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Appendix I : TDR derivation

We present a few derivations for the TDR method. The derivations differ by the assumptions used to solve for TDR. We use this section to show the conditions where the TDR method can be used. In addition, we use this section to walk through all of the mathematical steps in order to provide an easy reference for comparing the derivations of all four methods (TDR, SIM, ASM, and LDM). The original condition presented by Levin *et. al.* (1) is the last derivation described in this section.

Here we assume that we are considering conditions where population growth is not occurring. These conditions could involve an environment hindering cell division. Alternatively, the environment could promote growth, but we restrict the time period sufficiently so that population change is negligible. Or finally, if all strains possess the same growth rate, the population could be growing over longer periods of time but doing so in a continuous flow-through device (e.g., a chemostat) such that population density remains constant, see ref (1). Because we assume no plasmid loss of the plasmid, the donor population must remain constant

$$D_t = D_0, \tag{I.a}$$

for any time t under consideration. Importantly, even though growth is not occurring, conjugation can proceed. We assume $T_0 = 0$, but the population of transconjugants can increase over time. Because every transconjugant was formerly a recipient cell, it must be the case that

$$R_t + T_t = R_0,$$

for any time t under consideration. Therefore,

$$R_t = R_0 - T_{t.} \tag{I.b}$$

The dynamics of transconjugants is given by

$$\frac{dT_t}{dt} = \gamma_D D_t R_t + \gamma_T T_t R_t \tag{I.c}$$

By substituting terms from equations [I.a] and [I.b]

$$\frac{dT_t}{dt} = \gamma_D D_0 (R_0 - T_t) + \gamma_T T_t (R_0 - T_t),$$

$$\frac{dT_t}{dt} = (\gamma_D D_0 + \gamma_T T_t)(R_0 - T_t),$$

$$\frac{dT_t}{dt} = -\gamma_T \left(T_t + \frac{\gamma_D D_0}{\gamma_T}\right)(T_t - R_0),$$

We can solve this differential equation by a separation of variables:

$$\int_0^{\tilde{t}} \frac{dT_t}{-\gamma_T \left(T_t + \frac{\gamma_D D_0}{\gamma_T}\right)(T_t - R_0)} = \int_0^{\tilde{t}} dt.$$

The following identity is relevant here:

$$\frac{d\left\{\frac{1}{a(b-c)} \ln \frac{x-b}{x-c}\right\}}{dx} = \frac{1}{a(x-b)(x-c)}.$$

Letting $x = T_t$, $a = -\gamma_T$, $b = -\frac{\gamma_D D_0}{\gamma_T}$, and $c = R_0$, we can proceed as follows:

$$\left\{\frac{1}{\gamma_T\left(\frac{\gamma_D D_0}{\gamma_T}+R_0\right)}\ln\frac{T_t+\frac{\gamma_D D_0}{\gamma_T}}{T_t-R_0}\right\}\Bigg|_0^{\tilde{t}}=(t)|_0^{\tilde{t}},$$

$$\frac{1}{\gamma_T\left(\frac{\gamma_D D_0}{\gamma_T}+R_0\right)}\left(\ln\frac{T_{\tilde{t}}+\frac{\gamma_D D_0}{\gamma_T}}{T_{\tilde{t}}-R_0}-\ln\frac{T_0+\frac{\gamma_D D_0}{\gamma_T}}{T_0-R_0}\right)=\tilde{t}.$$

Because $T_0=0$,

$$\frac{1}{\gamma_T\left(\frac{\gamma_D D_0}{\gamma_T}+R_0\right)}\left(\ln\frac{T_{\tilde{t}}+\frac{\gamma_D D_0}{\gamma_T}}{T_{\tilde{t}}-R_0}-\ln\frac{\frac{\gamma_D D_0}{\gamma_T}}{-R_0}\right)=\tilde{t},$$

$$\frac{1}{\gamma_T\left(\frac{\gamma_D D_0}{\gamma_T}+R_0\right)}\left(\ln\frac{-R_0\left(T_{\tilde{t}}+\frac{\gamma_D D_0}{\gamma_T}\right)}{\frac{\gamma_D D_0}{\gamma_T}(T_{\tilde{t}}-R_0)}\right)=\tilde{t},$$

$$\ln\frac{1+\frac{\gamma_T T_{\tilde{t}}}{\gamma_D D_0}}{1-\frac{T_{\tilde{t}}}{R_0}}=(\gamma_D D_0+\gamma_T R_0)\tilde{t}, \qquad \text{[I.d]}$$

$$\frac{1+\frac{\gamma_T T_{\tilde{t}}}{\gamma_D D_0}}{1-\frac{T_{\tilde{t}}}{R_0}}=\exp\{(\gamma_D D_0+\gamma_T R_0)\tilde{t}\},$$

$$1+\frac{\gamma_T T_{\tilde{t}}}{\gamma_D D_0}=\left(1-\frac{T_{\tilde{t}}}{R_0}\right)\exp\{(\gamma_D D_0+\gamma_T R_0)\tilde{t}\},$$

$$\frac{\gamma_T T_{\tilde{t}}}{\gamma_D D_0}+\frac{T_{\tilde{t}}}{R_0}\exp\{(\gamma_D D_0+\gamma_T R_0)\tilde{t}\}=\exp\{(\gamma_D D_0+\gamma_T R_0)\tilde{t}\}-1,$$

$$T_{\tilde{t}}\left[\frac{\gamma_T}{\gamma_D D_0}+\frac{1}{R_0}\exp\{(\gamma_D D_0+\gamma_T R_0)\tilde{t}\}\right]=\exp\{(\gamma_D D_0+\gamma_T R_0)\tilde{t}\}-1,$$

$$T_{\tilde{t}}=\frac{R_0(\exp\{(\gamma_D D_0+\gamma_T R_0)\tilde{t}\}-1)}{\frac{\gamma_T R_0}{\gamma_D D_0}+\exp\{(\gamma_D D_0+\gamma_T R_0)\tilde{t}\}}. \qquad \text{[I.e]}$$

Thus, equation [I.e] is a general solution for the number of transconjugants at any time. If we assume that $\gamma_T=0$, then we can rewrite [I.d] as

$$\ln\frac{1}{1-\frac{T_{\tilde{t}}}{R_0}}=\gamma_D D_0\tilde{t},$$

$$-\ln\left(1-\frac{T_{\tilde{t}}}{R_0}\right)=\gamma_D D_0\tilde{t},$$

$$\gamma_D=\frac{-\ln\left(1-\frac{T_{\tilde{t}}}{R_0}\right)}{D_0\tilde{t}}. \qquad \text{[I.f]}$$

When $R_0\gg T_{\tilde{t}}$, a first-order Taylor approximation ensures $-\ln\left(1-\frac{T_{\tilde{t}}}{R_0}\right)\approx\frac{T_{\tilde{t}}}{R_0}$, and therefore

$$\gamma_D\approx\frac{\frac{T_{\tilde{t}}}{R_0}}{D_0\tilde{t}},$$

$$\gamma_D \approx \frac{T_{\tilde{t}}}{D_0 R_0 \tilde{t}}.$$

Because $D_{\tilde{t}} = D_0$ (see [I.a]) and $R_{\tilde{t}} \approx R_0$ (when $R_0 \gg T_{\tilde{t}}$ by [I.b]), we have

$$\gamma_D \approx \frac{T_{\tilde{t}}}{D_{\tilde{t}} R_{\tilde{t}} \tilde{t}}.$$

On the other hand, if we assume $\gamma_D = \gamma_T = \gamma$, then we can rewrite [I.d] as

$$\ln \frac{1 + \frac{T_{\tilde{t}}}{D_0}}{1 - \frac{T_{\tilde{t}}}{R_0}} = \gamma (D_0 + R_0)\tilde{t},$$

$$\gamma = \frac{1}{\tilde{t}(D_0 + R_0)} \ln \frac{1 + \frac{T_{\tilde{t}}}{D_0}}{1 - \frac{T_{\tilde{t}}}{R_0}},$$

$$\gamma = \frac{1}{\tilde{t}(D_0 + R_0)} \left\{ \ln\left(1 + \frac{T_{\tilde{t}}}{D_0}\right) - \ln\left(1 - \frac{T_{\tilde{t}}}{R_0}\right) \right\}. \tag{I.g}$$

When $D_0 \gg T_{\tilde{t}}$ and $R_0 \gg T_{\tilde{t}}$, first-order Taylor approximations ensure

$$\gamma \approx \frac{1}{\tilde{t}(D_0 + R_0)} \left(\frac{T_{\tilde{t}}}{D_0} + \frac{T_{\tilde{t}}}{R_0} \right),$$

$$\gamma \approx \frac{T_{\tilde{t}}}{\tilde{t}(D_0 + R_0)} \left(\frac{1}{D_0} + \frac{1}{R_0} \right),$$

$$\gamma \approx \frac{T_{\tilde{t}}}{\tilde{t}(D_0 + R_0)} \left(\frac{R_0 + D_0}{D_0 R_0} \right),$$

$$\gamma \approx \frac{T_{\tilde{t}}}{D_0 R_0 \tilde{t}}.$$

Because $D_{\tilde{t}} = D_0$ and $R_{\tilde{t}} \approx R_0$ (when $R_0 \gg T_{\tilde{t}}$), we have

$$\gamma \approx \frac{T_{\tilde{t}}}{D_{\tilde{t}} R_{\tilde{t}} \tilde{t}}.$$

So we have general expressions for donor conjugation rate when $\gamma_T = 0$ (equation [I.f]) or when $\gamma_D = \gamma_T$ (equation [I.g]). However, when $D_0 \gg T_t$ and $R_0 \gg T_t$, for all t under consideration, both of these measures are well approximated by equation [1.4]. Here we extend the application of equation [1.4] even further. When $R_0 \gg T_t$, then $R_t \approx R_0$. Let us assume $R_t = R_0$. We will also assume

$$\gamma_D D_0 R_0 \gg \gamma_T T_t R_0, \tag{I.h}$$

namely, the rate of formation of transconjugants by donors is much greater than the formation by transconjugants. Of course, if $0 \le \gamma_T \le \gamma_D$, then $D_0 \gg T_t$ ensures assumption [I.h]. In general, this inequality is satisfied when $T_0 = 0$, D_0 and R_0 are large, γ_T is not dramatically higher than γ_D, and the period is small. Under assumption [I.h], the dynamics can be well approximated by a simplified version of the differential equation [I.c]. (where the transconjugant conjugation term is gone). This is the differential equation originally solved by Levin *et. al.,*

$$\frac{dT_t}{dt} = \gamma_D D_0 R_0.$$

Because everything on the right-hand-side of the equation is a constant, the solution is straightforward:

$$\int_0^{\tilde{t}} dT_t = \int_0^{\tilde{t}} \gamma_D D_0 R_0 \, dt,$$

$$(T_{\tilde{t}})|_0^{\tilde{t}} = (\gamma_D D_0 R_0 t)|_0^{\tilde{t}},$$
$$T_{\tilde{t}} - T_0 = \gamma_D D_0 R_0 \tilde{t}.$$

Because $T_0 = 0$,

$$T_{\tilde{t}} = \gamma_D D_0 R_0 \tilde{t},$$
$$\gamma_D = \frac{T_{\tilde{t}}}{D_0 R_0 \tilde{t}}.$$

Because $D_{\tilde{t}} = D_0$ and $R_{\tilde{t}} = R_0$ (by assumption), we have recovered equation [1.4].

Appendix II : SIM derivation

In this section, we walk through the mathematical steps in the Simonsen *et. al.* derivation. We include this derivation as a quick reference to help the reader compare the derivations of all four methods (TDR, SIM, ASM, and LDM). Simonsen *et. al.* modified the model (equations [1]-[3]) by adding a dynamic variable for resource concentration (C). The dynamics of this resource incorporate an additional parameter for the amount of resource needed to produce a new cell (e). Both the growth rate and conjugation rate are taken to be functions of the resource concentration.

$$\frac{dD}{dt} = \psi(C)D, \qquad \text{[II.a]}$$

$$\frac{dR}{dt} = \psi(C)R - \gamma(C)R(D+T), \qquad \text{[II.b]}$$

$$\frac{dT}{dt} = \psi(C)T + \gamma(C)R(D+T), \qquad \text{[II.c]}$$

$$\frac{dC}{dt} = -\psi(C)(R+D+T)e. \qquad \text{[II.d]}$$

The other variables are consistent with their use in equations [1]-[3]. In Simonsen *et. al.*, when resources are depleted, growth and conjugation stop. A Monod function introduces batch culture dynamics (i.e., exponential and stationary phase) making growth and conjugation both increase in a saturated manner with resource concentration, where the resource concentration yielding ½ the maximal rate is given by the parameter Q. Importantly, conjugation and growth are assumed to have the same functional form:

$$\psi(C) = \frac{\psi_{max} C}{Q + C}, \qquad \text{[II.e]}$$

$$\gamma(C) = \frac{\gamma_{max} C}{Q + C}, \qquad \text{[II.f]}$$

where Q is the half saturation constant.

More generally, let us assume

$$\psi(C) = \psi^{\blacksquare} g(C), \qquad \text{[II.g]}$$

$$\gamma(C) = \gamma^{\blacksquare} g(C), \qquad \text{[II.h]}$$

where $\psi^{\blacksquare}$ and $\gamma^{\blacksquare}$ are constants and $g(C)$ is some function. We see that equations [II.e] and [II.f] are a special case of equations [II.g] and [II.h]. For the most general case, the ratio of growth rate to conjugation rate is a constant:

$$\frac{\psi(C)}{\gamma(C)} = \frac{\psi^{\blacksquare}}{\gamma^{\blacksquare}}.$$

Here we derive the estimation of the conjugation rate parameter $\gamma^{\blacksquare}$ for this general case. Note, we can connect equations [II.a]-[II.d] this to the equations [1]-[3] if we assume $\psi_D = \psi_R = \psi_T = \psi(C) = \psi^{\blacksquare} g(C)$ and $\gamma_D = \gamma_T = \gamma(C) = \gamma^{\blacksquare} g(C)$. Simonsen *et. al.* assume that all strains have the same growth rate, and conjugation rates from donors and transconjugants are the same. Additionally, Simonsen *et. al.* assume no segregative loss. We define $N_t = D_t + R_t + T_t$. Therefore, using equations [II.a]-[II.c], and droping the t subscripts for notational convenience, we have:

$$\frac{dN}{dt} = \frac{dD}{dt} + \frac{dR}{dt} + \frac{dT}{dt},$$

$$\frac{dN}{dt} = \psi(C)D + \psi(C)R - \gamma(C)R(D+T) + \psi(C)T + \gamma(C)R(D+T),$$

$$\frac{dN}{dt} = \psi(C)(D + R + T),$$

$$\frac{dN}{dt} = \psi(C)N. \qquad \text{[II.i]}$$

Letting $X_t = D_t/N_t$, we have the following by the quotient rule:

$$\frac{dX}{dt} = \frac{\frac{dD}{dt}N - \frac{dN}{dt}D}{N^2}$$

$$\frac{dX}{dt} = \frac{\psi(C)DN - \psi(C)ND}{N^2}$$

$$\frac{dX}{dt} = 0$$

Thus, X_t does not change over time (i.e., $X_t = X_0$ for all t).

Lastly, we define a fraction $Y_t = T_t/R_t$. Using equations [II.b] and [II.c],

$$\frac{dY}{dt} = \frac{\frac{dT}{dt}R - \frac{dR}{dt}T}{R^2},$$

$$\frac{dY}{dt} = \frac{\{\psi(C)T + \gamma(C)R(D+T)\}R - \{\psi(C)R - \gamma(C)R(D+T)\}T}{R^2},$$

$$\frac{dY}{dt} = \frac{\psi(C)TR + \gamma(C)(D+T)R^2 - \psi(C)TR + \gamma(C)(D+T)TR}{R^2},$$

$$\frac{dY}{dt} = \frac{\gamma(C)(D+T)R^2 + \gamma(C)(D+T)TR}{R^2},$$

$$\frac{dY}{dt} = \frac{\gamma(C)(D+T)R + \gamma(C)(D+T)T}{R},$$

$$\frac{dY}{dt} = \frac{\gamma(C)(DR + TR + DT + T^2)}{R},$$

$$\frac{dY}{dt} = \gamma(C)\frac{DT + RT + T^2 + DR}{R},$$

$$\frac{dY}{dt} = \gamma(C)\left(\frac{T(D+R+T)}{R} + D\right).$$

Because $N_t = D_t + R_t + T_t$,

$$\frac{dY}{dt} = \gamma(C)\left(\frac{TN}{R} + D\right),$$

$$\frac{dY}{dt} = \gamma(C)N\left(\frac{T}{R} + \frac{D}{N}\right).$$

Because $X_t = D_t/N_t$ and $Y_t = T_t/R_t$,

$$\frac{dY}{dt} = \gamma(C)N(Y+X),$$

$$\left(\frac{1}{Y+X}\right)\frac{dY}{dt} = \gamma(C)N.$$

Equation [II.i] ensures $N = \left(\frac{1}{\psi(C)}\right)\frac{dN}{dt}$, and along with equations [II.g] and [II.h], we have

$$\left(\frac{1}{Y+X}\right)\frac{dY}{dt} = \gamma(C)\left(\frac{1}{\psi(C)}\right)\frac{dN}{dt},$$

$$\left(\frac{1}{Y+X}\right)\frac{dY}{dt} = \gamma^{\blacksquare} g(C)\left(\frac{1}{\psi^{\blacksquare} g(C)}\right)\frac{dN}{dt},$$

$$\psi^{\blacksquare}\left(\frac{1}{Y+X}\right)\frac{dY}{dt} = \gamma^{\blacksquare}\frac{dN}{dt},$$

$$\gamma^{\blacksquare}(dN) = \psi^{\blacksquare}\left(\frac{dY}{Y+X}\right).$$

To emphasize that X is a constant, we write this as X_0 and then integrate both sides,

$$\gamma^{\blacksquare}\int_0^{\tilde{t}} dN = \psi^{\blacksquare}\int_0^{\tilde{t}}\left(\frac{dY}{Y+X_0}\right),$$

Making the time dependence of the variables explicit via subscripts

$$\gamma^{\blacksquare} N_t|_0^{\tilde{t}} = \psi^{\blacksquare}\ln(Y_t+X_0)|_0^{\tilde{t}},$$

$$\gamma^{\blacksquare}(N_{\tilde{t}}-N_0) = \psi^{\blacksquare}\{\ln(Y_{\tilde{t}}+X_0)-\ln(Y_0+X_0)\}.$$

Because $X_0 = X_{\tilde{t}}$

$$\gamma^{\blacksquare}(N_{\tilde{t}}-N_0) = \psi^{\blacksquare}\{\ln(Y_{\tilde{t}}+X_{\tilde{t}})-\ln(Y_0+X_{\tilde{t}})\},$$

$$\gamma^{\blacksquare}(N_{\tilde{t}}-N_0) = \psi^{\blacksquare}\ln\left(\frac{Y_{\tilde{t}}+X_{\tilde{t}}}{Y_0+X_{\tilde{t}}}\right).$$

Because $X_{\tilde{t}} = D_{\tilde{t}}/N_{\tilde{t}}$ and $Y_{\tilde{t}} = T_{\tilde{t}}/R_{\tilde{t}}$,

$$\gamma^{\blacksquare}(N_{\tilde{t}}-N_0) = \psi^{\blacksquare}\ln\left(\frac{\frac{T_{\tilde{t}}}{R_{\tilde{t}}}+\frac{D_{\tilde{t}}}{N_{\tilde{t}}}}{\frac{T_0}{R_0}+\frac{D_{\tilde{t}}}{N_{\tilde{t}}}}\right).$$

Because $T_0 = 0$,

$$\gamma^{\blacksquare}(N_{\tilde{t}}-N_0) = \psi^{\blacksquare}\ln\left(\frac{\frac{T_{\tilde{t}}}{R_{\tilde{t}}}+\frac{D_{\tilde{t}}}{N_{\tilde{t}}}}{\frac{D_{\tilde{t}}}{N_{\tilde{t}}}}\right),$$

$$\gamma^{\blacksquare}(N_{\tilde{t}}-N_0) = \psi^{\blacksquare}\ln\left(\frac{T_{\tilde{t}}}{R_{\tilde{t}}}\frac{N_{\tilde{t}}}{D_{\tilde{t}}}+1\right),$$

$$\gamma^{\blacksquare} = \psi^{\blacksquare}\ln\left(1+\frac{T_{\tilde{t}}}{R_{\tilde{t}}}\frac{N_{\tilde{t}}}{D_{\tilde{t}}}\right)\frac{1}{N_{\tilde{t}}-N_0}.$$

If we let $\psi^{\blacksquare} = \psi_{max}$ and $\gamma^{\blacksquare} = \gamma_{max}$ (with $g(C) = C/(Q+C)$) then we have recovered the SIM estimate for conjugation rate (equation [1.5]).

Appendix III : ASM derivation

In this section, we walk through all the mathematical steps in the Huisman *et. al.* (2) derivation. We include this derivation as a quick reference to help the reader compare the derivations of all four methods (TDR, SIM, ASM, and LDM). We start with a system of ordinary differential equations described by Huisman *et. al.,* the Extended Simonsen Model (ESM):

$$\frac{dD}{dt} = \psi_D(C)D, \qquad \text{[III.a]}$$

$$\frac{dR}{dt} = \psi_R(C)R - (\gamma_D(C)D + \gamma_T(C)T)R, \qquad \text{[III.b]}$$

$$\frac{dT}{dt} = \psi_T(C)T + (\gamma_D(C)D + \gamma_T(C)T)R, \qquad \text{[III.c]}$$

$$\frac{dC}{dt} = -(\psi_D(C)D + \psi_R(C)R + \psi_T(C)T)e, \qquad \text{[III.d]}$$

Where ψ subscripts specify population specific growth rates, γ subscripts specify donor and transconjugant specific conjugation rates, and other variables are consistent with equations [III.a]-[III.d]. As with the SIM, growth and conjugation rate are both dependent on resource concentration. When resources are depleted, growth and conjugation stop.

$$\psi_A(C) = \frac{\psi_{A,max}C}{Q + C},$$

$$\gamma_B(C) = \frac{\gamma_{B,max}C}{Q + C},$$

where $A \in \{D, R, T\}$ and $B \in \{D, T\}$.

Under the assumption that growth rate and conjugation rate are constant (where $\psi_A(C) = \psi_{A,max}$ and $\gamma_B(C) = \gamma_{B,max}$), equation [III.d] can be dropped. Although the maximal rates of growth and conjugation are assumed, in what follows, we drop the “max” subscript for notational convenience. This new set of simplified ordinary differential equations is termed the Approximate Simonsen *et. al.* Method (‘ASM’).

$$\frac{dD}{dt} = \psi_D D, \qquad \text{[III.e]}$$

$$\frac{dR}{dt} = \psi_R R - (\gamma_D D + \gamma_T T)R, \qquad \text{[III.f]}$$

$$\frac{dT}{dt} = \psi_T T + (\gamma_D D + \gamma_T T)R, \qquad \text{[III.g]}$$

If we assume that the recipient population is dominated by growth $\psi_R R \gg (\gamma_D D + \gamma_T T)R$ and the transconjugant population is dominated by growth and conjugation from donors $\psi_T T + \gamma_D DR \gg \gamma_T TR$, then we can replace equations [III.e]-[III.g] with the following set of differential equations, which do a good job approximating the dynamics:

$$\frac{dD}{dt} = \psi_D D, \qquad \text{[III.h]}$$

$$\frac{dR}{dt} = \psi_R R, \qquad \text{[III.i]}$$

$$\frac{dT}{dt} = \psi_T T + \gamma_D DR, \qquad \text{[III.j]}$$

The solutions to differential equations [III.h] and [III.i] are:

$$D_t = D_0 e^{\psi_D t} \qquad \text{[III.k]}$$

$$R_t = R_0 e^{\psi_R t} \qquad \text{[III.l]}$$

Here we will derive the solution for the differential equation [III.j] for transconjugant density T. We know that $D_t = D_0 e^{\psi_D t}$ and $R_t = R_0 e^{\psi_R t}$, therefore

$$\frac{dT}{dt} = \psi_T T + \gamma_D D_0 R_0 e^{(\psi_D + \psi_R)t} \qquad \text{[III.m]}$$

We propose that the transconjugant density can be written as a product of time dependent functions:

$$T_t = u_t v_t \qquad \text{[III.n]}$$

We'll drop the t subscripts for notational ease. By the product rule,

$$\frac{dT}{dt} = u\frac{dv}{dt} + v\frac{du}{dt} \qquad \text{[III.o]}$$

We can rewrite equation [III.m] by plugging in equations [III.n] and [III.o] as follows:

$$u\frac{dv}{dt} + v\frac{du}{dt} = \psi_T uv + \gamma_D D_0 R_0 e^{(\psi_D + \psi_R)t}$$

$$u\frac{dv}{dt} + v\left(\frac{du}{dt} - \psi_T u\right) = \gamma_D D_0 R_0 e^{(\psi_D + \psi_R)t} \qquad \text{[III.p]}$$

We have some freedom to pick u_t as we please. So, let's choose a function such that the second term of the left-hand side of equation [III.p] is zero:

$$\frac{du}{dt} - \psi_T u = 0$$

$$\frac{du}{dt} = \psi_T u$$

The solution to this differential equation is:

$$u_t = u_0 e^{\psi_T t} \qquad \text{[III.q]}$$

where u_0 is a constant.

Thus, we can rewrite equation [III.p] as:

$$u_0 e^{\psi_T t}\frac{dv}{dt} = \gamma_D D_0 R_0 e^{(\psi_D + \psi_R)t}$$

$$u_0 \frac{dv}{dt} = \frac{\gamma_D D_0 R_0 e^{(\psi_D + \psi_R)t}}{e^{\psi_T t}}$$

$$u_0 \frac{dv}{dt} = \gamma_D D_0 R_0 e^{(\psi_D + \psi_R - \psi_T)t}$$

To solve this equation, we integrate

$$u_0 \int dv = \gamma_D D_0 R_0 \int e^{(\psi_D + \psi_R - \psi_T)t} dt$$

$$u_0 v_t = \frac{\gamma_D D_0 R_0}{\psi_D + \psi_R - \psi_T} e^{(\psi_D + \psi_R - \psi_T)t} + c \qquad \text{[III.r]}$$

where c is a constant of the integration. To solve for c, plug in $t = 0$,

$$u_0 v_0 = \frac{\gamma_D D_0 R_0}{\psi_D + \psi_R - \psi_T} e^{(\psi_D + \psi_R - \psi_T)0} + c$$

$$u_0 v_0 = \frac{\gamma_D D_0 R_0}{\psi_D + \psi_R - \psi_T} + c$$

$$c = u_0 v_0 - \frac{\gamma_D D_0 R_0}{\psi_D + \psi_R - \psi_T}$$

Because $T_0 = u_0 v_0$,

$$c = T_0 - \frac{\gamma_D D_0 R_0}{\psi_D + \psi_R - \psi_T}$$

So, we now can find the solution for $v_{\tilde{t}}$ by plugging in our solution for c into equation [III.r]:

$$u_0 v_{\tilde{t}} = \frac{\gamma_D D_0 R_0}{\psi_D + \psi_R - \psi_T} e^{(\psi_D + \psi_R - \psi_T)\tilde{t}} + T_0 - \frac{\gamma_D D_0 R_0}{\psi_D + \psi_R - \psi_T}$$

$$u_0 v_{\tilde{t}} = T_0 + \frac{\gamma_D D_0 R_0}{\psi_D + \psi_R - \psi_T}\left\{e^{(\psi_D + \psi_R - \psi_T)\tilde{t}} - 1\right\}$$

$$v_{\tilde{t}} = \frac{1}{u_0}\left(T_0 + \frac{\gamma_D D_0 R_0}{\psi_D + \psi_R - \psi_T}\left\{e^{(\psi_D + \psi_R - \psi_T)\tilde{t}} - 1\right\}\right) \qquad \text{[III.s]}$$

Because $T_{\tilde{t}} = u_{\tilde{t}} v_{\tilde{t}}$ through substitution of equations [III.q] and [III.s] and, we have

$$T_{\tilde{t}} = \left[u_0 e^{\psi_T \tilde{t}}\right]\left[\frac{1}{u_0}\left(T_0 + \frac{\gamma_D D_0 R_0}{\psi_D + \psi_R - \psi_T}\left\{e^{(\psi_D + \psi_R - \psi_T)\tilde{t}} - 1\right\}\right)\right]$$

$$T_{\tilde{t}} = e^{\psi_T \tilde{t}}\left(T_0 + \frac{\gamma_D D_0 R_0}{\psi_D + \psi_R - \psi_T}\left\{e^{(\psi_D + \psi_R - \psi_T)\tilde{t}} - 1\right\}\right)$$

$$T_{\tilde{t}} = T_0 e^{\psi_T \tilde{t}} + \frac{\gamma_D D_0 R_0}{\psi_D + \psi_R - \psi_T}\left\{e^{(\psi_D + \psi_R)\tilde{t}} - e^{\psi_T \tilde{t}}\right\}$$

Because $T_0 = 0$, we arrive at the result in Huisman *et al*.

$$T_{\tilde{t}} = \frac{\gamma_D D_0 R_0}{\psi_D + \psi_R - \psi_T}\left\{e^{(\psi_D + \psi_R)\tilde{t}} - e^{\psi_T \tilde{t}}\right\}$$

Given that $D_{\tilde{t}} = D_0 e^{\psi_D \tilde{t}}$ and $R_{\tilde{t}} = R_0 e^{\psi_R \tilde{t}}$, this can be rewritten as

$$T_{\tilde{t}} = \frac{\gamma_D}{\psi_D + \psi_R - \psi_T}\left\{D_{\tilde{t}} R_{\tilde{t}} - D_0 R_0 e^{\psi_T \tilde{t}}\right\}$$

Solving for γ_D gives equation [1.9].

Appendix IV : The LDM MLE derivation

We start by focusing on $p_0(\tilde{t})$, the probability that a population will have no transconjugants at time $\tilde{t}$ (for notational convenience we'll drop the time variable). What we actually measure is the number of independent populations (or wells) that have no transconjugants (call this w) out of the total number of populations (or wells) tracked (call this W). What is our best estimate of p_0, given our data w? That is, what value p_0 maximizes the likelihood function:

$$\mathcal{L}(p_0) = \Pr\{w|p_0\} = \binom{\mathrm{W}}{w}(p_0)^w (1 - p_0)^{\mathrm{W}-w}$$

Because $-\ln(x)$ is a monotonic decreasing function, the value p_0 that maximizes $\mathcal{L}(p_0)$ will be the same value that minimizes:

$$\mathrm{L}(p_0) = -\ln\{\mathcal{L}(p_0)\}$$

This can be rewritten as follows:

$$\mathrm{L}(p_0) = -\ln\left\{\binom{\mathrm{W}}{w}(p_0)^w (1 - p_0)^{\mathrm{W}-w}\right\}$$

$$\mathrm{L}(p_0) = -\ln\binom{\mathrm{W}}{w} - w\ln p_0 - (\mathrm{W} - w)\ln(1 - p_0)$$

To find the maximum likelihood estimate, we find the critical points of L by setting its derivative to zero, or:

$$\frac{d\mathrm{L}}{dp_0} = -\frac{w}{p_0} + \frac{\mathrm{W} - w}{1 - p_0} = 0$$

The maximum likelihood estimate for p_0 (which we'll denote $\hat{p}_0$) solves the above equation, or

$$\frac{\mathrm{W}-w}{1-\hat{p}_0}=\frac{w}{\hat{p}_0}$$
$$(\mathrm{W}-w)\hat{p}_0=w(1-\hat{p}_0)$$
$$\mathrm{W}\hat{p}_0-w\hat{p}_0=w-w\hat{p}_0$$
$$\mathrm{W}\hat{p}_0=w$$
$$\hat{p}_0=\frac{w}{\mathrm{W}}$$
This answer makes intuitive sense: the most likely estimate for p_0 (the probability that a population has no transconjugants) is simply the fraction of the populations that have no transconjugants.

To double check that this estimate actually corresponds to a *minimum* of $\mathrm{L}(p_0)$, consider the second derivative:
$$\frac{d^2\mathrm{L}}{d{p_0}^2}=\frac{w}{{p_0}^2}+\frac{\mathrm{W}-w}{(1-p_0)^2}$$
Evaluating this derivative at the critical point yields:
$$\left.\frac{d^2\mathrm{L}}{d{p_0}^2}\right|_{p_0=\hat{p}_0}=\frac{w}{\left(\frac{w}{\mathrm{W}}\right)^2}+\frac{\mathrm{W}-w}{\left(\frac{\mathrm{W}-w}{\mathrm{W}}\right)^2}$$
$$\left.\frac{d^2\mathrm{L}}{d{p_0}^2}\right|_{p_0=\hat{p}_0}=\mathrm{W}^2\left(\frac{1}{w}+\frac{1}{\mathrm{W}-w}\right)$$
As long as $0<w<\mathrm{W}$,
$$\left.\frac{d^2\mathrm{L}}{d{p_0}^2}\right|_{p_0=\hat{p}_0}>0,$$
which means that L is convex at $\hat{p}_0$ and therefore, this value is a local minimum. In turn, this means that $\hat{p}_0$ is a local maximum for $\mathcal{L}$.

Appendix V : Derivations of the first and second central moments

In this section, we derive the equations for the moments using terminology close to what Keller and Antal (3) used (focusing on the case where $\kappa\notin\{1,2\}$). From SI section 7, $N=e^{\delta t}$ and with $\kappa=\frac{\delta}{\alpha}$, $N^{-1/\kappa}=e^{-\alpha t}$. Keller and Antal denote the number of mutants (analogous to our transconjugants) as B. Also, letting $\xi=\frac{z}{z-1}$ and $\mu=\frac{\nu}{\alpha}$ and dropping the time argument for notational convenience, the probability generating function (PGF) can be written as:

$$G_B(z)=\exp\left\{\frac{N\mu}{\kappa}\left[\frac{1}{N}F\left(1,\kappa;1+\kappa;\xi N^{-\frac{1}{\kappa}}\right)-F(1,\kappa;1+\kappa;\xi)\right]\right\}.$$
The expected value for the number of mutants can be obtained from the PGF in the usual way:
$$E[B]=G_B'(1-)=\lim_{z\to 1-}G_B(z)\frac{N\mu}{1+\kappa}\frac{1}{(z-1)^2}\Sigma,$$
where
$$\Sigma=-N^{-1-\frac{1}{\kappa}}F\left(2,1+\kappa;2+\kappa;\xi N^{-\frac{1}{\kappa}}\right)+F(2,1+\kappa;2+\kappa;\xi).$$
We use the following identity
$$F(a,b;c;z)=(1-z)^{c-a-b}F(c-a,c-b;c;z),$$
to obtain
$$F(2,1+\kappa;2+\kappa;\xi)=(1-\xi)^{-1}F(\kappa,1,2+\kappa,\xi)$$

$$= (1-z)F\left(\kappa, 1, 2+\kappa, \frac{z}{z-1}\right)$$

Using a related identity

$$F(a,b;c;z) = (1-z)^{-b}F\left(c-a, b; c; \frac{z}{z-1}\right),$$

we get:

$$F(2, 1+\kappa; 2+\kappa; \xi) = (1-z)F\left(\kappa, 1, 2+\kappa, \frac{z}{z-1}\right)$$

$$= (1-z)^2 F(2, 1, 2+\kappa, z)$$

We will use a similar procedure for the first term in Σ, obtaining:

$$F(2, 1+\kappa; 2+\kappa; \xi N^{-1/\kappa}) = (1-\xi N^{-1/\kappa})^{-1} F(\kappa, 1, 2+\kappa; \xi N^{-1/\kappa})$$

$$= (1-\xi N^{-1/\kappa})^{-1} F\left(\kappa, 1, 2+\kappa; \frac{x}{x-1}\right)$$

$$= (1-\xi N^{-1/\kappa})^{-1}(1-x)F(2, 1, 2+\kappa; x)$$

$$= \frac{(z-1)^2}{(zN^{-1/\kappa}-z+1)^2} F(2, 1; 2+\kappa; x)$$

where $x = \frac{zN^{-1/\kappa}}{zN^{-1/\kappa}-z+1}$.

In sum, we have shown that the first derivative of the PGF can be expressed in the following way:

$$G_B'(z) = G_B(z)\frac{N\mu}{1+\kappa}\left(-\frac{N^{-1-\frac{1}{\kappa}}}{(zN^{-\frac{1}{\kappa}}-z+1)^2}F(2, 1; 2+\kappa; x) + F(2, 1, 2+\kappa, z)\right). \qquad \text{[V.a]}$$

Using the fact that $\lim_{z \to 1-} G_B(z) = 1$ and the Gauss identity $F(a,b;c;1) = \frac{\Gamma(c)\Gamma(c-a-b)}{\Gamma(c-a)\Gamma(c-b)}$ (which holds if $c > a+b$) we obtain

$$E[B] = G_B'(1-) = \frac{N\mu}{\kappa-1}(-N^{-1+1/\kappa}+1).$$

To calculate the variance for the number of mutants, we note that

$$G_B''(1-) = E[B^2] - E[B],$$

and thus

$$\mathrm{Var}[B] = G_B''(1-) + E[B] - (E[B])^2$$

$$= G_B''(1-) + G_B'(1-) - (G_B'(1-))^2$$

From equation [V.a] we can express the first derivative of the PGF as:

$$G_B'(z) = G_B(z)\frac{N\mu}{1+\kappa}\Sigma_1.$$

It follows that

$$\mathrm{Var}[B] = G_B''(1-) + G_B'(1-) - (G_B'(1-))^2$$

$$= \frac{N\mu}{1+\kappa}\lim_{z \to 1-}(\Sigma_1 + \Sigma_1')$$

$$= E[B] + \frac{N\mu}{1+\kappa}\lim_{z \to 1-}\Sigma_1'$$

To calculate the derivative of Σ_1, we note that

$$\Sigma_1 = -\frac{N^{-1-\frac{1}{\kappa}}}{(zN^{-\frac{1}{\kappa}}-z+1)^2}F(2, 1; 2+\kappa; x) + F(2, 1, 2+\kappa, z).$$

We can calculate the derivative of the second term:

$$\frac{\partial F(2{,}1{,}2+\kappa,z)}{\partial z}=\frac{2}{2+\kappa}F(3{,}2;3+\kappa;z),$$

and of the first term:

$$\frac{\partial[-\frac{N^{-1-1/\kappa}}{(zN^{-1/\kappa}-z+1)^2}F(2{,}1;2+\kappa;x)]}{\partial z}$$

$$=-N^{-1-1/\kappa}\left(-\frac{2(N^{-1/\kappa}-1)}{(N^{-1/\kappa}z-z+1)^3}F(2{,}1;2+\kappa;x)\right.$$

$$\left.+\frac{2N^{-1/\kappa}}{(N^{-1/\kappa}z-z+1)^4}\frac{1}{2+\kappa}F(3{,}2;3+\kappa;x)\right)$$

Taken together, and using Gauss' equality,

$$\lim_{z\to1-}\Sigma_1'=2(N^{-1+1/\kappa}-N^{-1+2/\kappa})\frac{\kappa+1}{\kappa-1}+\frac{2}{2+\kappa}\frac{(\kappa+2)(\kappa+1)}{(\kappa-1)(\kappa-2)}(1-N^{-1+2/\kappa})$$

$$=2N^{-1+2/\kappa}\frac{\kappa+1}{\kappa-1}\left(-1-\frac{1}{\kappa-2}\right)+2N^{-1+1/\kappa}\frac{\kappa+1}{\kappa-1}+\frac{2(\kappa+1)}{(\kappa-1)(\kappa-2)}$$

$$=2N^{-1+2/\kappa}\frac{\kappa+1}{2-\kappa}+2N^{-1+1/\kappa}\frac{\kappa+1}{\kappa-1}+\frac{2(\kappa+1)}{(\kappa-1)(\kappa-2)}$$

Coming back to

$$\mathrm{Var}[B]=E[B]+\frac{N\mu}{1+\kappa}\lim_{z\to1-}\Sigma_1',$$

we obtain

$$\mathrm{Var}[B]=N\mu\left[\frac{2}{2-\kappa}N^{-1+\frac{2}{\kappa}}+\frac{1}{\kappa-1}N^{-1+\frac{1}{\kappa}}+\frac{\kappa}{(\kappa-1)(\kappa-2)}\right].$$

Making the appropriate substitutions yields our expressions for the mean and variance for our transconjugants in SI section 7.

Appendix VI : Behavior of the variance relative to the mean over time

In this section, we will show that the variance in transconjugant numbers grows relative to the mean over time. To do so, we will need to consider several cases.

Let's consider the ratio of the variance to the mean, which we denote $\rho_t=\frac{\mathrm{Var}[T_t]}{E[T_t]}$. Using the results from SI section 7, we will start by focusing on the case where $\psi_D+\psi_R\neq\psi_T$ and $\psi_D+\psi_R\neq 2\psi_T$:

$$\rho_t=\frac{\gamma_D D_0 R_0\left\{\frac{2e^{2\psi_T t}(\psi_T-(\psi_D+\psi_R))-e^{\psi_T t}(2\psi_T-(\psi_D+\psi_R))+(\psi_D+\psi_R)e^{(\psi_D+\psi_R)t}}{(2\psi_T-(\psi_D+\psi_R))(\psi_T-(\psi_D+\psi_R))}\right\}}{\frac{\gamma_D D_0 R_0(e^{(\psi_D+\psi_R)t}-e^{\psi_T t})}{\psi_D+\psi_R-\psi_T}}.$$

This can be simplified as follows:

$$\rho_t=\frac{2e^{2\psi_T t}(\psi_T-(\psi_D+\psi_R))-e^{\psi_T t}(2\psi_T-(\psi_D+\psi_R))+(\psi_D+\psi_R)e^{(\psi_D+\psi_R)t}}{(\psi_D+\psi_R-2\psi_T)(e^{(\psi_D+\psi_R)t}-e^{\psi_T t})}.$$

Letting $\kappa=\frac{\psi_D+\psi_R}{\psi_T}$,

$$\rho_t=\frac{2e^{2\psi_T t}(1-\kappa)-e^{\psi_T t}(2-\kappa)+\kappa e^{(\psi_D+\psi_R)t}}{(\kappa-2)(e^{(\psi_D+\psi_R)t}-e^{\psi_T t})},$$

$$\rho_t=\frac{\kappa e^{(\psi_D+\psi_R)t}-2(\kappa-1)e^{2\psi_T t}+(\kappa-2)e^{\psi_T t}}{(\kappa-2)(e^{(\psi_D+\psi_R)t}-e^{\psi_T t})}.$$

To determine the behavior of this ratio over time we take the derivative with respect to time:

$$\frac{d\rho_t}{dt}$$

$$= \frac{\left\{\begin{array}{c}\left(\kappa(\psi_D+\psi_R)e^{(\psi_D+\psi_R)t} - 4\psi_T(\kappa-1)e^{2\psi_T t} + (\kappa-2)\psi_T e^{\psi_T t}\right)(\kappa-2)\left(e^{(\psi_D+\psi_R)t} - e^{\psi_T t}\right) \\ -\left(\kappa e^{(\psi_D+\psi_R)t} - 2(\kappa-1)e^{2\psi_T t} + (\kappa-2)e^{\psi_T t}\right)(\kappa-2)\left((\psi_D+\psi_R)e^{(\psi_D+\psi_R)t} - \psi_T e^{\psi_T t}\right)\end{array}\right\}}{\left((\kappa-2)(e^{(\psi_D+\psi_R)t} - e^{\psi_T t})\right)^2}$$

$$\frac{d\rho_t}{dt} = \frac{\left\{\begin{array}{c}\left(\kappa(\psi_D+\psi_R)e^{(\psi_D+\psi_R)t} - 4\psi_T(\kappa-1)e^{2\psi_T t} + (\kappa-2)\psi_T e^{\psi_T t}\right)(\kappa-2)\left(e^{(\psi_D+\psi_R)t}\right) \\ -\left(\kappa(\psi_D+\psi_R)e^{(\psi_D+\psi_R)t} - 4\psi_T(\kappa-1)e^{2\psi_T t} + (\kappa-2)\psi_T e^{\psi_T t}\right)(\kappa-2)\left(e^{\psi_T t}\right) \\ -\left(\kappa e^{(\psi_D+\psi_R)t} - 2(\kappa-1)e^{2\psi_T t} + (\kappa-2)e^{\psi_T t}\right)(\kappa-2)\left((\psi_D+\psi_R)e^{(\psi_D+\psi_R)t}\right) \\ +\left(\kappa e^{(\psi_D+\psi_R)t} - 2(\kappa-1)e^{2\psi_T t} + (\kappa-2)e^{\psi_T t}\right)(\kappa-2)\left(\psi_T e^{\psi_T t}\right)\end{array}\right\}}{\left((\kappa-2)(e^{(\psi_D+\psi_R)t} - e^{\psi_T t})\right)^2},$$

$$\frac{d\rho_t}{dt} = \frac{\left\{\begin{array}{c}\left(-4\psi_T(\kappa-1)e^{2\psi_T t} + (\kappa-2)\psi_T e^{\psi_T t}\right)(\kappa-2)\left(e^{(\psi_D+\psi_R)t}\right) \\ -\left(\kappa(\psi_D+\psi_R)e^{(\psi_D+\psi_R)t} - 4\psi_T(\kappa-1)e^{2\psi_T t}\right)(\kappa-2)\left(e^{\psi_T t}\right) \\ -\left(-2(\kappa-1)e^{2\psi_T t} + (\kappa-2)e^{\psi_T t}\right)(\kappa-2)\left((\psi_D+\psi_R)e^{(\psi_D+\psi_R)t}\right) \\ +\left(\kappa e^{(\psi_D+\psi_R)t} - 2(\kappa-1)e^{2\psi_T t}\right)(\kappa-2)\left(\psi_T e^{\psi_T t}\right)\end{array}\right\}}{\left((\kappa-2)(e^{(\psi_D+\psi_R)t} - e^{\psi_T t})\right)^2},$$

$$\frac{d\rho_t}{dt} = \frac{\left\{\begin{array}{c}(\psi_D+\psi_R-2\psi_T)2(\kappa-1)(\kappa-2)e^{2\psi_T t}\left(e^{(\psi_D+\psi_R)t}\right) \\ -(\psi_D+\psi_R-\psi_T)(\kappa-2)^2 e^{\psi_T t}\left(e^{(\psi_D+\psi_R)t}\right) \\ -(\psi_D+\psi_R-\psi_T)\kappa(\kappa-2)e^{\psi_T t}\left(e^{(\psi_D+\psi_R)t}\right) \\ +2\psi_T(\kappa-1)(\kappa-2)e^{3\psi_T t}\end{array}\right\}}{\left((\kappa-2)(e^{(\psi_D+\psi_R)t} - e^{\psi_T t})\right)^2},$$

$$\frac{d\rho_t}{dt} = \frac{\left\{\begin{array}{c}(\psi_D+\psi_R-2\psi_T)2(\kappa-1)(\kappa-2)e^{2\psi_T t}\left(e^{(\psi_D+\psi_R)t}\right) \\ -(\psi_D+\psi_R-\psi_T)2(\kappa-1)(\kappa-2)e^{\psi_T t}\left(e^{(\psi_D+\psi_R)t}\right) \\ +2\psi_T(\kappa-1)(\kappa-2)e^{3\psi_T t}\end{array}\right\}}{\left((\kappa-2)(e^{(\psi_D+\psi_R)t} - e^{\psi_T t})\right)^2},$$

$$\frac{d\rho_t}{dt} = \frac{(\kappa-1)(\kappa-2)\left\{(\kappa-2)e^{(\psi_D+\psi_R+2\psi_T)t} - (\kappa-1)e^{(\psi_D+\psi_R+\psi_T)t} + e^{3\psi_T t}\right\}}{\left(\frac{1}{2\psi_T}\right)\left((\kappa-2)(e^{(\psi_D+\psi_R)t} - e^{\psi_T t})\right)^2},$$

$$\frac{d\rho_t}{dt} = \frac{(\kappa-1)(\kappa-2)e^{\psi_T t}\left\{(\kappa-2)e^{(\psi_D+\psi_R+\psi_T)t} - (\kappa-1)e^{(\psi_D+\psi_R)t} + e^{2\psi_T t}\right\}}{\left(\frac{1}{2\psi_T}\right)\left((\kappa-2)(e^{(\psi_D+\psi_R)t} - e^{\psi_T t})\right)^2},$$

$$\frac{d\rho_t}{dt} = \frac{(\kappa-1)(\kappa-2)\left\{(\kappa-2)e^{(\kappa+1)\psi_T t} - (\kappa-1)e^{\kappa\psi_T t} + e^{2\psi_T t}\right\}}{\left(\frac{e^{-\psi_T t}}{2\psi_T}\right)\left((\kappa-2)(e^{(\psi_D+\psi_R)t} - e^{\psi_T t})\right)^2}.$$

The denominator is always positive, so the sign of this derivative is governed by the numerator

$$\operatorname{sign}\left[\frac{d\rho_t}{dt}\right] = \operatorname{sign}\left[(\kappa-1)(\kappa-2)\left\{(\kappa-2)e^{(\kappa+1)\psi_T t} - (\kappa-1)e^{\kappa\psi_T t} + e^{2\psi_T t}\right\}\right].$$

For $\kappa > 2$, which is when the growth rate of the transconjugant is less than the average of the donor and recipient growth rates, we have

$$\operatorname{sign}\left[\frac{d\rho_t}{dt}\right] = \operatorname{sign}\left[(\kappa-2)e^{(\kappa+1)\psi_T t} - (\kappa-1)e^{\kappa\psi_T t} + e^{2\psi_T t}\right].$$

For any $t > 0$, for $\kappa = 2$

$$\operatorname{sign}\left[\frac{d\rho_t}{dt}\right] = \operatorname{sign}\left[0 - e^{2\psi_T t} + e^{2\psi_T t}\right] = 0.$$

Now letting $g(\kappa) = (\kappa - 2)e^{(\kappa+1)\psi_T t} - (\kappa - 1)e^{\kappa\psi_T t} + e^{2\psi_T t}$, we have

$$g'(\kappa) = e^{(\kappa+1)\psi_T t} + (\kappa - 2)\psi_T t e^{(\kappa+1)\psi_T t} - e^{\kappa\psi_T t} - (\kappa - 1)\psi_T t e^{\kappa\psi_T t},$$

$$g'(\kappa) = \{1 + (\kappa - 2)\psi_T t\}e^{(\kappa+1)\psi_T t} - \{1 + (\kappa - 1)\psi_T t\}e^{\kappa\psi_T t}.$$

Letting $h(x) = \{1 + (\kappa - 1 - x)\psi_T t\}e^{(\kappa+x)\psi_T t}$, we see

$$g'(\kappa) = h(1) - h(0).$$

But we see that

$$h'(x) = -\psi_T t e^{(\kappa+x)\psi_T t} + \{1 + (\kappa - 1 - x)\psi_T t\}\psi_T t e^{(\kappa+x)\psi_T t},$$

$$h'(x) = \psi_T t e^{(\kappa+x)\psi_T t}(-1 + \{1 + (\kappa - 1 - x)\psi_T t\}),$$

$$h'(x) = \psi_T t e^{(\kappa+x)\psi_T t}(\kappa - 1 - x)\psi_T t.$$

If $\kappa > 2$ and $t > 0$, then $h'(x) > 0$ for $0 \le x \le 1$. Since $h(x)$ is a continuous function, we must have

$$h(1) > h(0).$$

This implies that for $\kappa > 2$ and $t > 0$,

$$g'(\kappa) > 0.$$

Since $g(\kappa)$ is also continuous, and since $g(2) = 0$, we now know that for $\kappa > 2$ and $t > 0$,

$$g(\kappa) > 0.$$

Therefore $\operatorname{sign}\left[\frac{d\rho_t}{dt}\right] = 1$, or the derivative is positive for $t > 0$ and $\kappa > 2$, which means the variance grows relative to the mean over time.

For $1 < \kappa < 2$,

$$\operatorname{sign}\left[\frac{d\rho_t}{dt}\right] = \operatorname{sign}\left[-(\kappa - 2)e^{(\kappa+1)\psi_T t} + (\kappa - 1)e^{\kappa\psi_T t} - e^{2\psi_T t}\right].$$

Letting $\varphi = -(\kappa - 2)$, we know that $0 < \varphi < 1$, and we can rewrite the above

$$\operatorname{sign}\left[\frac{d\rho_t}{dt}\right] = \operatorname{sign}\left[\varphi e^{(3-\varphi)\psi_T t} + (1 - \varphi)e^{(3-(1+\varphi))\psi_T t} - e^{2\psi_T t}\right].$$

Because $e^{(3-x)\psi_T t}$ is convex $\left(t > 0 \Longrightarrow \frac{d^2 e^{(3-x)\psi_T t}}{dx^2} > 0\right)$, Jensen's inequality ensures

$$\varphi e^{(3-\varphi)\psi_T t} + (1 - \varphi)e^{(3-(1+\varphi))\psi_T t} - e^{2\psi_T t} > e^{\left(3-\left(\varphi^2+(1-\varphi)(1+\varphi)\right)\right)\psi_T t} - e^{2\psi_T t},$$

$$\varphi e^{(3-\varphi)\psi_T t} + (1 - \varphi)e^{(3-(1+\varphi))\psi_T t} - e^{2\psi_T t} > e^{\left(3-\left(\varphi^2+1-\varphi^2\right)\right)\psi_T t} - e^{2\psi_T t},$$

$$\varphi e^{(3-\varphi)\psi_T t} + (1 - \varphi)e^{(3-(1+\varphi))\psi_T t} - e^{2\psi_T t} > e^{2\psi_T t} - e^{2\psi_T t},$$

$$\varphi e^{(3-\varphi)\psi_T t} + (1 - \varphi)e^{(3-(1+\varphi))\psi_T t} - e^{2\psi_T t} > 0.$$

Therefore $\operatorname{sign}\left[\frac{d\rho_t}{dt}\right] = 1$, or the derivative is positive for $t > 0$ and $1 < \kappa < 2$, which means the variance grows relative to the mean over time.

Next, we turn to $0 < \kappa < 1$, where

$$\operatorname{sign}\left[\frac{d\rho_t}{dt}\right] = \operatorname{sign}\left[(\kappa - 2)e^{(\kappa+1)\psi_T t} - (\kappa - 1)e^{\kappa\psi_T t} + e^{2\psi_T t}\right].$$

For any $t > 0$, for $\kappa = 1$

$$\operatorname{sign}\left[\frac{d\rho_t}{dt}\right] = \operatorname{sign}\left[-e^{2\psi_T t} - 0 + e^{2\psi_T t}\right] = 0.$$

Now letting $g(\kappa) = (\kappa - 2)e^{(\kappa+1)\psi_T t} - (\kappa - 1)e^{\kappa\psi_T t} + e^{2\psi_T t}$, we have from above

$$g'(\kappa) = \{1 + (\kappa - 2)\psi_T t\}e^{(\kappa+1)\psi_T t} - \{1 + (\kappa - 1)\psi_T t\}e^{\kappa\psi_T t}.$$

Letting $h(x) = \{1 + (\kappa - 1 - x)\psi_T t\}e^{(\kappa+x)\psi_T t}$, we see

$$g'(\kappa) = h(1) - h(0).$$

But we see from above that

$$h'(x) = \psi_T t e^{(\kappa+x)\psi_T t}(\kappa - 1 - x)\psi_T t.$$

If $0 < \kappa < 1$ and $t > 0$, then $h'(x) < 0$ for $0 \le x \le 1$. Since $h(x)$ is a continuous function, we must have

$$h(1) < h(0).$$

This implies that for $0 < \kappa < 1$ and $t > 0$,

$$g'(\kappa) < 0.$$

Since $g(\kappa)$ is continuous, and since $g(1) = 0$, we now know that for $0 < \kappa < 1$ and $t > 0$, $g(\kappa) > 0$. Therefore $\operatorname{sign}\left[\frac{d\rho_t}{dt}\right] = 1$, or the derivative is positive for $t > 0$ and $0 < \kappa < 1$, which means the variance grows relative to the mean over time.

Now consider the special case of $\kappa = 2$

$$\rho_t = \frac{\dfrac{2\gamma_D D_0 R_0\left(e^{\psi_T t} - e^{2\psi_T t}\right)}{2\psi_T} + 2\gamma_D D_0 R_0 e^{2\psi_T t} t}{\dfrac{\gamma_D D_0 R_0 (e^{2\psi_T t} - e^{\psi_T t})}{2\psi_T - \psi_T}},$$

$$\rho_t = \frac{\left(e^{\psi_T t} - e^{2\psi_T t}\right) + 2\psi_T t e^{2\psi_T t}}{(e^{2\psi_T t} - e^{\psi_T t})},$$

$$\rho_t = \frac{(2\psi_T t - 1)e^{2\psi_T t} + e^{\psi_T t}}{(e^{2\psi_T t} - e^{\psi_T t})}.$$

Taking the derivative with respect to time yields

$$\frac{d\rho_t}{dt} = \frac{\left\{\begin{matrix}\left(2\psi_T e^{2\psi_T t} + 2\psi_T(2\psi_T t - 1)e^{2\psi_T t} + \psi_T e^{\psi_T t}\right)\left(e^{2\psi_T t} - e^{\psi_T t}\right) \\ -\left((2\psi_T t - 1)e^{2\psi_T t} + e^{\psi_T t}\right)\left(2\psi_T e^{2\psi_T t} - \psi_T e^{\psi_T t}\right)\end{matrix}\right\}}{(e^{2\psi_T t} - e^{\psi_T t})^2},$$

$$\frac{d\rho_t}{dt} = \psi_T \frac{\left(4\psi_T t e^{2\psi_T t} + e^{\psi_T t}\right)\left(e^{2\psi_T t} - e^{\psi_T t}\right) - \left((2\psi_T t - 1)e^{2\psi_T t} + e^{\psi_T t}\right)\left(2e^{2\psi_T t} - e^{\psi_T t}\right)}{(e^{2\psi_T t} - e^{\psi_T t})^2},$$

$$\frac{d\rho_t}{dt} = \psi_T \frac{\left\{\begin{matrix}4\psi_T t e^{4\psi_T t} + e^{3\psi_T t} - 4\psi_T t e^{3\psi_T t} - e^{2\psi_T t} \\ -2(2\psi_T t - 1)e^{4\psi_T t} - 2e^{3\psi_T t} + (2\psi_T t - 1)e^{3\psi_T t} + e^{2\psi_T t}\end{matrix}\right\}}{(e^{2\psi_T t} - e^{\psi_T t})^2},$$

$$\frac{d\rho_t}{dt} = \psi_T \frac{\{4\psi_T t - 2(2\psi_T t - 1)\}e^{4\psi_T t} - \{4\psi_T t + 1 - (2\psi_T t - 1)\}e^{3\psi_T t}}{(e^{2\psi_T t} - e^{\psi_T t})^2},$$

$$\frac{d\rho_t}{dt} = \psi_T \frac{2e^{4\psi_T t} - \{2\psi_T t + 2\}e^{3\psi_T t}}{(e^{2\psi_T t} - e^{\psi_T t})^2},$$

$$\frac{d\rho_t}{dt} = 2\psi_T e^{3\psi_T t} \frac{e^{\psi_T t} - \psi_T t - 1}{(e^{2\psi_T t} - e^{\psi_T t})^2}.$$

Using the Taylor expansion

$$\frac{d\rho_t}{dt} = 2\psi_T e^{3\psi_T t} \frac{\left(1 + \psi_T t + \frac{(\psi_T t)^2}{2!} + \frac{(\psi_T t)^3}{3!} + \frac{(\psi_T t)^4}{4!} \ldots\right) - \psi_T t - 1}{(e^{2\psi_T t} - e^{\psi_T t})^2},$$

$$\frac{d\rho_t}{dt} = 2\psi_T e^{3\psi_T t} \frac{\left(\frac{(\psi_T t)^2}{2!} + \frac{(\psi_T t)^3}{3!} + \frac{(\psi_T t)^4}{4!} \ldots\right)}{(e^{2\psi_T t} - e^{\psi_T t})^2}.$$

Therefore, $\frac{d\rho_t}{dt} > 0$ for $t > 0$ and $\kappa = 2$, which means the variance grows relative to the mean over time.

Finally, consider the special case of $\kappa = 1$

$$\rho_t = \frac{\frac{2\gamma_D D_0 R_0\left(e^{2\psi_T t} - e^{\psi_T t}\right)}{\psi_T} - \gamma_D D_0 R_0 e^{\psi_T t} t}{\gamma_D D_0 R_0 e^{\psi_T t} t},$$

$$\rho_t = \frac{2e^{2\psi_T t} - (2 + \psi_T t)e^{\psi_T t}}{\psi_T t e^{\psi_T t}},$$

$$\rho_t = \frac{2e^{\psi_T t} - (2 + \psi_T t)}{\psi_T t}.$$

Using the Taylor expansion

$$\rho_t = \frac{2\left(1 + \psi_T t + \frac{(\psi_T t)^2}{2!} + \frac{(\psi_T t)^3}{3!} + \frac{(\psi_T t)^4}{4!} \dots\right) - (2 + \psi_T t)}{\psi_T t},$$

$$\rho_t = \frac{\psi_T t + 2\left(\frac{(\psi_T t)^2}{2!} + \frac{(\psi_T t)^3}{3!} + \frac{(\psi_T t)^4}{4!} \dots\right)}{\psi_T t},$$

$$\rho_t = 1 + 2\left(\frac{\psi_T t}{2!} + \frac{(\psi_T t)^2}{3!} + \frac{(\psi_T t)^3}{4!} \dots\right).$$

Once again, the variance grows relative to the mean over time.

Overall, we have shown that for all $\kappa > 0$ and $t > 0$, the ratio of the transconjugant variance to the mean number of transconjugants is amplified over time.

Appendix VII : Derivations for estimate variance

In this appendix, we provide details for the derivation of the variance expressions for the LDM, SIM, and ASM estimates. Starting with the ASM estimate:

$$\gamma_D = \frac{\psi_D + \psi_R - \psi_T}{D_0 R_0\left(e^{(\psi_D+\psi_R)\tilde{t}} - e^{\psi_T \tilde{t}}\right)} T_{\tilde{t}},$$

which we can think about as a random variable Γ_{ASM}. Specifically,

$$\Gamma_{\mathrm{ASM}} = c_1 T_{\tilde{t}},$$

where the constant c_1 is

$$c_1 = \frac{\psi_D + \psi_R - \psi_T}{D_0 R_0\left(e^{(\psi_D+\psi_R)\tilde{t}} - e^{\psi_T \tilde{t}}\right)}.$$

The variance of the ASM estimate due to transconjugant variance is then

$$\mathrm{var}(\Gamma_{\mathrm{ASM}}) = {c_1}^2\{\mathrm{var}(T_{\tilde{t}})\}.$$

If $\psi_T \notin \{\psi_D + \psi_R,\ (\psi_D + \psi_R)/2\}$, we have:

$$\mathrm{var}(\Gamma_{\mathrm{ASM}}) = \left(\frac{\psi_D+\psi_R-\psi_T}{D_0R_0\left(e^{(\psi_D+\psi_R)\tilde{t}}-e^{\psi_T\tilde{t}}\right)}\right)^2 \gamma_D D_0 R_0 \left\{\frac{(\psi_D+\psi_R)e^{(\psi_D+\psi_R)\tilde{t}}}{(\psi_D+\psi_R-\psi_T)(\psi_D+\psi_R-2\psi_T)} + \frac{e^{\psi_T\tilde{t}}}{\psi_D+\psi_R-\psi_T} - \frac{2e^{2\psi_T\tilde{t}}}{\psi_D+\psi_R-2\psi_T}\right\},$$

$$\mathrm{var}(\Gamma_{\mathrm{ASM}}) = \frac{\gamma_D}{D_0R_0}\left(\frac{\psi_D + \psi_R - \psi_T}{e^{(\psi_D+\psi_R)\tilde{t}} - e^{\psi_T\tilde{t}}}\right)^2 \left\{\frac{(\psi_D + \psi_R)e^{(\psi_D+\psi_R)\tilde{t}} + (\psi_D + \psi_R - 2\psi_T)e^{\psi_T\tilde{t}} - (\psi_D + \psi_R - \psi_T)2e^{2\psi_T\tilde{t}}}{(\psi_D + \psi_R - \psi_T)(\psi_D + \psi_R - 2\psi_T)}\right\}$$

$$\mathrm{var}(\Gamma_{\mathrm{ASM}}) = \frac{\gamma_D(\psi_D+\psi_R-\psi_T)}{D_0R_0}\left\{\frac{(\psi_D+\psi_R)e^{(\psi_D+\psi_R)\tilde{t}}+(\psi_D+\psi_R-2\psi_T)e^{\psi_T\tilde{t}}-(\psi_D+\psi_R-\psi_T)2e^{2\psi_T\tilde{t}}}{(\psi_D+\psi_R-2\psi_T)\left(e^{(\psi_D+\psi_R)\tilde{t}}-e^{\psi_T\tilde{t}}\right)^2}\right\}.$$

The LDM estimate is expressed as follows:

$$\gamma_D = -\ln \hat{p}_0(\tilde{t}) \left(\frac{\psi_D + \psi_R}{D_0 R_0 \left(e^{(\psi_D + \psi_R)\tilde{t}} - 1 \right)} \right).$$

We measure the number of populations that have no transconjugants (w) out of the total number of populations tracked (W). The maximum likelihood estimate of $p_0(\tilde{t})$ is

$$\hat{p}_0(\tilde{t}) = \frac{w}{\mathrm{W}}.$$

Across experiments, there will be variance in the number of populations with no transconjugants. We define the random variable F to represent the fraction of total populations that have no transconjugants. The expectation of F is:

$$\mathrm{E}[F] = \sum_{w=0}^{\mathrm{W}} \binom{\mathrm{W}}{w} (p_0)^w (1 - p_0)^{\mathrm{W}-w} \left(\frac{w}{\mathrm{W}} \right),$$

$$\mathrm{E}[F] = \frac{1}{\mathrm{W}} \sum_{w=1}^{\mathrm{W}} \frac{\mathrm{W}!}{w!\,(\mathrm{W}-w)!} (p_0)^w (1 - p_0)^{\mathrm{W}-w}\, w,$$

$$\mathrm{E}[F] = \frac{1}{\mathrm{W}} \sum_{w=1}^{\mathrm{W}} \frac{\mathrm{W}!}{(\mathrm{w}-1)!\,(\mathrm{W}-w)!} (p_0)^w (1 - p_0)^{\mathrm{W}-w},$$

$$\mathrm{E}[F] = p_0 \sum_{w=1}^{\mathrm{W}} \frac{(\mathrm{W}-1)!}{(\mathrm{w}-1)!\,\big((\mathrm{W}-1)-(\mathrm{w}-1)\big)!} (p_0)^{w-1} (1 - p_0)^{(\mathrm{W}-1)-(w-1)}.$$

Letting $i = w - 1$, we have

$$\mathrm{E}[F] = p_0 \sum_{i=0}^{\mathrm{W}-1} \frac{(\mathrm{W}-1)!}{i!\,((\mathrm{W}-1)-i)!} (p_0)^i (1 - p_0)^{(\mathrm{W}-1)-i}.$$

However, because $\sum_{i=0}^{\mathrm{W}-1} \binom{\mathrm{W}-1}{i} (p_0)^i (1-p_0)^{(\mathrm{W}-1)-i} = 1$, we have

$$\mathrm{E}[F] = p_0,$$

which makes sense.

The variance of F is

$$\mathrm{var}[F] = \sum_{w=0}^{\mathrm{W}} \binom{\mathrm{W}}{w} (p_0)^w (1 - p_0)^{\mathrm{W}-w} \left(\frac{w}{\mathrm{W}} - p_0 \right)^2,$$

$$\mathrm{var}[F] = \sum_{w=0}^{\mathrm{W}} \binom{\mathrm{W}}{w} (p_0)^w (1 - p_0)^{\mathrm{W}-w} \left(\left(\frac{w}{\mathrm{W}} \right)^2 - 2p_0 \left(\frac{w}{\mathrm{W}} \right) + (p_0)^2 \right),$$

$$\mathrm{var}[F] = \sum_{w=0}^{\mathrm{W}} \binom{\mathrm{W}}{w} (p_0)^w (1 - p_0)^{\mathrm{W}-w} \left(\frac{w}{\mathrm{W}} \right)^2 - 2p_0 \sum_{w=0}^{\mathrm{W}} \binom{\mathrm{W}}{w} (p_0)^w (1 - p_0)^{\mathrm{W}-w} \left(\frac{w}{\mathrm{W}} \right)$$

$$+ (p_0)^2 \sum_{w=0}^{\mathrm{W}} \binom{\mathrm{W}}{w} (p_0)^w (1 - p_0)^{\mathrm{W}-w},$$

$$\mathrm{var}[F] = \left\{ \left(\frac{1}{\mathrm{W}^2} \right) \sum_{w=0}^{\mathrm{W}} \binom{\mathrm{W}}{w} (p_0)^w (1 - p_0)^{\mathrm{W}-w} w^2 \right\} - 2p_0 \mathrm{E}[F] + (p_0)^2,$$

$$\mathrm{var}[F] = \left\{ \left(\frac{1}{\mathrm{W}^2} \right) \sum_{w=0}^{\mathrm{W}} \binom{\mathrm{W}}{w} (p_0)^w (1 - p_0)^{\mathrm{W}-w} w(w - 1 + 1) \right\} - 2(p_0)^2 + (p_0)^2,$$

$$\text{var}[F] = \left\{\left(\frac{1}{\mathrm{W}^2}\right)\sum_{w=2}^{\mathrm{W}} \frac{\mathrm{W}!}{w!\,(\mathrm{W}-w)!}(p_0)^w(1-p_0)^{\mathrm{W}-w}w(w-1)\right.$$

$$\left. + \left(\frac{1}{\mathrm{W}^2}\right)\sum_{w=0}^{\mathrm{W}} \binom{\mathrm{W}}{w}(p_0)^w(1-p_0)^{\mathrm{W}-w}w\right\} - (p_0)^2,$$

$$\text{var}[F] = \left\{\left(\frac{1}{\mathrm{W}^2}\right)\sum_{w=2}^{\mathrm{W}} \frac{\mathrm{W}!}{(w-2)!\,(\mathrm{W}-w)!}(p_0)^w(1-p_0)^{\mathrm{W}-w}\right.$$

$$\left. + \left(\frac{1}{\mathrm{W}}\right)\sum_{w=0}^{\mathrm{W}} \binom{\mathrm{W}}{w}(p_0)^w(1-p_0)^{\mathrm{W}-w}\left(\frac{w}{\mathrm{W}}\right)\right\} - (p_0)^2,$$

$$\text{var}[F] = \left(\frac{\mathrm{W}(\mathrm{W}-1)(p_0)^2}{\mathrm{W}^2}\right)\left\{\sum_{w=2}^{\mathrm{W}} \frac{(\mathrm{W}-2)!}{(w-2)!\,((\mathrm{W}-2)-(w-2))!}(p_0)^{w-2}(1\right.$$

$$\left. - p_0)^{(\mathrm{W}-2)-(w-2)}\right\} + \frac{p_0}{\mathrm{W}} - (p_0)^2.$$

Letting $j = w - 2$, we have

$$\text{var}[F] = \left(\frac{(\mathrm{W}-1)(p_0)^2}{\mathrm{W}}\right)\left\{\sum_{j=0}^{\mathrm{W}-2} \binom{\mathrm{W}-2}{j}(p_0)^j(1-p_0)^{(\mathrm{W}-2)-j}\right\} + \frac{p_0}{\mathrm{W}} - (p_0)^2,$$

$$\text{var}[F] = \left(\frac{(\mathrm{W}-1)(p_0)^2}{\mathrm{W}}\right) + \frac{p_0}{\mathrm{W}} - (p_0)^2,$$

$$\text{var}[F] = \frac{(\mathrm{W}-1)(p_0)^2 + p_0 - \mathrm{W}(p_0)^2}{\mathrm{W}},$$

$$\text{var}[F] = \frac{-(p_0)^2 + p_0}{\mathrm{W}},$$

$$\text{var}[F] = \frac{p_0(1-p_0)}{\mathrm{W}}.$$

We represent the LDM estimate as a random variable Γ_{LDM},

$$\Gamma_{\mathrm{LDM}} = c_2 \ln F,$$

where the constant c_2 is

$$c_2 = -\left(\frac{\psi_D + \psi_R}{D_0 R_0\left(e^{(\psi_D+\psi_R)\tilde{t}} - 1\right)}\right).$$

The variance of the LDM estimate (due to the variance in transconjugant presence) is

$$\text{var}(\Gamma_{\mathrm{LDM}}) = {c_2}^2\{\text{var}(\ln F)\}.$$

Using a first-order Taylor series approximation for $\ln F$ centered at $\mathrm{E}[F]$

$$\ln F \approx \ln(\mathrm{E}[F]) + \frac{1}{\mathrm{E}[F]}(F - \mathrm{E}[F]),$$

$$\ln F \approx \frac{F}{\mathrm{E}[F]} + \ln(\mathrm{E}[F]) - 1.$$

Because $\ln(\mathrm{E}[F]) - 1$ is constant, we have

$$\text{var}[\ln F] \approx \text{var}\left\{\frac{F}{\mathrm{E}[F]}\right\},$$

$$\text{var}[\ln F] \approx \left(\frac{1}{\mathrm{E}[F]}\right)^2 \text{var}[F],$$

$$\mathrm{var}[\ln F] \approx \left(\frac{1}{p_0}\right)^2 \left(\frac{p_0(1-p_0)}{\mathrm{W}}\right),$$

$$\mathrm{var}[\ln F] \approx \frac{1}{\mathrm{W}}\left(\frac{1}{p_0} - 1\right).$$

The following is the expression for $p_0(\tilde{t})$:

$$p_0(\tilde{t}) = \exp\left\{\frac{-\gamma_D D_0 R_0}{\psi_D + \psi_R}\left(e^{(\psi_D+\psi_R)\tilde{t}} - 1\right)\right\}.$$

Reintroducing the time argument in F, and substituting the expression for $p_0(\tilde{t})$ yields

$$\mathrm{var}[\ln F_{\tilde{t}}] \approx \frac{1}{\mathrm{W}}\left(\exp\left\{\frac{\gamma_D D_0 R_0}{\psi_D + \psi_R}\left(e^{(\psi_D+\psi_R)\tilde{t}} - 1\right)\right\} - 1\right).$$

And therefore the variance for the LDM estimate is

$$\mathrm{var}(\Gamma_{\mathrm{LDM}}) \approx \frac{1}{\mathrm{W}}\left(\frac{\psi_D + \psi_R}{D_0 R_0\left(e^{(\psi_D+\psi_R)\tilde{t}} - 1\right)}\right)^2 \left(\exp\left\{\frac{\gamma_D D_0 R_0}{\psi_D + \psi_R}\left(e^{(\psi_D+\psi_R)\tilde{t}} - 1\right)\right\} - 1\right).$$

This can be written more compactly as

$$\mathrm{var}(\Gamma_{\mathrm{LDM}}) \approx \frac{{\xi_{\tilde{t}}}^2}{\mathrm{W}}\left(e^{\left(\frac{\gamma_D}{\xi_{\tilde{t}}}\right)} - 1\right),$$

with

$$\xi_{\tilde{t}} = \frac{\psi_D + \psi_R}{D_0 R_0\left(e^{(\psi_D+\psi_R)\tilde{t}} - 1\right)}.$$

To show mathematically that the LDM estimate is more precise for short times, we will approximate the expressions for the variance when $\tilde{t}$ is very small. This enables us to use a first-order Maclaurin approximation $e^{c\tilde{t}} \approx 1 + c\tilde{t}$. This allows the following approximation of the variance for the ASM estimate:

$$\mathrm{var}(\Gamma_{\mathrm{ASM}}) \approx \frac{\gamma_D(\psi_D + \psi_R - \psi_T)}{D_0 R_0}\left\{\frac{(\psi_D + \psi_R)(1 + (\psi_D + \psi_R)\tilde{t}) + (\psi_D + \psi_R - 2\psi_T)(1 + \psi_T\tilde{t}) - 2(\psi_D + \psi_R - \psi_T)(1 + 2\psi_T\tilde{t})}{(\psi_D + \psi_R - 2\psi_T)((\psi_D + \psi_R)\tilde{t} - \psi_T\tilde{t})^2}\right\}.$$

We can then simplify this expression:

$$\mathrm{var}(\Gamma_{\mathrm{ASM}}) \approx \frac{\gamma_D(\psi_D + \psi_R - \psi_T)}{D_0 R_0}\left\{\frac{(\psi_D + \psi_R)(\psi_D + \psi_R)\tilde{t} + (\psi_D + \psi_R - 2\psi_T)\psi_T\tilde{t} - 2(\psi_D + \psi_R - \psi_T)2\psi_T\tilde{t}}{(\psi_D + \psi_R - 2\psi_T)(\psi_D + \psi_R - \psi_T)^2\tilde{t}^2}\right\},$$

$$\mathrm{var}(\Gamma_{\mathrm{ASM}}) \approx \frac{\gamma_D}{D_0 R_0 \tilde{t}}\left\{\frac{(\psi_D + \psi_R)(\psi_D + \psi_R) + (\psi_D + \psi_R - 2\psi_T)\psi_T - 2(\psi_D + \psi_R - \psi_T)2\psi_T}{(\psi_D + \psi_R - 2\psi_T)(\psi_D + \psi_R - \psi_T)}\right\},$$

$$\mathrm{var}(\Gamma_{\mathrm{ASM}}) \approx \frac{\gamma_D}{D_0 R_0 \tilde{t}}\left\{\frac{(\psi_D + \psi_R - 2\psi_T)(\psi_D + \psi_R) + 2\psi_T(\psi_D + \psi_R) + (\psi_D + \psi_R - 2\psi_T)\psi_T - 2(\psi_D + \psi_R - \psi_T)2\psi_T}{(\psi_D + \psi_R - 2\psi_T)(\psi_D + \psi_R - \psi_T)}\right\},$$

$$\mathrm{var}(\Gamma_{\mathrm{ASM}}) \approx \frac{\gamma_D}{D_0 R_0 \tilde{t}}\left\{\frac{(\psi_D + \psi_R - 2\psi_T)(\psi_D + \psi_R) + 2\psi_T\psi_D + 2\psi_T\psi_R + \psi_T\psi_D + \psi_T\psi_R - 2{\psi_T}^2 - 4\psi_T\psi_D - 4\psi_T\psi_R + 4{\psi_T}^2}{(\psi_D + \psi_R - 2\psi_T)(\psi_D + \psi_R - \psi_T)}\right\},$$

$$\mathrm{var}(\Gamma_{\mathrm{ASM}}) \approx \frac{\gamma_D}{D_0 R_0 \tilde{t}}\left\{\frac{(\psi_D + \psi_R - 2\psi_T)(\psi_D + \psi_R) - \psi_T\psi_D - \psi_T\psi_R + 2{\psi_T}^2}{(\psi_D + \psi_R - 2\psi_T)(\psi_D + \psi_R - \psi_T)}\right\},$$

$$\mathrm{var}(\Gamma_{\mathrm{ASM}}) \approx \frac{\gamma_D}{D_0 R_0 \tilde{t}} \left\{ \frac{(\psi_D + \psi_R - 2\psi_T)(\psi_D + \psi_R) - (\psi_D + \psi_R - 2\psi_T)\psi_T}{(\psi_D + \psi_R - 2\psi_T)(\psi_D + \psi_R - \psi_T)} \right\},$$

$$\mathrm{var}(\Gamma_{\mathrm{ASM}}) \approx \frac{\gamma_D}{D_0 R_0 \tilde{t}} \left\{ \frac{(\psi_D + \psi_R - 2\psi_T)(\psi_D + \psi_R - \psi_T)}{(\psi_D + \psi_R - 2\psi_T)(\psi_D + \psi_R - \psi_T)} \right\},$$

$$\mathrm{var}(\Gamma_{\mathrm{ASM}}) \approx \frac{\gamma_D}{D_0 R_0 \tilde{t}}.$$

We now turn to the variance for the LDM (which we note is already an approximation). For very small $\tilde{t}$,

$$\xi_{\tilde{t}} \approx \frac{\psi_D + \psi_R}{D_0 R_0 (1 + (\psi_D + \psi_R)\tilde{t} - 1)},$$

$$\xi_{\tilde{t}} \approx \frac{1}{D_0 R_0 \tilde{t}}.$$

Thus, we have

$$\mathrm{var}(\Gamma_{\mathrm{LDM}}) \approx \frac{\left(\frac{1}{D_0 R_0 \tilde{t}}\right)^2}{\mathrm{W}} \left(e^{(\gamma_D D_0 R_0 \tilde{t})} - 1\right).$$

Using the Maclaurin approximation again yields

$$\mathrm{var}(\Gamma_{\mathrm{LDM}}) \approx \frac{\left(\frac{1}{D_0 R_0 \tilde{t}}\right)^2}{\mathrm{W}} (1 + \gamma_D D_0 R_0 \tilde{t} - 1),$$

$$\mathrm{var}(\Gamma_{\mathrm{LDM}}) \approx \frac{\gamma_D}{\mathrm{W} D_0 R_0 \tilde{t}}.$$

Our LDM assay requires $\mathrm{W} > 1$. Therefore when $\tilde{t}$ is very small

$$\mathrm{var}(\Gamma_{\mathrm{LDM}}) < \mathrm{var}(\Gamma_{\mathrm{ASM}}).$$

Again, we note the caveat that our estimate for the variance of the LDM estimate was already an approximation.

One can derive the variance for the SIM estimate in a way analogous to the ASM estimate, with the caveat that an approximation is needed (namely one that is similar to the approximation used for the variance of the LDM estimate). We will assume that the SIM estimate is obtained during exponential growth of all populations (which are assumed to grow at the same rate), which will allow us to connect the variance for the SIM to the variance for the ASM. We provide some of the details here.

If we focus solely on the contribution of transconjugant variation to estimate variance, we can represent the SIM estimate as a random variable Γ_{SIM}:

$$\Gamma_{\mathrm{SIM}} = \mathrm{A} \ln(1 + \mathrm{B} T_{\tilde{t}})$$

where the coefficients are treated as the following constants:

$$\mathrm{A} = \frac{\psi}{N_0 (e^{\psi \tilde{t}} - 1)},$$

$$\mathrm{B} = \frac{N_0}{D_0 R_0 e^{\psi \tilde{t}}}.$$

The variance of the estimate is then

$$\mathrm{var}(\Gamma_{\mathrm{SIM}}) = \mathrm{A}^2 \mathrm{var}[\ln(1 + \mathrm{B}T_{\tilde{t}})]$$

Using the first-order Taylor expansion centered at $E[T_{\tilde{t}}]$:

$$\ln(1 + \mathrm{B}T_{\tilde{t}}) \approx \ln(1 + \mathrm{B}E[T_{\tilde{t}}]) + \frac{B}{1 + \mathrm{B}E[T_{\tilde{t}}]}(T_{\tilde{t}} - E[T_{\tilde{t}}]).$$

And we have

$$\mathrm{var}[\ln(1 + \mathrm{B}T_{\tilde{t}})] \approx \left(\frac{\mathrm{B}}{1 + \mathrm{B}E[T_{\tilde{t}}]}\right)^2 \mathrm{var}(T_{\tilde{t}}).$$

Thus, we have

$$\mathrm{var}(\Gamma_{\mathrm{SIM}}) \approx \left(\frac{\mathrm{AB}}{1 + \mathrm{B}E[T_{\tilde{t}}]}\right)^2 \mathrm{var}(T_{\tilde{t}})$$

The quantity $E[T_{\tilde{t}}]$ is given in SI Section 7 (here we assume $\psi_D = \psi_R = \psi_T = \psi$). Plugging in the expressions for A, B, and $E[T_{\tilde{t}}]$ and simplifying yields,

$$\mathrm{var}(\Gamma_{\mathrm{SIM}}) \approx \frac{1}{\left(1 + \frac{\gamma_D(N_{\tilde{t}} - N_0)}{\psi}\right)^2} \left(\frac{\psi}{D_0 R_0 (e^{2\psi\tilde{t}} - e^{\psi\tilde{t}})}\right)^2 \mathrm{var}(T_{\tilde{t}})$$

The expression for variance of the ASM estimate (derived in SI Section 8) is:

$$\mathrm{var}(\Gamma_{\mathrm{ASM}}) = \left(\frac{\psi_D + \psi_R - \psi_T}{D_0 R_0 \left(e^{(\psi_D + \psi_R)\tilde{t}} - e^{\psi_T \tilde{t}}\right)}\right)^2 \mathrm{var}(T_{\tilde{t}})$$

If $\psi_D = \psi_R = \psi_T = \psi$ (as is assumed for the SIM estimate) we have

$$\mathrm{var}(\Gamma_{\mathrm{ASM}}) = \left(\frac{\psi}{D_0 R_0 \left(e^{2\psi\tilde{t}} - e^{\psi\tilde{t}}\right)}\right)^2 \mathrm{var}(T_{\tilde{t}})$$

Therefore,

$$\mathrm{var}(\Gamma_{\mathrm{SIM}}) \approx \frac{1}{\left(1 + \frac{\gamma_D(N_{\tilde{t}} - N_0)}{\psi}\right)^2} \mathrm{var}(\Gamma_{\mathrm{ASM}})$$

At the time of the end of the assay ($t = \tilde{t}$), the product of donors and recipients ($D_{\tilde{t}} R_{\tilde{t}}$) is in the vicinity of the reciprocal of the conjugation rate ($1/\gamma_D$), but the sum of donors and recipients is much smaller than the reciprocal of the conjugation rate ($D_{\tilde{t}} + R_{\tilde{t}} \ll 1/\gamma_D$). We note $N_t \approx D_t + R_t$. Therefore, for reasonable times in which the assay is ended and a reasonable growth rate:

$$N_{\tilde{t}} - N_0 \ll \frac{\psi}{\gamma_D}$$

In such a case, $1 + \frac{\gamma_D\left(N_{\tilde{t}} - N_0\right)}{\psi} \approx 1$, and

$$\mathrm{var}(\Gamma_{\mathrm{SIM}}) \approx \mathrm{var}(\Gamma_{\mathrm{ASM}})$$

Indeed, for an example close to that explored in SI Figure 10 (with $\psi_D = \psi_R = \psi_T = 1$, $D_0 = R_0 = 10^4$, and $\gamma_D = 10^{-12}$), the variances for the SIM and ASM estimates are virtually indistinguishable.

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