

Model:

$$Z_{ij} = a + b_A S_{ij}^A + b_B S_{ij}^B + d_{AB} U_{ij} + e_{ij} \quad (1)$$

Model:

$$Y_i = X_i \gamma + H_i^A \beta^A + H_i^B \beta^B + T_i \alpha + e_i \quad (2)$$

where  $X_i = (X_{i1}, X_{i2}, \dots, X_{in})$  is the covariant,  $H_i^A = (H_{i1}^A, H_{i2}^A, \dots, H_{i,l_A}^A)$  is the haplotype for Gene A and  $H_i^B = (H_{i1}^B, H_{i2}^B, \dots, H_{i,l_B}^B)$  is the haplotype for Gene B,  $\beta^A = (\beta_1^A, \beta_2^A, \dots, \beta_{l_A}^A)^T$  follows  $MN(0, \tau_A R_A)$ ,  $\beta^B = (\beta_1^B, \beta_2^B, \dots, \beta_{l_B}^B)^T$  follows  $MN(0, \tau_B R_B)$ ,  $T_i = (H_{i1}^A H_{i1}^B, \dots, H_{i1}^A H_{i,l_B}^B, H_{i2}^A H_{i1}^B, \dots, H_{i,l_A}^A H_{i,l_B}^B)$  records the interaction terms for the Gene A and Gene B.  $\alpha = (\alpha_1, \dots, \alpha_{l_A, l_B})^T$  follows  $MN(0, \phi Q)$

Re-parameter:

Let  $H_i = (H_i^A, H_i^B, T_i)$ ,  $\beta = (\beta^A, \beta^B, \alpha)^T$ , so (1) can be rewrite as following model:

$$Y_i = X_i \gamma + H_i \beta + e_i \quad (3)$$

$$\text{Let } R_\beta = \begin{pmatrix} \tau_A R_A & 0 & 0 \\ 0 & \tau_B R_B & 0 \\ 0 & 0 & \phi Q \end{pmatrix}, \text{ so } \beta \text{ follows } MN(0, R_\beta).$$

The rest derivation is almost the same with the model for just one gene:

Let  $u_i = E(Y_i | \beta, X_i, H_i)$ , so  $g(u_i) = X_i \gamma + H_i \beta$ . Define  $u_i^0 = g^{-1}(X_i \gamma)$ , we have

$$\begin{aligned} E(Y_i | X_i, H_i) &= E[E(Y_i | \beta, X_i, H_i)] \\ &= E(u_i) \\ &\approx E u_i^0 + [g'(u_i^0)]^{-1} H_i \beta \\ &= u_i^0 \end{aligned} \quad (4)$$

For two individuals i and j, we have

$$\begin{aligned} \text{cov}(Y_i, Y_j | X, H) &= E[Y_i - E(Y_i)][Y_j - E(Y_j)] \\ &\approx E[(Y_i - u_i^0)(Y_j - u_j^0)] \end{aligned} \quad (5)$$

The connection between the VC model and the similarity model is the definition of  $Z_{ij}$  which is

$$Z_{ij} = w_i(Y_i - u_i^0)w_j(Y_j - u_j^0)$$

$$\begin{aligned} E(Z_{ij} | X, H) &= E w_i(Y_i - u_i^0)w_j(Y_j - u_j^0) \\ &= w_i w_j E[(Y_i - u_i^0)(Y_j - u_j^0)] \\ &\approx \text{cov}(Y_i, Y_j | X, H) \end{aligned} \quad (6)$$

using the law of covariance, we have

$$\text{cov}(Y_i, Y_j | X, H) = E[\text{cov}(Y_i, Y_j | \beta, X, H)] + \text{cov}[E(Y_i | \beta, X, H), E(Y_j | \beta, X, H)] \quad (7)$$

Conditional on  $\beta$ ,  $\text{cov}(Y_i, Y_j | \beta, X, H)$  equals to 0, so we mainly focus on the second part of formula (7).

$$\begin{aligned}
\text{cov}[E(Y_i|\beta, X, H), E(Y_j|\beta, X, H)] &\approx \text{cov}[u_i^0 + [g'(u_i^0)]^{-1}H_i\beta, u_j^0 + [g'(u_j^0)]^{-1}H_j\beta] \\
&= \text{cov}[g'(u_i^0)]^{-1}H_i\beta, [g'(u_j^0)]^{-1}H_j\beta \\
&= [g'(u_i^0)g'(u_j^0)]^{-1}H_iR_\beta H_j^T
\end{aligned} \tag{8}$$

where

$$\begin{aligned}
H_iR_\beta H_j^T &= H_i^A R_A (H_j^A)^T + H_i^B R_B (H_j^B)^T + T_i Q T_j^T \\
&= \tau_A \sum_{h_A, k_A} H_{i, h_A} H_{j, k_A} r_{h_A, k_A} + \tau_B \sum_{h_B, k_B} H_{i, h_B} H_{j, k_B} r_{h_B, k_B} + \phi \sum_{h_A, k_A, h_B, k_B} H_{i, h_A} H_{i, h_B} H_{j, k_A} H_{j, k_B} r_{h_A, k_A} r_{h_B, k_B}
\end{aligned} \tag{9}$$

so if the  $l_A l_B \times l_A l_B$  matrix  $Q$  is

$$Q = \begin{pmatrix} r_{11}^A r_{11}^B & \dots & r_{11}^A r_{1l_B}^B & \dots & r_{1l_A}^A r_{1l_B}^B \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ r_{l_A 1}^A r_{11}^B & \dots & r_{l_A 1}^A r_{1l_B}^B & \dots & r_{l_A l_A}^A r_{1l_B}^B \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ r_{l_A 1}^A r_{l_B 1}^B & \dots & r_{l_A 1}^A r_{l_B l_B}^B & \dots & r_{l_A l_A}^A r_{l_B l_B}^B \end{pmatrix}$$

then we choose  $w_i = g'(u_i^0)$  then the two model are the same and  $\phi$  equals to  $d_{AB}$ .