1 **GitHub appendix**
2
3 **Appendix I : TDR derivation**
4 We present a few derivations for the TDR method. The derivations differ by the
5 assumptions used to solve for TDR. We use this section to show the conditions where
6 the TDR method can be used. In addition, we use this section to walk through all of the
7 mathematical steps in order to provide an easy reference for comparing the derivations
8 of all four methods (TDR, SIM, ASM, and LDM). The original condition presented by Levin
9 *et. al.* (1) is the last derivation described in this section.
10 Here we assume that we are considering conditions where population growth is
11 not occurring. These conditions could involve an environment hindering cell division.
12 Alternatively, the environment could promote growth, but we restrict the time period
13 sufficiently so that population change is negligible. Or finally, if all strains possess the
14 same growth rate, the population could be growing over longer periods of time but doing
15 so in a continuous flow-through device (e.g., a chemostat) such that population density
16 remains constant, see ref (1). Because we assume no plasmid loss of the plasmid, the
17 donor population must remain constant

$$D_t = D_0, \qquad [\text{I.a}]$$

18 for any time t under consideration. Importantly, even though growth is not occurring,
19 conjugation can proceed. We assume $T_0 = 0$, but the population of transconjugants can
20 increase over time. Because every transconjugant was formerly a recipient cell, it must
21 be the case that
22 $$R_t + T_t = R_0,$$
23 for any time t under consideration. Therefore,

$$R_t = R_0 - T_t. \qquad [\text{I.b}]$$

24 The dynamics of transconjugants is given by

$$\frac{dT_t}{dt} = \gamma_D D_t R_t + \gamma_T T_t R_t \qquad [\text{I.c}]$$

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

26 $$\frac{dT_t}{dt} = \gamma_D D_0 (R_0 - T_t) + \gamma_T T_t (R_0 - T_t),$$

27 $$\frac{dT_t}{dt} = (\gamma_D D_0 + \gamma_T T_t)(R_0 - T_t),$$

28 $$\frac{dT_t}{dt} = -\gamma_T \left(T_t + \frac{\gamma_D D_0}{\gamma_T} \right)(T_t - R_0),$$

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

30 $$\int_0^{\tilde{t}} \frac{dT_t}{-\gamma_T \left(T_t + \frac{\gamma_D D_0}{\gamma_T} \right)(T_t - R_0)} = \int_0^{\tilde{t}} dt.$$

31 The following identity is relevant here:

32 $$\frac{d\left\{ \frac{1}{a(b-c)} \ln \frac{x-b}{x-c} \right\}}{dx} = \frac{1}{a(x-b)(x-c)}.$$

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

1

34

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

35

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

36 Because $T_0=0$,

37

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

38

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

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

39

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

40

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

41

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

42

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

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

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

45

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

46

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

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

47 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
48 therefore

49

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

50
$$\gamma_D \approx \frac{T_{\tilde{t}}}{D_0 R_0 \tilde{t}}.$$

51 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

52
$$\gamma_D \approx \frac{T_{\tilde{t}}}{D_{\tilde{t}} R_{\tilde{t}} \tilde{t}}.$$

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

54
$$\ln \frac{1 + \dfrac{T_{\tilde{t}}}{D_0}}{1 - \dfrac{T_{\tilde{t}}}{R_0}} = \gamma(D_0 + R_0)\tilde{t},$$

55
$$\gamma = \frac{1}{\tilde{t}(D_0 + R_0)} \ln \frac{1 + \dfrac{T_{\tilde{t}}}{D_0}}{1 - \dfrac{T_{\tilde{t}}}{R_0}},$$

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

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

57
$$\gamma \approx \frac{1}{\tilde{t}(D_0 + R_0)} \left(\frac{T_{\tilde{t}}}{D_0} + \frac{T_{\tilde{t}}}{R_0} \right),$$

58
$$\gamma \approx \frac{T_{\tilde{t}}}{\tilde{t}(D_0 + R_0)} \left(\frac{1}{D_0} + \frac{1}{R_0} \right),$$

59
$$\gamma \approx \frac{T_{\tilde{t}}}{\tilde{t}(D_0 + R_0)} \left(\frac{R_0 + D_0}{D_0 R_0} \right),$$

60
$$\gamma \approx \frac{T_{\tilde{t}}}{D_0 R_0 \tilde{t}}.$$

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

62
$$\gamma \approx \frac{T_{\tilde{t}}}{D_{\tilde{t}} R_{\tilde{t}} \tilde{t}}.$$

63 So we have general expressions for donor conjugation rate when $\gamma_T = 0$ (equation [I.f])
64 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
65 consideration, both of these measures are well approximated by equation [1.4]. Here we
66 extend the application of equation [1.4] even further. When $R_0 \gg T_t$, then $R_t \approx R_0$. Let us
67 assume $R_t = R_0$. We will also assume

$$\gamma_D D_0 R_0 \gg \gamma_T T_t R_0, \qquad \text{[I.h]}$$

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

75
$$\frac{dT_t}{dt} = \gamma_D D_0 R_0.$$

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

78
$$\int_0^{\tilde{t}} dT_t = \int_0^{\tilde{t}} \gamma_D D_0 R_0 \, dt,$$

3

79
$$(T_{\tilde{t}})|_0^{\tilde{t}} = (\gamma_D D_0 R_0 t)|_0^{\tilde{t}},$$

80
$$T_{\tilde{t}} - T_0 = \gamma_D D_0 R_0 \tilde{t}.$$

81 Because $T_0 = 0$,

82
$$T_{\tilde{t}} = \gamma_D D_0 R_0 \tilde{t},$$

83
$$\gamma_D = \frac{T_{\tilde{t}}}{D_0 R_0 \tilde{t}}.$$

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

85

86 **Appendix II : SIM derivation**

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

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

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

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

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

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

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

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

100 where Q is the half saturation constant.
101 More generally, let us assume

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

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

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

105
$$\frac{\psi(C)}{\gamma(C)} = \frac{\psi^{\blacksquare}}{\gamma^{\blacksquare}}.$$

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

113
$$\frac{dN}{dt} = \frac{dD}{dt} + \frac{dR}{dt} + \frac{dT}{dt},$$

114
$$\frac{dN}{dt} = \psi(C)D + \psi(C)R - \gamma(C)R(D + T) + \psi(C)T + \gamma(C)R(D + T),$$

115
$$\frac{dN}{dt} = \psi(C)(D + R + T),$$

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

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

117
$$\frac{dX}{dt} = \frac{\frac{dD}{dt}N - \frac{dN}{dt}D}{N^2}$$

118
$$\frac{dX}{dt} = \frac{\psi(C)DN - \psi(C)ND}{N^2}$$

119
$$\frac{dX}{dt} = 0$$

120   Thus, X_t does not change over time (i.e., $X_t = X_0$ for all t).
121
122   Lastly, we define a fraction $Y_t = T_t/R_t$. Using equations [II.b] and [II.c],

123
$$\frac{dY}{dt} = \frac{\frac{dT}{dt}R - \frac{dR}{dt}T}{R^2},$$

124
$$\frac{dY}{dt} = \frac{\{\psi(C)T + \gamma(C)R(D + T)\}R - \{\psi(C)R - \gamma(C)R(D + T)\}T}{R^2},$$

125
$$\frac{dY}{dt} = \frac{\psi(C)TR + \gamma(C)(D + T)R^2 - \psi(C)TR + \gamma(C)(D + T)TR}{R^2},$$

126
$$\frac{dY}{dt} = \frac{\gamma(C)(D + T)R^2 + \gamma(C)(D + T)TR}{R^2},$$

127
$$\frac{dY}{dt} = \frac{\gamma(C)(D + T)R + \gamma(C)(D + T)T}{R},$$

128
$$\frac{dY}{dt} = \frac{\gamma(C)(DR + TR + DT + T^2)}{R},$$

129
$$\frac{dY}{dt} = \gamma(C)\frac{DT + RT + T^2 + DR}{R},$$

130
$$\frac{dY}{dt} = \gamma(C)\left(\frac{T(D + R + T)}{R} + D\right).$$

131   Because $N_t = D_t + R_t + T_t$,

132
$$\frac{dY}{dt} = \gamma(C)\left(\frac{TN}{R} + D\right),$$

133
$$\frac{dY}{dt} = \gamma(C)N\left(\frac{T}{R} + \frac{D}{N}\right).$$

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

5

$$135 \qquad \frac{dY}{dt} = \gamma(C) N (Y + X),$$

$$136 \qquad \left(\frac{1}{Y+X}\right) \frac{dY}{dt} = \gamma(C) N.$$

137 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

$$138 \qquad \left(\frac{1}{Y+X}\right) \frac{dY}{dt} = \gamma(C) \left(\frac{1}{\psi(C)}\right) \frac{dN}{dt},$$

$$139 \qquad \left(\frac{1}{Y+X}\right) \frac{dY}{dt} = \gamma^{\blacksquare} g(C) \left(\frac{1}{\psi^{\blacksquare} g(C)}\right) \frac{dN}{dt},$$

$$140 \qquad \psi^{\blacksquare} \left(\frac{1}{Y+X}\right) \frac{dY}{dt} = \gamma^{\blacksquare} \frac{dN}{dt},$$

$$141 \qquad \gamma^{\blacksquare} (dN) = \psi^{\blacksquare} \left(\frac{dY}{Y+X}\right).$$

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

$$143 \qquad \gamma^{\blacksquare} \int_0^{\tilde{t}} dN = \psi^{\blacksquare} \int_0^{\tilde{t}} \left(\frac{dY}{Y + X_0}\right),$$

144 Making the time dependence of the variables explicit via subscripts

$$145 \qquad \gamma^{\blacksquare} N_t |_0^{\tilde{t}} = \psi^{\blacksquare} \ln(Y_t + X_0) |_0^{\tilde{t}},$$

$$146 \qquad \gamma^{\blacksquare} (N_{\tilde{t}} - N_0) = \psi^{\blacksquare} \{ \ln(Y_{\tilde{t}} + X_0) - \ln(Y_0 + X_0) \}.$$

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

$$148 \qquad \gamma^{\blacksquare} (N_{\tilde{t}} - N_0) = \psi^{\blacksquare} \{ \ln(Y_{\tilde{t}} + X_{\tilde{t}}) - \ln(Y_0 + X_{\tilde{t}}) \},$$

$$149 \qquad \gamma^{\blacksquare} (N_{\tilde{t}} - N_0) = \psi^{\blacksquare} \ln\left(\frac{Y_{\tilde{t}} + X_{\tilde{t}}}{Y_0 + X_{\tilde{t}}}\right).$$

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

$$151 \qquad \gamma^{\blacksquare} (N_{\tilde{t}} - N_0) = \psi^{\blacksquare} \ln\left(\frac{\frac{T_{\tilde{t}}}{R_{\tilde{t}}} + \frac{D_{\tilde{t}}}{N_{\tilde{t}}}}{\frac{T_0}{R_0} + \frac{D_{\tilde{t}}}{N_{\tilde{t}}}}\right).$$

152 Because $T_0 = 0$,

$$153 \qquad \gamma^{\blacksquare} (N_{\tilde{t}} - N_0) = \psi^{\blacksquare} \ln\left(\frac{\frac{T_{\tilde{t}}}{R_{\tilde{t}}} + \frac{D_{\tilde{t}}}{N_{\tilde{t}}}}{\frac{D_{\tilde{t}}}{N_{\tilde{t}}}}\right),$$

$$154 \qquad \gamma^{\blacksquare} (N_{\tilde{t}} - N_0) = \psi^{\blacksquare} \ln\left(\frac{T_{\tilde{t}}}{R_{\tilde{t}}} \frac{N_{\tilde{t}}}{D_{\tilde{t}}} + 1\right),$$

$$155 \qquad \gamma^{\blacksquare} = \psi^{\blacksquare} \ln\left(1 + \frac{T_{\tilde{t}}}{R_{\tilde{t}}} \frac{N_{\tilde{t}}}{D_{\tilde{t}}}\right) \frac{1}{N_{\tilde{t}} - N_0}.$$

156

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

159

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

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

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

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

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

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

170
$$\psi_A(C) = \frac{\psi_{A,max}C}{Q + C},$$

171
$$\gamma_B(C) = \frac{\gamma_{B,max}C}{Q + C},$$

172 where $A \in \{D, R, T\}$ and $B \in \{D, T\}$.
173 Under the assumption that growth rate and conjugation rate are constant (where
174 $\psi_A(C) = \psi_{A,max}$ and $\gamma_B(C) = \gamma_{B,max}$), equation [III.d] can be dropped. Although the
175 maximal rates of growth and conjugation are assumed, in what follows, we drop the "max"
176 subscript for notational convenience. This new set of simplified ordinary differential
177 equations is termed the Approximate Simonsen *et. al.* Method ('ASM').

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

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

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

178 If we assume that the recipient population is dominated by growth $\psi_R R \gg (\gamma_D D +$
179 $\gamma_T T)R$ and the transconjugant population is dominated by growth and conjugation from
180 donors $\psi_T T + \gamma_D DR \gg \gamma_T TR$, then we can replace equations [III.e]-[III.g] with the following
181 set of differential equations, which do a good job approximating the dynamics:

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

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

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

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

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

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

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

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

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

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

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

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

188 We can rewrite equation [III.m] by plugging in equations [III.n] and [III.o] as follows:
189
$$u\frac{dv}{dt} + v\frac{du}{dt} = \psi_T u v + \gamma_D D_0 R_0 e^{(\psi_D + \psi_R)t}$$

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

190 We have some freedom to pick u_t as we please. So, let's choose a function such that the
191 second term of the left-hand side of equation [III.p] is zero:
192
$$\frac{du}{dt} - \psi_T u = 0$$

193
$$\frac{du}{dt} = \psi_T u$$

194 The solution to this differential equation is:

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

195 where u_0 is a constant.
196
197 Thus, we can rewrite equation [III.p] as:
198
$$u_0 e^{\psi_T t} \frac{dv}{dt} = \gamma_D D_0 R_0 e^{(\psi_D + \psi_R)t}$$

199
$$u_0 \frac{dv}{dt} = \frac{\gamma_D D_0 R_0 e^{(\psi_D + \psi_R)t}}{e^{\psi_T t}}$$

200
$$u_0 \frac{dv}{dt} = \gamma_D D_0 R_0 e^{(\psi_D + \psi_R - \psi_T)t}$$

201 To solve this equation, we integrate
202
$$u_0 \int dv = \gamma_D D_0 R_0 \int e^{(\psi_D + \psi_R - \psi_T)t} dt$$

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

203 where c is a constant of the integration. To solve for c, plug in $t = 0$,
204
$$u_0 v_0 = \frac{\gamma_D D_0 R_0}{\psi_D + \psi_R - \psi_T} e^{(\psi_D + \psi_R - \psi_T)0} + c$$

205
$$u_0 v_0 = \frac{\gamma_D D_0 R_0}{\psi_D + \psi_R - \psi_T} + c$$

206
$$c = u_0 v_0 - \frac{\gamma_D D_0 R_0}{\psi_D + \psi_R - \psi_T}$$

207   Because $T_0 = u_0 v_0$,

208
$$c = T_0 - \frac{\gamma_D D_0 R_0}{\psi_D + \psi_R - \psi_T}$$

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

210
$$u_0 v_{\tilde{t}} = \frac{\gamma_D D_0 R_0}{\psi_D + \psi_R - \psi_T} e^{(\psi_D + \psi_R - \psi_T)\tilde{t}} + T_0 - \frac{\gamma_D D_0 R_0}{\psi_D + \psi_R - \psi_T}$$

211
$$u_0 v_{\tilde{t}} = T_0 + \frac{\gamma_D D_0 R_0}{\psi_D + \psi_R - \psi_T} \left\{ e^{(\psi_D + \psi_R - \psi_T)\tilde{t}} - 1 \right\}$$

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

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

213
$$T_{\tilde{t}} = \left[u_0 e^{\psi_T \tilde{t}} \right] \left[\frac{1}{u_0} \left(T_0 + \frac{\gamma_D D_0 R_0}{\psi_D + \psi_R - \psi_T} \left\{ e^{(\psi_D + \psi_R - \psi_T)\tilde{t}} - 1 \right\} \right) \right]$$

214
$$T_{\tilde{t}} = e^{\psi_T \tilde{t}} \left(T_0 + \frac{\gamma_D D_0 R_0}{\psi_D + \psi_R - \psi_T} \left\{ e^{(\psi_D + \psi_R - \psi_T)\tilde{t}} - 1 \right\} \right)$$

215
$$T_{\tilde{t}} = T_0 e^{\psi_T \tilde{t}} + \frac{\gamma_D D_0 R_0}{\psi_D + \psi_R - \psi_T} \left\{ e^{(\psi_D + \psi_R)\tilde{t}} - e^{\psi_T \tilde{t}} \right\}$$

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

217
$$T_{\tilde{t}} = \frac{\gamma_D D_0 R_0}{\psi_D + \psi_R - \psi_T} \left\{ e^{(\psi_D + \psi_R)\tilde{t}} - e^{\psi_T \tilde{t}} \right\}$$

218   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

219
$$T_{\tilde{t}} = \frac{\gamma_D}{\psi_D + \psi_R - \psi_T} \left\{ D_{\tilde{t}} R_{\tilde{t}} - D_0 R_0 e^{\psi_T \tilde{t}} \right\}$$

220   Solving for γ_D gives equation [1.9].

221

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

229
$$\mathcal{L}(p_0) = \Pr\{w|p_0\} = \binom{W}{w} (p_0)^w (1 - p_0)^{W-w}$$

230   Because $-\ln(x)$ is a monotonic decreasing function, the value p_0 that maximizes $\mathcal{L}(p_0)$
231   will be the same value that minimizes:
232
$$L(p_0) = -\ln\{\mathcal{L}(p_0)\}$$

233   This can be rewritten as follows:

234
$$L(p_0) = -\ln\left\{ \binom{W}{w} (p_0)^w (1 - p_0)^{W-w} \right\}$$

235
$$L(p_0) = -\ln\binom{W}{w} - w \ln p_0 - (W - w) \ln(1 - p_0)$$

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

238
$$\frac{dL}{dp_0} = -\frac{w}{p_0} + \frac{W - w}{1 - p_0} = 0$$

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

241
$$\frac{W-w}{1-\hat{p}_0} = \frac{w}{\hat{p}_0}$$

242
$$(W-w)\hat{p}_0 = w(1-\hat{p}_0)$$

243
$$W\hat{p}_0 - w\hat{p}_0 = w - w\hat{p}_0$$

244
$$W\hat{p}_0 = w$$

245
$$\hat{p}_0 = \frac{w}{W}$$

246 This answer makes intuitive sense: the most likely estimate for p_0 (the probability that a
247 population has no transconjugants) is simply the fraction of the populations that have no
248 transconjugants.

249   To double check that this estimate actually corresponds to a *minimum* of $\mathrm{L}(p_0)$,
250 consider the second derivative:

251
$$\frac{d^2\mathrm{L}}{dp_0{}^2} = \frac{w}{p_0{}^2} + \frac{W-w}{(1-p_0)^2}$$

252 Evaluating this derivative at the critical point yields:

253
$$\left.\frac{d^2\mathrm{L}}{dp_0{}^2}\right|_{p_0=\hat{p}_0} = \frac{w}{\left(\frac{w}{W}\right)^2} + \frac{W-w}{\left(\frac{W-w}{W}\right)^2}$$

254
$$\left.\frac{d^2\mathrm{L}}{dp_0{}^2}\right|_{p_0=\hat{p}_0} = W^2\left(\frac{1}{w} + \frac{1}{W-w}\right)$$

255 As long as $0 < w < W$,

256
$$\left.\frac{d^2\mathrm{L}}{dp_0{}^2}\right|_{p_0=\hat{p}_0} > 0,$$

257 which means that L is convex at $\hat{p}_0$ and therefore, this value is a local minimum. In turn,
258 this means that $\hat{p}_0$ is a local maximum for $\mathcal{L}$.

259

260 **Appendix V : Derivations of the first and second central moments**
261 In this section, we derive the equations for the moments using terminology close to what
262 Keller and Antal (3) used (focusing on the case where $\kappa \notin \{1,2\}$). From SI section 7, $N =$
263 $e^{\delta t}$ and with $\kappa = \frac{\delta}{\alpha}$, $N^{-1/\kappa} = e^{-\alpha t}$. Keller and Antal denote the number of mutants
264 (analogous to our transconjugants) as B. Also, letting $\xi = \frac{z}{z-1}$ and $\mu = \frac{\nu}{\alpha}$ and dropping the
265 time argument for notational convenience, the probability generating function (PGF) can
266 be written as:

267

268
$$G_B(z) = \exp\left\{\frac{N\mu}{\kappa}\left[\frac{1}{N}F\left(1,\kappa;1+\kappa;\xi N^{-\frac{1}{\kappa}}\right) - F(1,\kappa;1+\kappa;\xi)\right]\right\}.$$

269 The expected value for the number of mutants can be obtained from the PGF in the usual
270 way:

271
$$E[B] = G_B'(1-) = \lim_{z\to 1-} G_B(z)\frac{N\mu}{1+\kappa}\frac{1}{(z-1)^2}\Sigma,$$

272 where

273
$$\Sigma = -N^{-1-\frac{1}{\kappa}}F\left(2,1+\kappa;2+\kappa;\xi N^{-\frac{1}{\kappa}}\right) + F(2,1+\kappa;2+\kappa;\xi).$$

274 We use the following identity

275
$$F(a,b;c;z) = (1-z)^{c-a-b}F(c-a,c-b;c;z),$$

276 to obtain

277
$$F(2,1+\kappa;2+\kappa;\xi) = (1-\xi)^{-1}F(\kappa,1;2+\kappa,\xi)$$

278    $$= (1-z)F\left(\kappa, 1, 2+\kappa, \frac{z}{z-1}\right)$$

279   Using a related identity

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

281   we get:

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

283    $$= (1-z)^2 F(2,1,2+\kappa, z)$$

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

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

286    $$= (1-\xi N^{-1/\kappa})^{-1}F\left(\kappa, 1, 2+\kappa; \frac{x}{x-1}\right)$$

287    $$= (1-\xi N^{-1/\kappa})^{-1}(1-x)F(2,1,2+\kappa; x)$$

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

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

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

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

[V.a]

$$\left. + F(2,1,2+\kappa, z)\right).$$

292   Using the fact that $\lim_{z\to1-} G_B(z) = 1$ and the Gauss identity $F(a, b; c; 1) = \frac{\Gamma(c)\Gamma(c-a-b)}{\Gamma(c-a)\Gamma(c-b)}$ (which
293   holds if $c > a + b$) we obtain

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

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

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

297   and thus

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

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

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

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

302   It follows that

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

304    $$= \frac{N\mu}{1+\kappa}\lim_{z\to1-}(\Sigma_1 + \Sigma_1')$$

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

306   To calculate the derivative of Σ_1, we note that

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

308   We can calculate the derivative of the second term:

11

309
$$\frac{\partial F(2,1,2+\kappa,z)}{\partial z} = \frac{2}{2+\kappa} F(3,2;3+\kappa;z),$$

310 and of the first term:

311
$$\frac{\partial\left[-\frac{N^{-1-1/\kappa}}{(zN^{-1/\kappa}-z+1)^2} F(2,1;2+\kappa;x)\right]}{\partial z}$$

312
$$= -N^{-1-1/\kappa}\left(-\frac{2(N^{-1/\kappa}-1)}{(N^{-1/\kappa}z-z+1)^3} F(2,1;2+\kappa;x)\right.$$

313
$$\left. +\frac{2N^{-1/\kappa}}{(N^{-1/\kappa}z-z+1)^4}\frac{1}{2+\kappa} F(3,2;3+\kappa;x)\right)$$

314 Taken together, and using Gauss' equality,

315
$$\lim_{z\to1-}\Sigma_1' = 2(N^{-1+1/\kappa}-N^{-1+2/\kappa})\frac{\kappa+1}{\kappa-1}+\frac{2}{2+\kappa}\frac{(\kappa+2)(\kappa+1)}{(\kappa-1)(\kappa-2)}(1-N^{-1+2/\kappa})$$

316
$$= 2N^{-1+2/\kappa}\frac{\kappa+1}{\kappa-1}\left(-1-\frac{1}{\kappa-2}\right)+2N^{-1+1/\kappa}\frac{\kappa+1}{\kappa-1}+\frac{2(\kappa+1)}{(\kappa-1)(\kappa-2)}$$

317
$$= 2N^{-1+2/\kappa}\frac{\kappa+1}{2-\kappa}+2N^{-1+1/\kappa}\frac{\kappa+1}{\kappa-1}+\frac{2(\kappa+1)}{(\kappa-1)(\kappa-2)}$$

318 Coming back to

319
$$\text{Var}[B] = E[B] + \frac{N\mu}{1+\kappa}\lim_{z\to1-}\Sigma_1',$$

320 we obtain

321
$$\text{Var}[B] = N\mu\left[\frac{2}{2-\kappa}N^{-1+\frac{2}{\kappa}}+\frac{1}{\kappa-1}N^{-1+\frac{1}{\kappa}}+\frac{\kappa}{(\kappa-1)(\kappa-2)}\right].$$

322 Making the appropriate substitutions yields our expressions for the mean and variance
323 for our transconjugants in SI section 7.
324
325 **Appendix VI : Behavior of the variance relative to the mean over time**
326 In this section, we will show that the variance in transconjugant numbers grows relative
327 to the mean over time. To do so, we will need to consider several cases.
328
329 Let's consider the ratio of the variance to the mean, which we denote $\rho_t = \frac{\text{Var}[T_t]}{E[T_t]}$. Using
330 the results from SI section 7, we will start by focusing on the case where $\psi_D+\psi_R \neq \psi_T$
331 and $\psi_D+\psi_R \neq 2\psi_T$:

332
$$\rho_t = \frac{\gamma_D D_0 R_0\left\{\frac{2e^{2\psi_T t}(\psi_T-(\psi_D+\psi_R))-e^{\psi_T t}(2\psi_T-(\psi_D+\psi_R))+(\psi_D+\psi_R)e^{(\psi_D+\psi_R)t}}{(2\psi_T-(\psi_D+\psi_R))(\psi_T-(\psi_D+\psi_R))}\right\}}{\frac{\gamma_D D_0 R_0(e^{(\psi_D+\psi_R)t}-e^{\psi_T t})}{\psi_D+\psi_R-\psi_T}}.$$

333 This can be simplified as follows:

334
$$\rho_t = \frac{2e^{2\psi_T t}(\psi_T-(\psi_D+\psi_R))-e^{\psi_T t}(2\psi_T-(\psi_D+\psi_R))+(\psi_D+\psi_R)e^{(\psi_D+\psi_R)t}}{(\psi_D+\psi_R-2\psi_T)(e^{(\psi_D+\psi_R)t}-e^{\psi_T t})}.$$

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

336
$$\rho_t = \frac{2e^{2\psi_T t}(1-\kappa)-e^{\psi_T t}(2-\kappa)+\kappa e^{(\psi_D+\psi_R)t}}{(\kappa-2)(e^{(\psi_D+\psi_R)t}-e^{\psi_T t})},$$

337
$$\rho_t = \frac{\kappa e^{(\psi_D+\psi_R)t}-2(\kappa-1)e^{2\psi_T t}+(\kappa-2)e^{\psi_T t}}{(\kappa-2)(e^{(\psi_D+\psi_R)t}-e^{\psi_T t})}.$$

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

12

$340 \quad \dfrac{d\rho_t}{dt}$

$$341 \quad = \frac{\left\{\begin{array}{l}\left(\kappa(\psi_D + \psi_R)e^{(\psi_D+\psi_R)t} - 4\psi_T(\kappa-1)e^{2\psi_T t} + (\kappa-2)\psi_T e^{\psi_T t}\right)(\kappa-2)\left(e^{(\psi_D+\psi_R)t} - e^{\psi_T t}\right) \\ -\left(\kappa e^{(\psi_D+\psi_R)t} - 2(\kappa-1)e^{2\psi_T t} + (\kappa-2)e^{\psi_T t}\right)(\kappa-2)\left((\psi_D+\psi_R)e^{(\psi_D+\psi_R)t} - \psi_T e^{\psi_T t}\right)\end{array}\right\}}{\left((\kappa-2)(e^{(\psi_D+\psi_R)t} - e^{\psi_T t})\right)^2}$$

$$342 \quad \frac{d\rho_t}{dt} = \frac{\left\{\begin{array}{l}\left(\kappa(\psi_D + \psi_R)e^{(\psi_D+\psi_R)t} - 4\psi_T(\kappa-1)e^{2\psi_T t} + (\kappa-2)\psi_T e^{\psi_T t}\right)(\kappa-2)\left(e^{(\psi_D+\psi_R)t}\right) \\ -\left(\kappa(\psi_D + \psi_R)e^{(\psi_D+\psi_R)t} - 4\psi_T(\kappa-1)e^{2\psi_T t} + (\kappa-2)\psi_T e^{\psi_T t}\right)(\kappa-2)\left(e^{\psi_T t}\right) \\ -\left(\kappa e^{(\psi_D+\psi_R)t} - 2(\kappa-1)e^{2\psi_T t} + (\kappa-2)e^{\psi_T t}\right)(\kappa-2)\left((\psi_D+\psi_R)e^{(\psi_D+\psi_R)t}\right) \\ +\left(\kappa e^{(\psi_D+\psi_R)t} - 2(\kappa-1)e^{2\psi_T t} + (\kappa-2)e^{\psi_T t}\right)(\kappa-2)\left(\psi_T e^{\psi_T t}\right)\end{array}\right\}}{\left((\kappa-2)(e^{(\psi_D+\psi_R)t} - e^{\psi_T t})\right)^2},$$

$$343 \quad \frac{d\rho_t}{dt} = \frac{\left\{\begin{array}{l}\left(-4\psi_T(\kappa-1)e^{2\psi_T t} + (\kappa-2)\psi_T e^{\psi_T t}\right)(\kappa-2)\left(e^{(\psi_D+\psi_R)t}\right) \\ -\left(\kappa(\psi_D + \psi_R)e^{(\psi_D+\psi_R)t} - 4\psi_T(\kappa-1)e^{2\psi_T t}\right)(\kappa-2)\left(e^{\psi_T t}\right) \\ -\left(-2(\kappa-1)e^{2\psi_T t} + (\kappa-2)e^{\psi_T t}\right)(\kappa-2)\left((\psi_D+\psi_R)e^{(\psi_D+\psi_R)t}\right) \\ +\left(\kappa e^{(\psi_D+\psi_R)t} - 2(\kappa-1)e^{2\psi_T t} + (\kappa-2)e^{\psi_T t}\right)(\kappa-2)\left(\psi_T e^{\psi_T t}\right)\end{array}\right\}}{\left((\kappa-2)(e^{(\psi_D+\psi_R)t} - e^{\psi_T t})\right)^2},$$

$$344 \quad \frac{d\rho_t}{dt} = \frac{\left\{\begin{array}{l}(\psi_D + \psi_R - 2\psi_T)2(\kappa-1)(\kappa-2)e^{2\psi_T t}\left(e^{(\psi_D+\psi_R)t}\right) \\ -(\psi_D + \psi_R - \psi_T)(\kappa-2)^2 e^{\psi_T t}\left(e^{(\psi_D+\psi_R)t}\right) \\ -(\psi_D + \psi_R - \psi_T)\kappa(\kappa-2)e^{\psi_T t}\left(e^{(\psi_D+\psi_R)t}\right) \\ +2\psi_T(\kappa-1)(\kappa-2)e^{3\psi_T t}\end{array}\right\}}{\left((\kappa-2)(e^{(\psi_D+\psi_R)t} - e^{\psi_T t})\right)^2},$$

$$345 \quad \frac{d\rho_t}{dt} = \frac{\left\{\begin{array}{l}(\psi_D + \psi_R - 2\psi_T)2(\kappa-1)(\kappa-2)e^{2\psi_T t}\left(e^{(\psi_D+\psi_R)t}\right) \\ -(\psi_D + \psi_R - \psi_T)2(\kappa-1)(\kappa-2)e^{\psi_T t}\left(e^{(\psi_D+\psi_R)t}\right) \\ +2\psi_T(\kappa-1)(\kappa-2)e^{3\psi_T t}\end{array}\right\}}{\left((\kappa-2)(e^{(\psi_D+\psi_R)t} - e^{\psi_T t})\right)^2},$$

$$346 \quad \frac{d\rho_t}{dt} = \frac{(\kappa-1)(\kappa-2)\left\{(\kappa-2)e^{(\psi_D+\psi_R+2\psi_T)t} - (\kappa-1)e^{(\psi_D+\psi_R+\psi_T)t} + e^{3\psi_T t}\right\}}{\left(\frac{1}{2\psi_T}\right)\left((\kappa-2)(e^{(\psi_D+\psi_R)t} - e^{\psi_T t})\right)^2},$$

$$347 \quad \frac{d\rho_t}{dt} = \frac{(\kappa-1)(\kappa-2)e^{\psi_T t}\left\{(\kappa-2)e^{(\psi_D+\psi_R+\psi_T)t} - (\kappa-1)e^{(\psi_D+\psi_R)t} + e^{2\psi_T t}\right\}}{\left(\frac{1}{2\psi_T}\right)\left((\kappa-2)(e^{(\psi_D+\psi_R)t} - e^{\psi_T t})\right)^2},$$

$$348 \quad \frac{d\rho_t}{dt} = \frac{(\kappa-1)(\kappa-2)\left\{(\kappa-2)e^{(\kappa+1)\psi_T t} - (\kappa-1)e^{\kappa\psi_T t} + e^{2\psi_T t}\right\}}{\left(\frac{e^{-\psi_T t}}{2\psi_T}\right)\left((\kappa-2)(e^{(\psi_D+\psi_R)t} - e^{\psi_T t})\right)^2}.$$

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

$$351 \quad \text{sign}\left[\frac{d\rho_t}{dt}\right] = \text{sign}\left[(\kappa-1)(\kappa-2)\left\{(\kappa-2)e^{(\kappa+1)\psi_T t} - (\kappa-1)e^{\kappa\psi_T t} + e^{2\psi_T t}\right\}\right].$$

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

$$354 \quad \text{sign}\left[\frac{d\rho_t}{dt}\right] = \text{sign}\left[(\kappa-2)e^{(\kappa+1)\psi_T t} - (\kappa-1)e^{\kappa\psi_T t} + e^{2\psi_T t}\right].$$

13

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

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

357 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

358 $$g'(\kappa) = e^{(\kappa+1)\psi_T t} + (\kappa - 2)\psi_T t e^{(\kappa+1)\psi_T t} - e^{\kappa\psi_T t} - (\kappa - 1)\psi_T t e^{\kappa\psi_T t},$$

359 $$g'(\kappa) = \{1 + (\kappa - 2)\psi_T t\}e^{(\kappa+1)\psi_T t} - \{1 + (\kappa - 1)\psi_T t\}e^{\kappa\psi_T t}.$$

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

361 $$g'(\kappa) = h(1) - h(0).$$

362 But we see that

363 $$h'(x) = -\psi_T t e^{(\kappa+x)\psi_T t} + \{1 + (\kappa - 1 - x)\psi_T t\}\psi_T t e^{(\kappa+x)\psi_T t},$$

364 $$h'(x) = \psi_T t e^{(\kappa+x)\psi_T t}(-1 + \{1 + (\kappa - 1 - x)\psi_T t\}),$$

365 $$h'(x) = \psi_T t e^{(\kappa+x)\psi_T t}(\kappa - 1 - x)\psi_T t.$$

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

368 $$h(1) > h(0).$$

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

370 $$g'(\kappa) > 0.$$

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

372 $$g(\kappa) > 0.$$

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

375 For $1 < \kappa < 2$,

376 $$\text{sign}\left[\frac{d\rho_t}{dt}\right] = \text{sign}\left[-(\kappa - 2)e^{(\kappa+1)\psi_T t} + (\kappa - 1)e^{\kappa\psi_T t} - e^{2\psi_T t}\right].$$

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

378 $$\text{sign}\left[\frac{d\rho_t}{dt}\right] = \text{sign}\left[\varphi e^{(3-\varphi)\psi_T t} + (1 - \varphi)e^{(3-(1+\varphi))\psi_T t} - e^{2\psi_T t}\right].$$

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

380 $$\varphi e^{(3-\varphi)\psi_T t} + (1 - \varphi)e^{(3-(1+\varphi))\psi_T t} - e^{2\psi_T t} > e^{\left(3 - \left(\varphi^2 + (1-\varphi)(1+\varphi)\right)\right)\psi_T t} - e^{2\psi_T t},$$

381 $$\varphi e^{(3-\varphi)\psi_T t} + (1 - \varphi)e^{(3-(1+\varphi))\psi_T t} - e^{2\psi_T t} > e^{\left(3 - (\varphi^2 + 1 - \varphi^2)\right)\psi_T t} - e^{2\psi_T t},$$

382 $$\varphi e^{(3-\varphi)\psi_T t} + (1 - \varphi)e^{(3-(1+\varphi))\psi_T t} - e^{2\psi_T t} > e^{2\psi_T t} - e^{2\psi_T t},$$

383 $$\varphi e^{(3-\varphi)\psi_T t} + (1 - \varphi)e^{(3-(1+\varphi))\psi_T t} - e^{2\psi_T t} > 0.$$

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

386

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

388 $$\text{sign}\left[\frac{d\rho_t}{dt}\right] = \text{sign}\left[(\kappa - 2)e^{(\kappa+1)\psi_T t} - (\kappa - 1)e^{\kappa\psi_T t} + e^{2\psi_T t}\right].$$

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

390 $$\text{sign}\left[\frac{d\rho_t}{dt}\right] = \text{sign}\left[-e^{2\psi_T t} - 0 + e^{2\psi_T t}\right] = 0.$$

391 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

392 $$g'(\kappa) = \{1 + (\kappa - 2)\psi_T t\}e^{(\kappa+1)\psi_T t} - \{1 + (\kappa - 1)\psi_T t\}e^{\kappa\psi_T t}.$$

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

394 $$g'(\kappa) = h(1) - h(0).$$

395 But we see from above that

14

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

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 $\text{sign}\left[\frac{d\rho_t}{dt}\right] = 1$, 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

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

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

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

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

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

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

Using the Taylor expansion

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

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

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 $\kappa = 1$

$$424 \quad \rho_t = \frac{\frac{2\gamma_D D_0 R_0 \left(e^{2\psi_T t} - e^{\psi_T t}\right)}{\psi_T} - \gamma_D D_0 R_0 e^{\psi_T t} t}{\gamma_D D_0 R_0 e^{\psi_T t} t},$$

$$425 \quad \rho_t = \frac{2e^{2\psi_T t} - (2 + \psi_T t)e^{\psi_T t}}{\psi_T t e^{\psi_T t}},$$

$$426 \quad \rho_t = \frac{2e^{\psi_T t} - (2 + \psi_T t)}{\psi_T t}.$$

427   Using the Taylor expansion

$$428 \quad \rho_t = \frac{2\left(1 + \psi_T t + \frac{(\psi_T t)^2}{2!} + \frac{(\psi_T t)^3}{3!} + \frac{(\psi_T t)^4}{4!} \cdots\right) - (2 + \psi_T t)}{\psi_T t},$$

$$429 \quad \rho_t = \frac{\psi_T t + 2\left(\frac{(\psi_T t)^2}{2!} + \frac{(\psi_T t)^3}{3!} + \frac{(\psi_T t)^4}{4!} \cdots\right)}{\psi_T t},$$

$$430 \quad \rho_t = 1 + 2\left(\frac{\psi_T t}{2!} + \frac{(\psi_T t)^2}{3!} + \frac{(\psi_T t)^3}{4!} \cdots\right).$$

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

432

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

435

436   **Appendix VII : Derivations for estimate variance**
437   In this appendix, we provide details for the derivation of the variance expressions for the
438   LDM and ASM estimates. Starting with the ASM estimate:

$$439 \quad \gamma_D = \frac{\psi_D + \psi_R - \psi_T}{D_0 R_0 \left(e^{(\psi_D + \psi_R)\tilde{t}} - e^{\psi_T \tilde{t}}\right)} T_{\tilde{t}},$$

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

$$441 \quad \Gamma_{ASM} = c_1 T_{\tilde{t}},$$

442   where the constant c_1 is

$$443 \quad c_1 = \frac{\psi_D + \psi_R - \psi_T}{D_0 R_0 \left(e^{(\psi_D + \psi_R)\tilde{t}} - e^{\psi_T \tilde{t}}\right)}.$$

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

$$445 \quad \text{var}(\Gamma_{ASM}) = c_1^2 \{\text{var}(T_{\tilde{t}})\}.$$

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

$$447 \quad \text{var}(\Gamma_{ASM}) = \left(\frac{\psi_D + \psi_R - \psi_T}{D_0 R_0 \left(e^{(\psi_D + \psi_R)\tilde{t}} - e^{\psi_T \tilde{t}}\right)}\right)^2 \gamma_D D_0 R_0 \left\{\frac{(\psi_D + \psi_R)e^{(\psi_D + \psi_R)\tilde{t}}}{(\psi_D + \psi_R - \psi_T)(\psi_D + \psi_R - 2\psi_T)} + \frac{e^{\psi_T \tilde{t}}}{\psi_D + \psi_R - \psi_T} - \right.$$

$$448 \quad \left. \frac{2e^{2\psi_T \tilde{t}}}{\psi_D + \psi_R - 2\psi_T}\right\},$$

449

$$450 \quad \text{var}(\Gamma_{ASM})$$

$$451 \quad = \frac{\gamma_D}{D_0 R_0}\left(\frac{\psi_D + \psi_R - \psi_T}{e^{(\psi_D + \psi_R)\tilde{t}} - e^{\psi_T \tilde{t}}}\right)^2 \left\{\frac{(\psi_D + \psi_R)e^{(\psi_D + \psi_R)\tilde{t}} + (\psi_D + \psi_R - 2\psi_T)e^{\psi_T \tilde{t}} - (\psi_D + \psi_R - \psi_T)2e^{2\psi_T \tilde{t}}}{(\psi_D + \psi_R - \psi_T)(\psi_D + \psi_R - 2\psi_T)}\right\}$$

452

$$453 \quad \text{var}(\Gamma_{ASM}) = \frac{\gamma_D(\psi_D + \psi_R - \psi_T)}{D_0 R_0}\left\{\frac{(\psi_D + \psi_R)e^{(\psi_D + \psi_R)\tilde{t}} + (\psi_D + \psi_R - 2\psi_T)e^{\psi_T \tilde{t}} - (\psi_D + \psi_R - \psi_T)2e^{2\psi_T \tilde{t}}}{(\psi_D + \psi_R - 2\psi_T)\left(e^{(\psi_D + \psi_R)\tilde{t}} - e^{\psi_T \tilde{t}}\right)^2}\right\}.$$

454

455   The LDM estimate is expressed as follows:

$$456 \qquad \gamma_D = -\ln \hat{p}_0(\tilde{t}) \left(\frac{\psi_D + \psi_R}{D_0 R_0 \left(e^{(\psi_D + \psi_R)\tilde{t}} - 1 \right)} \right).$$

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

$$459 \qquad \hat{p}_0(\tilde{t}) = \frac{w}{W}.$$

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

$$463 \qquad \mathrm{E}[F] = \sum_{w=0}^{W} \binom{W}{w} (p_0)^w (1 - p_0)^{W-w} \left(\frac{w}{W} \right),$$

$$464 \qquad \mathrm{E}[F] = \frac{1}{W} \sum_{w=1}^{W} \frac{W!}{w!\,(W-w)!} (p_0)^w (1 - p_0)^{W-w} w,$$

$$465 \qquad \mathrm{E}[F] = \frac{1}{W} \sum_{w=1}^{W} \frac{W!}{(w-1)!\,(W-w)!} (p_0)^w (1 - p_0)^{W-w},$$

$$466 \qquad \mathrm{E}[F] = p_0 \sum_{w=1}^{W} \frac{(W-1)!}{(w-1)!\,\big((W-1)-(w-1)\big)!} (p_0)^{w-1} (1 - p_0)^{(W-1)-(w-1)}.$$

467 Letting $i = w - 1$, we have

$$468 \qquad \mathrm{E}[F] = p_0 \sum_{i=0}^{W-1} \frac{(W-1)!}{i!\,\big((W-1)-i\big)!} (p_0)^i (1 - p_0)^{(W-1)-i}.$$

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

$$470 \qquad \mathrm{E}[F] = p_0,$$

471 which makes sense.
472
473 The variance of F is

$$474 \qquad \mathrm{var}[F] = \sum_{w=0}^{W} \binom{W}{w} (p_0)^w (1 - p_0)^{W-w} \left(\frac{w}{W} - p_0 \right)^2,$$

$$475 \qquad \mathrm{var}[F] = \sum_{w=0}^{W} \binom{W}{w} (p_0)^w (1 - p_0)^{W-w} \left(\left(\frac{w}{W}\right)^2 - 2p_0 \left(\frac{w}{W}\right) + (p_0)^2 \right),$$

$$476 \qquad \mathrm{var}[F] = \sum_{w=0}^{W} \binom{W}{w} (p_0)^w (1 - p_0)^{W-w} \left(\frac{w}{W}\right)^2 - 2p_0 \sum_{w=0}^{W} \binom{W}{w} (p_0)^w (1 - p_0)^{W-w} \left(\frac{w}{W}\right)$$

$$477 \qquad + (p_0)^2 \sum_{w=0}^{W} \binom{W}{w} (p_0)^w (1 - p_0)^{W-w},$$

$$478 \qquad \mathrm{var}[F] = \left\{ \left(\frac{1}{W^2}\right) \sum_{w=0}^{W} \binom{W}{w} (p_0)^w (1 - p_0)^{W-w} w^2 \right\} - 2p_0 \mathrm{E}[F] + (p_0)^2,$$

$$479 \qquad \mathrm{var}[F] = \left\{ \left(\frac{1}{W^2}\right) \sum_{w=0}^{W} \binom{W}{w} (p_0)^w (1 - p_0)^{W-w} w(w - 1 + 1) \right\} - 2(p_0)^2 + (p_0)^2,$$

480
$$\text{var}[F] = \left\{ \left(\frac{1}{W^2}\right) \sum_{w=2}^{W} \frac{W!}{w!\,(W-w)!} (p_0)^w (1-p_0)^{W-w} w(w-1) \right.$$

481
$$\left. + \left(\frac{1}{W^2}\right) \sum_{w=0}^{W} \binom{W}{w} (p_0)^w (1-p_0)^{W-w} w \right\} - (p_0)^2,$$

482
$$\text{var}[F] = \left\{ \left(\frac{1}{W^2}\right) \sum_{w=2}^{W} \frac{W!}{(w-2)!\,(W-w)!} (p_0)^w (1-p_0)^{W-w} \right.$$

483
$$\left. + \left(\frac{1}{W}\right) \sum_{w=0}^{W} \binom{W}{w} (p_0)^w (1-p_0)^{W-w} \left(\frac{w}{W}\right) \right\} - (p_0)^2,$$

484
$$\text{var}[F] = \left(\frac{W(W-1)(p_0)^2}{W^2}\right) \left\{ \sum_{w=2}^{W} \frac{(W-2)!}{(w-2)!\,((W-2)-(w-2))!} (p_0)^{w-2} (1 \right.$$

485
$$\left. - p_0)^{(W-2)-(w-2)} \right\} + \frac{p_0}{W} - (p_0)^2.$$

486
Letting $j = w - 2$, we have

487
$$\text{var}[F] = \left(\frac{(W-1)(p_0)^2}{W}\right) \left\{ \sum_{j=0}^{W-2} \binom{W-2}{j} (p_0)^j (1-p_0)^{(W-2)-j} \right\} + \frac{p_0}{W} - (p_0)^2,$$

488
$$\text{var}[F] = \left(\frac{(W-1)(p_0)^2}{W}\right) + \frac{p_0}{W} - (p_0)^2,$$

489
$$\text{var}[F] = \frac{(W-1)(p_0)^2 + p_0 - W(p_0)^2}{W},$$

490
$$\text{var}[F] = \frac{-(p_0)^2 + p_0}{W},$$

491
$$\text{var}[F] = \frac{p_0(1-p_0)}{W}.$$

492

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

494
$$\Gamma_{\text{LDM}} = c_2 \ln F,$$

495 where the constant c_2 is

496
$$c_2 = -\left(\frac{\psi_D + \psi_R}{D_0 R_0 \left(e^{(\psi_D + \psi_R)\tilde{t}} - 1\right)}\right).$$

497

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

499
$$\text{var}(\Gamma_{\text{LDM}}) = c_2{}^2 \{\text{var}(\ln F)\}.$$

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

501
$$\ln F \approx \ln(\text{E}[F]) + \frac{1}{\text{E}[F]} (F - \text{E}[F]),$$

502
$$\ln F \approx \frac{F}{\text{E}[F]} + \ln(\text{E}[F]) - 1.$$

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

504
$$\text{var}[\ln F] \approx \text{var}\left\{\frac{F}{\text{E}[F]}\right\},$$

505
$$\text{var}[\ln F] \approx \left(\frac{1}{\text{E}[F]}\right)^2 \text{var}[F],$$

506
$$\text{var}[\ln F] \approx \left(\frac{1}{p_0}\right)^2 \left(\frac{p_0(1-p_0)}{W}\right),$$

507
$$\text{var}[\ln F] \approx \frac{1}{W}\left(\frac{1}{p_0} - 1\right).$$

508
509   The following is the expression for $p_0(\tilde{t})$:

510
$$p_0(\tilde{t}) = \exp\left\{\frac{-\gamma_D D_0 R_0}{\psi_D + \psi_R}\left(e^{(\psi_D + \psi_R)\tilde{t}} - 1\right)\right\}.$$

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

512
$$\text{var}[\ln F_{\tilde{t}}] \approx \frac{1}{W}\left(\exp\left\{\frac{\gamma_D D_0 R_0}{\psi_D + \psi_R}\left(e^{(\psi_D + \psi_R)\tilde{t}} - 1\right)\right\} - 1\right).$$

513   And therefore the variance for the LDM estimate is

514
$$\text{var}(\Gamma_{\text{LDM}}) \approx \frac{1}{W}\left(\frac{\psi_D + \psi_R}{D_0 R_0\left(e^{(\psi_D + \psi_R)\tilde{t}} - 1\right)}\right)^2 \left(\exp\left\{\frac{\gamma_D D_0 R_0}{\psi_D + \psi_R}\left(e^{(\psi_D + \psi_R)\tilde{t}} - 1\right)\right\} - 1\right).$$

515
516   This can be written more compactly as

517
$$\text{var}(\Gamma_{\text{LDM}}) \approx \frac{\xi_{\tilde{t}}^2}{W}\left(e^{\left(\frac{\gamma_D}{\xi_{\tilde{t}}}\right)} - 1\right),$$

518   with

519
$$\xi_{\tilde{t}} = \frac{\psi_D + \psi_R}{D_0 R_0\left(e^{(\psi_D + \psi_R)\tilde{t}} - 1\right)}.$$

520
521   To show mathematically that the LDM estimate is more precise for short times, we will
522   approximate the expressions for the variance when $\tilde{t}$ is very small. This enables us to
523   use a first-order Maclaurin approximation $e^{c\tilde{t}} \approx 1 + c\tilde{t}$.   This allows the following
524   approximation of the variance for the ASM estimate:

525
526     $\text{var}(\Gamma_{\text{ASM}})$
527
$$\approx \frac{\gamma_D(\psi_D + \psi_R - \psi_T)}{D_0 R_0}\left\{\frac{(\psi_D + \psi_R)(1 + (\psi_D + \psi_R)\tilde{t}) + (\psi_D + \psi_R - 2\psi_T)(1 + \psi_T\tilde{t}) - 2(\psi_D + \psi_R - \psi_T)(1 + 2\psi_T\tilde{t})}{(\psi_D + \psi_R - 2\psi_T)((\psi_D + \psi_R)\tilde{t} - \psi_T\tilde{t})^2}\right\}.$$

528
529   We can then simplify this expression:

530
$$\text{var}(\Gamma_{\text{ASM}}) \approx \frac{\gamma_D(\psi_D + \psi_R - \psi_T)}{D_0 R_0}\left\{\frac{(\psi_D + \psi_R)(\psi_D + \psi_R)\tilde{t} + (\psi_D + \psi_R - 2\psi_T)\psi_T\tilde{t} - 2(\psi_D + \psi_R - \psi_T)2\psi_T\tilde{t}}{(\psi_D + \psi_R - 2\psi_T)(\psi_D + \psi_R - \psi_T)^2\tilde{t}^2}\right\},$$

531
532
$$\text{var}(\Gamma_{\text{ASM}}) \approx \frac{\gamma_D}{D_0 R_0 \tilde{t}}\left\{\frac{(\psi_D + \psi_R)(\psi_D + \psi_R) + (\psi_D + \psi_R - 2\psi_T)\psi_T - 2(\psi_D + \psi_R - \psi_T)2\psi_T}{(\psi_D + \psi_R - 2\psi_T)(\psi_D + \psi_R - \psi_T)}\right\},$$

533
534     $\text{var}(\Gamma_{\text{ASM}})$
535
$$\approx \frac{\gamma_D}{D_0 R_0 \tilde{t}}\left\{\frac{(\psi_D + \psi_R - 2\psi_T)(\psi_D + \psi_R) + 2\psi_T(\psi_D + \psi_R) + (\psi_D + \psi_R - 2\psi_T)\psi_T - 2(\psi_D + \psi_R - \psi_T)2\psi_T}{(\psi_D + \psi_R - 2\psi_T)(\psi_D + \psi_R - \psi_T)}\right\},$$

536
537     $\text{var}(\Gamma_{\text{ASM}})$
538
$$\approx \frac{\gamma_D}{D_0 R_0 \tilde{t}}\left\{\frac{(\psi_D + \psi_R - 2\psi_T)(\psi_D + \psi_R) + 2\psi_T\psi_D + 2\psi_T\psi_R + \psi_T\psi_D + \psi_T\psi_R - 2\psi_T^2 - 4\psi_T\psi_D - 4\psi_T\psi_R + 4\psi_T^2}{(\psi_D + \psi_R - 2\psi_T)(\psi_D + \psi_R - \psi_T)}\right\},$$

539
540
$$\text{var}(\Gamma_{\text{ASM}}) \approx \frac{\gamma_D}{D_0 R_0 \tilde{t}}\left\{\frac{(\psi_D + \psi_R - 2\psi_T)(\psi_D + \psi_R) - \psi_T\psi_D - \psi_T\psi_R + 2\psi_T^2}{(\psi_D + \psi_R - 2\psi_T)(\psi_D + \psi_R - \psi_T)}\right\},$$

541

19

542
$$\text{var}(\Gamma_{\text{ASM}}) \approx \frac{\gamma_D}{D_0 R_0 \tilde{t}} \left\{ \frac{(\psi_D + \psi_R - 2\psi_T)(\psi_D + \psi_R) - (\psi_D + \psi_R - 2\psi_T)\psi_T}{(\psi_D + \psi_R - 2\psi_T)(\psi_D + \psi_R - \psi_T)} \right\},$$

543
$$\text{var}(\Gamma_{\text{ASM}}) \approx \frac{\gamma_D}{D_0 R_0 \tilde{t}} \left\{ \frac{(\psi_D + \psi_R - 2\psi_T)(\psi_D + \psi_R - \psi_T)}{(\psi_D + \psi_R - 2\psi_T)(\psi_D + \psi_R - \psi_T)} \right\},$$

544
$$\text{var}(\Gamma_{\text{ASM}}) \approx \frac{\gamma_D}{D_0 R_0 \tilde{t}}.$$

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

547
$$\xi_{\tilde{t}} \approx \frac{\psi_D + \psi_R}{D_0 R_0 (1 + (\psi_D + \psi_R)\tilde{t} - 1)},$$

548
$$\xi_{\tilde{t}} \approx \frac{1}{D_0 R_0 \tilde{t}}.$$

549 Thus, we have

550
$$\text{var}(\Gamma_{\text{LDM}}) \approx \frac{\left(\frac{1}{D_0 R_0 \tilde{t}}\right)^2}{W} \left(e^{(\gamma_D D_0 R_0 \tilde{t})} - 1\right).$$

551 Using the Maclaurin approximation again yields

552
$$\text{var}(\Gamma_{\text{LDM}}) \approx \frac{\left(\frac{1}{D_0 R_0 \tilde{t}}\right)^2}{W} (1 + \gamma_D D_0 R_0 \tilde{t} - 1),$$

553
$$\text{var}(\Gamma_{\text{LDM}}) \approx \frac{\gamma_D}{W D_0 R_0 \tilde{t}}.$$

554 Our LDM assay requires $W > 1$. Therefore when $\tilde{t}$ is very small
555
$$\text{var}(\Gamma_{\text{LDM}}) < \text{var}(\Gamma_{\text{ASM}}).$$

556 Again, we note the caveat that our estimate for the variance of the LDM estimate was
557 already an approximation.
558

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