

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 γ_{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 ρ , 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

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

with the initial condition $z_1(0) = 0$. Using the method of variation of constants, we find

$$\begin{aligned} z_1(\tau') \approx & \frac{1}{2} + \frac{1}{2} \frac{1}{(1 + z\tau')^2} + \left(1 - \frac{z}{x}\right) \frac{z\tau'}{(1 + z\tau')^2} + \left(1 - \frac{z}{y}\right) \frac{z\tau'}{(1 + z\tau')^2} \\ & + \left(1 - \frac{z}{x}\right)^2 \frac{\ln(1 + x\tau')}{(1 + z\tau')^2} + \left(1 - \frac{z}{y}\right)^2 \frac{\ln(1 + y\tau')}{(1 + z\tau')^2}. \end{aligned} \quad (14)$$

Thus, to the lowest order in ρ , from Eq. (3) the numerator of $\Lambda(f_0)$ follows as

$$\begin{aligned}
\left\langle f_{Ab}f_{aB}f_{AB} \cdot e^{-\frac{f_A+f_B}{f_0}} \right\rangle &\approx -\theta^2 f_0^4 \int_0^\tau d\tau' \partial_x \partial_y \partial_z [-\rho z_0 \Phi_x \Phi_y + \rho z_1 \Phi_x + \rho z_1 \Phi_y] \Bigg|_{\substack{x=1 \\ y=1 \\ z=2 \\ \tau=\infty}} \\
&\approx \rho \theta^2 f_0^4 \left[\int_0^\tau d\tau' \partial_x \Phi_x \partial_y \Phi_y \partial_z \frac{z}{1+z\tau'} \right. \\
&\quad + \int_0^\tau d\tau' \partial_x \Phi_x \partial_y \partial_z \frac{z}{y} \frac{z\tau'}{(1+z\tau')^2} \\
&\quad + \int_0^\tau d\tau' \partial_y \Phi_y \partial_x \partial_z \frac{z}{x} \frac{z\tau'}{(1+z\tau')^2} \\
&\quad - \int_0^\tau d\tau' \partial_x \Phi_x \partial_y \partial_z \left(1 - \frac{z}{y}\right)^2 \frac{\ln(1+y\tau')}{(1+z\tau')^2} \\
&\quad \left. - \int_0^\tau d\tau' \partial_y \Phi_y \partial_x \partial_z \left(1 - \frac{z}{x}\right)^2 \frac{\ln(1+x\tau')}{(1+z\tau')^2} \right] \Bigg|_{\substack{x=1 \\ y=1 \\ z=2 \\ \tau=\infty}} \\
&= \rho \theta^2 f_0^4 \left[\frac{1}{2} - \frac{1}{2} - \frac{1}{2} + \frac{3}{4} + \frac{3}{4} \right] = \rho \theta^2 f_0^4.
\end{aligned} \tag{15}$$

where have used

$$\partial_x \Phi_x \Bigg|_{\substack{x=1 \\ \tau=\infty}} = \frac{(\tau - \tau')^2}{(1+x\tau)^2} \Bigg|_{\substack{x=1 \\ \tau=\infty}} = 1, \tag{16a}$$

$$\partial_y \Phi_y \Bigg|_{\substack{y=1 \\ \tau=\infty}} = \frac{(\tau - \tau')^2}{(1+y\tau)^2} \Bigg|_{\substack{y=1 \\ \tau=\infty}} = 1. \tag{16b}$$

To the lowest order in θ , f_0 , and ρ , from Eq. (3) the denominator of $\Lambda(f_0)$ follows as

$$\left\langle f_A^2 f_B^2 \cdot e^{-\frac{f_A+f_B}{f_0}} \right\rangle \approx \theta^2 f_0^4 \partial_x^2 \partial_y^2 H_A H_B \Bigg|_{\substack{x=1 \\ y=1 \\ \tau=\infty}} = \theta^2 f_0^4 \frac{1}{x^2 y^2} \Bigg|_{\substack{x=1 \\ y=1}} = \theta^2 f_0^4. \tag{17}$$

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

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

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

$$\partial_u z(u) = -z(u) - \epsilon z^2(u) + \alpha \xi(u) \quad (18)$$

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

$$\xi(u) = \frac{\beta_A x e^{-\beta_A u}}{\beta_A + \epsilon x (1 - e^{-\beta_A u})} + \frac{\beta_B y e^{-\beta_B u}}{\beta_B + \epsilon y (1 - e^{-\beta_B u})} \quad (19)$$

is a function independent of z .

We can solve Eq. (18) using a perturbation expansion in ϵ , defining

$$z(u) \approx \sum_{i=0}^{\infty} \epsilon^i z_i(u) \quad (20)$$

and, if $\gamma_A, \gamma_B \gg 1$,

$$\begin{aligned} \xi(u) &\approx \sum_{i=0}^{\infty} \epsilon^i \xi_i(u) \\ &= x e^{-\beta_A u} \sum_{i=0}^{\infty} \left(-\epsilon/\beta_A x (1 - e^{-\beta_A u}) \right)^i + y e^{-\beta_B u} \sum_{i=0}^{\infty} \left(-\epsilon/\beta_B y (1 - e^{-\beta_B u}) \right)^i. \end{aligned} \quad (21)$$

In order to find $\Lambda(f_0)$ to the lowest order in ϵ , we need to calculate the first three terms in each series above. At zeroth order in ϵ ,

$$\partial_u z_0(u) = -z_0(u) + \alpha \xi_0(u) \quad (22)$$

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

$$z_0(u) = z e^{-u} + \alpha e^{-u} \int_0^u e^{u'} \xi_0(u') du'. \quad (23)$$

At first order in ϵ ,

$$\partial_u z_1(u) = -z_1(u) - z_0^2(u) + \alpha \xi_1(u) \quad (24)$$

with the initial condition $z_1(0) = 0$ and hence

$$z_1(u) = \alpha e^{-u} \int_0^u e^{u'} \xi_1(u') du' - e^{-u} \int_0^u e^{u'} z_0^2(u') du'. \quad (25)$$

At second order in ϵ ,

$$\partial_u z_2(u) = -z_2(u) - 2z_0(u)z_1(u) + \alpha \xi_2(u) \quad (26)$$

with the initial condition $z_2(0) = 0$ and hence

$$z_2(u) = \alpha e^{-u} \int_0^u e^{u'} \xi_2(u') du' - 2e^{-u} \int_0^u e^{u'} z_0(u') z_1(u') du'. \quad (27)$$

To the lowest order in ϵ , the numerator of $\Lambda(f_0)$ follows from Eq. (3) as

$$\begin{aligned} \left\langle f_{Ab} f_{aB} f_{AB} \cdot e^{-\frac{f_A + f_B}{f_0}} \right\rangle &\approx -\theta^2 f_0^4 \int_0^{\tau/\epsilon} du \partial_x \partial_y \partial_z \left[-\alpha z_0 \Phi_x \Phi_y - \alpha \epsilon z_1 \Phi_x \Phi_y - \alpha \epsilon^2 z_2 \Phi_x \Phi_y \right. \\ &\quad \left. + \epsilon^2 z_1 \Phi_x + \epsilon^2 z_1 \Phi_y + \epsilon^3 z_2 \Phi_x + \epsilon^3 z_2 \Phi_y \right] \Bigg|_{\substack{x=1 \\ y=1 \\ z=2 \\ \tau=\infty}} \\ &\approx \frac{\alpha \epsilon^4 \theta^2 f_0^4}{\beta_A^2 \beta_B^2 (1 + \beta_A + \beta_B)} \left[1 + \frac{\beta_A (\alpha + \beta_A)}{(1 + \beta_B)(1 + \beta_B/2)} + \frac{\beta_B (\alpha + \beta_B)}{(1 + \beta_A)(1 + \beta_A/2)} \right. \\ &\quad \left. + \frac{2\alpha \beta_A \beta_B (\alpha + \beta_A + \beta_B)(2 + \beta_A + \beta_B)}{(1 + \beta_A)(1 + \beta_B)} \right] + \mathcal{O}(\epsilon^5), \end{aligned} \quad (28)$$

where we have used

$$\Phi_x \Big|_{\tau=\infty} \approx -\frac{\epsilon}{\beta_A} + \mathcal{O}(\epsilon^2), \quad (29a)$$

$$\Phi_y \Big|_{\tau=\infty} \approx -\frac{\epsilon}{\beta_B} + \mathcal{O}(\epsilon^2), \quad (29b)$$

$$\partial_x \Phi_x \Big|_{\tau=\infty} \approx \frac{\epsilon^2}{\beta_A^2} e^{-\beta_A u} + \mathcal{O}(\epsilon^3), \quad (29c)$$

$$\partial_y \Phi_y \Big|_{\tau=\infty} \approx \frac{\epsilon^2}{\beta_B^2} e^{-\beta_B u} + \mathcal{O}(\epsilon^3). \quad (29d)$$

The denominator of $\Lambda(f_0)$ follows from Eq. (3) as

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

$\Lambda(f_0)$ then follows as

$$\Lambda(f_0) \approx \frac{\alpha}{1 + \beta_A + \beta_B} \quad (31)$$

$$\begin{aligned}
& \times \left[1 + \frac{2\beta_A(\alpha + \beta_A)}{(1 + \beta_B)(2 + \beta_B)} + \frac{2\beta_B(\alpha + \beta_B)}{(1 + \beta_A)(2 + \beta_A)} + \frac{2\alpha\beta_A\beta_B(\alpha + \beta_A + \beta_B)(2 + \beta_A + \beta_B)}{(1 + \beta_A)(1 + \beta_B)} \right] \\
& = \frac{\rho}{\rho + \gamma_A + \gamma_B + \gamma_{AB}} \\
& \times \left[1 + \frac{\gamma_A(\rho + \gamma_A)}{(\rho + \gamma_B + \gamma_{AB})(\rho + 1/2\gamma_B + \gamma_{AB})} + \frac{\gamma_B(\rho + \gamma_B)}{(\rho + \gamma_A + \gamma_{AB})(\rho + 1/2\gamma_A + \gamma_{AB})} \right. \\
& \left. + \frac{4\rho\gamma_A\gamma_B(\rho + \gamma_A + \gamma_B)(\rho + 1/2\gamma_A + 1/2\gamma_B + \gamma_{AB})}{(\rho + \gamma_A + \gamma_{AB})(\rho + \gamma_B + \gamma_{AB})(\rho + \gamma_{AB})^3} \right].
\end{aligned}$$

The approximation above holds for any ρ as long as $\gamma_A, \gamma_B \gg 1$. If $\rho \gg \gamma_A, \gamma_B$, then

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

If $\rho \ll \gamma_A, \gamma_B$, $\gamma_A = \gamma_B = \gamma$, $\gamma_{AB} = 2\gamma$, then

$$\Lambda(f_0) \approx \frac{19}{60} \frac{\rho}{\gamma}. \quad (33)$$

In the limit that $\gamma_A \gg 1, \gamma_B = 0$, we can solve Eq. (18) expanding

$$\xi(u) \approx \sum_{i=0}^{\infty} \epsilon^i \xi_i(u) = x e^{-\beta_A u} \sum_{i=0}^{\infty} \left(-\epsilon/\beta_A x (1 - e^{-\beta_A u}) \right)^i + y \sum_{i=0}^{\infty} (-\epsilon u)^i. \quad (34)$$

To the lowest order in ϵ , the numerator of $\Lambda(f_0)$ follows from Eq. (3) as

$$\left\langle f_{Ab} f_{aB} f_{AB} \cdot e^{-\frac{f_A + f_B}{f_0}} \right\rangle \approx -\theta^2 f_0^4 \int_0^{\tau/\epsilon} du \partial_x \partial_y \partial_z \left[-\alpha z_0 \Phi_x \Phi_y - \alpha \epsilon z_1 \Phi_x \Phi_y + \epsilon^2 z_1 \Phi_y \right] \Bigg|_{\substack{x=1 \\ y=1 \\ z=2 \\ \tau=\infty}} \quad (35)$$

$$\approx \frac{\alpha \epsilon^2 \theta^2 f_0^4}{\beta_A^2 (1 + \beta_A)} [1 - \beta_A (\alpha + \beta_A)] + \mathcal{O}(\epsilon^3),$$

where we have used

$$\Phi_x \Big|_{\tau=\infty} \approx -\frac{\epsilon}{\beta_A} + \mathcal{O}(\epsilon^2), \quad (36a)$$

$$\Phi_y \Big|_{\tau=\infty} \approx -\frac{1}{y} + \mathcal{O}(\epsilon), \quad (36b)$$

$$\partial_x \Phi_x \Big|_{\tau=\infty} \approx \frac{\epsilon^2}{\beta_A^2} e^{-\beta_A u} + \mathcal{O}(\epsilon^3), \quad (36c)$$

$$\partial_y \Phi_y \Big|_{\tau=\infty} \approx \frac{1}{y^2} + \mathcal{O}(\epsilon). \quad (36d)$$

The denominator of $\Lambda(f_0)$ follows from Eq. (3) as

$$\left\langle f_A^2 f_B^2 \cdot e^{-\frac{f_A + f_B}{f_0}} \right\rangle \approx \theta^2 f_0^4 \partial_x^2 \partial_y^2 H_A H_B \Big|_{\substack{x=1 \\ y=1 \\ \tau=\infty}} = \frac{\epsilon^2 \theta^2 f_0^4}{\beta_A^2} \frac{1}{x^2 y^2} \Big|_{\substack{x=1 \\ y=1}} = \frac{\epsilon^2 \theta^2 f_0^4}{\beta_A^2}. \quad (37)$$

$\Lambda(f_0)$ then follows as

$$\Lambda(f_0) \approx \frac{\alpha}{1 + \beta_A} [1 - \beta_A(\alpha + \beta_A)] = \frac{\rho}{\rho + \gamma_A + \gamma_{AB}} \left[1 - \frac{\rho \gamma_A (\rho + \gamma_A)}{(\rho + \gamma_{AB})^3} \right]. \quad (38)$$

If $\rho \gg \gamma_A$, then

$$\Lambda(f_0) \approx 1. \quad (39)$$

If $\rho \ll \gamma_A$, $\gamma_{AB} = \gamma_A = \gamma$, then

$$\Lambda(f_0) \approx \frac{1}{2} \frac{\rho}{\gamma}. \quad (40)$$