Linkage Score for Cox Partial Likelihood

For linkage, the first derivative of the efficient score for the partial likelihood (8) vanishes, and the second derivative produces

$$\begin{aligned}
\ddot{\ell}(\beta_0; v_t \,|\, Y) &= \sum_{i=1}^{n}\sum_{j=1}^{n} \mathbb{E}_0[\kappa_{ij} \,|\, Y]\big\{\mathbb{E}_0[U_i U_j \,|\, v_t] - \mathbb{E}_0\big[U_i U_j\big]\big\} \\
&= \sum_{i=1}^{n}\sum_{j=1}^{n} \mathbb{E}_0[\kappa_{ij} \,|\, Y]\big\{(\hat{\Phi}_{ij} - \Phi_{ij})\sigma^2_{\mathrm{A:U}} + (\hat{\Delta}_{ij} - \Delta_{ij})\sigma^2_{\mathrm{D:U}}\big\} \,,
\end{aligned}$$

where

$$\begin{aligned}
\kappa_{ij} &= \sum_{k=1}^{n} \hat{p}_{ki}\hat{p}_{kj}\delta_k 1_{\{i\in\mathcal{R}_k\}} 1_{\{j\in\mathcal{R}_k\}} + \delta_i\delta_j + \sum_{k=1}^{n}\sum_{l=1}^{n} \hat{p}_{ki}\hat{p}_{lj}\delta_k\delta_l 1_{\{i\in\mathcal{R}_k\}} 1_{\{j\in\mathcal{R}_l\}} \\
&\quad - \sum_{l=1}^{n} \delta_i\delta_l 1_{\{j\in\mathcal{R}_l\}}\hat{p}_{lj} - \sum_{k=1}^{n} \delta_j\delta_k 1_{\{i\in\mathcal{R}_k\}}\hat{p}_{ki} \,.
\end{aligned}$$

Normal Distribution

We give here some technical details of the example involving the normal distribution. Under the assumption that the random effects G and E have normal distributions with mean 0 and covariance Σ_{G} and Σ_{E}, respectively, η and Y have a multivariate normal distribution with mean $\mu = z\beta_{\mathrm{z}}$ and covariance matrix:

$$\begin{pmatrix} \Sigma & R \\ R & R \end{pmatrix},$$

where $R = \Sigma_{\mathrm{G}} + \Sigma_{\mathrm{E}}$ and $\Sigma = R + \sigma_e^2 I$.

The conditional distribution of ϵ given Y has mean

$$\frac{1}{\sigma_e^2}\Big\{Y - \big[\mu + R\Sigma^{-1}\big(Y-\mu\big)\big]\Big\} = \frac{1}{\sigma_e^2}\big[I - R\Sigma^{-1}\big]\big(Y-\mu\big) = \Sigma^{-1}\big(Y-\mu\big)\ ,$$

and the statistic can be written as

$$\dot{\ell}(\beta_0; U\,|\,Y) = \big(Y-\mu\big)'\Sigma^{-1}\big(U - \mathbb{E}_0 U\big)\ .$$

When Y is measured in pedigrees, the polygenic random effect G is often assumed to have covariance structure $\Sigma_{\mathrm{G}} = \sigma_{\mathrm{G}}^2\Phi$, where Φ is the coefficient of relationship matrix. For simplicity, we set $\beta_{\mathrm{E}} = 0$ in what follows to correspond to a standard genetic variance component model, so $\Sigma = \sigma_{\mathrm{G}}^2\Phi + \sigma_e^2 I$. The statistic to test for association in this context is

$$\dot{\ell}(\beta_0; U\,|\,Y) = \big(Y-\mu\big)'\big(\sigma_{\mathrm{G}}^2\Phi + \sigma_e^2 I\big)^{-1}\big(U - \mathbb{E}_0 U\big)\ .$$

When the observations are from a collection of pedigrees, under the assumption of independence of G and U, Φ is a block diagonal matrix and the preceding expression reduces to a sum of terms of the indicated form, where each term corresponds to a pedigree.

In the context of linkage analysis, we can write the efficient score as

$$\begin{aligned}
\ddot{\ell}(\beta_0; v_t\,|\,Y) &= \sum_{i=1}^{n}\sum_{j=1}^{n}\mathbb{E}_0[\epsilon_i\epsilon_j\,|\,Y]\big\{\mathbb{E}_0[U_iU_j|v_t] - \mathbb{E}_0[U_iU_j]\big\} \\
&= \sum_{i=1}^{n}\sum_{j=1}^{n}\mathbb{E}_0[\epsilon_i\epsilon_j\,|\,Y]\big[(\hat{\Phi}_{ij} - \Phi_{ij})\sigma_{\mathrm{A:U}}^2 + (\hat{\Delta}_{ij} - \Delta_{ij})\sigma_{\mathrm{D:U}}^2\big]\ .
\end{aligned}$$

We can rewrite this as

$$\mathrm{tr}\Big\{\mathbb{E}_0\Big[\Big(\frac{Y-\eta}{\sigma_e^2}\Big)\Big(\frac{Y-\eta}{\sigma_e^2}\Big)'\,\Big|\,Y\Big]\big[(\hat{\Phi} - \Phi)\sigma_{\mathrm{A:U}}^2 + (\hat{\Delta} - \Delta)\sigma_{\mathrm{D:U}}^2\big]\Big\}\ .$$

Let $\hat{\mu}$ be the conditional expectation of η given Y, then

$$\begin{aligned}
\mathbb{E}_0\Big[\Big(\frac{Y-\eta}{\sigma_e^2}\Big)\Big(\frac{Y-\eta}{\sigma_e^2}\Big)'\,\Big|\,Y\Big] &= \mathbb{E}_0\Big[\Big(\frac{Y-\hat{\mu}+\hat{\mu}-\eta}{\sigma_e^2}\Big)\Big(\frac{Y-\hat{\mu}+\hat{\mu}-\eta}{\sigma_e^2}\Big)'\,\Big|\,Y\Big] \\
&= \Big(\frac{Y-\hat{\mu}}{\sigma_e^2}\Big)\Big(\frac{Y-\hat{\mu}}{\sigma_e^2}\Big)' + \sigma_e^{-4}\mathbb{V}\mathrm{ar}(\eta\,|\,Y) \\
&= \big[\Sigma^{-1}(Y-\mu)\big]\big[\Sigma^{-1}(Y-\mu)\big]' + \sigma_e^{-2}\Sigma^{-1}R
\end{aligned}$$

so, after putting $\hat{\Sigma} = (Y-\mu)(Y-\mu)'$, the score statistic reduces to

$$\begin{aligned}
&\ddot{\ell}(\beta_0; v_t\,|\,Y) = \\
&\qquad \mathrm{tr}\Big\{\big[\Sigma^{-1}\hat{\Sigma}\Sigma^{-1} + \sigma_e^{-2}\Sigma^{-1}R\big]\big[(\hat{\Phi}-\Phi)\sigma^2_{\mathrm{A:U}} + (\hat{\Delta}-\Delta)\sigma^2_{\mathrm{D:U}}\big]\Big\} \\
&= \mathrm{tr}\Big\{\big[\Sigma^{-1}\hat{\Sigma}\Sigma^{-1} + \sigma_e^{-2}\Sigma^{-1}\big(\Sigma-\sigma_e^2 I\big)\big]\big[(\hat{\Phi}-\Phi)\sigma^2_{\mathrm{A:U}} + (\hat{\Delta}-\Delta)\sigma^2_{\mathrm{D:U}}\big]\Big\} \\
&= \mathrm{tr}\Big\{\big[\big(\Sigma^{-1}\hat{\Sigma}-I\big)\Sigma^{-1} + \sigma_e^{-2}I\big]\big[(\hat{\Phi}-\Phi)\sigma^2_{\mathrm{A:U}} + (\hat{\Delta}-\Delta)\sigma^2_{\mathrm{D:U}}\big]\Big\} \\
&= \mathrm{tr}\Big\{\big[\big(\Sigma^{-1}\hat{\Sigma}-I\big)\Sigma^{-1}\big]\big[(\hat{\Phi}-\Phi)\sigma^2_{\mathrm{A:U}} + (\hat{\Delta}-\Delta)\sigma^2_{\mathrm{D:U}}\big]\Big\}\,.
\end{aligned}$$