is just the variance of the sum of the two random variables $(b_{0i} + b_{1i}t_{ij})$ and e_{ij} , so that we get

$$var(b_{0i} + b_{1i}t_{ij}) + var(e_{ij}) + 2cov\{(b_{0i} + b_{1i}t_{ij}), e_{ij}\}.$$

Now, because b_i and e_i are independent, clearly the covariance in the last term must be equal to 0, as it is a covariance between a function of the elements of b_i and an element of e_i . By the same result on the variance of a sum, the first term is equal to

$$var(b_{0i} + b_{1i}t_{ij}) = var(b_{0i}) + var(b_{1i}t_{ij}) + 2cov(b_{0i}, b_{1i}t_{ij}).$$

We have immediately that $var(b_{0i}) = D_{11}$, $var(b_{1i}t_{ij}) = t_{ij}^2 D_{22}$, and $var(e_{ij}) = \sigma^2$. So we only need to evaluate $cov(b_{0i}, b_{1i}t_{ij})$. Because both b_{0i} and b_{1i} have mean zero, we have $cov(b_{0i}, b_{1i}t_{ij}) = E(b_{0i}b_{1i}t_{ij})$, which, because $E(b_{0i}b_{1i} = cov(b_{0i}, b_{1i})$, is just equal to $t_{ij}D_{12}$. Putting all this together yields the result that

$$var(Y_{ij}) = D_1 + D_{22}t_{ij}^2 + 2D_{12}t_{ij} + \sigma^2.$$

To find $cov(Y_{ij}, Y_{ik})$, note that, as $E(Y_{ij}) = \beta_0 + \beta_1 t_{ij}$, and similarly for Y_{ik} , by the definition of covariance we can write this as

$$E\{(b_{0i}+b_{1i}t_{ij}+e_{ij})(b_{0i}+b_{1i}t_{ik}+e_{ik})\}.$$

Multiplying all this out and collecting terms gives

$$E(b_{0i}^2) + E(b_{1i}^2 t_{ij} t_{ik}) + E(e_{ij} e_{ik}) + E\{b_{0i} + b_{1i} t_{ij}\} e_{ik}\} + E\{b_{0i} + b_{1i} t_{ik}\} e_{ij}\} + E(b_{0i} b_{1i} t_{ij}) + E(b_{0i} b_{1i} t_{ik}) e_{ij}\} + E(b_{0i} b_{1i} t_{ij}) + E(b_{0i} b_{1i} t_{ik}) e_{ij}\} e_{ik}$$

Using the result that E(be) = E(b)E(e) if b and e are independent and the fact that b_{0i} , b_{1i} , e_{ij} , and e_{ik} all have mean zero, and that $cov(e_{ij}, e_{ik}) = 0$, it follows that the middle three expectations are zero. We are left with

$$E(b_{0i}^2) + E(b_{1i}^2 t_{ij} t_{ik}) + E(b_{0i} b_{1i} t_{ij}) + E(b_{0i} b_{1i} t_{ik}),$$

which is equal to $D_{11} + t_{ij}t_{ik}D_{22} + (t_{ij} + t_{ik})D_{12}$, the result

(b) If $D_{12} = 0$, $cov(Y_{ij}, Y_{ik})$ becomes

$$D_{11} + D_{22}t_{ij}t_{ik} + \sigma^2.$$

This is clearly non-zero in general. Thus, even if the individual-specific intercepts and slopes are uncorrelated in the population, there is still non-zero correlation between elements of Y_i . This makes intuitive sense. Whether $D_{12}=0$ or not, the elements of Y_i all share a common dependence on the random effects b_{0i} and b_{1i} . Thus, they would be expected to be associated with one another on this basis alone.

(c) In our derivation of $\text{var}(Y_{ij})$, everything stays the same except that now $\text{var}(e_{ij}) = \sigma_1^2 + \sigma_2^2$. So we find that

$$var(Y_{ij}) = D_1 + D_{22}t_{ij}^2 + 2D_{12}t_{ij} + \sigma_1^2 + \sigma_2^2.$$

For $cov(Y_{ij}, Y_{ik})$, everything is the same except that now $cov(e_{ij}, e_{ik}) = E(e_{ij}e_{ik}) \neq 0$. Rather, according to the Markov structure, $cov(e_{ij}, e_{ik}) = \sigma_2^2 \rho^{d_{ijk}}$, say, where $d_{ijk} = |t_{ij} - t_{ik}|$. Thus, the covariance becomes

$$D_{11} + t_{ij}t_{ik}D_{22} + (t_{ij} + t_{ik})D_{12} + \sigma_2^2 \rho^{d_{ijk}}.$$

) (a) Random Intercepts

$$\begin{split} Y_{ij} &= \beta_0 + t_{ij} + b_{0i} + \epsilon_{ij} \quad , \\ b_{0i} &\sim \mathcal{N}(0, \tau^2) \ (iid), \\ \epsilon_{ij} &\sim \mathcal{N}(0, \sigma^2) \ (iid), \end{split}$$

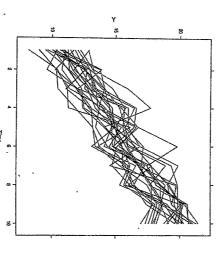
where b_{0i} and ϵ_{ij} are mutually independent.

 Σ is the following result. Y_{ij} and Y_{ik} for $j \neq k$ is τ^2 because $Cov(b_{0i}, b_{0i}) = Var(b_{0i}) = \tau^2$. Thus, the general form for (solution) For a fixed i, $Var(Y_{ij}) = Var(b_{0i}) + Var(\epsilon_{ij}) = r^2 + \sigma^2$. Also, the covariance of · Give the general form for the covariance matrix $\mathcal{L} = Cov(Y_i)$.

· Give Y_i and plot (lines) versus t_i for m=25 using $\sigma=1.0$ and $\tau=1.0$.

, which is a 10×10 matrix.





there is an increasing trend overall. In the above figure, the red line represents a LOESS smoothing curve for 25 subjects. I think

Biostatistics (Longitudinal Data Analysis)

(solution) Give Y_i and plot (lines) versus t_i for m=25 using $\sigma=1.0$ and $\tau=2.0$.

Plot of Y vs. Time with LOESS smoothing curve

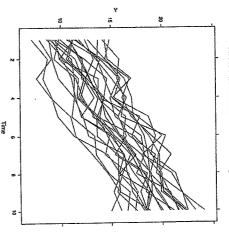
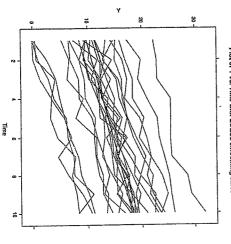


figure in the above question($\tau = 1.0$), although two τ 's are different, two figures look very Like the preceding, we can see that there is an increasing trend. When comparing with the

· Give Y_i and plot (lines) versus t_i for m=25 using $\sigma=1.0$ and $\tau=5.0$.

Plot of Y vs. Time with LOESS smoothing curve



this b_{0i} has variance 5.0. It is greater than two values of above b_{0i} s' variances. two figures, this figure has greater variation than others. The difference comes from the fact that Also, in this figure, we can conclude that there is an increasing trend. However, unlike above

(b) Random Intercepts and Slopes

$$Y_{ij} = eta_0 + eta_1 t_{ij} + b_{0i} + b_{1i} t_{ij} + \epsilon_{ij}$$
, $b \sim N(0, D)$, $\epsilon_{ij} \sim N(0, \sigma^2)$ (iid),

where $b = (b_{0i}, b_{1i})$ and ϵ_{ij} are mutually independent.

· Give the general form for the covariance matrix $\Sigma = Cov(Y_i)$.

(solution) Let
$$D=\begin{bmatrix} d_{00}\,d_{01}\\d_{10}\,d_{11} \end{bmatrix}$$
 , where $d_{00}=Var(b_{0i})$, $d_{01}=d_{10}=Cbv(b_{0i}\,b_{1i})$, and $d_{11}=Var(b_{1i})$. First, left find the variance of Y_{ij} .

$$a_{11} = Var(b_{1i})$$
. First, let's find the variance of Y_{ij} .
$$Var(Y_{ij}) = Var(\beta_0 + \beta_1 t_{ij} + b_{0i} + b_1 t_{ij} + \epsilon_{ij})$$

$$= Var(b_{0i}) + Var(b_{1i}t_{ij}) + Var(e_{ij}) + 2Cov(b_{0i}, b_{1i}t_{ij})$$

$$= d_{00} + t_{0j}^2d_{11} + \sigma^2 + 2t_{0j}d_{01}$$

$$=d_{00}+j^2d_{11}+\sigma^2+2jd_{01}$$
 (because $t_{ij}=j$ in the problem.)

Also, the covariance of Y_{ij} and Y_{ik} for $j \neq k$ is as follows.

$$Cov(Y_{ij}, Y_{ik}) = Cov(b_{0i} + b_{1i}t_{ij} + \epsilon_{ij}, b_{0i} + b_{1i}t_{ik} + \epsilon_{ik})$$

$$= Var(b_{0i}) + Cov(b_{1}\dot{x}_{0i}, b_{1}\dot{x}_{ji}) + Cov(b_{0i}, b_{1}\dot{x}_{0i}) + Cov(b_{1}\dot{x}_{0j}, b_{0i})$$

$$= d_{00} + t_{ij}t_{ik}d_{i1} + t_{ik}d_{01} + t_{ij}d_{01}$$

Thus, the general form for Σ can be constructed as follows. $=d_{00}+jkd_{11}+(k+j)d_{01}$ (because $t_{ij}=j$ and $t_{ik}=k$.)

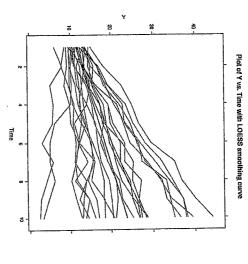
$$\Sigma = \begin{bmatrix} d_{00} + d_{11} + \sigma^2 + 2d_{01} & d_{00} + 2d_{11} + 3d_{01} & \dots & d_{00} + 10d_{11} + 11d_{01} \\ d_{00} + 2d_{11} + 3d_{01} & d_{00} + 4d_{11} + \sigma^2 + 4d_{01} & \dots & d_{00} + 20d_{11} + 12d_{01} \\ \vdots & \vdots & \vdots & \vdots \\ d_{00} + 10d_{11} + 11d_{01} & d_{00} + 20d_{11} + 12d_{01} & \dots & d_{00} + 10d_{11} + \sigma^2 + 20d_{01} \end{bmatrix} \quad \text{, which is a } 10$$

 $\times 10$ matrix. Only diagonal elements have σ^2 .

Generate
$$Y_i$$
 and plot (lines) versus t_i for $m=25$ using $\sigma=1.0,\ D=\begin{bmatrix} 2.0 & 0\\ 0 & 2.0 \end{bmatrix}$.

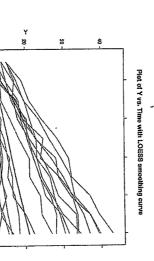
has its own intercept and slope, a LOESS curve doesn't have many meanings. red line means a LOESS curve and it shows an increasing trend of Y_i . But since each subject (solution) We can see that the variation of Y_i over time is not constant from this figure. The

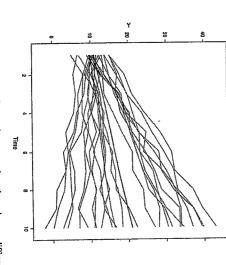
Biostatistics (Longitudinal Data Analysis)



Generate Y_i and plot (lines) versus t_i for m=25 using $\sigma=1.0,\ D=\begin{bmatrix} 2.0 & -0.2 \\ -0.2 & 2.0 \end{bmatrix}$

(solution)



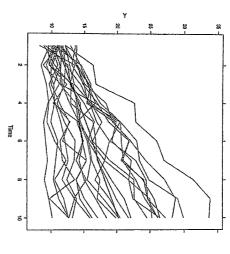


curve shows still an increase of Y_i over time and Y_i has heteroscedasticity over time. This figures even though b_{1i} and b_{1i} are correlated(but, the correlation is almost zero.). A LOESS figure looks like a right-opening megaphone. When comparing with the above figure, it seems that there is no difference between two

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· Generate Y_i and plot (lines) versus t_i for m=25 using $\sigma=1.0,\ D=\begin{bmatrix} 0.5 & 0 \\ 0 & 0.4 \end{bmatrix}$ (solution)





Since $Var(b_{ii})$ and $Var(b_{1i})$ are different(but, they are almost same!), the shape of dispersion of Y_i over time is a little bit different from above two figures. But, still Y_i has different variation as time passes.

(c) Serial Correlation

$$\begin{split} Y_{ij} &= \beta_0 + \beta_1 t_{ij} + W_i'(t_{ij}') + \epsilon_{ij} \quad , \\ W_i &\sim N(0, D) \; , \\ Var[\ W_i'(t_{ij})] &= \tau^2 \; , \\ Cov[\ W_i'(t_{ij}), \ W_i'(t_{ik})] &= \tau^2 \rho^{\left[t_{ij} - t_{ik}\right]} \; , \\ \epsilon_{ij} &\sim N(0, \ \sigma^2) \; (iid), \end{split}$$

where W_i and ϵ_{ij} are mutually independent.

· Give the general form for the covariance matrix $\Sigma = Cbv(Y_i)$. (colution) For a specific subject i led find the variance of V

(solution) For a specific subject
$$i$$
, let's find the variance of Y_{ij} .
$$Var(Y_{ij}) = Var[\beta_0 + \beta_1 t_{ij} + W_i(t_{ij}) + \epsilon_{ij}]$$

$$= Var[W_i(t_{ij})] + Var(\epsilon_{ij})$$

 $= \eta^2 + \sigma^2$

And, $Cov(Y_{ij}, Y_{ik})$ could be obtained like the following for $j \neq k$.

$$\begin{aligned} Cov(Y_{ij}, \ Y_{ik}) &= Cov[\beta_0 + \beta_1 t_{ij} + W_i(t_{ij}) + \epsilon_{ij}, \ \beta_0 + \beta_i t_{ik} + W_i(t_{ik}) + \epsilon_{ik}] \\ &= Cov[W_i(t_{ij}), \ W_i(t_{ik})] \end{aligned}$$

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$$= \tau^2 \rho^{|t_{ij} - t_{kl}|}$$

$$= \tau^2 \rho^{|j-k|} \text{ (because } t_{ij} = j \text{ and } t_{ik} = k.)$$

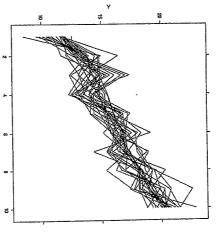
Therefore, the covariance matrix $\Sigma = Cov(Y_i)$ has the following form

$$\hat{J} = \begin{bmatrix}
\tau^{2} + \sigma^{3} & \tau^{2} \rho & \cdots & \tau^{2} \rho^{3} \\
\tau^{2} \rho & \tau^{2} + \sigma^{2} & \cdots & \tau^{2} \rho^{3} \\
\vdots & \vdots & \vdots & \vdots \\
\tau^{2} \rho^{9} & \tau^{2} \rho^{8} & \cdots & \tau^{2} + \sigma^{2}
\end{bmatrix}$$

have ρ .

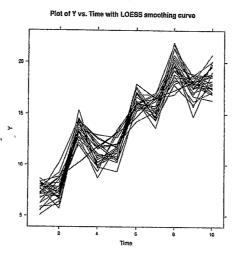
• Generate Y_i and plot (lines) versus t_i for m=25 using $\sigma=1.0$, $\tau=2.0$, and $\rho=0.7$. (solution)

Plot of Y vs. Time with LOESS smoothing curve

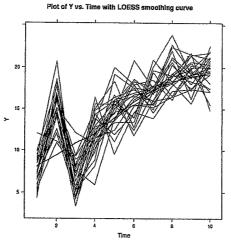


As we saw before, the covariance matrix of Y_i is very similar to the one in the first question of (a). The only different part is whether $Cov(Y_{ij}, Y_{ik})$ has the correlation $\rho^{|j-k|}$ or not. Due to the effect of this correlation, this figure has denser than the one in the first question of (a). Note that the red line is a LOESS curve.

• Generate Y_i and plot (lines) versus t_i for m=25 using $\sigma=1.0$, $\tau=2.0$, and $\rho=0.9$. (solution) When Comparing with the above figure, we can see a more fluctuation of $Y_{\dot{\theta}^i}$. It has a deeper valley than the above one.



• Generate Y_i and plot (lines) versus t_i for m=25 using $\sigma=2.0$, $\tau=2.0$, and $\rho=0.9$. (solution)



Since the standard deviation of a measurement error is bigger than the above two cases, this figure shows the greatest fluctuation of Y_{ij} over time. The variation of Y_{ij} tends to decrease as time passes because $\rho^{|j-h|}$ decreases.

- (a) From the spaghetti plots, each child's lead level profile looks like it reasonably come from an overall "inherent" straight-line trend, with some "jitter." So it seems like this is a reasonable model.
 - (b) As in the notes, we may think of e_i as being the sum of two components, $e_i = e_{1i} + e_{2i}$. Model assumptions (i) and (ii) mean the following:
 - (i) implies that we believe that b_i and e_{2i} are independent and that the variance of measurement errors is constant regardless of the lead level for the child
 - (ii) Implies that the elements of e_{1i} are uncorrelated with constant variance over time and are independent of b_i and e_{2i} .

Under (i) and (ii), we thus have that \mathbf{R}_i is of the general form on the bottom of page \mathfrak{A}_5 , $\mathfrak{I}_{n_i} = \sigma_1^2 \mathbf{I}_{n_i} + \sigma_2^2 \mathbf{I}_{n_i}$.

Under the first assumption on (iii) and (iv), D is the same for all strategies and σ_1^2 is the same for all treatments, so that the total within-child variance $\sigma_1^2 + \sigma_2^2 = \sigma^2$ is the same for all treatments.

Under the second assumption on (iii) and (iv), D is the same for all treatments but now σ_1^2 might be different, so that total within-child variance $\sigma_1^2 + \sigma_2^2$ is possibly different.

Under the third assumption on (iii) and (iv), D is possibly different for all treatments but σ_1^2 is the same for all strategies, so that the total within-mouse variance $\sigma_1^2 + \sigma_2^2 = \sigma^2$ is the same for all treatments.

Under the fourth assumption on (iii) and (iv), D is possibly different for all treatments and σ_1^2 might be different.

The attached SAS program fits the model under these three different assumptions.

(c) From the output, we have

| Model | AIC | BIC |
|--|--------|--------|
| Same D and same within-child variance | 3106.9 | 3118.0 |
| Same D and different within-child variance | 3108.2 | 3124.9 |
| Different D and same within-child variance | 3113.1 | 3140.9 |
| Both D and within-child variance different | 3115.8 | 3149.2 |

Both criteria prefer that model with the same D (variation/covariation of intercepts/slopes) same in each treatment and same within-child variance (reflecting that magnitude of within-child fluctuations is similar in each treatment). This is the "usual" model that is generally (but not always correctly!) assumed in mixed model analyses.

(d) We have included in each fit a contrast statement for the comparison of the three "typical" mean slopes. From the contrast statement for the fit of the model in (c), $T_L = 7.64$ with an associated p-value of 0.02. At level of significance 0.05, there is evidence to support the contention that there is a difference in lead level patterns, as represented by mean slope for each treatment. From the Solution for Fixed Effects for this model, informally, it appears that this is because both low- and high-dose succimer seem to lead to more dramatic rates of (decreasing) lead levels than placebo (so seem to be having an effect relative to placebo).