Text S1: Multiplicative Model

I first calculate the expected contribution under a multiplicative model to the prevalence $E(K_L)$ and the recurrence risk $E(K_L K_{LR})$ for a pair of individuals with relationship R. Then I show the individual terms for calculating $Pr(AA_R|H,S)$ that are used in equation (8).

The contribution to prevalence can be calculated by integrating over all possible effect sizes

$$\begin{aligned} E(K_L) &= \int [p^2(\omega_1\omega_2) + 2p(1-p)\omega_1 + (1-p)^2]\, f(\omega_1)f(\omega_2)d\omega_1 d\omega_2 \\ &= p^2 \int \omega_1 \int [\omega_2\, f(\omega_2\,)d\omega_2] f(\omega_1)d\omega_1 + 2p(1-p)\int \omega_1 f(\omega_1\,)d\omega_1 + (1-p)^2 \\ &= p^2\mu^2 + 2p(1-p)\mu + (1-p)^2 = (p\mu + 1 - p)^2 = \big(1 + p(\mu - 1)\big)^2 \end{aligned}$$

To calculate $E(K_L K_{LR})$ I apply the law of total probability by conditioning on the number S of chromosomes shared between the relatives. For $S = 0$

$$E(K_L K_{LR}|S=0) = E(K_L)^2 = \big(1 + p(\mu - 1)\big)^4.$$

When considering relative pairs with shared carrier chromosomes, some risk haplotypes may occur in multiple individuals IBD. The contribution of these chromosomes to the overall penetrance includes the term $\int \omega_S^2 f(\omega)d\omega = \mu^2 + \sigma^2$. When conditioning on $S = 1$, I consider the relative risk ω_S of shared chromosome and the penetrances ω_1, ω_2 of the 2 non-shared chromosomes.

$$E(K_L\, K_{LR}|S=1) =$$

$$= (1-p)^3 + p(1-p)^2 \int \omega_1\ f(\omega_1)d\omega_1 + p(1-p)^2 \int \omega_2\ f(\omega_2)d\omega_2$$

$$+p(1-p)^2 \int \omega_S^2\, f(\omega_S\,)d\omega_S + p^2\,(1-p)\int (\omega_1\,\omega_S\,)\omega_S\, f(\omega_1\,)f(\omega_S\,)d\omega_1\, d\omega_S$$

$$+p^2\,(1-p)\int (\omega_2\omega_S\,)\omega_S\, f(\omega_2\,)f(\omega_S\,)d\omega_1\, d\omega_S + p^2\,(1-p)\int \omega_1\,\omega_2\, f(\omega_1\,)f(\omega_2\,)d\omega_1\, d\omega_2 +$$

$$+p^3 \int (\omega_1\omega_S\,)(\omega_2\omega_S\,)f(\omega_1\,)f(\omega_2\,)f(\omega_S\,)d\omega_1\, d\omega_2\, d\omega_S =$$

$$= (1-p)^3 + 2(1-p)^2\, p\mu + (1-p)p^2\mu^2 + (1-p)^2\, p(\mu^2 + \sigma^2\,) + 2(1-p)p^2\, \mu(\mu^2 + \sigma^2\,) +$$

$$p^3\, \mu^2\, (\mu^2 + \sigma^2\,) = (1-p)((1-p)^2 + 2(1-p)p\mu + p^2\,\mu^2\,) + p(\mu^2 + \sigma^2\,)\big((1-p) + p\,\mu\,\big)^2 =$$

$$= \big((1-p) + p\,\mu\,\big)^2\big((1-p) + p(\mu^2 + \sigma^2)\big) = E(K_L)(1 + p(\mu^2 + \sigma^2 - 1))$$

When conditioning on two shared chromosomes, I integrate over the penetrances ω_{S1}, ω_{S2}.

$$E(K_L K_{LR}|S=2)$$

$$= (1-p)^2 + 2p(1-p)\int \omega_{S1}^2 f(\omega_{S1}) d\omega_{S1} + p^2 \int \omega_{S1}^2\, \omega_{S2}^2 \quad f(\omega_{S1}) f(\omega_{S2}) d\omega_{S1} d\omega_{S2}$$

$$= \left(1 + p(\mu^2 + \sigma^2 - 1)\right)^2$$

Then the expectation of $K_L K_{LR}$ can be calculated by summing over S:

$$E(K_L K_{LR}) = \sum_S E(K_L K_{LR}|S) P(S|R)$$

To calculate the probability of observing H risk haplotypes in the sampled individual requires calculating $\sum_S \Pr(AA_R|H,S) \Pr(S)$. Under a multiplicative model, $\Pr(AA_R|H,S)$ can be calculated up to a constant that depends on the overall prevalence and relative recurrence risk (See equation (7)) by integrating over the genotype in the affected relative H_R. Conditional on $S=0$, the additive effect of all risk haplotypes is independent. Hence:

$$P(AA_R|H=h_1, H_R=h_2, S=0) \propto \mu^{h_1+h_2}$$

To account for such shared risk chromosomes for $S>0$, define H_S as the number of shared risk haplotypes ($H_S \leq S$). Then

$$P(AA_R|H=h_1, H_R=h_2, H_S=h_s) \propto \mu^{h_1+h_2} + 1_{h_S>0}\mu^{h_1+h_2-2h_S}\sigma^{2h_S}.$$

From this we can then calculate by integrating over H_R.

$$Pr(AA_R|H=0, S=0) \propto (1-p)^2 + 2p(1-p)\mu + p^2\mu^2 = (1+p(\mu-1))^2$$

$$Pr(AA_R|H=1, S=0) \propto (1-p)^2\mu + 2p(1-p)\mu^2 + p^2\mu^3 = \mu(1+p(\mu-1))^2$$

$$Pr(AA_R|H=2, S=0) \propto (1-p)^2\mu^2 + 2p(1-p)\mu^3 + p^2\mu^4 = \mu^2(1+p(\mu-1))^2$$

$$Pr(AA_R|H=0, S=1) \propto 1-p+(p\mu) = 1+p(\mu-1)$$

$$Pr(AA_R|H=1, S=1) \propto \tfrac{1}{2}\left((1-p)\mu + p\mu^2\right) + \tfrac{1}{2}\left((1-p)(\mu^2+\sigma^2) + p\mu(\mu^2+\sigma^2)\right)$$

$$Pr(AA_R|H=2, S=1) \propto \left((1-p)\mu(\mu^2+\sigma^2) + p\mu^2(\mu^2+\sigma^2)\right)$$

$$Pr(AA_R|H=0, S=2) \propto 1$$

$$Pr(AA_R|H=1, S=2) \propto (\mu^2+\sigma^2)$$

$Pr(AA_R|H = 2, S = 2) \propto (\mu^2 + \sigma^2)^2$

Based on these equations, the probability of observing h risk haplotypes in an individual is

$$Pr(H = h|AA_R) = Pr(AA_R|H = h)\frac{\Pr(H = h)}{\sum_H Pr(AA_R|H)\Pr(H)};$$

here the normalizing constant cancels.