ASV proportions response $\mathbf{y}_i = (y_{i1}, \ldots, y_{ij}, \ldots, y_{ip})^T_{(np\times 1)} \sim \text{Dirichlet}(\alpha_{i1}, \ldots, \alpha_{ip})$

$$E(y_{ij}) = \mu_{ij} = \frac{\alpha_{ij}}{\alpha_{i1}}$$

where $\alpha_{i0} = \sum_{j=1}^{p} \alpha_{i0}$.

Indeces:

- Number of Samples: $i = 1, \ldots, n$.
- Number of OTUs: $j = 1, \ldots, p$
- Number of covariates, $k = 1, \ldots, q$

Define the design matrix $\mathbf{X}_{np\times(pq)}$ through the measurements for each sample $\mathbf{x}_i$ the p rows for a given sample:

$$\mathbf{x}_i = \begin{pmatrix} x_{k=1} & \cdots & x_{k=q} & 0 & \cdots & 0 & 0 & \cdots & 0 \\ 0 & \cdots & 0 & x_1 & \cdots & x_q & 0 & \cdots & 0 \\ \vdots \\ 0 & \cdots & 0 & 0 & \cdots & 0 & x_1 & \cdots & x_q \end{pmatrix}_{p\times pq}$$

$$\boldsymbol{\beta} = \begin{pmatrix} \beta_{j=1,k=1} \\ \beta_{j=1,k=2} \\ \vdots \\ \beta_{j=1,k=q} \\ \beta_{j=2,k=1} \\ \beta_{j=2,k=2} \\ \vdots \\ \beta_{j=p,k=1} \\ \vdots \end{pmatrix}_{pq\times 1}$$

For notation, consider $\mathbf{x}_{ij}$ to denote the jth row of $\mathbf{x}_i$, but note that the nonzero values of each $\mathbf{x}_{ij}$ are the same for all j

Link covarites to α's:

$$\log(\alpha_{ij_{1\times 1}}) = \mathbf{x_{ij_{1\times pq}}} \boldsymbol{\beta}_{pq\times 1}$$

and

$$\alpha_{ij} = e^{\mathbf{x_{ij}}\boldsymbol{\beta}}$$

Where only the corresponding j elements of β will have corresponding non-zero elements of $\mathbf{x}_{ij}$

Then the GEE equations are

$$\sum_{i=1}^{n}\left(\frac{\partial \boldsymbol{\mu}_i}{\partial \boldsymbol{\beta}}\right)^T \mathbf{V}_i^{-1}(\mathbf{Y_i}-\boldsymbol{\mu}_i)=0$$

Where $\boldsymbol{V}_i = A_i^{\frac{1}{2}} R_i A_i^{\frac{1}{2}}$
Then,

$$\begin{aligned}
\frac{\partial \boldsymbol{\mu}_i}{\partial \boldsymbol{\beta}} &= \frac{\partial}{\partial \boldsymbol{\beta}}\frac{\boldsymbol{\alpha}_i}{\alpha_{i0}} \\
&= \frac{\partial}{\partial \boldsymbol{\beta}}\frac{e^{\mathbf{x}_i\boldsymbol{\beta}}}{\sum_{j=1}^{p} e^{\mathbf{x_{ij}}\boldsymbol{\beta}}} \\
&= \begin{pmatrix}
\frac{\partial}{\partial \boldsymbol{\beta}_{j=1,k=1}}\frac{e^{\mathbf{x}_{i1}\boldsymbol{\beta}}}{\sum_{j=1}^{p} e^{\mathbf{x}_{ij}\boldsymbol{\beta}}} & \cdots & \frac{\partial}{\partial \boldsymbol{\beta}_{1,1}}\frac{e^{\mathbf{x}_{ip}\boldsymbol{\beta}}}{\sum_{j=1}^{p} e^{\mathbf{x}_{ij}\boldsymbol{\beta}}} \\
\frac{\partial}{\partial \boldsymbol{\beta}_{j=1,k=2}}\frac{e^{\mathbf{x}_{i1}\boldsymbol{\beta}}}{\sum_{j=1}^{p} e^{\mathbf{x}_{ij}\boldsymbol{\beta}}} & \vdots & \vdots \\
\vdots & \vdots & \vdots \\
\frac{\partial}{\partial \boldsymbol{\beta}_{j=p,k=q}}\frac{e^{\mathbf{x}_{i1}\boldsymbol{\beta}}}{\sum_{j=1}^{p} e^{\mathbf{x}_{ij}\boldsymbol{\beta}}} & \cdots & \frac{\partial}{\partial \boldsymbol{\beta}}\frac{e^{\mathbf{x}_{ip}\boldsymbol{\beta}_{p,q}}}{\sum_{j=1}^{p} e^{\mathbf{x}_{ij}\boldsymbol{\beta}}}
\end{pmatrix}_{np\times p} \\
&= \frac{1}{\left(\sum_{j=1}^{p} e^{\mathbf{x}_{ij}\boldsymbol{\beta}}\right)^2}
\begin{pmatrix}
x_{i1}\alpha_{i1}\alpha_{i0} - x_{iq}\alpha_{i1}\alpha_{i1} & \cdots & -x_{i1}\alpha_{i1}\alpha_{ip} \\
\vdots & \vdots & \vdots \\
-x_{i1}\alpha_{i1}\alpha_{i2} & x_{i2}\alpha_{i0}\alpha_{i2} - x_{i2}\alpha_{i2}\alpha_{i2} & \cdots \\
\vdots & \ddots & \vdots \\
-x_{i1}\alpha_{i1}\alpha_{ip} & \cdots & x_{iq}\alpha_{ip}\alpha_{i0} - x_{iq}\alpha_{ip}\alpha_{ip} \\
\vdots & \ddots & \vdots
\end{pmatrix}
\end{aligned}$$