

## Perturbative solution of the generating function for small $f_0$

We are interested in the linkage equilibrium statistic  $\Lambda(f_0)$ , defined as

$$\Lambda(f_0) \equiv \frac{\left\langle f_{ab}f_{Ab}f_{aB}f_{AB} \cdot e^{-\frac{f_A+f_B}{f_0}} \right\rangle}{\left\langle f_A^2(1-f_A)^2 f_B^2(1-f_B)^2 \cdot e^{-\frac{f_A+f_B}{f_0}} \right\rangle}, \quad (1)$$

where  $f_A \equiv f_{Ab} + f_{aB}$ ,  $f_B \equiv f_{aB} + f_{AB}$  and  $f_A, f_B \lesssim f_0$ . In the limit that  $f_{Ab}, f_{aB}, f_{AB} \ll 1$ ,

$$\Lambda(f_0) \approx \frac{\left\langle f_{Ab}f_{aB}f_{AB} \cdot e^{-\frac{f_A+f_B}{f_0}} \right\rangle}{\left\langle f_A^2 f_B^2 \cdot e^{-\frac{f_A+f_B}{f_0}} \right\rangle}. \quad (2)$$

The moments follows from

$$\left\langle f_{Ab}^i f_{aB}^j f_{AB}^k \cdot e^{-\frac{f_A+f_B}{f_0}} \right\rangle = -f_0^{(i+j+k)} \partial_x^i \partial_y^j \partial_z^k H(x, y, z, t) \Big|_{\substack{x=1 \\ y=1 \\ z=2 \\ t=\infty}}, \quad (3)$$

where

$$H(x, y, z, t) \equiv \left\langle e^{-x \frac{f_{Ab}(t)}{f_0} - y \frac{f_{aB}(t)}{f_0} - z \frac{f_{AB}(t)}{f_0}} \right\rangle \quad (4)$$

is the joint moment generating function.

In the limit that  $\theta = 2N\mu$  and  $f_0$  are both small compared to one,

$$H(x, y, z, \tau) \approx 1 - \theta(H_A + H_B) + \frac{\theta^2}{2} (H_A + H_B)^2 \quad (5)$$

$$+ \theta^2 f_0 \Upsilon + \theta^2 f_0 \int_0^\tau d\tau' z(\tau') [\Phi_x(\tau') + \Phi_y(\tau') - \rho \Phi_x(\tau') \Phi_y(\tau')] \\ + \mathcal{O}(f_0^2) + \mathcal{O}(\theta^3),$$

where  $\tau = t/2Nf_0$ ,  $\gamma_A = 2Ns_A f_0$ ,  $\gamma_B = 2Ns_B f_0$ ,  $\rho = 2NRf_0$ , and

$$H_A(x, \tau) \equiv \ln \left[ 1 + \frac{x(1 - e^{-\gamma_A \tau})}{\gamma_A} \right], \quad (6a)$$

$$H_B(y, \tau) \equiv \ln \left[ 1 + \frac{y(1 - e^{-\gamma_B \tau})}{\gamma_B} \right], \quad (6b)$$

$$\Phi_x(\tau') \equiv -\frac{[1 - e^{-\gamma_A(\tau - \tau')}] [\gamma_A + x(1 - e^{-\gamma_A \tau})]}{\gamma_A [\gamma_A + x(1 - e^{-\gamma_A \tau})]}, \quad (7a)$$

$$\Phi_y(\tau') \equiv -\frac{[1 - e^{-\gamma_B(\tau - \tau')}] [\gamma_B + y(1 - e^{-\gamma_B \tau'})]}{\gamma_A [\gamma_B + y(1 - e^{-\gamma_B \tau})]}, \quad (7b)$$

$$\Upsilon(x, y, \tau) = \int_0^\tau d\tau' \rho [x(\tau') + y(\tau')] \Phi_x(\tau') \Phi_y(\tau'). \quad (8)$$

The characteristic  $z(\tau')$  is defined by

$$\partial_{\tau'} z(\tau') = -(\gamma_{AB} + \rho)z(\tau') - z^2(\tau') + \rho \frac{\gamma_A x e^{-\gamma_A \tau'}}{\gamma_A + x(1 - e^{-\gamma_A \tau'})} + \rho \frac{\gamma_B y e^{-\gamma_B \tau'}}{\gamma_B + y(1 - e^{-\gamma_B \tau'})} \quad (9)$$

with the initial condition  $z(0) = z$ , where  $\gamma_{AB}$  is the rescaled fitness of the double mutant.

### Perturbative solution for $\Lambda(f_0)$ for neutral loci and weak recombination

In the absence of recombination, the equation above has an exact solution,

$$z_0(\tau') = \frac{\gamma_{AB} z e^{-\gamma_{AB} \tau'}}{\gamma_{AB} + z(1 - e^{-\gamma_{AB} \tau'})}. \quad (10)$$

In the limit that  $\rho \ll 1$ , corrections to the zeroth-order solution can be found by perturbatively expanding  $z(\tau')$  as

$$z(\tau') \approx z_0(\tau') + \sum_{i=1}^{\infty} \rho^i z_i(\tau'). \quad (11)$$

Plugging the series expansion in the equation for  $z(\tau')$  and matching the coefficients in front powers of  $\rho$ , we obtain for the first-order correction

$$\partial_{\tau'} z_1(\tau') \approx -\gamma_{AB} z_1(\tau') - 2z_0(\tau') z_1(\tau') - z_0(\tau') + \frac{\gamma_A x e^{-\gamma_A \tau'}}{\gamma_A + x(1 - e^{-\gamma_A \tau'})} + \frac{\gamma_B y e^{-\gamma_B \tau'}}{\gamma_B + y(1 - e^{-\gamma_B \tau'})}. \quad (12)$$

In the neutral limit, the equation above reduces to

$$\partial_{\tau'} z_1(\tau') \approx -\frac{2z}{1 + z\tau'} z_1(\tau') - \frac{z}{1 + z\tau'} + \frac{x}{1 + x\tau'} + \frac{y}{1 + y\tau'}. \quad (13)$$

This inhomogeneous linear ordinary differential equation can be solved by the method of variation of constants. The corresponding homogeneous equation

$$\partial_{\tau'} z_1(\tau') \approx -\frac{2z}{1 + z\tau'} z_1(\tau') \quad (14)$$

has solution in the form

$$z_1(\tau') \approx \frac{\phi(\tau')}{(1 + z\tau')^2}, \quad (15)$$

where  $\phi(\tau')$  is some function of  $\tau'$ . Plugging Eq. (15) into Eq. (13), we obtain

$$\partial_{\tau'} \phi(\tau') \approx -z(1 + z\tau') + \frac{x(1 + z\tau')^2}{1 + x\tau'} + \frac{y(1 + z\tau')^2}{1 + y\tau'}, \quad (16)$$

from where

$$\begin{aligned} \phi(\tau') &\approx - \int z(1 + z\tau') d\tau' + \int \frac{x(1 + z\tau')^2}{1 + x\tau'} d\tau' + \int \frac{y(1 + z\tau')^2}{1 + y\tau'} d\tau' \\ &= \frac{1}{2}(1 + z\tau')^2 + z\tau' \left(1 - \frac{z}{x}\right) + z\tau' \left(1 - \frac{z}{y}\right) \\ &\quad + \left(1 - \frac{z}{x}\right)^2 \ln(1 + x\tau') + \left(1 - \frac{z}{y}\right)^2 \ln(1 + y\tau') + C, \end{aligned} \quad (17)$$

where  $C = \frac{1}{2}$  is a constant determined by the initial condition  $\phi(0) = 0$ . Then,

$$\begin{aligned} z_1(\tau') &\approx \frac{1}{2} + \frac{1}{2} \frac{1}{(1 + z\tau')^2} + \left(1 - \frac{z}{x}\right) \frac{z\tau'}{(1 + z\tau')^2} + \left(1 - \frac{z}{y}\right) \frac{z\tau'}{(1 + z\tau')^2} \\ &\quad + \left(1 - \frac{z}{x}\right)^2 \frac{\ln(1 + x\tau')}{(1 + z\tau')^2} + \left(1 - \frac{z}{y}\right)^2 \frac{\ln(1 + y\tau')}{(1 + z\tau')^2}. \end{aligned} \quad (18)$$

Substituting Eq. (18) into Eq. (11), we find

$$\begin{aligned} z(\tau') &\approx \frac{z}{1 + z\tau'} + \frac{\rho}{2} + \frac{\rho}{2} \frac{1}{(1 + z\tau')^2} \\ &\quad + \rho \left(1 - \frac{z}{x}\right) \frac{z\tau'}{(1 + z\tau')^2} + \rho \left(1 - \frac{z}{y}\right) \frac{z\tau'}{(1 + z\tau')^2} \\ &\quad + \rho \left(1 - \frac{z}{x}\right)^2 \frac{\ln(1 + x\tau')}{(1 + z\tau')^2} + \rho \left(1 - \frac{z}{y}\right)^2 \frac{\ln(1 + y\tau')}{(1 + z\tau')^2}. \end{aligned} \quad (19)$$

Thus, to the lowest order in  $\rho$ , the numerator of  $\Lambda(f_0)$  follows as

$$\begin{aligned} \left\langle f_{Ab} f_{aB} f_{AB} \cdot e^{-\frac{f_A + f_B}{f_0}} \right\rangle &\approx -\rho \theta^2 f_0^4 \left[ - \int_0^\tau d\tau' \partial_x \Phi_x \partial_y \Phi_y \partial_z \frac{z}{1 + z\tau'} \right. \\ &\quad - \int_0^\tau d\tau' \partial_x \Phi_x \partial_y \partial_z \frac{z}{y} \frac{z\tau'}{(1 + z\tau')^2} - \int_0^\tau d\tau' \partial_y \Phi_y \partial_x \partial_z \frac{z}{x} \frac{z\tau'}{(1 + z\tau')^2} \\ &\quad \left. + \int_0^\tau d\tau' \partial_x \Phi_x \partial_y \partial_z \left(1 - \frac{z}{y}\right)^2 \frac{\ln(1 + y\tau')}{(1 + z\tau')^2} \right] \end{aligned} \quad (20)$$

$$\begin{aligned}
& + \int_0^\tau d\tau' \partial_y \Phi_y \partial_x \partial_z \left( 1 - \frac{z}{x} \right)^2 \frac{\ln(1 + x\tau')}{(1 + z\tau')^2} \Bigg|_{\substack{x=1 \\ y=1 \\ z=2 \\ \tau=\infty}} \\
& = -\rho\theta^2 f_0^4 \left[ -\int_0^\infty \frac{1}{(1 + 2\tau')^2} d\tau + 2 \int_0^\infty \frac{4\tau'}{(1 + 2\tau')^3} d\tau' \right. \\
& \quad \left. + 2 \int_0^\tau \frac{2\tau' - 2(3 + 2\tau') \ln(1 + \tau')}{(1 + 2\tau')^3} d\tau' \right] \\
& = -\rho\theta^2 f_0^4 \left[ -\frac{1}{2} + 1 - \frac{3}{2} \right] = \rho\theta^2 f_0^4.
\end{aligned}$$

where have used

$$\partial_x \Phi_x \Bigg|_{\substack{x=1 \\ \tau=\infty}} = -\frac{(\tau - \tau')^2}{(1 + x\tau)^2} \Bigg|_{\substack{x=1 \\ \tau=\infty}} = 1, \quad (21a)$$

$$\partial_y \Phi_y \Bigg|_{\substack{y=1 \\ \tau=\infty}} = -\frac{(\tau - \tau')^2}{(1 + y\tau)^2} \Bigg|_{\substack{y=1 \\ \tau=\infty}} = 1. \quad (21b)$$

To the lowest order in  $\theta$ ,  $f_0$ , and  $\rho$ , the denominator of  $\Lambda(f_0)$  can be found as

$$\left\langle f_A^2 f_B^2 \cdot e^{-\frac{f_A + f_B}{f_0}} \right\rangle \approx \theta^2 f_0^4 \partial_x^2 \partial_y^2 H_A H_B \Bigg|_{\substack{x=1 \\ y=1 \\ \tau=\infty}} = \theta^2 f_0^4 \frac{1}{x^2 y^2} \Bigg|_{\substack{x=1 \\ y=1}} = \theta^2 f_0^4. \quad (22)$$

Thus, in the neutral limit for small  $\rho$ ,  $\Lambda(f_0) \approx \rho$ .

### Perturbative solution for $\Lambda(f_0)$ for strong selection or recombination

In the limit that  $\gamma_{AB}$  or  $\rho$  are large compared to one, we can rescale time in Eq. (9) so that

$$\partial_u z(u) = -z(u) - \epsilon z^2(u) + \alpha \xi(u) \quad (23)$$

with the initial condition  $z(0) = z$ , where  $u = \tau'/\epsilon$  is the rescaled time,  $\epsilon = 1/(\gamma_{AB} + \rho)$ ,  $\alpha = \epsilon\rho$ ,  $\beta_A = \epsilon\gamma_A$ ,  $\beta_B = \epsilon\gamma_B$ , and

$$\xi(u) = \frac{\beta_A x e^{-\beta_A u}}{\beta_A + \epsilon x (1 - e^{-\beta_A u})} + \frac{\beta_B y e^{-\beta_B u}}{\beta_B + \epsilon y (1 - e^{-\beta_B u})} \quad (24)$$

is a function independent of  $z$ .

We can solve Eq. (23) using a perturbation expansion in  $\epsilon$ , defining

$$z(u) \approx \sum_{i=0}^{\infty} \epsilon^i z_i(u) \quad (25a)$$

and

$$\xi(u) \approx \sum_{i=0}^{\infty} \epsilon^i \xi_i(u). \quad (25b)$$

At zeroth order,

$$\partial_u z_0(u) = -z_0(u) + \alpha \xi_0(u) \quad (26)$$

with the initial condition  $z_0(0) = z$  and hence

$$z_0(u) = z e^{-u} + \alpha e^{-u} \int_0^u e^{u'} \xi_0(u') du'. \quad (27)$$

The numerator of  $\Lambda(f_0)$  then follows as

$$\begin{aligned} \left\langle f_{Ab} f_{aB} f_{AB} \cdot e^{-\frac{f_A + f_B}{f_0}} \right\rangle &\approx \alpha \theta^2 f_0^4 \int_0^{\tau/\epsilon} e^{-u} du \partial_x \Phi_x \partial_y \Phi_y \partial_z z \Phi_x \Phi_y \Big|_{\substack{x=1 \\ y=1 \\ z=2 \\ \tau=\infty}} \\ &= \frac{\epsilon^2 \alpha \theta^2 f_0^4}{\beta_A^2 \beta_B^2 (1 + \beta_A + \beta_B)}, \end{aligned} \quad (28)$$

where we have used

$$\partial_x \Phi_x \Big|_{\substack{x=1 \\ \tau=\infty}} = e^{-\beta_A u} \left[ \frac{1 - e^{-\beta_A(\tau/\epsilon - u)}}{x(1 - e^{-\beta_A \tau/\epsilon}) + \beta_A/\epsilon} \right]^2 \Big|_{\substack{x=1 \\ \tau=\infty}} = \frac{\epsilon^2}{\beta_A^2} e^{-\beta_A u}, \quad (29a)$$

$$\partial_y \Phi_y \Big|_{\substack{y=1 \\ \tau=\infty}} = e^{-\beta_B u} \left[ \frac{1 - e^{-\beta_B(\tau/\epsilon - u)}}{x(1 - e^{-\beta_B \tau/\epsilon}) + \beta_B/\epsilon} \right]^2 \Big|_{\substack{y=1 \\ \tau=\infty}} = \frac{\epsilon^2}{\beta_B^2} e^{-\beta_B u}. \quad (29b)$$

The denominator of  $\Lambda(f_0)$  can be found as

$$\left\langle f_A^2 f_B^2 \cdot e^{-\frac{f_A + f_B}{f_0}} \right\rangle \approx \theta^2 f_0^4 \partial_x^2 \partial_y^2 H_A H_B \Big|_{\substack{x=1 \\ y=1 \\ \tau=\infty}} = \frac{\epsilon^2 \theta^2 f_0^4}{\beta_A^2 \beta_B^2} \frac{1}{x^2 y^2} \Big|_{\substack{x=1 \\ y=1}} = \frac{\epsilon^4 \theta^2 f_0^4}{\beta_A^2 \beta_B^2}. \quad (30)$$

$\Lambda(f_0)$  then follows as

$$\Lambda(f_0) \approx \frac{\alpha}{1 + \beta_A + \beta_B} = \frac{\rho}{\rho + \gamma_A + \gamma_B + \gamma_{AB}}. \quad (31)$$

The approximation above holds for any  $\rho$  as long as  $\gamma_{AB} \gg 1$ . If  $\rho \gg \gamma_A, \gamma_B, \gamma_{AB}$ , then

$$\Lambda(f_0) \approx 1 \quad (32)$$

for any  $\gamma_A, \gamma_B, \gamma_{AB}$ . If  $1 \ll \rho \ll \gamma_A, \gamma_B, \gamma_{AB}$ , Eq. (31) reduces to

$$\Lambda(f_0) \approx \frac{\rho}{\gamma_A + \gamma_B + \gamma_{AB}}. \quad (33)$$

Is this too simple?

It seems that the only regime that we have not thought about yet is small recombination, strong selection but no epistasis?