Perturbative solution of the generating function for small f_0

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

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

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}, $f_{AB} \ll 1$,

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

The moments follows from

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

where

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

is the joint moment generating function.

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

$$\begin{aligned} H(x,y,z,\tau) \approx{}& 1 - \theta(H_A + H_B) + \frac{\theta^2}{2}\left(H_A + H_B\right)^2 \\ &+ \theta^2 f_0 \Upsilon + \theta^2 f_0 \int_0^\tau d\tau' z(\tau') \left[\Phi_x(\tau') + \Phi_y(\tau') - \rho\Phi_x(\tau')\Phi_y(\tau')\right] \\ &+ \mathcal{O}(f_0^2) + \mathcal{O}(\theta^3), \end{aligned} \tag{5}$$

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

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

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

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

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

$$\Upsilon(x,y,\tau) = \int_0^\tau d\tau' \rho \left[x(\tau') + y(\tau')\right] \Phi_x(\tau')\Phi_y(\tau'). \tag{8}$$

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

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

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,

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

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

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

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

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

In the neutral limit, the equation above reduces to

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

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

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

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

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

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

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

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

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

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

is a function independent of z.

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

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

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

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

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

$$\partial_u z_0(u) = -z_0(u) + \alpha\xi_0(u) \tag{22}$$

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

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

At first order in ϵ,

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

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

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

At second order in ϵ,

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

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

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

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

$$\begin{aligned}\left\langle f_{Ab} f_{aB} f_{AB} \cdot e^{-\frac{f_A+f_B}{f_0}} \right\rangle &\approx -\theta^2 f_0^4 \int_0^{\tau/\epsilon} du\, \partial_x \partial_y \partial_z \left[-\alpha z_0 \Phi_x \Phi_y - \alpha \epsilon z_1 \Phi_x \Phi_y - \alpha \epsilon^2 z_2 \Phi_x \Phi_y \right. \\ &\quad \left. + \epsilon^2 z_1 \Phi_x + \epsilon^2 z_1 \Phi_y + \epsilon^3 z_2 \Phi_x + \epsilon^3 z_2 \Phi_y \right] \Bigg|_{\substack{x=1\\y=1\\z=2\\\tau=\infty}} \\ &\approx \frac{\alpha \epsilon^4 \theta^2 f_0^4}{\beta_A^2 \beta_B^2 (1+\beta_A+\beta_B)} \left[1 + \frac{\beta_A(\alpha+\beta_A)}{(1+\beta_B)(1+{}^{\beta_B}/_2)} + \frac{\beta_B(\alpha+\beta_B)}{(1+\beta_A)(1+{}^{\beta_A}/_2)} \right. \\ &\quad \left. + \frac{2\alpha\beta_A\beta_B(\alpha+\beta_A+\beta_B)(2+\beta_A+\beta_B)}{(1+\beta_A)(1+\beta_B)} \right] + \mathcal{O}(\epsilon^5),\end{aligned} \tag{28}$$

where we have used used

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

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

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

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

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

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

$\Lambda(f_0)$ then follows as

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

$$\times\left[1+\frac{2\beta_A(\alpha+\beta_A)}{(1+\beta_B)(2+\beta_B)}+\frac{2\beta_B(\alpha+\beta_B)}{(1+\beta_A)(2+\beta_A)}+\frac{2\alpha\beta_A\beta_B(\alpha+\beta_A+\beta_B)(2+\beta_A+\beta_B)}{(1+\beta_A)(1+\beta_B)}\right]$$

$$=\frac{\rho}{\rho+\gamma_A+\gamma_B+\gamma_{AB}}$$

$$\times\left[1+\frac{\gamma_A(\rho+\gamma_A)}{(\rho+\gamma_B+\gamma_{AB})(\rho+{}^1\!/\!_2\gamma_B+\gamma_{AB})}+\frac{\gamma_B(\rho+\gamma_B)}{(\rho+\gamma_A+\gamma_{AB})(\rho+{}^1\!/\!_2\gamma_A+\gamma_{AB})}\right.$$

$$\left.+\frac{4\rho\gamma_A\gamma_B(\rho+\gamma_A+\gamma_B)(\rho+{}^1\!/\!_2\gamma_A+{}^1\!/\!_2\gamma_B+\gamma_{AB})}{(\rho+\gamma_A+\gamma_{AB})(\rho+\gamma_B+\gamma_{AB})(\rho+\gamma_{AB})^3}\right].$$

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

$$\Lambda(f_0) \approx 1. \tag{32}$$

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

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

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

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

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

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

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

where we have used used

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

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

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

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

$\Lambda(f_0)$ then follows as

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

If $\rho \gg \gamma_A$, then

$$\Lambda(f_0) \approx 1. \tag{39}$$

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

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

Finally, in the limit that both loci are neutral, but either recombination is strong or epistasis is strong, expanding

$$\xi(u) \approx \sum_{i=0}^{\infty} \epsilon^i \xi_i(u) = (x+y)\sum_{i=0}^{\infty}(-\epsilon u)^i \tag{41}$$

we obtain the numerator and the denominator of Λ from Eq. (3) to the lowest order in ϵ as

$$\left\langle f_{Ab} f_{aB} f_{AB} \cdot e^{-\frac{f_A+f_B}{f_0}} \right\rangle \approx \alpha\theta^2 f_0^4 \int_0^{\tau/\epsilon} du\, \partial_x \partial_y \partial_z z_0 \Phi_x \Phi_y \Bigg|_{\substack{x=1\\y=1\\z=2\\\tau=\infty}} \approx \alpha\theta^2 f_0^4 + \mathcal{O}(\epsilon), \tag{42}$$

$$\left\langle f_A^2 f_B^2 \cdot e^{-\frac{f_A+f_B}{f_0}} \right\rangle \approx \theta^2 f_0^4 \partial_x^2 \partial_y^2 H_A H_B \Bigg|_{\substack{x=1\\y=1\\\tau=\infty}} = \theta^2 f_0^4 \frac{1}{x^2y^2}\Bigg|_{\substack{x=1\\y=1}} = \theta^2 f_0^4. \tag{43}$$

$\Lambda(f_0)$ then follows as

$$\Lambda(f_0) \approx \alpha = \frac{\rho}{\rho+\gamma_{AB}}. \tag{44}$$

If $\rho \gg \gamma_A B$, then

$$\Lambda(f_0) \approx 1. \tag{45}$$

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

$$\Lambda(f_0) \approx \frac{\rho}{\gamma}. \tag{46}$$