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,

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

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

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

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

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

has solution in the form

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

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

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

from where

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

where

$$C = \frac{1}{2} \tag{18}$$

is a constant determined by the initial condition $\phi(0) = 0$. Then,

$$\begin{aligned}z_1(\tau') &\approx \frac{1}{2} + \frac{1}{2}\frac{1}{(1+z\tau')^2} + \left(1-\frac{z}{x}\right)\frac{z\tau'}{(1+z\tau')^2} + \left(1-\frac{z}{y}\right)\frac{z\tau'}{(1+z\tau')^2} \\ &\quad + \left(1-\frac{z}{x}\right)^2 \frac{\ln(1+x\tau')}{(1+z\tau')^2} + \left(1-\frac{z}{y}\right)^2 \frac{\ln(1+y\tau')}{(1+z\tau')^2}.\end{aligned} \tag{19}$$

Substituting Eq. (19) into Eq. (11), we find

$$\begin{aligned}z(\tau') &\approx \frac{z}{1+z\tau'} + \frac{\rho}{2} + \frac{\rho}{2}\frac{1}{(1+z\tau')^2} \\ &\quad + \rho\left(1-\frac{z}{x}\right)\frac{z\tau'}{(1+z\tau')^2} + \rho\left(1-\frac{z}{y}\right)\frac{z\tau'}{(1+z\tau')^2} \\ &\quad + \rho\left(1-\frac{z}{x}\right)^2 \frac{\ln(1+x\tau')}{(1+z\tau')^2} + \rho\left(1-\frac{z}{y}\right)^2 \frac{\ln(1+y\tau')}{(1+z\tau')^2}.\end{aligned} \tag{20}$$

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

$$\left\langle f_{Ab} f_{aB} f_{AB} \cdot e^{-\frac{f_A+f_B}{f_0}} \right\rangle \approx -\,\rho\theta^2 f_0^4 \left[-\int_0^{\tau} d\tau'\, \partial_x\Phi_x\, \partial_y\Phi_y\, \partial_z \frac{z}{1+z\tau'} \right. \tag{21}$$

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

where

$$
\partial_x \Phi_x \Bigg|_{\substack{x=1\\\tau=\infty}} = -\frac{(\tau-\tau')^2}{(1+x\tau)^2} \Bigg|_{\substack{x=1\\\tau=\infty}} = 1, \tag{22a}
$$

$$
\partial_y \Phi_y \Bigg|_{\substack{y=1\\\tau=\infty}} = -\frac{(\tau-\tau')^2}{(1+y\tau)^2} \Bigg|_{\substack{y=1\\\tau=\infty}} = 1. \tag{22b}
$$

The first integral in Eq. (21) evaluates to

$$
- \int_0^\tau d\tau' \, \partial_x \Phi_x \, \partial_y \Phi_y \, \partial_z \frac{z}{1+z\tau'} \Bigg|_{\substack{x=1\\y=1\\z=2\\\tau=\infty}} = - \int_0^\infty \frac{1}{(1+2\tau')^2} \, d\tau = -\frac{1}{2}. \tag{23}
$$

The second (and third) integral in Eq. (21) can be evaluated as

$$
- \int_0^\tau d\tau' \, \partial_x \Phi_x \, \partial_y \partial_z \frac{z}{y} \frac{z\tau'}{(1+z\tau')^2} \Bigg|_{\substack{x=1\\y=1\\z=2\\\tau=\infty}} = \int_0^\infty \frac{4\tau'}{(1+2\tau')^3} \, d\tau' = \frac{1}{2}. \tag{24}
$$

Finally, we find the last (and the second to last) integral in Eq. (21) as

$$
\int_0^\tau d\tau' \, \partial_y \Phi_y \, \partial_x \partial_z \left(1 - \frac{z}{x}\right)^2 \frac{\ln(1+x\tau')}{(1+z\tau')^2} \Bigg|_{\substack{x=1\\y=1\\z=2\\\tau=\infty}} = \int_0^\tau \frac{2\tau' - 2(3+2\tau')\ln(1+\tau')}{(1+2\tau')^3} d\tau' = -\frac{3}{4}. \tag{25}
$$

Substituting Eq. (23), Eq. (24), and Eq. (25) into Eq. (21), we obtain

$$\left\langle f_{Ab}f_{aB}f_{AB}\cdot e^{-\frac{f_A+f_B}{f_0}}\right\rangle \approx -\rho\theta^2 f_0^4\left[-\frac{1}{2}+\frac{1}{2}+\frac{1}{2}-\frac{3}{4}-\frac{3}{4}\right]=\rho\theta^2 f_0^4. \tag{26}$$

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

$$\left\langle f_A^2 f_B^2\cdot e^{-\frac{f_A+f_B}{f_0}}\right\rangle \approx \theta^2 f_0^4\partial_x^2\partial_y^2 H_A H_B\Bigg|_{\substack{x=1\\y=1\\\tau=\infty}} = \theta^2 f_0^4\frac{1}{x^2y^2}\Bigg|_{\substack{x=1\\y=1}} = \theta^2 f_0^4. \tag{27}$$

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

$$\partial_u z(u) = -z(u)-\epsilon z^2(u)+\alpha f(u) \tag{28}$$

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

$$f(u)=\frac{\beta_A x e^{-\beta_A u}}{\beta_A+\epsilon x(1-e^{-\beta_A u})}+\frac{\beta_B y e^{-\beta_B u}}{\beta_B+\epsilon y(1-e^{-\beta_B u})} \tag{29}$$

is a function independent of z.

We can solve Eq. (28) using a perturbation expansion in ϵ, defining

$$z(u)\approx\sum_{i=0}^{\infty}\epsilon^i z_i(u) \tag{30a}$$

and

$$f(u)\approx\sum_{i=0}^{\infty}\epsilon^i f_i(u). \tag{30b}$$

At zeroth order,

$$\partial_u z_0(u) = -z_0(u)+\alpha f_0(u) \tag{31}$$

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

$$z_0(u) = ze^{-u} + \alpha e^{-u} \int_0^u e^{u'} f_0(u') du'. \tag{32}$$

If $\gamma_A, \gamma_B \gg 1$, then the first term in Eq. (30b) can be found as

$$f_0(u) = xe^{-\beta_A u} + ye^{-\beta_B u}, \tag{33}$$

and hence

$$z_0(u) = ze^{-u} - \frac{\alpha x}{1-\beta_A}\left(e^{-u} - e^{-\beta_A u}\right) - \frac{\alpha y}{1-\beta_B}\left(e^{-u} - e^{-\beta_B u}\right). \tag{34}$$

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

$$\begin{aligned}\left\langle f_{Ab} f_{aB} f_{AB} \cdot e^{-\frac{f_A+f_B}{f_0}} \right\rangle &\approx \alpha\theta^2 f_0^4 \int_0^{\tau/\epsilon} e^{-u} du \, \partial_x \Phi_x \, \partial_y \Phi_y \, \partial_z z \Phi_x \Phi_y \Bigg|_{\substack{x=1\\y=1\\z=2\\\tau=\infty}} \\ &= \frac{\epsilon^2 \alpha \theta^2 f_0^4}{\beta_A^2 \beta_B^2 (1+\beta_A+\beta_B)},\end{aligned} \tag{35}$$

where

$$\partial_x \Phi_x \Bigg|_{\substack{x=1\\\tau=\infty}} = e^{-\beta_A u} \left[\frac{1-e^{-\beta_A(\tau/\epsilon - u)}}{x(1-e^{-\beta_A \tau/\epsilon}) + \beta_A/\epsilon}\right]^2 \Bigg|_{\substack{x=1\\\tau=\infty}} = \frac{\epsilon^2}{\beta_A^2} e^{-\beta_A u}, \tag{36a}$$

$$\partial_y \Phi_y \Bigg|_{\substack{y=1\\\tau=\infty}} = e^{-\beta_B u} \left[\frac{1-e^{-\beta_B(\tau/\epsilon - u)}}{x(1-e^{-\beta_B \tau/\epsilon}) + \beta_B/\epsilon}\right]^2 \Bigg|_{\substack{y=1\\\tau=\infty}} = \frac{\epsilon^2}{\beta_B^2} e^{-\beta_B u}. \tag{36b}$$

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

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

$\Lambda(f_0)$ then follows as

$$\Lambda(f_0) \approx \frac{\alpha}{1+\beta_A+\beta_B} = \frac{\rho}{\rho+\gamma_A+\gamma_B+\gamma_{AB}}. \tag{38}$$

The approximation above holds for any ρ as long as $\gamma_A, \gamma_B, \gamma_{AB} \gg 1$. If $\gamma_{AB} = 0$ and $\gamma_A, \gamma_B \gg \rho \gg 1$, Eq. (38) reduces to

$$\Lambda(f_0) \approx \frac{\rho}{\gamma_A + \gamma_B}. \tag{39}$$

If $\gamma_{AB} = 0$ and $\rho \gg \gamma_A, \gamma_B \gg 1$,

$$\Lambda(f_0) \approx 1. \tag{40}$$

Is this too simple?

Can also look at $\gamma_A, \gamma_B = 0$, $\rho + \gamma_{AB} \gg 1$. It seems that the only regime that we have not thought about yet is small recombination, strong selection but no epistasis?