Genetic paths to evolutionary rescue and the distribution of fitness effects along them

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Dependencies

Directories

```
SetDirectory[NotebookDirectory[]];
(*sets current directory to be location of this file*)
datadir = "data/";(*directory with simulation data*)
figdir = "../main/";(*directory to save figures in*)
supfigdir = "../supplementary/";(*directory to save supplementary figures in*)
```

Plot styles

```
labelstyle = Directive[12, FontFamily → "Helvetica"];
defaultcolors = ColorData[1, "ColorList"];
braceLabel[{p1_, p2_}, lbl_, scale_: .02] :=
 {Arrowheads[{{scale, 0, {Graphics@Circle[{1, -1}, 1, {Pi / 2, Pi}], -1}}, {scale, 1,
     {Graphics[{Circle[{-1, 1}, 1, {-Pi / 2, 0}], Inset[lbl, {0, 2}]}], 1}}}],
  Arrow[{p1, (p1 + p2) / 2}], Arrowheads[
   {{scale, 0, {Graphics@Circle[{1, 1}, 1, {Pi, 3 Pi / 2}], -1}}, {scale, 1,
     {Graphics@Circle[{-1, -1}, 1, {0, Pi / 2}], 1}}}], Arrow[{(p1 + p2) / 2, p2}]}
```

Functions (derived below)

```
fs[s_, so_, λ_, n_] :=
 2/λ PDF[NoncentralChiSquareDistribution[n, 2 so/λ], 2/λ (so - s)] HeavisideTheta[so - s]
fm[m_, mwt_, mmax_, λ_, n_] :=
 Simplify[fs[s, so, λ, n] /. s → m - mwt /. so → mmax - mwt, {mmax > m, λ > 0}]

prescue = 1 - (1 - p0)^N0;
```

```
prescueApp = 1 - e^(-N0 p0);

pest[m_] := (1 - Exp[-2 m]) HeavisideTheta[m]

prescuem[m_, Λ_] := 1 - e^((1 - Sqrt[1 + 2 Λ/Abs[m]^2]) Abs[m])

Λ1[m0_?NumericQ, mmax_, λ_, n_, U_] :=
 U NIntegrate[fm[m, m0, mmax, λ, n] pest[m], {m, 0, mmax}]
PR1[m0_?NumericQ] := prescue /. p0 → prescuem[m0, Λ1[m0, mmax, λ, n, U]]
PR1App[m0_?NumericQ] := prescueApp /. p0 → prescuem[m0, Λ1[m0, mmax, λ, n, U]]
```

$$f\psi = \frac{e^{-\frac{1}{4}\rho max\,(\psi-\psi wt)^2}\sqrt{\rho max}\left(\frac{2-\psi}{2-\psi wt}\right)^{-\frac{1}{2}+\theta}}{2\sqrt{\pi}};$$

$$AnciauxEqnA12 = U\,\frac{\left(1-\frac{\psi wt}{2}\right)^{\frac{1}{2}-\theta}}{1-\frac{\psi wt}{4}}\left(\frac{Exp[-\alpha]}{\sqrt{\pi\,\alpha}} - Erfc\left[\sqrt{\alpha}\right]\right);$$

```
Λ2[m0_?NumericQ, mmax_, λ_, n_, U_] := U NIntegrate[
   fm[m, m0, mmax, λ, n] (1 - pest[m]) prescuem[m, Λ1[m, mmax, λ, n, U]], {m, -∞, mmax}]
```

$$\Lambda 0approx = \frac{2\,U\sqrt{mmax\,\lambda}}{\sqrt{\pi}};$$

$$small\psi approxRescue = -\left(e^{-\frac{mmax\left(1-\sqrt{1-\frac{mwt}{mmax}}\right)^2}{\lambda}}\left(1-\frac{mwt}{mmax}\right)^{\frac{1-n}{2}} U\,Log\left[\frac{1-\sqrt{1+\frac{\sqrt{U\sqrt{mmax\,\lambda}}}{mmax\,\pi^{1/4}}}}{1-\sqrt{1-\frac{mwt}{mmax}}}\right]\right)\Big/$$

$$\left(\left(1+\frac{1}{2}\left(-1+\sqrt{1-\frac{mwt}{mmax}}\right)\right)\pi\right);$$

$$verylarge\rho approxRescue = -\left(2\,e^{-\frac{mmax\left(1-\sqrt{1-\frac{mwt}{mmax}}\right)^2}{2\lambda}}\left(1-\frac{mwt}{mmax}\right)^{\frac{1-n}{2}}\sqrt{\frac{2}{\pi}}\;U\right)\Big/$$

$$\left(\left(1-\sqrt{1-\frac{mwt}{mmax}}\right)^3\left(1+\frac{1}{2}\left(-1+\sqrt{1-\frac{mwt}{mmax}}\right)\right)\left(\frac{mmax}{\lambda}\right)^{3/2}\right);$$

$$\text{small}\psi\text{approxRescueSuper} = \left(e^{-\frac{\text{mmax}\left(1-\sqrt{1-\frac{\text{mwt}}{\text{mmax}}}\right)^2}{\lambda}} \left(1-\frac{\text{mwt}}{\text{mmax}}\right)^{\frac{1-n}{2}} U \right.$$

$$\left. \text{Log}\left[\frac{1}{\sqrt{2}\sqrt{\frac{\text{mmax}}{\lambda}}\left(1-\sqrt{1-\frac{\sqrt{U\sqrt{\text{mmax}\,\lambda}}}{\text{mmax}\,\pi^{1/4}}}\right)}\right]\right) \Big/ \left(\left(1+\frac{1}{2}\left(-1+\sqrt{1-\frac{\text{mwt}}{\text{mmax}}}\right)\right)\pi\right);$$

$$\text{g1m} = \frac{U\,\text{fm}[m, \text{mwt}, \text{mmax}, \lambda, n]\,\text{pest}[m]}{\Lambda 1[\text{mwt}, \text{mmax}, \lambda, n, U]};$$

$$\text{g1mApp} = \frac{e^{\alpha-\frac{1}{4}\rho\text{max}\,(\psi-\psi\text{wt})^2}\sqrt{\alpha\,\rho\text{max}}\;\psi}{\sqrt{1-\frac{m}{\text{mmax}}}\;\text{mmax}\,\psi\text{wt}\left(-1+e^{\alpha}\sqrt{\pi}\sqrt{\alpha}\;\text{Erfc}\left[\sqrt{\alpha}\right]\right)};$$

```
g2numerator[m0_, m2_?NumericQ] := U NIntegrate[fm[m, m0, mmax, λ, n]
      (1 - pest[m]) prescuem[m, U fm[m2, m, mmax, λ, n] pest[m2]], {m, -∞, mmax}];
g2denominator[m0_?NumericQ] := NIntegrate[U fm[m, m0, mmax, λ, n] (1 - pest[m])
     prescuem[m, U fm[m2, m, mmax, λ, n] pest[m2]], {m, -∞, mmax}, {m2, 0, mmax}];
```

Example simulations

1-step rescue (figure 1)

Population size dynamics (panel A)

Total population size for many replicates

```
n0 = "10000";
n = "4";
U = "0.000100";
Es = "0.01000";
mmax = "0.50";
mwt = "-0.10";
mutmax = "2";
nreps = 100;

data = Table[
    Import[datadir <> "alleles_N" <> n0 <> "_n" <>
        n <> "_U" <> U <> "_Es" <> Es <> "_mmax" <> mmax <> "_mwt" <> mwt <>
        "_mutmax" <> mutmax <> "_rep" <> ToString[rep] <> ".csv"][[All, 1]],
    {rep, 1, nreps}
   ];

rescued = Select[data, #[[-1]] > 1000 &];
extinct = Select[data, #[[-1]] < 1000 &];

genmax = 500;
nmax = n0;

fig1a = Show[
  ListLogPlot[
   extinct,
   Joined → True,
   PlotRange → {{0, genmax}, {1, nmax}},
   Frame → {True, True, False, False},
   FrameLabel → {"", "Number of individuals"},
   PlotStyle → Gray, LabelStyle → labelstyle,
   FrameTicksStyle → {FontColor → White, Automatic, Automatic, Automatic},
   Epilog →
    Text[Style["A", 14, Bold, FontFamily → "Helvetica"], Scaled@{0.05, 0.95}]
  ],
  ListLogPlot[
   rescued,
   Joined → True,
   PlotStyle → Thickness[0.005]
  ],
  PlotRange → {{0, genmax}, Log@{2, 10^4}}
 ]

Clear[n0, n, U, Es, mmax, mwt, r, mutmax, nreps, genmax, nmax]
```

Mutation dynamics (panel B)

example of allele dynamics for one rescued replicate

```
n0 = "10000";
n = "4";
U = "0.000100";
Es = "0.01000";
mmax = "0.50";
mwt = "-0.10";
mutmax = "2";
rep = "83";

genmax = 500;
nmax = 1000;

Import[datadir <> "alleles_N" <> n0 <> "_n" <> n <> "_U" <> U <> "_Es" <> Es <> "_mmax" <>
   mmax <> "_mwt" <> mwt <> "_mutmax" <> mutmax <> "_rep" <> rep <> ".csv"];
alleles = Transpose[PadRight[%]];

Import[datadir <> "kmuts_N" <> n0 <> "_n" <> n <> "_U" <> U <> "_Es" <> Es <> "_mmax" <>
   mmax <> "_mwt" <> mwt <> "_mutmax" <> mutmax <> "_rep" <> rep <> ".csv"];
allmuts = Transpose[PadRight[%]];

rescuemut = Ordering[alleles[[2 ;;]][[All, -1]], -1];

fig1b = Show[
  ListLogPlot[
   alleles[[2 ;;]][[rescuemut]],
   Joined → True,
   PlotRange → {{0, genmax}, {1, 10^4}},
   Frame → {True, True, False, False},
   FrameLabel → {"Generation", "Number of copies of allele"},
   LabelStyle → labelstyle,
   Epilog →
    Text[Style["B", 14, Bold, FontFamily → "Helvetica"], Scaled@{0.05, 0.95}],
   PlotStyle → Directive[Thickness[0.005], defaultcolors[[3]]]
  ],
  ListLogPlot[
   Drop[alleles[[2 ;;]], rescuemut],
   Joined → True,
   PlotStyle → Directive[Thickness[0.002], Black]
  ],
  ListLogPlot[
   allmuts[[1]],
   Joined → True,
   PlotStyle → {Gray, Thickness[0.005]}
  ]
 ]

Clear[n0, n, U, Es, mmax, mwt, r, mutmax, rep, genmax, nmax]
```

Figure 1

```
GraphicsColumn[{fig1a, fig1b}, Spacings → -30, ImageSize → 350]
Export[figdir <> "Figure1.eps", %];
```

2-step rescue (figure 2)

Population size dynamics (panel A)

```
n0 = "10000";
n = "4";
U = "0.010000";
Es = "0.01000";
mmax = "0.50";
mwt = "-0.30";
mutmax = "2";
intrep = 500;
endrep = 1000;
nrescued = 1000;

data = Table[
    Import[datadir <> "alleles_N" <> n0 <> "_n" <>
        n <> "_U" <> U <> "_Es" <> Es <> "_mmax" <> mmax <> "_mwt" <> mwt <>
        "_mutmax" <> mutmax <> "_rep" <> ToString[rep] <> ".csv"][[All, 1]],
    {rep, intrep, endrep}
   ];

rescued = Select[data, #[[-1]] > 1000 &];
extinct = Select[data, #[[-1]] < 1000 &];

genmax = 150;
nmax = n0;

fig2a = Show[
   ListLogPlot[
    extinct,
    Joined → True,
    PlotRange → {{0, genmax}, {1, nmax}},
    Frame → {True, True, False, False},
    FrameLabel → {"", "Number of individuals"},
    PlotStyle → Gray,
    LabelStyle → labelstyle,
    FrameTicksStyle → {FontColor → White, Automatic, Automatic, Automatic},
    Epilog →
     Text[Style["A", 14, Bold, FontFamily → "Helvetica"], Scaled@{0.05, 0.95}]],
   ListLogPlot[rescued, Joined → True, PlotStyle → Thickness[0.005]
   ],
   PlotRange → {{0, genmax}, Log@{2, 10^4}}
  ]

Clear[n0, n, U, Es, mmax, mwt, r, mutmax, nreps, genmax, nmax, nrescued]
```

A
Number of individuals
10^4
1000
100
10

Mutation dynamics (panel B)

```
n0 = "10000";
n = "4";
U = "0.010000";
Es = "0.01000";
mmax = "0.50";
mwt = "-0.30";
mutmax = "2";
rep = "675";

genmax = 150;
nmax = 1000;
ymax = 10^4;

Import[datadir <> "alleles_N" <> n0 <> "_n" <> n <> "_U" <> U <> "_Es" <> Es <> "_mmax" <>
   mmax <> "_mwt" <> mwt <> "_mutmax" <> mutmax <> "_rep" <> rep <> ".csv"];
alleles = Transpose[PadRight[%]];

Import[datadir <> "kmuts_N" <> n0 <> "_n" <> n <> "_U" <> U <> "_Es" <> Es <> "_mmax" <>
   mmax <> "_mwt" <> mwt <> "_mutmax" <> mutmax <> "_rep" <> rep <> ".csv"];
allmuts = Transpose[PadRight[%]];

rescuemuts = Ordering[alleles[[2 ;;]][[All, -1]], -2];

fig2b = Show[
  ListLogPlot[Drop[alleles[[2 ;;]], {rescuemuts[[1]]}, {rescuemuts[[2]]}],
   Joined → True, PlotStyle → Directive[Black, Thickness[0.002]],
   PlotRange → {{0, genmax}, {1, ymax}},
   Frame → {True, True, False, False},
   FrameLabel → {"Generation", "Number of copies of allele"},
   LabelStyle → labelstyle,
   Epilog →
    Text[Style["B", 14, Bold, FontFamily → "Helvetica"], Scaled@{0.05, 0.95}]
  ],
  ListLogPlot[
   alleles[[2 ;;]][[rescuemuts]],
   Joined → True,
   PlotStyle → {Directive[Thickness[0.005], defaultcolors[[2]], Dashing[Medium]],
     Directive[Thickness[0.005], defaultcolors[[2]]]}
  ],
  ListLogPlot[allmuts[[1]], Joined → True, PlotStyle → {Gray, Thickness[0.005]}]
 ]

Clear[n0, n, U, Es, mmax, mwt, r, mutmax, rep, genmax, nmax, ymax]
```

Note that the first mutation is subcritical, but the second mutation makes the double mutant supercritical (we can see this because we keep track of what is supercritical in the sims):

```
n0 = "10000";
n = "4";
U = "0.010000";
Es = "0.01000";
mmax = "0.50";
mwt = "-0.30";
mutmax = "2";
rep = "675";

genmax = 150;
nmax = 1000;
ymax = 10^4;

Import[datadir <> "supercrit_kmuts_N" <> n0 <> "_n" <> n <> "_U" <> U <> "_Es" <> Es <>
   "_mmax" <> mmax <> "_mwt" <> mwt <> "_mutmax" <> mutmax <> "_rep" <> rep <> ".csv"];
supermuts = Transpose[PadRight[%]];

ListLogPlot[supermuts, Joined → True,
 PlotRange → {{0, genmax}, {0, nmax}}, Frame → {True, True, False, False},
 FrameLabel → {"Generation", "Number of copies of allele"},
 LabelStyle → labelstyle]

Clear[n0, n, U, Es, mmax, mwt, r, mutmax, rep, genmax, nmax, ymax]
```

The blue replicate is also 2-step rescue

```
n0 = "10000";
n = "4";
U = "0.010000";
Es = "0.01000";
mmax = "0.50";
mwt = "-0.30";
mutmax = "2";
rep = "629";

genmax = 150;
nmax = 1000;
ymax = 10^4;

Import[datadir <> "alleles_N" <> n0 <> "_n" <> n <> "_U" <> U <> "_Es" <> Es <> "_mmax" <>
   mmax <> "_mwt" <> mwt <> "_mutmax" <> mutmax <> "_rep" <> rep <> ".csv"];
alleles = Transpose[PadRight[%]];

Import[datadir <> "kmuts_N" <> n0 <> "_n" <> n <> "_U" <> U <> "_Es" <> Es <> "_mmax" <>
   mmax <> "_mwt" <> mwt <> "_mutmax" <> mutmax <> "_rep" <> rep <> ".csv"];
allmuts = Transpose[PadRight[%]];

Show[
 ListLogPlot[alleles[[2 ;;]], Joined → True,
  PlotRange → {{0, genmax}, {1, ymax}}, Frame → {True, True, False, False},
  FrameLabel → {"Generation", "Number of copies of allele"}, LabelStyle →
   labelstyle, (*Epilog→Text[Style["B",14,Bold],Scaled@{0.05,0.95}],*)
  PlotStyle → Thickness[0.005]
 ],
 ListLogPlot[allmuts[[1]], Joined → True, PlotStyle → {Gray, Thickness[0.005]}]
]

Import[datadir <> "supercrit_kmuts_N" <> n0 <> "_n" <> n <> "_U" <> U <> "_Es" <> Es <>
   "_mmax" <> mmax <> "_mwt" <> mwt <> "_mutmax" <> mutmax <> "_rep" <> rep <> ".csv"];
supermuts = Transpose[PadRight[%]];

ListLogPlot[supermuts, Joined → True,
 PlotRange → {{0, genmax}, {0, nmax}}, Frame → {True, True, False, False},
 FrameLabel → {"Generation", "Number of copies of allele"},
 LabelStyle → labelstyle]

Clear[n0, n, U, Es, mmax, mwt, r, mutmax, rep, genmax, nmax, ymax]
```

but the yellow replicate is 1-step

```
n0 = "10000";
n = "4";
U = "0.010000";
Es = "0.01000";
mmax = "0.50";
mwt = "-0.30";
mutmax = "2";
rep = "752";

genmax = 150;
nmax = 1000;
ymax = 10^4;

Import[datadir <> "alleles_N" <> n0 <> "_n" <> n <> "_U" <> U <> "_Es" <> Es <> "_mmax" <>
   mmax <> "_mwt" <> mwt <> "_mutmax" <> mutmax <> "_rep" <> rep <> ".csv"];
alleles = Transpose[PadRight[%]];

Import[datadir <> "kmuts_N" <> n0 <> "_n" <> n <> "_U" <> U <> "_Es" <> Es <> "_mmax" <>
   mmax <> "_mwt" <> mwt <> "_mutmax" <> mutmax <> "_rep" <> rep <> ".csv"];
allmuts = Transpose[PadRight[%]];

Show[
 ListLogPlot[alleles[[2 ;;]], Joined → True,
  PlotRange → {{0, genmax}, {1, ymax}}, Frame → {True, True, False, False},
  FrameLabel → {"Generation", "Number of copies of allele"}, LabelStyle →
   labelstyle, (*Epilog→Text[Style["B",14,Bold],Scaled@{0.05,0.95}],*)
  PlotStyle → Thickness[0.005]
 ],
 ListLogPlot[allmuts[[1]], Joined → True, PlotStyle → {Gray, Thickness[0.005]}]
]

Import[datadir <> "supercrit_kmuts_N" <> n0 <> "_n" <> n <> "_U" <> U <> "_Es" <> Es <>
   "_mmax" <> mmax <> "_mwt" <> mwt <> "_mutmax" <> mutmax <> "_rep" <> rep <> ".csv"];
supermuts = Transpose[PadRight[%]];

ListLogPlot[supermuts, Joined → True,
 PlotRange → {{0, genmax}, {0, nmax}}, Frame → {True, True, False, False},
 FrameLabel → {"Generation", "Number of copies of allele"},
 LabelStyle → labelstyle]

Clear[n0, n, U, Es, mmax, mwt, r, mutmax, rep, genmax, nmax, ymax]
```

Number of copies of allele
Generation

Number of copies of allele
Generation

Figure 2

```
GraphicsColumn[{fig2a, fig2b}, Spacings → -30, ImageSize → 350]
Export[figdir <> "Figure2.eps", %];
```

Background

Distribution of mutant growth rates (equation 1)

In FGM, the PDF of selective effects of new mutations, s = $m - m_{wt}$, is (Martin & Lenormand 2015 Evolution)

```
fs[s_, so_, λ_, n_] :=
  2/λ PDF[NoncentralChiSquareDistribution[n, 2 so/λ], 2/λ (so - s)] HeavisideTheta[so - s];
```

where so = $m_{max} - m_{wt}$ is the selection coefficient of the optimum phenotype, λ is the mutational variance per trait, and n is the number of traits under selection.

We can translate this into the PDF of mutant growth rates (see also Anciaux et al 2018 Genetics)

```
fm[m_, mwt_, mmax_, λ_, n_] :=
 Simplify[fs[s, so, λ, n] /. s → m - mwt /. so → mmax - mwt, {mmax > m, λ > 0}]
```

Simulate some mutants

```
n = 4; η = n / 2;(*phenotypic dimensions*)
Es = 0.01;(*mean mutational selective efffect*)
λ = 2 Es / n;(*mutational variance, i.e., scaled size*)
uo = 0 UnitVector[n, 1];(*mean mutational size; set to all zeros*)

Idn = IdentityMatrix[n];(*matrix to make variance multidimensional*)
NT = 10^5;(*number of mutants to create*)
dz = RandomReal[MultinormalDistribution[uo, λ Idn], NT];

Clear[λ, n, Es, η, uo, Idn, NT]
```

Calculate selection coefficient given mutant vectors dz and vector to optimum zopt

```
ss[dz_, zopt_] := Table[dz[[i]].zopt - dz[[i]].dz[[i]]/2, {i, 1, Length[dz]}];
```

Check distributions with simulated mutants:

```
n = 4; η = n / 2; (*phenotypic dimensions*)
Es = 0.01; (*mean mutational selective efffect*)
λ = 2 Es / n; (*mutational variance per trait*)

mmax = 0.5; (*max growth rate*)
mwts = {-0.3, -0.2, -0.1}; nmwts = Length[mwts]; (*scaled*)
zis = Table[Sqrt[2 (mmax - mwts[[i]])] UnitVector[n, 1], {i, nmwts}];
(*vector from wildtype from the optimum along trait 1 axis*)

color = {Darker[Blue, 0.7], Lighter[Orange], Red}; (*colors*)
styl = {FontFamily → "Times", FontSize → 10}; (*styles of axes and legend*)

legends = Table[StringForm["m_wt = ``", NumberForm[mwts[[i]], 3]], {i, nmwts}];
simuls = Histogram[Table[mwts[[i]] + ss[dz, zis[[i]]], {i, nmwts}], 500,
  "PDF", ChartStyle → color, PlotRange → {{-2, 0.5}, All}, Axes → False,
  ChartLegends → Placed[legends, {0.2, 0.8}]]; (*simulation results*)

Table[fm[m, mwts[[i]], mmax, λ, n], {i, nmwts}];
theory = Plot[%, {m, -1, 0.5}, PlotRange → {{-0.7, 0.2}, All},
   PlotStyle → color, Frame → {True, True, False, False}, FrameLabel → {"m"}];

Show[{theory, simuls, theory}, LabelStyle → styl, AxesLabel → {, "f(m | m_wt)"}]
(*Export[imagedir<>"fmmwt.pdf",%];*)

Clear[λ, n, η, Es, mmax, mwts, nmwts, zis, color, styl, legends, simuls, theory]
```

Probability of rescue (equations 2 and 3)

Let p0 be the probability a wildtype individual has descendants that rescue the population. If we start with N0 wildtypes the probability of rescue is then

```
prescue = 1 - (1 - p0)^N0;
```

which with small p0 and large N0 is approximately

```
prescueApp = Series[1 - (1 - p0)^N0 /. p0 → p0 ϵ /. N0 → N0 / ϵ, {ϵ, 0, 0}] // Normal
```

$1 - e^{-N0\, p0}$

Let there be X[t,m] individuals in a lineage time t after it arose, given growth rate m. Then the total number of individuals in the lineage is $\int_0^\tau X[t, m]\, dt$, where τ is the time of extinction. The distribution of the random variable Y[m] = $\int_0^\tau X[t, m]\, dt$ is known (see Martin et al 2013 Phil Trans B sup mat); its MGF is

```
MomentGeneratingFunction[InverseGaussianDistribution[Abs[1 / m], 1], z]
```

$e^{\left(1-\sqrt{1-\frac{2 z}{\text{Abs}[m]^2}}\right) \text{Abs}[m]}$

Let an individual with growth rate m produce rescue mutants at rate Λ(m). The probability its lineage rescues the population is then $1 - \mathbb{E}_Y\left[e^{-Y(m)\,\Lambda(m)}\right] = 1 - M_Y[-\Lambda(m)]$ where $M_Y$is the MGF of Y. Thus evaluating our MGF above at $z = -\Lambda(m)$ we have the probability of rescue from a genotype with growth rate m

```
prescuem[m_, Λ_] :=
 1 - MomentGeneratingFunction[InverseGaussianDistribution[Abs[1 / m], 1], -Λ]
```

Probability of establishment (equation 4)

Using the Feller diffusion approximation (see Martin et al 2013 Phil Trans B sup mat for details), the probability a mutant establishes is

```
1 - Exp[-2 r / σ]
```

$1 - e^{-\frac{2 r}{\sigma}}$

where r is the infinitesimal mean and σ is the infinitesimal variance in mutant growth rate.

In our discrete generation Poisson process, r is

```
Expectation[X - 1, X ≈ PoissonDistribution[Exp[m]]]
```

$-1 + e^m$

and σ is

```
Expectation[(X - 1)^2, X ≈ PoissonDistribution[Exp[m]]] -
   Expectation[X - 1, X ≈ PoissonDistribution[Exp[m]]]^2 // Simplify // Simplify
```

e^m

When m is small these are roughly

```
Series[Exp[m] - 1, {m, 0, 1}] // Normal
```

m

and

```
Series[Exp[m], {m, 0, 0}] // Normal
```

1

Then the probability of establishment for m>0 is roughly

```
1 - Exp[-2 r / σ] /. r → m /. σ → 1
```

$1 - e^{-2\,m}$

and this is zero when m<0.

```
pest[m_] := (1 - Exp[-2 m]) HeavisideTheta[m]
```

Note that this reduces to both Haldane's (1927 Mathematical Proceedings of the Cambridge Philosophical Society) constant population size result and Otto & Whitlock's (1997 Genetics) changing population size result when m is small

```
Normal[Series[1 - Exp[-2 m], {m, 0, 1}]] /. m → m_wt + s /. m_wt → 0
```

2 s

```
Normal[Series[1 - Exp[-2 m], {m, 0, 1}]] /. m → m_wt + s
```

$2\,(s + m_{wt})$

Mutant lineage dynamics

Probability generating function

Here we use a continuous time birth (λ) death (μ) process to approximate the dynamics of our discrete time Poisson process (nonoverlapping generations with expected offspring exp(m)). To align these two approaches we need m = λ - μ and, as discussed in Uecker & Hermisson 2016 Genetics and Uecker et al 2014 Am Nat, λ + μ = 1. The latter requirement ensures both processes have the same amount of drift. We follow these studies in equally distributing m between λ and μ, such that λ = (1 + m)/2 and μ = (1 - m)/2. Note that this is only valid for |m|<1.

For a continuous-time birth death process starting from N0 individuals $(F[s, 0] == s^{N0})$ the PGF for the number of individuals at time t can be solved for explicitly

```
fst = DSolve[{D[F[s, t], t] == D[F[s, t], s] (λ s^2 - (λ + μ) s + μ), F[s, 0] == s^N0},
   F[s, t], {s, t}] // Flatten
```

$$\left\{F[s,t] \to \left(\left(e^{\frac{\mu\,(t\,\lambda - t\,\mu + \mathrm{Log}[-1+s] - \mathrm{Log}[s\,\lambda-\mu])}{\lambda-\mu}} - e^{\frac{\lambda\,(t\,\lambda - t\,\mu + \mathrm{Log}[-1+s] - \mathrm{Log}[s\,\lambda-\mu])}{\lambda-\mu}}\,\mu\right) \Big/ \left(e^{\frac{\mu\,(t\,\lambda - t\,\mu + \mathrm{Log}[-1+s] - \mathrm{Log}[s\,\lambda-\mu])}{\lambda-\mu}} - e^{\frac{\lambda\,(t\,\lambda - t\,\mu + \mathrm{Log}[-1+s] - \mathrm{Log}[s\,\lambda-\mu])}{\lambda-\mu}}\,\lambda\right)\right)^{N0}\right\}$$

Probability of persistence

The probability of extinction at time t can be obtained from the PGF

```
pextt = F[s, t] /. fst /. s → 0 // Factor // FullSimplify
```

$$\left(1 + \frac{-\lambda + \mu}{\lambda - e^{t\,(-\lambda+\mu)}\,\mu}\right)^{N0}$$

Evaluating at s=0 as t goes to infinity gives the probabilty the lineage ever goes extinct. When birth rate is greater than death rate, λ>μ ie m>0, we have

```
pextinction = Limit[F[s, t] /. fst /. s → 0, t → ∞, Assumptions → {λ > μ, μ > 0}]
1 - % /. λ → (1 + m)/2 /. μ → (1 - m)/2 /. N0 → 1;
Series[%, {m, 0, 1}]
```

$$\left(\frac{\mu}{\lambda}\right)^{N0}$$

$$2\,m + O[m]^2$$

(giving Haldane's classic 2m approximation for the probability of establishment)

and when death rate is greater than birth rate we have

```
Limit[F[s, t] /. fst /. s → 0, t → ∞, Assumptions → {λ < μ, μ > 0}]
```

1

The probability of persistence to time t is just one minus the probability of extinction by time t

```
probpersist = 1 - pextt
```

$$1 - \left(1 + \frac{-\lambda + \mu}{\lambda - e^{t\,(-\lambda+\mu)}\,\mu}\right)^{N0}$$

Distribution of extinction times (equation 21)

When |m| << 1/t << 1, ie |1/m| >> t >> 1 (that is, at late times but while the mutant is still effectively critical) the probability that a new mutant persists to time t is approximately

```
pestapp1 =
 Normal[Series[probpersist /. λ → (1 + m)/2 /. μ → (1 - m)/2 /. N0 → 1 /. m → m ϵ^2 /. t → t /ϵ,
    {ϵ, 0, 1}]] /. ϵ → 1
```

$$\frac{2}{t}$$

And when -m t >>1, ie -m >> 1/t (that is, when the mutant is effectively subcritical) we have roughly

```
pestapp2 = Simplify[probpersist /. λ → (1 + m)/2 /. μ → (1 - m)/2 /. N0 → 1] /.
   1 + e^(-m t) (-1 + m) + m → e^(-m t) (-1 + m) /. -1 + m → -1
```

$$-2\,e^{m\,t}\,m$$

Visually check the critical (red) and subcritical (green) approximations of the true solution (blue)

```
Show[
 LogPlot[probpersist /. λ → (1 + m)/2 /. μ → (1 - m)/2 /. N0 → 1 /. m → -0.01,
  {t, 0, 1000}, PlotRange → {10^-4, 1}],
 LogPlot[pestapp1 /. m → -0.01, {t, 0, 1000}, PlotRange → All, PlotStyle → Red],
 LogPlot[pestapp2 /. m → -0.01, {t, 0, 1000}, PlotRange → All, PlotStyle → Green]
]
```

Our equations for persistence times line-up with Weissman et al 2010 Genetics eq A2, but with an additional factor of 2 because we have b+d=2 while they have b+d=1. They point out that the distribution of persistence time has a long tail (like 1/t) before falling off exponentially when t > -1 / m (as can be seen in the plot above). Thus we can essentially say that a mutant lineage will not persist past t = -1 / m.

Distribution of lineage sizes

The probability that there is 1 individual at time t is

```
pn1 = D[F[s, t] /. fst, {s, n}] / n! /. n → 1 /. s → 0 /. λ → (1 + m)/2 /. μ → (1 - m)/2 /. N0 → 1 //
  Simplify
```

$$\frac{4\, e^{m t}\, m^2}{\left(-1 + m + e^{m t}\,(1 + m)\right)^2}$$

and two individuals

```
pn2 = D[F[s, t] /. fst, {s, n}] / n! /. n → 2 /. s → 0 /. λ → (1 + m)/2 /. μ → (1 - m)/2 /. N0 → 1 //
  Simplify
```

$$\frac{4\, e^{m t}\,\left(-1 + e^{m t}\right) m^2\,(1 + m)}{\left(-1 + m + e^{m t}\,(1 + m)\right)^3}$$

three

```
D[F[s, t] /. fst, {s, n}] / n! /. n → 3 /. s → 0 /. λ → (1 + m)/2 /. μ → (1 - m)/2 /. N0 → 1 // Simplify
```

$$\frac{4\, e^{m t}\, (-1 + e^{m t})^2\, m^2\, (1 + m)^2}{(-1 + m + e^{m t}\, (1 + m))^4}$$

From this series we can see that we can write the probability of n individuals at time t like

```
pnt = pn1 (pn2 / pn1)^(n-1)
```

$$\frac{4\, e^{m t}\, m^2 \left(\frac{(-1+e^{m t})\,(1+m)}{-1+m+e^{m t}\,(1+m)}\right)^{-1+n}}{(-1 + m + e^{m t}\, (1 + m))^2}$$

Check for n=4:

```
pnt / (D[F[s, t] /. fst, {s, n}] / n!) /. n → 4 /. s → 0 /. λ → (1 + m)/2 /. μ → (1 - m)/2 /. N0 → 1 //
 Simplify
```

1

Distribution of lineage sizes given persistence (equation 22)

Dividing the probability of having n individuals at time t by the probability of survival to time t gives the conditional probability of having n individuals at time t given a mutant lineage lives to time t

```
pntgt = pnt / probpersist /. λ → (1 + m)/2 /. μ → (1 - m)/2 /. N0 → 1 // FullSimplify
```

$$\frac{2\, m \left(1 - \frac{2\, m}{-1+m+e^{m t}\,(1+m)}\right)^n}{(-1 + e^{m t})\,(1 + m)}$$

When t << |1/m| (effectively critical) this is approximately

```
pntgtapp1 = Normal[Series[pntgt /. m → m ϵ, {ϵ, 0, 0}]] /. ϵ → 1 // FullSimplify
Simplify[% == 2 (1/t) (1 + 2/t)^(-n), {t > 0, n > 0}]
```

$2\, t^{-1+n}\, (2 + t)^{-n}$

True

with expectation

```
Sum[n pntgtapp1, {n, 0, ∞}]
```

$$\frac{2 + t}{2}$$

Using this expectation, the cumulative number of individuals over T generations is roughly

```
Sum[t / 2, {t, 0, T}]
```

$$\frac{1}{4}\, T\, (1 + T)$$

Or when -1/m << t (ie subcritical mutants) we have approximately

```
pntgtapp2 = pntgt /. -1 + m + ⅇ^(m t) (1 + m) → -1 + m /. -1 + ⅇ^(m t) → -1 // Simplify;
% /. 1 - m → 1
```

$$-2\,m\,(1+m)^{-1+n}$$

with expectation

```
Sum[n pntgtapp2, {n, 0, ∞}]
```

$$\frac{-1+m}{2\,m}$$

Visually check critical (red) and subcritical (green) approximations against true solution (blue) for n=20 across time

```
Show[
 Plot[pntgt /. m → -0.01 /. n → 20, {t, 0, 500}, PlotRange → All],
 Plot[pntgtapp1 /. m → -0.01 /. n → 20,
  {t, 0, 500}, PlotRange → All, PlotStyle → Red],
 Plot[pntgtapp2 /. m → -0.01 /. n → 20, {t, 0, 500}, PlotRange → All, PlotStyle → Green]
]
```

Check distribution of n at 3 different times

```
nmax = 100;
Show[
 LogPlot[pntgt /. m → -0.01 /. t → 2,
  {n, 0, nmax}, PlotStyle → Blue, PlotRange → {10^-4, 10}],
 LogPlot[pntgt /. m → -0.01 /. t → 20, {n, 0, nmax},
  PlotStyle → {Blue, Dashed}, PlotRange → All],
 LogPlot[pntgt /. m → -0.01 /. t → 200, {n, 0, nmax},
  PlotStyle → {Blue, Dotted, Thick}, PlotRange → All],
 LogPlot[pntgtapp1 /. m → -0.01 /. t → 2, {n, 0, nmax},
  PlotRange → All, PlotStyle → Red],
 LogPlot[pntgtapp1 /. m → -0.01 /. t → 20, {n, 0, nmax},
  PlotRange → All, PlotStyle → {Red, Dashed}],
 LogPlot[pntgtapp1 /. m → -0.01 /. t → 200, {n, 0, nmax},
  PlotRange → All, PlotStyle → {Red, Dotted, Thick}],
 LogPlot[pntgtapp2 /. m → -0.01, {n, 0, nmax}, PlotRange → All, PlotStyle → Green]
]
```

These lineage sizes given persistence align with eq A3 in Weissman et al 2010. As they pointed out, the distribution of n given persistence to t and m is roughly geometric in both cases (t<<|1/m| and t>>-1/m), with p=1/t or p=-m respectively, which implies that the probability of n drops off exponentially when n>min(t, -1/m). Thus n will essentially never be greater than the minimum of t or -1/m, eg mutants with large -m will be restricted to small sizes.

Probability of rescue

1-step rescue (equation 5)

The probability that a mutant with growth rate in [m,m+dm] rescues the popuation is $f[m \mid m_{wt}]$ $p_{est}[m]$ dm. Integrating over all m>0 gives the probability of 1-step rescue from an individual with growth rate m0

```
Clear[Λ1]
```

```
Λ1[m0_?NumericQ, mmax_, λ_, n_, U_] :=
 U NIntegrate[fm[m, m0, mmax, λ, n] pest[m], {m, 0, mmax}]
```

The total probability of 1-step rescue is then

```
PR1[m0_?NumericQ] := prescue /. p0 → prescuem[m0, Λ1[m0, mmax, λ, n, U]]
```

And we can approximate this as

```
PR1App[m0_?NumericQ] := prescueApp /. p0 → prescuem[m0, Λ1[m0, mmax, λ, n, U]]
```

Numerical example

```
N0 = 10^4;
U = 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;

LogPlot[
 {PR1[m0], PR1App[m0]},
 {m0, -0.3, -0.01},
 Frame → {True, False, False, True},
 FrameLabel → {"Wildtype growth rate (m0)", "", "", "Probability of rescue"},
 FrameTicks → {True, False, False, True},
 PerformanceGoal → "Speed"
]

Clear[N0, U, mmax, λ, Es, n, mwt]
```

2-step rescue (equation 6)

The rate of 2-step rescue from a single individual with growth rate m0 is the probability of a mutation to growth rate m, which does not establish, but then creates a second mutation that does

```
Λ2[m0_?NumericQ, mmax_, λ_, n_, U_] := U NIntegrate[
   fm[m, m0, mmax, λ, n] (1 - pest[m]) prescuem[m, Λ1[m, mmax, λ, n, U]], {m, -∞, mmax}]
```

Numerical comparison with probability of 1-step rescue

```
N0 = 10^4;
U = 2 * 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;

Table[{m0, prescue /. p0 → prescuem[m0, Λ2[m0, mmax, λ, n, U]]},
  {m0, -0.3, -0.01, 0.1}];
plot1 = ListLogPlot[%, Joined → True, PlotStyle → Red];

plot2 = LogPlot[PR1[m0], {m0, -0.3, -0.01}, Frame → {True, False, False, True},
   FrameLabel → {"Wildtype growth rate (m0)", "", "", "Probability of rescue"},
   FrameTicks → {True, False, False, True}, PerformanceGoal → "Speed"];

Show[plot2, plot1]

Clear[mmax, λ, Es, n, N0, U]
```

k-step rescue (equation 7)

One can carry on the logic used for 2-step rescue to get the probability of k-step rescue, e.g., 3-step is

```
Λ3[m0_?NumericQ, mmax_, λ_, n_, U_] := U NIntegrate[
   fm[m, m0, mmax, λ, n] (1 - pest[m]) prescuem[m, Λ2[m, mmax, λ, n, U]], {m, -∞, mmax}]
```

and 4-step is

```
Λ4[m0_?NumericQ, mmax_, λ_, n_, U_] := U NIntegrate[
   fm[m, m0, mmax, λ, n] (1 - pest[m]) prescuem[m, Λ3[m, mmax, λ, n, U]], {m, -∞, mmax}]
```

etc

Plot probability as a function of wildtype growth rate (figure 3)

Interpolation function

The probability of rescue by k steps involves k integrals, and so with even small k (e.g, k=3) they are very slow to compute in their exact form. We can, however, combine an approximation (don't integrate

below mmin) with interpolation functions to greatly speed things up (with some loss of accuaracy)

```
mTempmin = -0.4;
mTempmax = -0.01;
step = 0.01;
mmin = mTempmin;

Clear[Λ1Interpolated, Λ2Interpolated, Λ3Interpolated, Λ4Interpolated]

Λ1Interpolated[m0_, mmax_, λ_, n_, U_] :=
 Λ1Interpolated[m0, mmax, λ, n, U] = Block[{},
   f = Interpolation[Table[{mTemp, U NIntegrate[fm[m, mTemp, mmax, λ, n] pest[m],
          {m, 0, mmax}, Method → {Automatic, "SymbolicProcessing" → 0}]},
       {mTemp, mTempmin, mTempmax, step}]];
   f[m0]
  ]

Λ2Interpolated[m0_, mmax_, λ_, n_, U_] :=
 Λ2Interpolated[m0, mmax, λ, n, U] = Block[{},
   f = Interpolation[Table[{mTemp, U NIntegrate[fm[m, mTemp, mmax, λ, n]
           (1 - pest[m]) prescuem[m, Λ1Interpolated[m, mmax, λ, n, U]],
          {m, mmin, mmax}, Method → {Automatic, "SymbolicProcessing" → 0}]},
       {mTemp, mTempmin, mTempmax, step}]];
   f[m0]
  ]

Λ3Interpolated[m0_, mmax_, λ_, n_, U_] :=
 Λ3Interpolated[m0, mmax, λ, n, U] = Block[{},
   f = Interpolation[Table[{mTemp, U NIntegrate[fm[m, mTemp, mmax, λ, n]
           (1 - pest[m]) prescuem[m, Λ2Interpolated[m, mmax, λ, n, U]],
          {m, mmin, mmax}, Method → {Automatic, "SymbolicProcessing" → 0}]},
       {mTemp, mTempmin, mTempmax, step}]];
   f[m0]
  ]

Λ4Interpolated[m0_, mmax_, λ_, n_, U_] :=
 Λ4Interpolated[m0, mmax, λ, n, U] = Block[{},
   f = Interpolation[Table[{mTemp, U NIntegrate[fm[m, mTemp, mmax, λ, n]
           (1 - pest[m]) prescuem[m, Λ3Interpolated[m, mmax, λ, n, U]],
          {m, mmin, mmax}, Method → {Automatic, "SymbolicProcessing" → 0}]},
       {mTemp, mTempmin, mTempmax, step}]];
   f[m0]
  ]
```

Numerical data

```
(*N0=10^4;
mmax=0.5;
λ=2Es/n;
Es=0.01;
n=4;
U=2*10^-3;

m0min=mTempmin;
m0max=mTempmax;
mstep=step;
rate4=Table[{m0,Λ4Interpolated[m0,mmax,λ,n,U]},{m0,m0min,m0max,mstep}];
rate3=Table[{m0,Λ3Interpolated[m0,mmax,λ,n,U]},{m0,m0min,m0max,mstep}];
rate2=Table[{m0,Λ2Interpolated[m0,mmax,λ,n,U]},{m0,m0min,m0max,mstep}];
rate1=Table[{m0,Λ1Interpolated[m0,mmax,λ,n,U]},{m0,m0min,m0max,mstep}];
m0list=Table[m0,{m0,m0min,m0max,mstep}];
theory={
  Table[{m0list[[i]],prescue/.p0→prescuem[m0list[[i]],rate1[[i,2]]]},
   {i,Length[m0list]}],
  Table[{m0list[[i]],prescue/.p0→prescuem[m0list[[i]],rate2[[i,2]]]},
   {i,Length[m0list]}],
  Table[{m0list[[i]],prescue/.p0→prescuem[m0list[[i]],rate3[[i,2]]]},
   {i,Length[m0list]}],
  Table[{m0list[[i]],prescue/.p0→prescuem[m0list[[i]],rate4[[i,2]]]},
   {i,Length[m0list]}]
 };
alltheory=
 Table[{m0list[[i]],prescue/.p0→prescuem[m0list[[i]],rate1[[i,2]]+rate2[[i,2]]+
       rate3[[i,2]]+rate4[[i,2]]]},{i,Length[m0list]}];

Clear[N0,mmax,λ,Es,n,U,m0min,m0max]*)
```

```
theory = {{{-0.4`, 5.472398814099222`*^-7}, {-0.39`, 9.745688406281872`*^-7},
    {-0.38`, 1.7238895513305152`*^-6}, {-0.37`, 3.0285772651961196`*^-6},
    {-0.36000000000000004`, 5.2841014319682245`*^-6}, {-0.35000000000000003`,
     9.155420059081543`*^-6}, {-0.34`, 0.00001575188019520279 4`},
    {-0.33`, 0.00002690955788409166`}, {-0.32`, 0.00004564308357801749 6`},
    {-0.31000000000000005`, 0.0000768622102641503`},
    {-0.30000000000000004`, 0.00012849810996373723`},
    {-0.29000000000000004`, 0.0002132574731799064`},
    {-0.28`, 0.0003513291377449379`}, {-0.27`, 0.00057452097472376 9`},
    {-0.26`, 0.0009325213318174264`}, {-0.25`, 0.0015022797840921198`},
    {-0.24000000000000002`, 0.0024019086800984857`},
    {-0.23`, 0.0038110379258926574`}, {-0.22000000000000003`,
     0.00600020901304088`}, {-0.21000000000000002`, 0.00937261491044139`},
    {-0.2`, 0.014522096798011974`}, {-0.19000000000000003`, 0.022311337733202485`},
    {-0.18000000000000002`, 0.03397263148001661`},
    {-0.17`, 0.0512283883233019`}, {-0.16000000000000003`, 0.07641581098977057`},
    {-0.15000000000000002`, 0.11257347217569635`},
    {-0.14`, 0.16339795924448708`}, {-0.13`, 0.23289952993154328`},
    {-0.12`, 0.3244893834485655`}, {-0.11000000000000004`, 0.43919411790398366`},
    {-0.10000000000000003`, 0.5729341370203966`},
    {-0.09000000000000002`, 0.7137213876566558`},
```

```
 {-0.08000000000000002`, 0.8414602539868381`}, {-0.07`, 0.9344415307620567`},
 {-0.06`, 0.9829032755970813`}, {-0.04999999999999999`, 0.9979187459679042`},
 {-0.040000000000000036`, 0.9999341480370483`},
 {-0.030000000000000027`, 0.9999998505645212`},
 {-0.020000000000000018`, 0.9999999999991431`}, {-0.010000000000000009`, 1.`}},
{{-0.4`, 7.1817194564616216`*^-6}, {-0.39`, 0.00001038286843568769 8`},
 {-0.38`, 0.000015004899198478583`}, {-0.37`, 0.000021674932411452907`},
 {-0.36000000000000004`, 0.000031295722740964926`},
 {-0.35000000000000003`, 0.00004516336475557381`},
 {-0.34`, 0.00006513527103491068`}, {-0.33`, 0.00009386674884392932`},
 {-0.32`, 0.00013514257904490012`}, {-0.31000000000000005`,
  0.0001943394640103735`}, {-0.30000000000000004`, 0.00027906144855771586`},
 {-0.29000000000000004`, 0.0004000224444989930 5`},
 {-0.28`, 0.0005722318522486392`}, {-0.27`, 0.0008166042269467377`},
 {-0.26`, 0.0011621019720312598`}, {-0.25`, 0.0016485639043937184`},
 {-0.24000000000000002`, 0.002330394186973561`},
 {-0.23`, 0.0032813120522319217`}, {-0.22000000000000003`,
  0.0046003825714453495`}, {-0.21000000000000002`, 0.006419557828723499`},
 {-0.2`, 0.008912948912746632`}, {-0.19000000000000003`, 0.012308013245967753`},
 {-0.18000000000000002`, 0.01689876878901897`}, {-0.17`, 0.02306102686962941`},
 {-0.16000000000000003`, 0.031269462419949656`},
 {-0.15000000000000002`, 0.042116115688766054`}, {-0.14`, 0.05632965853148175`},
 {-0.13`, 0.07479449506069946`}, {-0.12`, 0.09856854888921651`},
 {-0.11000000000000004`, 0.12889844527072303`}, {-0.10000000000000003`,
  0.1672306176682965`}, {-0.09000000000000002`, 0.21521607762716344`},
 {-0.08000000000000002`, 0.2747032194313106`}, {-0.07`, 0.3477011299288638`},
 {-0.06`, 0.4362577296013713`}, {-0.04999999999999999`, 0.5420788502184701`},
 {-0.040000000000000036`, 0.6653477290582192`},
 {-0.030000000000000027`, 0.8010818232849237`}, {-0.020000000000000018`,
  0.9286233811012167`}, {-0.010000000000000009`, 0.9962496646879948`}},
{{-0.4`, 2.672518644497579`*^-6}, {-0.39`, 3.6200066483305093`*^-6},
 {-0.38`, 4.9024286813414975`*^-6}, {-0.37`, 6.639033992561494`*^-6},
 {-0.36000000000000004`, 8.99229424278225`*^-6}, {-0.35000000000000003`,
  0.000012183830842893428`}, {-0.34`, 0.000016516674993138913`},
 {-0.33`, 0.00002240514549411987`}, {-0.32`, 0.00003041648537960295 3`},
 {-0.31000000000000005`, 0.00004132735255646391 4`},
 {-0.30000000000000004`, 0.00005620069935863281`},
 {-0.29000000000000004`, 0.00007648968361839703`},
 {-0.28`, 0.0001041772194614321`}, {-0.27`, 0.00014196192976223543`},
 {-0.26`, 0.00019350379587734778`}, {-0.25`, 0.0002637455775598152`},
 {-0.24000000000000002`, 0.0003593290092440693`},
 {-0.23`, 0.0004891277868906974`},
 {-0.22000000000000003`, 0.0006649222935298793`}, {-0.21000000000000002`,
  0.0009022438378168962`}, {-0.2`, 0.0012214190541605108`},
 {-0.19000000000000003`, 0.0016488487049626244`}, {-0.18000000000000002`,
  0.0022185608705778126`}, {-0.17`, 0.0029740895246452848`},
 {-0.16000000000000003`, 0.003970751527472172`}, {-0.15000000000000002`,
  0.0052784386334274735`}, {-0.14`, 0.006985125056896413`},
 {-0.13`, 0.009201449505447323`}, {-0.12`, 0.012067026227695399`},
 {-0.11000000000000004`, 0.015759693621743676`}, {-0.10000000000000003`,
  0.020509966391728862`}, {-0.09000000000000002`, 0.02662504581244618`},
 {-0.08000000000000002`, 0.03453108060938248`}, {-0.07`, 0.04485200223554198`},
 {-0.06`, 0.0585665300648599`}, {-0.04999999999999999`, 0.0773474840786541`},
 {-0.040000000000000036`, 0.10438028623999529`},
 {-0.030000000000000027`, 0.14667096966766024`},
```

```
 {-0.020000000000000018`, 0.2233073280524227`},
 {-0.010000000000000009`, 0.4098900908454398`}},
{{-0.4`, 3.665400664099039`*^-7}, {-0.39`, 4.882948413387211`*^-7},
 {-0.38`, 6.507825516255394`*^-7}, {-0.37`, 8.679175866888045`*^-7},
 {-0.36000000000000004`, 1.1585392625246271`*^-6}, {-0.35000000000000003`,
  1.548213704460899`*^-6}, {-0.34`, 2.071738417153135`*^-6},
 {-0.33`, 2.776581790708832`*^-6}, {-0.32`, 3.727611290194055`*^-6},
 {-0.31000000000000005`, 5.013589215119296`*^-6},
 {-0.30000000000000004`, 6.756030736299046`*^-6},
 {-0.29000000000000004`, 9.12124881535803`*^-6},
 {-0.28`, 0.00001233658455390696`}, {-0.27`, 0.000016712145389896627`},
 {-0.26`, 0.00002266963795427568`}, {-0.25`, 0.000030780242171069006`},
 {-0.24000000000000002`, 0.00004181381972367948`},
 {-0.23`, 0.000056802136495281985`},
 {-0.22000000000000003`, 0.00007711911056884624`}, {-0.21000000000000002`,
  0.00010458146610448082`}, {-0.2`, 0.0001415735100674942`},
 {-0.19000000000000003`, 0.00019120021529694942`}, {-0.18000000000000002`,
  0.0002574735404686779`}, {-0.17`, 0.00034553832838446485`},
 {-0.16000000000000003`, 0.0004619470399811476`}, {-0.15000000000000002`,
  0.0006149981944676419`}, {-0.14`, 0.0008151642974213447`},
 {-0.13`, 0.0010756555359718867`}, {-0.12`, 0.0014132038091301258`},
 {-0.11000000000000004`, 0.0018492239194836113`},
 {-0.10000000000000003`, 0.002411647781310755`},
 {-0.09000000000000002`, 0.003138005818001832`},
 {-0.08000000000000002`, 0.004080917925158634`},
 {-0.07`, 0.005318491045821605`}, {-0.06`, 0.006975434272220693`},
 {-0.04999999999999999`, 0.009269923451119766`},
 {-0.040000000000000036`, 0.012631023980203326`},
 {-0.030000000000000027`, 0.01804961542287531`},
 {-0.020000000000000018`, 0.0284671089107692`},
 {-0.010000000000000009`, 0.05823795851907776`}}};
```

```
alltheory = {{-0.4`, 0.00001076798963850489 3`}, {-0.39`, 0.00001546568025267980 3`},
   {-0.38`, 0.00002228187795860758 8`}, {-0.37`, 0.00003221020658283891`},
   {-0.36000000000000004`, 0.00004673011156652862`}, {-0.35000000000000003`,
    0.00006804965109896699`}, {-0.34`, 0.00009947299961354794`},
   {-0.33`, 0.0001459524027258574`}, {-0.32`, 0.00021491729975098295`},
   {-0.31000000000000005`, 0.00031751489398534893`},
   {-0.30000000000000004`, 0.0004704543728014654`},
   {-0.29000000000000004`, 0.0006987523028609832`},
   {-0.28`, 0.0010397647754660788`}, {-0.27`, 0.0015491068347829318`},
   {-0.26`, 0.0023092555158806816`}, {-0.25`, 0.0034419561736643844`},
   {-0.24000000000000002`, 0.005125934145003619`},
   {-0.23`, 0.007621874910163862`}, {-0.22000000000000003`, 0.011307117362613917`},
   {-0.21000000000000002`, 0.01672286182842886`},
   {-0.2`, 0.024636589665609887`}, {-0.19000000000000003`, 0.03612111665412221`},
   {-0.18000000000000002`, 0.0526478810505413`}, {-0.17`, 0.07618321541025108`},
   {-0.16000000000000003`, 0.10925842311524103`},
   {-0.15000000000000002`, 0.154951959045035`}, {-0.14`, 0.21667029213726385`},
   {-0.13`, 0.29754827077524637`}, {-0.12`, 0.39924782631433087`},
   {-0.11000000000000004`, 0.5200288215021587`},
   {-0.10000000000000003`, 0.6524246688522214`},
   {-0.09000000000000002`, 0.7819169338181124`},
   {-0.08000000000000002`, 0.8893420776854711`}, {-0.07`, 0.9592948833994817`},
   {-0.06`, 0.9909501188644341`}, {-0.04999999999999999`, 0.9991194054587093`},
   {-0.040000000000000036`, 0.9999799413255674`},
   {-0.030000000000000027`, 0.999999972757273`},
   {-0.020000000000000018`, 0.9999999999999342`}, {-0.010000000000000009`, 1.`}};
```

Figure 3

```
N0 = 10^4;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
U = 2 * 10^-3;

dat1 = Import[datadir <>
     "prescue_poisson_N10000_n4_U0.00200_Es0.01_mmax0.50_mutmax10_nreps1000.csv"];
dat2 = Import[datadir <>
     "prescue_poisson_N10000_n4_U0.00200_Es0.01_mmax0.50_mutmax10_nreps10000.csv"];
dat3 = Import[datadir <>
     "prescue_poisson_N10000_n4_U0.00200_Es0.01_mmax0.50_mutmax10_nreps100000.csv"];
alldat = Flatten[{dat1, dat2, dat3}, {1, 2}];
alldat =
  Select[Select[Select[alldat, #[[1]] ≠ -0.1 &], #[[1]] ≠ -0.2 &], #[[1]] ≠ -0.3 &];

dat = Import[datadir <>
     "int_dfe_poisson_N10000_n4_U0.00200_Es0.01_mmax0.50_mwt-0.10_mutmax10
       _nreps100000.csv"];
nreps = 100 000;
onestep = Length[Select[dat, #[[2]] == 1 &]] / nreps;
twostep = Length[Select[dat, #[[2]] == 2 &]] / nreps;
threestep = Length[Select[dat, #[[2]] == 3 &]] / nreps;
fourstep = Length[Select[dat, #[[2]] == 4 &]] / nreps;
```

```
total = onestep + twostep + threestep + fourstep;
k1 = {onestep, twostep, threestep, fourstep, total} // N;
Table[{{-0.1, k1[[i]]}}, {i, Length[k1]}];
k1plot = ListLogPlot[%, PlotMarkers → {
      Graphics[{Circle[], defaultcolors[[1]]}, ImageSize → 10],
      Graphics[{Circle[], defaultcolors[[2]]}, ImageSize → 10],
      Graphics[{Circle[], defaultcolors[[3]]}, ImageSize → 10],
      Graphics[{Circle[], defaultcolors[[4]]}, ImageSize → 10],
      Graphics[{Black, Disk[]}, ImageSize → 8]
     }];

dat = Import[datadir <>
     "int_dfe_poisson_N10000_n4_U0.00200_Es0.01_mmax0.50_mwt-0.20_mutmax10
       _nreps100000.csv"];
nreps = 100 000;
onestep = Length[Select[dat, #[[2]] == 1 &]] / nreps;
twostep = Length[Select[dat, #[[2]] == 2 &]] / nreps;
threestep = Length[Select[dat, #[[2]] == 3 &]] / nreps;
fourstep = Length[Select[dat, #[[2]] == 4 &]] / nreps;
total = onestep + twostep + threestep + fourstep;
k2 = {onestep, twostep, threestep, fourstep, total} // N;
Table[{{-0.2, k2[[i]]}}, {i, Length[k2]}];
k2plot = ListLogPlot[%, PlotMarkers → {
      Graphics[{Circle[], defaultcolors[[1]]}, ImageSize → 10],
      Graphics[{Circle[], defaultcolors[[2]]}, ImageSize → 10],
      Graphics[{Circle[], defaultcolors[[3]]}, ImageSize → 10],
      Graphics[{Circle[], defaultcolors[[4]]}, ImageSize → 10],
      Graphics[{Black, Disk[]}, ImageSize → 8]
     }];

dat = Import[datadir <>
     "int_dfe_poisson_N10000_n4_U0.00200_Es0.01_mmax0.50_mwt-0.30_mutmax10
       _nreps1000000.csv"];
nreps = 1 000 000;
onestep = Length[Select[dat, #[[2]] == 1 &]] / nreps;
twostep = Length[Select[dat, #[[2]] == 2 &]] / nreps;
threestep = Length[Select[dat, #[[2]] == 3 &]] / nreps;
fourstep = Length[Select[dat, #[[2]] == 4 &]] / nreps;
total = onestep + twostep + threestep + fourstep;
k3 = {onestep, twostep, threestep, fourstep, total} // N;
Table[{{-0.3, k3[[i]]}}, {i, Length[k3]}];
k3plot =
  ListLogPlot[%,
   PlotMarkers → {
      Graphics[{Circle[], defaultcolors[[1]]}, ImageSize → 10],
      Graphics[{Circle[], defaultcolors[[2]]}, ImageSize → 10],
      Graphics[{Circle[], defaultcolors[[3]]}, ImageSize → 10],
      Graphics[{Circle[], defaultcolors[[4]]}, ImageSize → 10],
      Graphics[{Black, Disk[]}, ImageSize → 8]
     }
  ];

Show[
 ListLogPlot[
```

```
    theory,
    Joined → True,
    PlotStyle → Thick,
    PlotRange → {{-0.4, 0}, {5 * 10^-7, 1}},
    Frame → {True, False, False, True},
    FrameLabel → {"Wildtype growth rate", , , "Probability of rescue"},
    FrameTicks → {True, False, False, True},
    LabelStyle → labelstyle,
    PlotLegends → Placed[LineLegend[Style[#, 12, FontFamily → "Helvetica"] & /@
        {"1-step", "2-step", "3-step", "4-step"}], Scaled@{0.85, 0.23}]
   ],
   ListLogPlot[alltheory, Joined → True, PlotStyle → {Black, Thick},
    PlotLegends → Placed[LineLegend[
       Style[#, 12, FontFamily → "Helvetica"] & /@ {"total"}], Scaled@{0.56, 0.23}]
   ],
   ListLogPlot[alldat, PlotMarkers → Graphics[{Black, Disk[]}, ImageSize → 8]],
   k1plot, k2plot, k3plot,
   Epilog ->
    braceLabel[{{-0.125, Log@10^-6}, {-0.125, Log@(2 * 10^-4)}}, Style["", Larger]],
   ImageSize → 350
  ]

Export[figdir <> "Figure3.eps", %];

Clear[N0, mmax, λ, Es, n, U, m0min, m0max]
```

Plot probability as a function of mutation rate (figure S1)

Interpolation functions

We again use interpolation functions to speed things up, this time across U instead of m0

```
Umin = -5;
Umax = 1;
Ustep = 0.1;
mmin = -0.4;

Clear[Λ1InterpolatedU, Λ2InterpolatedU, Λ3InterpolatedU, Λ4InterpolatedU]

Λ1InterpolatedU[m0_, mmax_, λ_, n_, x_] :=
 Λ1InterpolatedU[m0, mmax, λ, n, x] = Block[{},
   f = Interpolation[Table[
      {xtemp, 10^xtemp NIntegrate[fm[m, m0, mmax, λ, n] pest[m], {m, 0, mmax}, Method →
           {Automatic, "SymbolicProcessing" → 0}]}, {xtemp, Umin, Umax, Ustep}]];
   f[x]
  ]

Λ2InterpolatedU[m0_, mmax_, λ_, n_, x_] :=
 Λ2InterpolatedU[m0, mmax, λ, n, x] = Block[{},
   f = Interpolation[
     Table[{xtemp, 10^xtemp NIntegrate[fm[m, m0, mmax, λ, n] (1 - pest[m]) prescuem[
            m, Λ1Interpolated[m, mmax, λ, n, 10^xtemp]], {m, mmin, mmax}, Method →
           {Automatic, "SymbolicProcessing" → 0}]}, {xtemp, Umin, Umax, Ustep}]];
   f[x]
  ]

Λ3InterpolatedU[m0_, mmax_, λ_, n_, x_] :=
 Λ3InterpolatedU[m0, mmax, λ, n, x] = Block[{},
   f = Interpolation[
     Table[{xtemp, 10^xtemp NIntegrate[fm[m, m0, mmax, λ, n] (1 - pest[m]) prescuem[
            m, Λ2Interpolated[m, mmax, λ, n, 10^xtemp]], {m, mmin, mmax}, Method →
           {Automatic, "SymbolicProcessing" → 0}]}, {xtemp, Umin, Umax, Ustep}]];
   f[x]
  ]

Λ4InterpolatedU[m0_, mmax_, λ_, n_, x_] :=
 Λ4InterpolatedU[m0, mmax, λ, n, x] = Block[{},
   f = Interpolation[
     Table[{xtemp, 10^xtemp NIntegrate[fm[m, m0, mmax, λ, n] (1 - pest[m]) prescuem[
            m, Λ3Interpolated[m, mmax, λ, n, 10^xtemp]], {m, mmin, mmax}, Method →
           {Automatic, "SymbolicProcessing" → 0}]}, {xtemp, Umin, Umax, Ustep}]];
   f[x]
  ]
```

Numerical data for panel A

```
(*N0=10^4;
m0=-0.1;
mmax=0.5;
λ=2Es/n;
Es=0.01;
n=4;

rate4=Table[Λ4InterpolatedU[m0,mmax,λ,n,x],{x,Umin,Umax,Ustep}];
rate3=Table[Λ3InterpolatedU[m0,mmax,λ,n,x],{x,Umin,Umax,Ustep}];
rate2=Table[Λ2InterpolatedU[m0,mmax,λ,n,x],{x,Umin,Umax,Ustep}];
rate1=Table[Λ1InterpolatedU[m0,mmax,λ,n,x],{x,Umin,Umax,Ustep}];
Ulist=Table[10^x,{x,Umin,Umax,Ustep}];
theory={
  Table[{Ulist[[i]],prescue/.p0→prescuem[m0,rate1[[i]]]},{i,Length[Ulist]}],
  Table[{Ulist[[i]],prescue/.p0→prescuem[m0,rate2[[i]]]},{i,Length[Ulist]}],
  Table[{Ulist[[i]],prescue/.p0→prescuem[m0,rate3[[i]]]},{i,Length[Ulist]}],
  Table[{Ulist[[i]],prescue/.p0→prescuem[m0,rate4[[i]]]},{i,Length[Ulist]}]
 };
alltheory=Table[{Ulist[[i]],
   prescue/.p0→prescuem[m0,rate1[[i]]+rate2[[i]]+rate3[[i]]+rate4[[i]]]},{i,
   Length[Ulist]}];

Clear[mmax,λ,Es,n,m0,N0,U]*)
```

```
theory = {{{0.00001`, 0.004246842378678117`},
    {0.00001258925411794166 1`, 0.005343512240509662 4`},
    {0.00001584893192461114`, 0.006722418845097056`}, {0.00001995262314968878 6`,
     0.008455638902157614`}, {0.00002511886431509582`, 0.010633329634670008`},
    {0.00003162277660168379 5`, 0.013368073668290736`},
    {0.00003981071705534969 5`, 0.01680015577769267`},
    {0.00005011872336272725`, 0.021103903488885356`},
    {0.00006309573444801929`, 0.026495197360892786`},
    {0.00007943282347242822`, 0.03324019208311246`},
    {0.0001`, 0.04166516094921757`}, {0.00012589254117941674`,
     0.05216714629405583`}, {0.00015848931924611142`, 0.06522471323417367`},
    {0.00019952623149688788`, 0.08140749078007126`},
    {0.00025118864315095822`, 0.10138225267144507`},
    {0.00031622776601683794`, 0.12591194417039553`},
    {0.00039810717055349735`, 0.15584223469333813`},
    {0.00050118723362727 25`, 0.19206791297501513`},
    {0.00063095734448019 3`, 0.2354690490355157`},
    {0.00079432823472428 22`, 0.2868051576697973`},
    {0.001`, 0.3465563408388336`}, {0.0012589254117941675`, 0.4147065687699266`},
    {0.00158489319246111 4`, 0.49048019295427137`},
    {0.00199526231496887 97`, 0.5720729042194002`},
    {0.00251188643150958 2`, 0.6564634113805501`},
    {0.00316227766016837 94`, 0.7394414586022069`},
    {0.00398107170553497 3`, 0.8160091713130636`},
    {0.00501187233627272 5`, 0.8812494467922933`},
    {0.00630957344480193 6`, 0.9315527837690738`},
    {0.00794328234724282`, 0.9657778626534119`}, {0.01`, 0.9856911478435505`},
    {0.01258925411794167 5`, 0.9952212549506977`},
```

```
{0.01584893192461114`, 0.9987965255597829`},
{0.01995262314968881`, 0.9997873527267671`}, {0.025118864315095822`,
 0.9999759117384616`}, {0.03162277660168379`, 0.9999984370833104`},
{0.039810717055349734`, 0.999999949529219`}, {0.05011872336272725`,
 0.9999999993188536`}, {0.06309573444801936`, 0.9999999999969065`},
{0.07943282347242822`, 0.9999999999999963`}, {0.1`, 1.`},
{0.12589254117941687`, 1.`}, {0.15848931924611143`, 1.`},
{0.1995262314968879`, 1.`}, {0.25118864315095824`, 1.`},
{0.31622776601683794`, 1.`}, {0.39810717055349776`, 1.`},
{0.5011872336272725`, 1.`}, {0.6309573444801942`, 1.`},
{0.7943282347242822`, 1.`}, {1.`, 1.`}, {1.2589254117941688`, 1.`},
{1.584893192461114`, 1.`}, {1.9952623149688828`, 1.`}, {2.5118864315095824`,
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```
{0.06309573444801936`, 1.`}, {0.07943282347242822`, 1.`},
{0.1`, 1.`}, {0.12589254117941687`, 1.`}, {0.15848931924611143`, 1.`},
{0.1995262314968879`, 1.`}, {0.25118864315095824`, 1.`}, {0.31622776601683794`,
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{0.03162277660168379`, 0.9999999968287793` + 0.` i},
{0.039810717055349734`, 0.9999999999999953` + 0.` i},
{0.05011872336272725`, 1.` + 0.` i}, {0.06309573444801936`, 1.` + 0.` i},
{0.07943282347242822`, 1.` + 0.` i}, {0.1`, 1.` + 0.` i},
{0.12589254117941687`, 1.` + 2.764473032650923`*^-174 i},
{0.15848931924611143`, 1.` + 6.954318481178101`*^-245 i}, {0.1995262314968879`,
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   99999999999999999999999999999999999999999999954195095086510902148319599150 3:
   6357191551341868`355.29367778426564 +
  2.087234795303845338146796740467790237`15.954589770191005*^-349
   i}, {0.25118864315095824`,
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   99999999999999999999999999999999999999997869595226336442133848083962353580 6:
   351`498.62612764362206 +
  2.681074505449572837767527147147354826589274784238`15.954589770191005*^-491
   i}, {0.31622776601683794`,
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  2.539896689642180875850744251914858 94`15.653559774527023*^-677
   i}, {0.39810717055349776`,
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   99999999999999999999987633434402601386607801705650442636671`922.561310611644:
   8 +
  3.267081179152030997800556896689657305758004063373 5`15.653559774527023*^-9:
    14 i}, {0.5011872336272725`,
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  .021869852722 +
 1.8193598254427304438526633857817872957 27`14.750064822519922*^-9131
  i}, {3.9810717055349776`,
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  810733058578378411597116577272 9`10481.933514092443 +
 1.683359027075080317440328012987895118975533909444 7`14.750164321868958*^-104:
   70 i}, {3.1622776601683795`,
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    999999999999999999999999999999999999999999999999999999999999999999999999999999999999999999999:
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```
{0.0000630957, 0.0267881 + 0. i}, {0.0000794328, 0.0336897 + 0. i},
{0.0001, 0.0423535 + 0. i}, {0.000125893, 0.0532182 + 0. i},
{0.000158489, 0.0668243 + 0. i}, {0.000199526, 0.083832 + 0. i},
{0.000251189, 0.105039 + 0. i}, {0.000316228, 0.131392 + 0. i},
{0.000398107, 0.163992 + 0. i}, {0.000501187, 0.20407 + 0. i},
{0.000630957, 0.252925 + 0. i}, {0.000794328, 0.31179 + 0. i},
{0.001, 0.381589 + 0. i}, {0.00125893, 0.462531 + 0. i},
{0.00158489, 0.553517 + 0. i}, {0.00199526, 0.651399 + 0. i},
{0.00251189, 0.750314 + 0. i}, {0.00316228, 0.841674 + 0. i},
{0.00398107, 0.915717 + 0. i}, {0.00501187, 0.965252 + 0. i},
{0.00630957, 0.990206 + 0. i}, {0.00794328, 0.998448 + 0. i},
{0.01, 0.999899 + 0. i}, {0.0125893, 0.999998 + 0. i}, {0.0158489, 1. + 0. i},
{0.0199526, 1. + 0. i}, {0.0251189, 1. + 0. i}, {0.0316228, 1. + 0. i},
{0.0398107, 1. + 0. i}, {0.0501187, 1. + 0. i}, {0.0630957, 1. + 0. i},
{0.0794328, 1. + 7.92512 × 10^-192 i}, {0.1, 1. + 1.32585 × 10^-265 i}, {0.125893,
 0.99999999999999999999999999999999999999999999999999999999999999999999999999999999:
   
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```
    999999999999999999990433160262793884 + 3.874942183534860 × 10^-1036 i}, {0.316228,
  0.99999999999999999999
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```
N0 = 10^4;
m0 = -0.1;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
letter = "A";

dat = Import[datadir <> ToString[StringForm[
      "prescue_poisson_N``_n``_Es``_mmax``_mwt``_mutmax10_nreps10000.csv",
      NumberForm[N0, 1], n, Es, NumberForm[mmax, {3, 2}], NumberForm[m0, {3, 2}]]]];
dat[[All, {1}]] = dat[[All, {1}]] * Uc /. Uc → n^2 λ / 4 /. λ → 2 Es / n;

figS1a = Show[
  ListLogLogPlot[Re[theory], Joined → True, PlotStyle → Thick,
   PlotRange → {{10^-5, 1}, {10^-6, 1}},
   Frame → {True, True, False, False},
   FrameLabel → {, "Probability of rescue", ,},
   FrameTicks → {True, True, False, False},
   LabelStyle → labelstyle,
   FrameTicksStyle → {FontColor → White, Automatic, Automatic, Automatic},
   PlotLegends → Placed[LineLegend[Style[#, 12, FontFamily → "Helvetica"] & /@
       {"1-step", "2-step", "3-step", "4-step"}], Scaled@{0.85, 0.23}]
  ],
  ListLogLogPlot[Re[alltheory], Joined → True, PlotStyle → {Thick, Black},
   PlotLegends → Placed[LineLegend[
      Style[#, 12, FontFamily → "Helvetica"] & /@ {"total"}], Scaled@{0.56, 0.23}]
  ],
  ListLogLogPlot[dat, PlotMarkers → {Automatic, Medium}, PlotStyle → Black],
  Epilog → {
    Text[Style[letter, 14, Bold, FontFamily → "Helvetica"], Scaled@{0.05, 0.95}],
    Text[Style[StringForm["m0=``", m0], 12, FontFamily → "Helvetica"],
     Scaled@{2 / 10, 9.5 / 10}], braceLabel[{{Log@(3 * 10^-2), Log@(2 * 10^-6)},
      {Log@(3 * 10^-2), Log@(3 * 10^-4)}}, Style["", Larger]]
   }
 ]

Clear[mmax, λ, Es, n, m0, N0, U, letter]
```

Numerical data for panel B

```
(*N0=10^4;
m0=-0.2;
mmax=0.5;
λ=2Es/n;
Es=0.01;
n=4;

rate4=Table[Λ4InterpolatedU[m0,mmax,λ,n,x],{x,Umin,Umax,Ustep}];
rate3=Table[Λ3InterpolatedU[m0,mmax,λ,n,x],{x,Umin,Umax,Ustep}];
rate2=Table[Λ2InterpolatedU[m0,mmax,λ,n,x],{x,Umin,Umax,Ustep}];
rate1=Table[Λ1InterpolatedU[m0,mmax,λ,n,x],{x,Umin,Umax,Ustep}];
Ulist=Table[10^x,{x,Umin,Umax,Ustep}];
theory={
  Table[{Ulist[[i]],prescue/.p0→prescuem[m0,rate1[[i]]]},{i,Length[Ulist]}],
  Table[{Ulist[[i]],prescue/.p0→prescuem[m0,rate2[[i]]]},{i,Length[Ulist]}],
  Table[{Ulist[[i]],prescue/.p0→prescuem[m0,rate3[[i]]]},{i,Length[Ulist]}],
  Table[{Ulist[[i]],prescue/.p0→prescuem[m0,rate4[[i]]]},{i,Length[Ulist]}]
 };
alltheory=Table[{Ulist[[i]],
   prescue/.p0→prescuem[m0,rate1[[i]]+rate2[[i]]+rate3[[i]]+rate4[[i]]]},{i,
   Length[Ulist]}];

Clear[mmax,λ,Es,n,m0,N0,U]*)

theory = {{{0.00001`, 0.00007314046372652871`}, {0.00001258925411794166 1`,
     0.00009207751649298324`}, {0.00001584893192461114`, 0.00011591734214455585`},
    {0.00001995262314968878 6`, 0.00014592909698574186`},
    {0.00002511886431509582 2`, 0.00018371037608155838`},
    {0.00003162277660168379 5`, 0.00023127215734253248`},
    {0.00003981071705534969 5`, 0.0002911456743308616`},
    {0.00005011872336272725`, 0.0003665168639935823`},
    {0.00006309573444801929`, 0.00046139548729717816`},
    {0.00007943282347242822`, 0.0005808277843870613`},
    {0.0001`, 0.0007311638383529218`}, {0.00012589254117941674`,
     0.0009203935461855606`}, {0.00015848931924611142`, 0.0011585686548950536`},
    {0.00019952623149688788`, 0.0014583325790454849`},
    {0.0002511886431509582`, 0.0018355850219021752`},
```

```
 {0.00031622776601683794`, 0.0023103149524704714`},
 {0.00039810717055349735`, 0.002907643335313459`},
 {0.0005011872336272725`, 0.003659126474774843`},
 {0.000630957344480193`, 0.0046043820138911284`},
 {0.0007943282347242822`, 0.0057931125466891276`},
 {0.001`, 0.007287616255093221`}, {0.0012589254117941675`,
  0.009165889373952796`}, {0.001584893192461114`, 0.011525440245827356`},
 {0.0019952623149688807`, 0.014487946773210414`},
 {0.002511886431509582`, 0.01820489368806233`},
 {0.0031622776601683794`, 0.022864315726856432`},
 {0.003981071705534973`, 0.028698735439603107`},
 {0.005011872336272725`, 0.03599430063226294`},
 {0.006309573444801936`, 0.04510096739305791`},
 {0.00794328234724282`, 0.056443297210017174`},
 {0.01`, 0.07053098067476249`}, {0.012589254117941675`, 0.08796748609482852`},
 {0.01584893192461114`, 0.10945416429540689`},
 {0.01995262314968881`, 0.1357856297038481`},
 {0.025118864315095822`, 0.16783024246560252`},
 {0.03162277660168379`, 0.20648715014405516`},
 {0.039810717055349734`, 0.2526090657216514`}, {0.05011872336272725`,
  0.30687886115628715`}, {0.06309573444801936`, 0.36963028456950564`},
 {0.07943282347242822`, 0.44061216795489566`}, {0.1`, 0.5187159793971413`},
 {0.12589254117941687`, 0.601722269310496`}, {0.15848931924611143`,
  0.6861703279391542`}, {0.1995262314968879`, 0.7675000901966439`},
 {0.25118864315095824`, 0.8406145024006825`}, {0.31622776601683794`,
  0.9009027165105612`}, {0.39810717055349776`, 0.9455114221673739`},
 {0.5011872336272725`, 0.9743314137635509`}, {0.6309573444801942`,
  0.9900452733886792`}, {0.7943282347242822`, 0.9969771393163126`},
 {1.`, 0.9993251282747677`}, {1.2589254117941688`, 0.9998976462095102`},
 {1.584893192461114`, 0.9999904503291296`}, {1.9952623149688828`,
  0.9999995159676723`}, {2.5118864315095824`, 0.9999999885937381`},
 {3.1622776601683795`, 0.9999999998971417`}, {3.9810717055349776`,
  0.9999999999997217`}, {5.011872336272725`, 0.9999999999999998`},
 {6.309573444801943`, 1.`}, {7.943282347242821`, 1.`}, {10.`, 1.`}},
{{0.00001`, 3.9781170735331273`*^-7}, {0.000012589254117941661`,
  6.185083899490351`*^-7}, {0.000015848931924611114`, 9.61248396325054`*^-7},
 {0.000019952623149688786`, 1.4932866104766518`*^-6},
 {0.000025118864315095822`, 2.318803576040196`*^-6},
 {0.000031622776601683795`, 3.5990879018177324`*^-6},
 {0.000039810717055349695`, 5.58370016112697`*^-6},
 {0.0000501187233627272 5`, 8.65857304854778`*^-6},
 {0.0000630957344480192 9`, 0.00001342014829053273`},
 {0.0000794328234724282 2`, 0.00002078963603246997`},
 {0.0001`, 0.00003218888321243618`},
 {0.0001258925411794167 4`, 0.00004981092503608675`},
 {0.0001584893192461114 2`, 0.00007703575809892005`},
 {0.0001995262314968878 8`, 0.00011906869870936809`},
 {0.0002511886431509582`, 0.00018391942155249197`},
 {0.0003162277660168379 4`, 0.00028390177851211895`},
 {0.0003981071705534973 5`, 0.00043792830910882596`},
 {0.0005011872336272725`, 0.00067501510905843`},
 {0.000630957344480193`, 0.0010396256017933814`},
 {0.0007943282347242822`, 0.0015997982802221644`},
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  0.0037771032309573682`}, {0.001584893192461114`, 0.005793606427017428`},
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{0.003981071705534973`, 0.03149081520058106`},
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{0.006309573444801936`, 0.07192223617335669`},
{0.007943282347242822`, 0.10757853682236074`}, {0.01`, 0.15917061625964812`},
{0.012589254117941675`, 0.23185456326841936`},
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{0.01995262314968881`, 0.4558346040848027`},
{0.025118864315095822`, 0.6024970158096243`}, {0.03162277660168379`,
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{0.05011872336272725`, 0.9588369814985114`}, {0.06309573444801936`,
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{0.1`, 0.9999813038111507`}, {0.12589254117941687`, 0.9999999193463172`},
{0.15848931924611143`, 0.9999999999759245`},
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{0.5011872336272725`, 1.`}, {0.6309573444801942`, 1.`},
{0.7943282347242822`, 1.`}, {1.`, 1.`}, {1.2589254117941688`,
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  .695137022301}, {1.584893192461114`,
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  91976254710858119626780887650113228 78`459.74918264081526},
{1.9952623149688828`,
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  99999999999999976603776150930508469417845337141613986322448801 24`622.28441\
  40065977}, {2.5118864315095824`,
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  9969331811173820341382790706965428944139476417917786 3`830.8658416502892},
{3.1622776601683795`,
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{0.01584893192461114`, 0.24458809905274304` + 0.` i},
{0.01995262314968881`, 0.39573140534593476` + 0.` i},
{0.025118864315095822`, 0.5936310952527153` + 0.` i},
{0.03162277660168379`, 0.7984973396002573` + 0.` i},
{0.03981071705534973 4`, 0.9412974796998601` + 0.` i},
{0.05011872336272725`, 0.9932004560943932` + 0.` i},
{0.06309573444801936`, 0.9998390291644069` + 0.` i}, {0.07943282347242822`,
 0.9999997465953634` + 0.` i}, {0.1`, 0.9999999999959165` + 0.` i},
{0.12589254117941687`, 1.` + 3.225142491954387`*^-45 i},
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{0.1995262314968879`, 1.` + 7.604814167737124`*^-70 i},
{0.25118864315095824`, 1.` + 3.4186641276386514`*^-104 i},
{0.31622776601683794`, 1.` + 1.6705852639120784`*^-160 i},
{0.39810717055349776`, 1.` + 1.9661773118882585`*^-246 i}, {0.5011872336272725`,
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   712305:
   604818580492902246398046612848729 95`379.4956583690775 +
  3.404873167236419132637909246147329242146344614966 1`15.954589770191005*^-3:
    74 i}, {0.6309573444801942`,
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   99999999999999999999999999999999999999999999999999999999999999999999999999999:
   99999999999999999999999999995523615408085422972636192859771959154234876047:
   198756`561.3036623779981 +
  1.253146533628167840796821230577701305529206`15.954589770191005*^-555
   i}, {0.7943282347242822`,
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  47205663873612672`4574.322483399568 +
 8.986172143414903153655593302490237426`15.051499781605775*^-4568
  i}, {3.9810717055349776`,
0.99999999999999999999999999999999999999999999999999999999999999999999999999
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{0.003981071705534973`, 0.0015005492160643508` + 0.` i},
{0.005011872336272725`, 0.0032656369054233636` + 0.` i},
{0.006309573444801936`, 0.007054707193345888` + 0.` i},
{0.00794328234724282`, 0.015103878234248191` + 0.` i},
{0.01`, 0.031956051712924816` + 0.` i},
{0.012589254117941675`, 0.06645640724050006` + 0.` i},
{0.01584893192461114`, 0.1344537697107403` + 0.` i},
{0.01995262314968881`, 0.2595533496434107` + 0.` i},
{0.025118864315095822`, 0.4617769931813598` + 0.` i},
{0.03162277660168379`, 0.7175599832462397` + 0.` i},
{0.039810717055349734`, 0.9221463977852586` + 0.` i},
{0.05011872336272725`, 0.9938850508244099` + 0.` i},
{0.06309573444801936`, 0.999956983609777` + 0.` i},
{0.07943282347242822`, 0.9999999968384369` + 1.7850516780818037`*^-34 i},
{0.1`, 1.` + 2.9584802576422846`*^-28 i},
{0.12589254117941687`, 1.` + 1.5155454541289638`*^-39 i},
{0.15848931924611143`, 1.` + 5.072815104828867`*^-64 i},
{0.1995262314968879`, 1.` + 2.470293036725584`*^-108 i},
{0.25118864315095824`, 1.` + 1.1399923207647062`*^-184 i},
{0.31622776601683794`, 1.` + 1.1831176358187376`*^-306 i},
{0.39810717055349776`,
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  i}, {5.011872336272725`,
0.99999999999
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 7.8921985158576491948926486790106970277832 09`14.750433055105809*^-13001
  i}, {7.943282347242821`,
0.99999999999
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{0.25118864315095824`, 1.` + 9.713609093068933`*^-281 i}, {0.31622776601683794`,
 0.99999999999999999999999999999999999999999999999999999999999999999999999999999:
   99999999999999999999999999999999999999999999999999999999999999999999999999999:
   99999999999999999999999999999999999999999999999999999999999999999999999999999:
   
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  50039403377`5991.516549667056 +
 9.534151258495109078002545419437881647355669215271`14.750463180173256*^-5982
  i}, {2.5118864315095824`,
0.99999999999999999999999999999999999999999999999999999999999999999999999999999999999
  
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  999999999999999999999999999999999999999999999999999999999999999999999999999999999999999999999:
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```
 3.636952782628991608359483837882486100145811786127 5`14.750463328921363*^-11:
   317 i}, {5.011872336272725`,
0.99999999999999999999999999999999999999999999999999999999999999999999999999999:
  99999999999999999999999999999999999999999999999999999999999999999999999999999:
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```
N0 = 10^4;
m0 = -0.2;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
letter = "B";

dat = Import[datadir <> ToString[StringForm[
      "prescue_poisson_N``_n``_Es``_mmax``_mwt``_mutmax10_nreps10000.csv",
      NumberForm[N0, 1], n, Es, NumberForm[mmax, {3, 2}], NumberForm[m0, {3, 2}]]]];
dat[[All, {1}]] = dat[[All, {1}]] * Uc /. Uc → n^2 λ / 4 /. λ → 2 Es / n;

figS1b = Show[
  ListLogLogPlot[Re[theory], Joined → True, PlotStyle → Thick,
   PlotRange → {{10^-5, 1}, {10^-6, 1}},
   Frame → {True, True, False, False},
   FrameLabel → {, "Probability of rescue", ,},
   FrameTicks → {True, True, False, False},
   LabelStyle → labelstyle,
   Epilog →
    {Text[Style[letter, 14, Bold, FontFamily → "Helvetica"], Scaled@{0.05, 0.95}],
     Text[Style[StringForm["m0=``", m0], 12, FontFamily → "Helvetica"],
      Scaled@{2 / 10, 9.5 / 10}]},
   FrameTicksStyle → {FontColor → White, Automatic, Automatic, Automatic}
  ],
  ListLogLogPlot[Re[alltheory], Joined → True, PlotStyle → {Thick, Black}],
  ListLogLogPlot[dat, PlotMarkers → {Automatic, Medium}, PlotStyle → Black]
 ]

Clear[mmax, λ, Es, n, m0, N0, U, letter]
```

Numerical data for panel C

```
(*N0=10^4;
m0=-0.3;
mmax=0.5;
λ=2Es/n;
Es=0.01;
n=4;

rate4=Table[Λ4InterpolatedU[m0,mmax,λ,n,x],{x,Umin,Umax,Ustep}];
rate3=Table[Λ3InterpolatedU[m0,mmax,λ,n,x],{x,Umin,Umax,Ustep}];
rate2=Table[Λ2InterpolatedU[m0,mmax,λ,n,x],{x,Umin,Umax,Ustep}];
rate1=Table[Λ1InterpolatedU[m0,mmax,λ,n,x],{x,Umin,Umax,Ustep}];
Ulist=Table[10^x,{x,Umin,Umax,Ustep}];
theory={
  Table[{Ulist[[i]],prescue/.p0→prescuem[m0,rate1[[i]]]},{i,Length[Ulist]}],
  Table[{Ulist[[i]],prescue/.p0→prescuem[m0,rate2[[i]]]},{i,Length[Ulist]}],
  Table[{Ulist[[i]],prescue/.p0→prescuem[m0,rate3[[i]]]},{i,Length[Ulist]}],
  Table[{Ulist[[i]],prescue/.p0→prescuem[m0,rate4[[i]]]},{i,Length[Ulist]}]
 };
alltheory=Table[{Ulist[[i]],
   prescue/.p0→prescuem[m0,rate1[[i]]+rate2[[i]]+rate3[[i]]+rate4[[i]]]},{i,
   Length[Ulist]}];

Clear[mmax,λ,Es,n,m0,N0,U]*)

theory = {{{0.00001`, 6.425313789915066`*^-7},
    {0.00001258925411794166 1`, 8.088992932142602`*^-7}, {0.00001584893192461114`,
     1.018343781855613`*^-6}, {0.00001995262314968878 6`, 1.2820181188866187`*^-6},
    {0.00002511886431509582`, 1.6139654472890896`*^-6},
    {0.00003162277660168379 5`, 2.031861507045818`*^-6},
    {0.00003981071705534969 5`, 2.557961690463628`*^-6},
    {0.00005011872336272725`, 3.220282207117009`*^-6},
    {0.00006309573444801929`, 4.054093288852201`*^-6},
    {0.00007943282347242822`, 5.103798812799987`*^-6},
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    {0.00019952623149688788`, 0.00001282011392511606 1`},
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    {0.00079432823472428 22`, 0.00005103681593787712`},
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    {0.0025118864315095 82`, 0.00016138367485374339`},
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  999999999
```

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  999999999
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  999999999
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9999999999

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  999999999
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9999999999

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  99999999999
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  999999999
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```
  999999999
```

9999999999

9999999999

9999999999

```
 999999999
```

```
N0 = 10^4;
m0 = -0.3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
letter = "C";

dat = Import[datadir <> ToString[StringForm[
      "prescue_poisson_N``_n``_Es``_mmax``_mwt``_mutmax10_nreps10000.csv",
      NumberForm[N0, 1], n, Es, NumberForm[mmax, {3, 2}], NumberForm[m0, {3, 2}]]]];
dat[[All, {1}]] = dat[[All, {1}]] * Uc /. Uc → n^2 λ / 4 /. λ → 2 Es / n;

figS1c = Show[
  ListLogLogPlot[Re[theory], Joined → True, PlotStyle → Thick,
   PlotRange → {{10^-5, 1}, {10^-6, 1}},
   Frame → {True, True, False, False},
   FrameLabel → {"Mutation probability", "Probability of rescue", ,},
   FrameTicks → {True, True, False, False},
   LabelStyle → labelstyle,
   Epilog →
    {Text[Style[letter, 14, Bold, FontFamily → "Helvetica"], Scaled@{0.05, 0.95}],
     Text[Style[StringForm["m0=``", m0], 12, FontFamily → "Helvetica"],
      Scaled@{2 / 10, 9.5 / 10}]}
  ],
  ListLogLogPlot[Re[alltheory], Joined → True, PlotStyle → {Thick, Black}],
  ListLogLogPlot[dat, PlotMarkers → {Automatic, Medium}, PlotStyle → Black]
 ]

Clear[mmax, λ, Es, n, m0, N0, U, letter]
```

Figure S1

```
GraphicsColumn[{figS1a, figS1b, figS1c}, Spacings → -30, ImageSize → 350]
Export[supfigdir <> "FigureS1.eps", %];
```

Approximating the probability of 1-step rescue

Replicating Anciaux et al 2018, Genetics

Change of variables

We first introduce the variables y = m/mmax, ywt = mwt/mmax, ρmax = mmax/λ, θ = n/2. The distribution of y among new mutations is then

```
fy = e^(-(2-y-ywt) ρmax) ρmax^θ (1 - y)^(θ-1)
   HypergeometricOF1Regularized[θ, (1 - y) (1 - ywt) ρmax^2];
Simplify[fy == fm[y mmax, ywt mmax, mmax, mmax / ρmax, 2 θ] / D[m/mmax, m], {ρmax > 0, 0 < y < 1}]
fy /. y → m / mmax /. ywt → mwt / mmax /. ρmax → mmax / λ /. θ → n / 2;
Simplify[% D[m / mmax, m] == fm[m, mwt, mmax, λ, n], {mmax > 0, λ > 0}]
```

```
True

True
```

Approximate hypergeometric function

We next want to approximate the hypergeometric function in fy.

Note first that Hypergeometric0F1Regularized[θ,z] is defined in *Mathematica* as Hypergeometric0F1[θ,z]/Gamma[θ]:

```
HypergeometricOF1Regularized[θ, z];
HypergeometricOF1[θ, z] / Gamma[θ];
FullSimplify[% / %%]
```

```
1
```

Next note that Hypergeometric0F1[θ,z] can be written as $\frac{\text{Gamma}[\theta]}{\left(\sqrt{z}\right)^{\theta-1}}$ BesselI$\left[\theta-1,\ 2\sqrt{z}\right]$ using 9.6.47 of Abramowitz and Stegun (1964):

```
HypergeometricOF1[θ, z];
Gamma[θ] / (Sqrt[z])^(θ-1) BesselI[θ - 1, 2 Sqrt[z]];
FullSimplify[% / %%]
```

```
1
```

Thus, the Hypergeometric0F1Regularized[θ,z] can be written as $\frac{1}{\left(\sqrt{z}\right)^{\theta-1}}$ BesselI$\left[\theta-1,\ 2\sqrt{z}\right]$:

```
HypergeometricOF1Regularized[θ, z];
```

$$\frac{1}{\left(\sqrt{z}\right)^{\theta-1}}\,\text{BesselI}\left[\theta-1,\,2\sqrt{z}\right];$$

```
FullSimplify[% / %%]
```

1

Finally, 9.7.1 of Abramowitz and Stegun (1964) gives an asymptotic expansion for BesselI that holds for large |z|:

$$\text{BesselI}[\theta-1,\,2\,\text{Sqrt}[z]]\ /.\ \text{BesselI}\to\text{Function}\left[\{v,\,x\},\ \frac{e^{x}}{\sqrt{2\,\pi\,x}}\left(1-\frac{\mu-1}{8\,x}+\frac{(\mu-1)\,(\mu-9)}{2!\,(8\,x)^{2}}-\frac{(\mu-1)\,(\mu-9)\,(\mu-25)}{3!\,(8\,x)^{3}}+\text{added}\right)\ /.\ \mu\to 4\,v^{2}\right];$$

where the kth term added to “1” is obtained by taking the previous term and multiplying by $-\frac{\left(\mu-(2\,k-1)^{2}\right)}{k\,(8\,z)}$.

For large z, the Bessel function will be dominated by the leading term:

$$\text{BesselI}[\theta-1,\,2\,\text{Sqrt}[z]]\ /.\ \text{BesselI}\to\text{Function}\left[\{v,\,x\},\ \frac{e^{x}}{\sqrt{2\,\pi\,x}}\right]$$

$$\frac{e^{2\sqrt{z}}}{2\sqrt{\pi}\,z^{1/4}}$$

This allows us to conclude that $\text{HypergeometricOF1Regularized}[\theta,\,z]=\frac{1}{\left(\sqrt{z}\right)^{\theta-1}}\,\text{BesselI}\left[\theta-1,\,2\sqrt{z}\right]$ can be approximated for z large as $\frac{1}{\left(\sqrt{z}\right)^{\theta-1}}\,\frac{e^{2\sqrt{z}}}{2\sqrt{\pi}\,z^{1/4}}$, which upon rearranging gives $\frac{e^{2\sqrt{z}}\,z^{\frac{1}{4}(1-2\theta)}}{2\sqrt{\pi}}$.

We can therefore use the following approximation as ρmax = mmax/λ goes to infinity, i.e., mutant growth rates are much less than maximal

```
fya = FullSimplify[
  fy /. HypergeometricOF1Regularized → Function[{θ, z}, 1/(2 Sqrt[π]) z^((1-2 θ)/4) e^(2 Sqrt[z])] //
   PowerExpand, 0 < y < 1 && ρmax > 0 && ywt < 0 && θ ≥ 1 / 2]
FullSimplify[% == e^(-v[y]) (1 - y)^(θ/2 - 3/4) (1 - ywt)^(1/4 - θ/2) Sqrt[ρmax] / (2 Sqrt[π]) /.
  v[y] → (2 - ywt - 2 Sqrt[(1 - ywt) (1 - y)] - y) ρmax,
 {ρmax > 0, ywt < 0, 0 < y < 1, θ ≥ 1 / 2}] (*compare to eqn A9*)
```

$$-\left(e^{\left(-2+y+2\sqrt{(-1+y)\,(-1+ywt)}+ywt\right)\rho max}\left(\frac{-1+y}{-1+ywt}\right)^{\theta/2}(-1+ywt)\sqrt{\rho max}\right)\Big/\left(2\sqrt{\pi}\,((-1+y)\,(-1+ywt))^{3/4}\right)$$

```
True
```

This does great for large ρmax, especially at the tails

```
θ = 2; ywt = -0.2; ρmax = {3, 10, 20}; fy;
Plot[%, {y, -3, 1}, PlotRange → All, PlotLegends → LineLegend[
    Table[StringForm["ρmax = ``", Round[ρmax[[i]]]], {i, Length[ρmax]}]]];
fya;
Plot[%, {y, -3, 1}, PlotRange → All, PlotStyle → {{Dashed, Black}}];
Show[%%%, %, AxesLabel → {y, "fy[y]"}]
    fy
 ------------;
 fy /. y → 0
Plot[%, {y, 0, 1}, PlotRange → All, PlotLegends → LineLegend[
    Table[StringForm["ρmax = ``", Round[ρmax[[i]]]], {i, Length[ρmax]}]]];
    fya
 ------------;
 fya /. y → 0
Plot[%, {y, 0, 1}, PlotRange → All, PlotStyle → {{Dashed, Black}}];
Show[%%%, %, AxesLabel → {y, "fy[y]/fy[0]"}]
θ =.; ywt =.; ρmax =.;
```

Change of variables

We now consider the variable $\psi = 2\left(1 - \sqrt{1 - y}\right)$, which varies between 0 and 2 as y varies between 0 and 1, and is $2\,\frac{A}{B}$, where A is the phenotypic distance to the closest critical phenotype and B is the distance from a critical phenotype to the optimal

```
2 (Sqrt[1 - y] - 1) /. y → m/mmax // Expand
FullSimplify[
 2 (x0 - xc)/xc == % /. Flatten[Solve[{Sqrt[2 (mmax - m)] == x0, Sqrt[2 mmax] == xc}, {mmax, m}]] //
  Expand, x0 > 0 && xc > 0]
```

$$-2 + 2\sqrt{1 - \frac{m}{mmax}}$$

True

The pdf of ψ is then approximately

```
Solve[{2 (1 - Sqrt[1 - y]) == ψ, 2 (1 - Sqrt[1 - ywt]) == ψwt}, {y, ywt}] // Flatten
Simplify[Abs[D[y /. %, ψ]] fya /. %, {0 < ψ < 2, ψwt < 0, ρmax > 0, θ ≥ 1 / 2}]
FullSimplify[% == (e^(-1/4 ρmax (ψ-ψwt)^2) Sqrt[ρmax] ((2-ψ)/(2-ψwt))^(-1/2+θ))/(2 Sqrt[π]), {0 < ψ < 2, ψwt < 0, ρmax > 0, θ ≥ 1 / 2}]
(*compare to eqn A10*)
fψ = (e^(-1/4 ρmax (ψ-ψwt)^2) Sqrt[ρmax] ((2-ψ)/(2-ψwt))^(-1/2+θ))/(2 Sqrt[π]);
```

$$\left\{y \to \frac{1}{4}\left(4\,\psi - \psi^2\right),\ ywt \to \frac{1}{4}\left(4\,\psi wt - \psi wt^2\right)\right\}$$

$$-\frac{e^{-\frac{1}{4}\rho max\,(\psi-\psi wt)^2}\sqrt{\rho max}\left(\frac{-2+\psi}{-2+\psi wt}\right)^{1+\theta}(-2+\psi wt)^3}{2\sqrt{\pi}\left((-2+\psi)^2\,(-2+\psi wt)^2\right)^{3/4}}$$

True

Note that this is a normal distribution, with mean ψwt and variance $\frac{2}{\rho max}$, as $\left(\frac{-2+\psi}{-2+\psi wt}\right)^{-\frac{1}{2}+\theta} \to 1$ (which is reasonable when the absolute values of ψ and ψwt are much less than 2, i.e., growth rates small relative to max, or when θ is 1/2, i.e., when dimensionality is low).

```
fψ /. ((2 - ψ)/(2 - ψwt))^(-1/2+θ) → 1;

Simplify[% == Simplify[PDF[NormalDistribution[ψwt, Sqrt[2/ρmax]], ψ], ρmax > 0],
 {0 < ψ < 2, ψwt < 0, ρmax > 0, θ > 1 / 2}]
```

```
True
```

Laplace approximation and compact form (equations 19 and 20)

Anciaux et al's equation A5 is the integral of the following over y from 0 to 1

```
U/(-mwt) pest[m] fy /. m → mmax y
```

$$-\frac{1}{\text{mwt}}\, e^{(-2+y+\text{ywt})\,\rho\text{max}}\left(1-e^{-2\,\text{mmax}\,y}\right) U\,(1-y)^{-1+\theta}\,\rho\text{max}^{\theta}\,\text{HeavisideTheta}[\text{mmax}\,y]\,\text{Hypergeometric0F1Regularized}\left[\theta,\,(1-y)\,(1-\text{ywt})\,\rho\text{max}^2\right]$$

which, using the approximation in equation A9, is nearly

```
U/(-mwt) pest[m] fya /. m → mmax y
```

$$\left(e^{\left(-2+y+2\sqrt{(-1+y)\,(-1+\text{ywt})}+\text{ywt}\right)\rho\text{max}}\left(1-e^{-2\,\text{mmax}\,y}\right) U\left(\frac{-1+y}{-1+\text{ywt}}\right)^{\theta/2}(-1+\text{ywt})\,\sqrt{\rho\text{max}}\,\text{HeavisideTheta}[\text{mmax}\,y]\right)\Big/\left(2\,\text{mwt}\,\sqrt{\pi}\,\left((-1+y)\,(-1+\text{ywt})\right)^{3/4}\right)$$

which is roughly the integral of the following over ψ from 0 to 2 (A10)

$$\frac{U}{-\text{mwt}}\,\frac{e^{-\frac{1}{4}\rho\text{max}\,(\psi-\psi\text{wt})^2}\sqrt{\rho\text{max}}\left(\frac{2-\psi}{2-\psi\text{wt}}\right)^{-\frac{1}{2}+\theta}}{2\sqrt{\pi}}$$

$$-\frac{e^{-\frac{1}{4}\rho\text{max}\,(\psi-\psi\text{wt})^2}\,U\sqrt{\rho\text{max}}\left(\frac{2-\psi}{2-\psi\text{wt}}\right)^{-\frac{1}{2}+\theta}}{2\,\text{mwt}\,\sqrt{\pi}}$$

Anciuaux et al 2018 say we can write this as (A11)

```
h[ψ_] := ((1 - ψ / 2)/(1 - ψwt / 2))^(θ - 1/2) (1 - e^(-2 mmax y)) /. y → ψ (1 - ψ / 4)
q[ψ_] := 1/4 (ψ - ψwt)^2
U/(-mwt) Sqrt[ρmax]/(2 Sqrt[π]) h[ψ] Exp[-ρmax q[ψ]]
```

$$-\frac{1}{2\,\mathrm{mwt}\,\sqrt{\pi}}\,e^{-\frac{1}{4}\rho\mathrm{max}\,(\psi-\psi\mathrm{wt})^2}\left(1-e^{-2\,\mathrm{mmax}\left(1-\frac{\psi}{4}\right)\psi}\right)\mathrm{U}\sqrt{\rho\mathrm{max}}\left(\frac{1-\frac{\psi}{2}}{1-\frac{\psi\mathrm{wt}}{2}}\right)^{-\frac{1}{2}+\theta}$$

which appears to be true only when we ignore this second term they have in h (but this will drop out anyway when we take the leading order in the next step)

$$\mathrm{Simplify}\left[\left(-\frac{1}{2\,\mathrm{mwt}\,\sqrt{\pi}}\,e^{-\frac{1}{4}\rho\mathrm{max}\,(\psi-\psi\mathrm{wt})^2}\left(1-e^{-2\,\mathrm{mmax}\left(1-\frac{\psi}{4}\right)\psi}\right)\mathrm{U}\sqrt{\rho\mathrm{max}}\left(\frac{1-\frac{\psi}{2}}{1-\frac{\psi\mathrm{wt}}{2}}\right)^{-\frac{1}{2}+\theta}\right)\Big/\left(\frac{\mathrm{U}}{-\mathrm{mwt}}\,\frac{e^{-\frac{1}{4}\rho\mathrm{max}\,(\psi-\psi\mathrm{wt})^2}\sqrt{\rho\mathrm{max}}\left(\frac{2-\psi}{2-\psi\mathrm{wt}}\right)^{-\frac{1}{2}+\theta}}{2\sqrt{\pi}}\right)\right]$$

$$1-e^{\frac{1}{2}\mathrm{mmax}\,(-4+\psi)\,\psi}$$

As ρmax=mmax/λ goes to ∞ the Exp term dominates and we take the leading order of h

```
h0 = Normal[Series[h[ψ], {ψ, 0, 1}]]
```

$$2\,\mathrm{mmax}\,\psi\left(\frac{1}{1-\frac{\psi\mathrm{wt}}{2}}\right)^{-\frac{1}{2}+\theta}$$

Now taking the integral over ψ from 0 to ∞ we get A12

```
Integrate[U/(-mwt) Sqrt[ρmax]/(2 Sqrt[π]) h0 Exp[-ρmax q[ψ]], {ψ, 0, ∞},
   Assumptions → {ρmax > 0, ψwt < 0}] /. mwt → ψwt (1 - ψwt / 4) mmax;
```

$$\mathrm{FullSimplify}\left[\%==\mathrm{U}\,\frac{\left(1-\frac{\psi\mathrm{wt}}{2}\right)^{\frac{1}{2}-\theta}}{1-\frac{\psi\mathrm{wt}}{4}}\left(\frac{\mathrm{Exp}[-\alpha]}{\sqrt{\pi\,\alpha}}-\mathrm{Erfc}\left[\sqrt{\alpha}\right]\right)\ /.\ \alpha\text{ -> }\frac{\rho\mathrm{max}\,\psi\mathrm{wt}^2}{4},\ \{\psi\mathrm{wt}<0,\ \rho\mathrm{max}>0,\ \mathrm{U}>0\}\right]$$

```
True
```

$$\mathrm{AnciauxEqnA12} = \mathrm{U}\,\frac{\left(1-\frac{\psi\mathrm{wt}}{2}\right)^{\frac{1}{2}-\theta}}{1-\frac{\psi\mathrm{wt}}{4}}\left(\frac{\mathrm{Exp}[-\alpha]}{\sqrt{\pi\,\alpha}}-\mathrm{Erfc}\left[\sqrt{\alpha}\right]\right);$$

As m0 and thus ψwt gets small, the rate of 1-step rescue becomes

```
Simplify[
 Series[m0 AnciauxEqnA12 /. m0 → mmax ψwt (1 - ψwt / 4) /. α → ρmax ψwt^2/4, {ψwt, 0, 0}] /.
   ρmax → mmax / λ // Normal, {mmax > 0, λ > 0}]
```

$$\frac{2\,U\sqrt{\text{mmax}\,\lambda}}{\sqrt{\pi}}$$

Approximating the probability of 2-step rescue

Defining "sufficiently critical" and "sufficiently non-critical" regimes (equation 8)

The probability of rescue from a new lineage with growth rate m and rescue rate Λ is

```
prescuem[m, Λ]
```

$$1 - e^{\left(1-\sqrt{1+\frac{2\Lambda}{\text{Abs}[m]^2}}\right)\text{Abs}[m]}$$

Let's now consider single mutants with growth rates far from 0, such that $\Lambda(m) << m^2$. We can then approximate this by

```
Normal[Series[prescuem[m, Λ] /. Λ → ϵ Abs[m]^2, {ϵ, 0, 1}]] /. ϵ → Λ/Abs[m]^2
```

$$\frac{\Lambda}{\text{Abs}[m]}$$

Alternatively, consider single mutants with growth rates sufficiently near 0, such that $\Lambda(m) >> m^2$. We then have approximately

```
Limit[prescuem[m, Λ], m → 0]
Normal[Series[% /. Λ → x^2, {x, 0, 1}]] /. x → Sqrt[Λ]
```

$$1 - e^{-\sqrt{2}\sqrt{\Lambda}}$$

$$\sqrt{2}\sqrt{\Lambda}$$

So we should transition from one approx to the other at

```
Solve[Sqrt[2 Λ] == Λ / m, m] // Flatten
```

$$\left\{m \to \frac{\sqrt{\Lambda}}{\sqrt{2}}\right\}$$

Check approximations and transition point (for given Λ)

```
prescuem[m, Λ] /. Λ → {10^-3, 10^-4, 10^-5};
Show[LogLogPlot[%, {m, 0.0001, 1}, PlotRange → All(*,
  PlotLegends→LineLegend[{"U_R = 10^-3","U_R = 10^-4","U_R = 10^-5"}]*)],
 LogLogPlot[If[m < Sqrt[# / 2], Sqrt[2 #], # / Abs[m]] & /@ {10^-3, 10^-4, 10^-5},
  {m, 0.0001, 1}, PlotStyle → {Dashed, Black}], AxesLabel → {"|m|", "p_2"}]
```

Approximate probability of rescue: sufficiently critical single mutants

House of Cards approximation (equation 9)

When $m << \sqrt{\Lambda/2}$ the probability of 2-step rescue from this single mutant lineage, as calculated above, is $\sqrt{2\,\Lambda}$. In this circumstance we can further approximate, since $\Lambda[m] \sim \Lambda[0]$, f(m|m0) ~ f(0|m0), and pest(m)~0. So the rate of 2-step "sufficiently critical" rescue from single mutants is roughly

```
U Integrate[fm[0, m0, mmax, λ, n] Sqrt[2 Λ0], {m, -Sqrt[Λ0 / 2], Sqrt[Λ0 / 2]}];
% == 2 U fm[0, m0, mmax, λ, n] Λ0
True
```

with $\Lambda 0 = \Lambda 1[0,\text{mmax},\lambda,n,U]$.

Check integration bounds:

```
U = 2 * 10^-5;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;

{mneg = FindRoot[2 m^2 - Λ1[m, mmax, λ, n, U], {m, -0.1}],
 mpos = FindRoot[2 m^2 - Λ1[m, mmax, λ, n, U], {m, 0.1}]}
pr0 = Sqrt[Λ1[0, mmax, λ, n, U] / 2];

Plot[{Abs[m], pr0, Sqrt[Λ1[m, mmax, λ, n, U] / 2]}, {m, 2 m /. mneg, 2 m /. mpos},
 PlotRange → {0, 1.2 pr0}, PerformanceGoal → "Speed"]

Clear[mmax, λ, Es, n, n0, U]
```

```
{{m → -0.000655285}, {m → 0.00066309}}
```

Now check the contribution of single mutant growth rates to 2-step sufficiently critical rescue

```
U = 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
m0 = -0.3;

{mneg = FindRoot[2 m^2 - Λ1[m, mmax, λ, n, U], {m, -0.1}],
  mpos = FindRoot[2 m^2 - Λ1[m, mmax, λ, n, U], {m, 0.1}]};
pr0 = Sqrt[Λ1[0, mmax, λ, n, U] / 2 ];

{
  fm[m, m0, mmax, λ, n] (1 - pest[m]) prescuem[m, Λ1[m, mmax, λ, n, U]],
  fm[m, m0, mmax, λ, n] (1 - pest[m]) Sqrt[2 Λ1[m, mmax, λ, n, U]]
   HeavisideTheta[(m - (m /. mneg)) ((m /. mpos) - m)],
   fm[0, m0, mmax, λ, n] Sqrt[2 Λ1[0, mmax, λ, n, U]] HeavisideTheta[(m + pr0) (pr0 - m)],
  fm[0, m0, mmax, λ, n] (1 - pest[m]) prescuem[m, Λ1[m, mmax, λ, n, U]]
 };

Plot[%, {m, 10 m /. mneg, 10 m /. mpos}, PlotRange → {0, All}, Filling → Bottom,
 PlotLegends → LineLegend[{"exact", "critical", "critical approx.", "HoC"}],
 PerformanceGoal → "Speed"]

Clear[mmax, λ, Es, n, U, m0]
```

Finally, let’s check the total rates of rescue across all m

```
U = 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;

{mneg = FindRoot[2 m^2 - Λ1[m, mmax, λ, n, U], {m, -0.1}],
  mpos = FindRoot[2 m^2 - Λ1[m, mmax, λ, n, U], {m, 0.1}]};
pr0 = Sqrt[Λ1[0, mmax, λ, n, U] / 2];

{

  Table[{m0, NIntegrate[fm[m, m0, mmax, λ, n] (1 - pest[m]) Sqrt[2 Λ1[m, mmax, λ, n, U]],
      {m, m /. mneg, m /. mpos}]}, {m0, -0.8 mmax, -0.1 mmax, 0.1 mmax}]

 };

Show[
 ListLogPlot[%],
 LogPlot[2 fm[0, m0, mmax, λ, n] Λ1[0, mmax, λ, n, U],
  {m0, -0.8 mmax, -0.1 mmax}, PerformanceGoal → "Speed"]
]

Clear[mmax, λ, Es, n, U, n0]
```

Closed form approximation (equations 10 and 11)

OK, so a good approximation for sufficiently critical rescue from a mutant is

```
2 Λ0 fm[0, m0, mmax, λ, n];
```

with Λ0=Λ1[0,mmax,λ,n,U]

but note that, while this has reduced a lot of complexity, $\Lambda 0 = U \int f(m \mid 0)\, p_{\text{est}}(m)\, dm$ is still an integral we have to compute. Fortunately however, we can just use the approximations Anciaux et al used (and we replicated above), so that when we take m=mmax $\psi(1-\psi/4)$ to zero we have Λ0 as roughly

```
(*multiply by m because anciaux A12 accounts for number
 of individuals in lineage, which they estimate as 1/m*)
```

$$m\,\text{AnciauxEqnA12} \;/.\; \psi wt \to \psi \;/.\; m \to mmax\,\psi\,(1-\psi/4) \;/.\; \alpha \to \frac{\rho max\,\psi^2}{4};$$

```
Limit[%, ψ → 0];
Simplify[% /. ρmax → mmax / λ, {mmax > 0, λ > 0}]
```

$$\frac{2\,U\,\sqrt{mmax\,\lambda}}{\sqrt{\pi}}$$

so that when we include mutation rate from the wildtype we have

$$4\,U^2\,fm[0,\,m0,\,mmax,\,\lambda,\,n]\,\sqrt{mmax\,\lambda/\pi};$$

We can further approximate fm to give a simpler analytic form. Using the approximation over ψ above (and incorporating the change in scale as we have integrated over fm above) we get

$$\text{Simplify}\Big[4\,U^2\,\sqrt{mmax\,\lambda/\pi}\,\left(D\left[2\left(1-\sqrt{1-m/mmax}\right),m\right]f\psi \;/.\; \psi\to 0\right) \;/.\; mmax\to\rho max\,\lambda \;/.\; m\to 0,$$
$$\{\lambda>0,\,\theta>1/2,\,\psi wt<0\}\Big] \;/.\; -\frac{\rho max\,\psi wt^2}{4} \to -\alpha\,(*/.\theta\to n/2*) \;/.\; \psi wt\to\psi_0 \;//\; \text{Simplify}$$

$$\text{FullSimplify}\left[U^2\left(1-\frac{\psi_0}{2}\right)^{\frac{1}{2}-\theta} e^{-\alpha}\,\frac{2}{\pi} == \%\right]$$

$$\frac{2^{\frac{1}{2}+\theta}\,e^{-\alpha}\,U^2\,(2-\psi_0)^{\frac{1}{2}-\theta}}{\pi}$$

```
True
```

Check contributions across m

```
Clear[m0]
```

```
U = 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
m0 = -0.3;

{mneg = FindRoot[2 m^2 - Λ1[m, mmax, λ, n, U], {m, -0.1}],
  mpos = FindRoot[2 m^2 - Λ1[m, mmax, λ, n, U], {m, 0.1}]};
pr0 = Sqrt[Λ1[0, mmax, λ, n, U] / 2];

{
  fm[m, m0, mmax, λ, n] (1 - pest[m]) prescuem[m, Λ1[m, mmax, λ, n, U]],
  fm[m, m0, mmax, λ, n] (1 - pest[m]) Sqrt[2 Λ1[m, mmax, λ, n, U]]
   HeavisideTheta[(m - (m /. mneg)) ((m /. mpos) - m)],
   fm[0, m0, mmax, λ, n] Sqrt[2 Λ1[0, mmax, λ, n, U]] HeavisideTheta[(m + pr0) (pr0 - m)],
  fm[0, m0, mmax, λ, n] (1 - pest[m]) prescuem[m, Λ1[m, mmax, λ, n, U]],
  fm[0, m0, mmax, λ, n] Sqrt[2 (2 U Sqrt[mmax λ]) / Sqrt[π]]
   HeavisideTheta[(m + Sqrt[(U Sqrt[mmax λ]) / Sqrt[π]]) (Sqrt[(U Sqrt[mmax λ]) / Sqrt[π]] - m)],
  (D[2 (1 - Sqrt[1 - m / mmax]), m] fψ /. ψ → 0 /. ψwt → 2 (1 - Sqrt[1 - m0 / mmax]) /.
      ρmax → mmax / λ /. θ → n / 2 /. m → 0) Sqrt[2 (2 U Sqrt[mmax λ]) / Sqrt[π]]
   HeavisideTheta[(m + Sqrt[(U Sqrt[mmax λ]) / Sqrt[π]]) (Sqrt[(U Sqrt[mmax λ]) / Sqrt[π]] - m)]
 };

Plot[%, {m, 10 m /. mneg, 10 m /. mpos}, PlotRange → {0, All}, Filling → Bottom,
 PlotLegends → LineLegend[{"exact", "critical", "critical approx.", "HoC",
    "critical closed form", "simpler closed form"}], PerformanceGoal → "Speed"]

Clear[mmax, λ, Es, n, U, m0]
```

And check total rate

```
U = 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;

{mneg = FindRoot[2 m^2 - Λ1[m, mmax, λ, n, U], {m, -0.1}],
  mpos = FindRoot[2 m^2 - Λ1[m, mmax, λ, n, U], {m, 0.1}]};
pr0 = Sqrt[Λ1[0, mmax, λ, n, U] / 2];

{
  Table[{m0, NIntegrate[U fm[m, m0, mmax, λ, n] (1 - pest[m]) Sqrt[2 Λ1[m, mmax, λ, n, U]],
      {m, m /. mneg, m /. mpos}]}, {m0, -0.8 mmax, -0.1 mmax, 0.1 mmax}]
 };

Show[
 LogPlot[
  {U 2 Λ0approx fm[0, m0, mmax, λ, n],
   U^2 (1 - ψ0/2)^(1/2 - θ) e^-α 2/π /. α → ρmax ψ0^2 / 4 /. ψ0 → 2 (1 - Sqrt[1 - m0 / mmax]) /. ρmax → mmax / λ /.
    θ → n / 2}, {m0, -0.8 mmax, -0.1 mmax},
  PlotStyle → Thick,
  Frame → {True, False, False, True},
  FrameLabel → {"Wildtype growth rate", , , "Rate of rescue"},
  FrameTicks → {True, False, False, True},
  LabelStyle → labelstyle,
  PlotLegends → Placed[LineLegend[Style[#, 12, FontFamily → "Helvetica"] & /@
      {"approx", "simpler approx"}], Scaled@{3 / 4, 1 / 4}],
  PerformanceGoal → "Speed"
 ],
 ListLogPlot[%, PlotMarkers → {Automatic, Medium}, PlotStyle → Black]
]

Clear[mmax, λ, Es, n, U, mwt]
```

Approximate probability of rescue: sufficiently non-critical single mutants

Approximation 1

When $m >> \sqrt{\Lambda/2}$ the probability of 2-step rescue from this single mutant lineage, as calculated above, is roughly $\frac{\Lambda}{\text{Abs}[m]}$.

We have seen above that the solutions to $m^2 = \Lambda[m]/2$ can be approximated well by $m = \pm\sqrt{\Lambda[0]/2}$.

Check the contribution of single mutant growth rates to 2-step sufficiently critical rescue

```
U = 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
mwt = -0.3;

{mneg = FindRoot[2 m1^2 - Λ1[m1, mmax, λ, n, U], {m1, -0.1}],
  mpos = FindRoot[2 m1^2 - Λ1[m1, mmax, λ, n, U], {m1, 0.1}]};
pr0 = Sqrt[Λ1[0, mmax, λ, n, U] / 2 ];

{
  fm[m1, mwt, mmax, λ, n] (1 - pest[m1]) prescuem[m1, Λ1[m1, mmax, λ, n, U]],
  fm[m1, mwt, mmax, λ, n] (1 - pest[m1])
    Λ1[m1, mmax, λ, n, U] / Abs[m1] HeavisideTheta[(-pr0 - m1) (pr0 - m1)]

 };

Plot[%, {m1, 50 m1 /. mneg, 10 m1 /. mpos}, PlotRange → {0, All}, Filling → Bottom,
 PlotLegends → LineLegend[{"exact", "non-critical"}], PerformanceGoal → "Speed"]

Clear[mmax, λ, Es, n, U, mwt]
```

And let’s check the total rates of rescue across all m1

```
n0 = 10^4;
U = 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;

{mneg = FindRoot[2 m1^2 - Λ1[m1, mmax, λ, n, U], {m1, -0.1}],
  mpos = FindRoot[2 m1^2 - Λ1[m1, mmax, λ, n, U], {m1, 0.1}]};
pr0 = Sqrt[Λ1[0, mmax, λ, n, U] / 2];

{

  Table[{mwt, NIntegrate[
      fm[m1, mwt, mmax, λ, n] (1 - pest[m1]) prescuem[m1, Λ1[m1, mmax, λ, n, U]],
      {m1, mwt, mmax}]}, {mwt, -0.8 mmax, -0.1 mmax, 0.1 mmax}],
  Table[{mwt, NIntegrate[fm[m1, mwt, mmax, λ, n] Λ1[m1, mmax, λ, n, U]/Abs[m1]
       , {m1, mwt, -pr0}] +
      NIntegrate[fm[m1, mwt, mmax, λ, n] (1 - pest[m1]) Λ1[m1, mmax, λ, n, U]/Abs[m1]
       , {m1, pr0, mmax}]}, {mwt, -0.8 mmax, -0.1 mmax, 0.1 mmax}]

 };

Show[
 ListLogPlot[%, PlotLegends → LineLegend[{"exact", "non-critical"}]]
]

Clear[mmax, λ, Es, n, U, n0]
```

Approximation 2

We can next borrow the approximation of Λ1 from Anciaux et al. (their eqn A12 without the 1/mwt term)

```
Abs[mwt] AnciauxEqnA12
```

$$\frac{U\left(1-\frac{\psi wt}{2}\right)^{\frac{1}{2}-\Theta}\,\mathrm{Abs}[mwt]\left(\frac{e^{-\alpha}}{\sqrt{\pi}\,\sqrt{\alpha}}-\mathrm{Erfc}\left[\sqrt{\alpha}\right]\right)}{1-\frac{\psi wt}{4}}$$

Check contributions of m1

```
U = 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
mwt = -0.3;

{mneg = FindRoot[2 m1^2 - Λ1[m1, mmax, λ, n, U], {m1, -0.1}],
  mpos = FindRoot[2 m1^2 - Λ1[m1, mmax, λ, n, U], {m1, 0.1}]};
pr0 = Sqrt[Λ1[0, mmax, λ, n, U] / 2 ];

{
  fm[m1, mwt, mmax, λ, n] (1 - pest[m1]) prescuem[m1, Λ1[m1, mmax, λ, n, U]],
  fm[m1, mwt, mmax, λ, n] (1 - pest[m1])
    Λ1[m1, mmax, λ, n, U] / Abs[m1] HeavisideTheta[(-pr0 - m1) (pr0 - m1)],
  (fm[m1, mwt, mmax, λ, n] (1 - pest[m1]) (Abs[m1] AnciauxEqnA12) / Abs[m1] /. ψwt → ψ /.
        m → mmax ψ (1 - ψ / 4) /. α → ρmax ψ^2 / 4 /. ψ → 2 (1 - Sqrt[1 - m / mmax]) /.
      ρmax → mmax / λ /. θ → n / 2 /. m → m1) HeavisideTheta[(-pr0 - m1) (pr0 - m1)]
 };

Plot[%, {m1, 50 m1 /. mneg, 10 m1 /. mpos}, PlotRange → {0, All}, Filling → Bottom,
 PlotLegends → LineLegend[{"exact", "non-critical", "non-critical anciaux"}],
 PerformanceGoal → "Speed"]

Clear[mmax, λ, Es, n, U, mwt]
```

and try with smaller mwt

```
U = 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
mwt = -0.2;

{mneg = FindRoot[2 m1^2 - Λ1[m1, mmax, λ, n, U], {m1, -0.1}],
  mpos = FindRoot[2 m1^2 - Λ1[m1, mmax, λ, n, U], {m1, 0.1}]};
pr0 = Sqrt[Λ1[0, mmax, λ, n, U] / 2 ];

{
  fm[m1, mwt, mmax, λ, n] (1 - pest[m1]) prescuem[m1, Λ1[m1, mmax, λ, n, U]],
  fm[m1, mwt, mmax, λ, n] (1 - pest[m1])
    Λ1[m1, mmax, λ, n, U] / Abs[m1] HeavisideTheta[(-pr0 - m1) (pr0 - m1)],
  (fm[m1, mwt, mmax, λ, n] (1 - pest[m1]) (Abs[m1] AnciauxEqnA12) / Abs[m1] /. ψwt → ψ /.
        m → mmax ψ (1 - ψ / 4) /. α → ρmax ψ^2 / 4 /. ψ → 2 (1 - Sqrt[1 - m / mmax]) /.
      ρmax → mmax / λ /. θ → n / 2 /. m → m1) HeavisideTheta[(-pr0 - m1) (pr0 - m1)]
 };

Plot[%, {m1, 50 m1 /. mneg, 10 m1 /. mpos}, PlotRange → {0, All}, Filling → Bottom,
 PlotLegends → LineLegend[{"exact", "non-critical", "non-critical anciaux"}],
 PerformanceGoal → "Speed"]

Clear[mmax, λ, Es, n, U, mwt]
```

Closed form approximation - subcriticals (equations 12 and 13)

For the subcriticals our approximation for $\Lambda 2$ is now the integral of

fm[m, mwt, mmax, λ, n] AnciauxEqnA12

$$-\left(e^{\frac{m-2\,\text{mmax}+\text{mwt}}{\lambda}}\,U\left(\frac{-m+\text{mmax}}{\lambda}\right)^{n/2}\left(1-\frac{\psi\text{wt}}{2}\right)^{\frac{1}{2}-\theta}\left(\frac{e^{-\alpha}}{\sqrt{\pi}\,\sqrt{\alpha}}-\text{Erfc}\left[\sqrt{\alpha}\right]\right)\right.$$
$$\left.\text{Hypergeometric0F1Regularized}\left[\frac{n}{2},\ \frac{(-m+\text{mmax})\ (\text{mmax}-\text{mwt})}{\lambda^2}\right]\right)\Big/\left((m-\text{mmax})\left(1-\frac{\psi\text{wt}}{4}\right)\right)$$

over m from -∞ to -m*, with α dependent on m.

As before we can approximately write fm in the ψ scale, leaving us with the integral of

$$\mathbf{f\psi\ AnciauxEqnA12\ /.\ \alpha \to \frac{\rho\text{max}\ \psi^2}{4}}$$

$$\mathbf{constant = \frac{U\sqrt{\rho\text{max}}}{2\sqrt{\pi}\ (1-\psi\text{wt}/4)\ (1-\psi\text{wt}/2)^{-1+2\theta}};}$$

$$\mathbf{\psi term = e^{-\frac{1}{4}\rho\text{max}\ (\psi-\psi\text{wt})^2}\ (1-\psi/2)^{-\frac{1}{2}+\theta}\left(\frac{2\,e^{-\frac{\rho\text{max}\ \psi^2}{4}}}{\sqrt{\pi}\ \sqrt{\rho\text{max}\ \psi^2}}-\text{Erfc}\left[\frac{\sqrt{\rho\text{max}\ \psi^2}}{2}\right]\right);}$$

$$\mathbf{Simplify}\Bigg[\left(e^{-\frac{1}{4}\rho\text{max}\ (\psi-\psi\text{wt})^2}\,U\sqrt{\rho\text{max}}\left(\frac{2-\psi}{2-\psi\text{wt}}\right)^{-\frac{1}{2}+\theta}\left(1-\frac{\psi\text{wt}}{2}\right)^{\frac{1}{2}-\theta}\left(\frac{2\,e^{-\frac{\rho\text{max}\ \psi^2}{4}}}{\sqrt{\pi}\ \sqrt{\rho\text{max}\ \psi^2}}-\text{Erfc}\left[\frac{\sqrt{\rho\text{max}\ \psi^2}}{2}\right]\right)\right)\Big/$$
$$\left(2\sqrt{\pi}\left(1-\frac{\psi\text{wt}}{4}\right)\right)==\text{constant}\ \psi\text{term},\ \{\psi\text{wt}<0\}\Bigg]$$

$$\left(e^{-\frac{1}{4}\rho\text{max}\ (\psi-\psi\text{wt})^2}\,U\sqrt{\rho\text{max}}\left(\frac{2-\psi}{2-\psi\text{wt}}\right)^{-\frac{1}{2}+\theta}\left(1-\frac{\psi\text{wt}}{2}\right)^{\frac{1}{2}-\theta}\left(\frac{2\,e^{-\frac{\rho\text{max}\ \psi^2}{4}}}{\sqrt{\pi}\ \sqrt{\rho\text{max}\ \psi^2}}-\text{Erfc}\left[\frac{\sqrt{\rho\text{max}\ \psi^2}}{2}\right]\right)\right)\Big/$$
$$\left(2\sqrt{\pi}\left(1-\frac{\psi\text{wt}}{4}\right)\right)$$

True

over ψ between -∞ and ψ*

$$\mathbf{Simplify}\left[2\left(1-\sqrt{1-\frac{m}{\text{mmax}}}\right)\ /.\ m\to\{-\infty,\ -m^*\},\ \text{mmax}>0\right]$$

$$\left\{-\infty,\ 2-2\sqrt{\frac{\text{mmax}+m^*}{\text{mmax}}}\right\}$$

We make 2 different approximations. When ψ-ψwt and ψ ρmax = ψ $\frac{\text{mmax}}{\lambda}$ = ψ $\frac{\text{mmax}*n}{2\,\text{Es}}$ are really small we

have

```
ψterm /. ψ - ψwt → ψwt + dψ ϵ  /. ψ → ψ ϵ;
Simplify[Normal[Series[%, {ϵ, 0, -1}]] /. ϵ → 1, {ψ < 0}]
```

$$-\frac{2\, e^{-\frac{\rho\max\, \psi wt^2}{4}}}{\sqrt{\pi}\, \sqrt{\rho\max}\, \psi}$$

And when ψ is small but ρmax is really large we have

```
ψterm /. ρmax -> ρmax / ϵ;
Simplify[Normal[Series[%, {ϵ, 0, 2}]] /. ϵ → 1, {ψ < 0}] /. (1 - ψ/2)^θ → 1 /.
 2 π - π ψ →  2 π
```

$$-\frac{4\, e^{-\frac{1}{4}\rho\max\, \left(\psi^2+(\psi-\psi wt)^2\right)}}{\sqrt{\pi}\, \rho\max^{3/2}\, \psi^3}$$

Compare numerically over m (from ψwt to ψ*)

```
U = 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
mwt = -0.1;
m* = Sqrt[Λ1[0, mmax, λ, n, U] / 2];
```

$$\left\{\psi\text{term},\ -\frac{2\,e^{-\frac{\rho\max\,\psi\text{wt}^2}{4}}}{\sqrt{\pi}\,\sqrt{\rho\max}\,\psi},\ -\frac{4\,e^{-\frac{1}{4}\rho\max\left(\psi^2+(\psi-\psi\text{wt})^2\right)}}{\sqrt{\pi}\,\rho\max^{3/2}\,\psi^3}\right\}\ /.\ \rho\max\to\text{mmax}/\lambda\ /.\ \theta\to n/2\ /.$$

$$\psi\text{wt}\to 2\left(1-\sqrt{1-\frac{\text{mwt}}{\text{mmax}}}\right);$$

$$\text{Plot}\left[\%,\ \left\{\psi,\ 2\left(1-\sqrt{1-\frac{\text{mwt}}{\text{mmax}}}\right),\ 2-2\sqrt{\frac{\text{mmax}+m^*}{\text{mmax}}}\right\},\ \text{PlotRange}\to\{0,\ \text{Automatic}\}\right]$$

```
Clear[mmax, λ, Es, n, U, mwt]
```

And compare integrals across range of mwt. We see the nice transition from the small ψ approx to the large ρmax approx as we increase ρmax:

For ρmax = 10

```
U = 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.1;
n = 4;
m* = Sqrt[Λ1[0, mmax, λ, n, U] / 2];
mmax / λ
```

$$\left\{\psi term,\ -\frac{2\, e^{-\frac{\rho max\, \psi wt^2}{4}}}{\sqrt{\pi}\ \sqrt{\rho max}\ \psi},\ -\frac{4\, e^{-\frac{1}{4}\rho max\left(\psi^2+(\psi-\psi wt)^2\right)}}{\sqrt{\pi}\ \rho max^{3/2}\ \psi^3}\right\} /.\ \rho max \to mmax / \lambda /.\ \theta \to n / 2 /.$$

$$\psi wt \to 2\left(1-\sqrt{1-\frac{mwt}{mmax}}\right);$$

$$Table\left[Table\left[\left\{mwt,\ NIntegrate\left[\%[[i]],\ \left\{\psi,\ 2\left(1-\sqrt{1-\frac{mwt}{mmax}}\right),\ 2-2\sqrt{\frac{mmax+m^*}{mmax}}\right\}\right]\right\},\ \{mwt,\ -0.3,\ -0.1,\ 0.01\}\right],\ \{i,\ Length[\%]\}\right];$$

```
ListLogPlot[%, Joined → True]

Clear[mmax, λ, Es, n, U, mwt]
```

10.

For ρmax=100

```
U = 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
m* = Sqrt[Λ1[0, mmax, λ, n, U] / 2];
mmax / λ
```

$$\left\{\psi term,\ -\frac{2\, e^{-\frac{\rho max\, \psi wt^2}{4}}}{\sqrt{\pi}\ \sqrt{\rho max}\ \psi},\ -\frac{4\, e^{-\frac{1}{4}\rho max\left(\psi^2+(\psi-\psi wt)^2\right)}}{\sqrt{\pi}\ \rho max^{3/2}\ \psi^3}\right\}\ /.\ \rho max \to mmax / \lambda\ /.\ \theta \to n / 2\ /.$$

$$\psi wt \to 2\left(1-\sqrt{1-\frac{mwt}{mmax}}\right);$$

$$Table\left[Table\left[\left\{mwt,\ NIntegrate\left[\%[[i]],\ \left\{\psi,\ 2\left(1-\sqrt{1-\frac{mwt}{mmax}}\right),\ 2-2\sqrt{\frac{mmax+m^*}{mmax}}\right\}\right]\right\},\ \{mwt,\ -0.3,\ -0.1,\ 0.01\}\right],\ \{i,\ Length[\%]\}\right];$$

```
ListLogPlot[%, Joined → True]

Clear[mmax, λ, Es, n, U, mwt]
```

100.

for ρmax=1000

```
U = 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.001;
n = 4;
m* = Sqrt[Λ1[0, mmax, λ, n, U] / 2];
mmax / λ
```

$$\left\{\psi term,\ -\frac{2\, e^{-\frac{\rho max\, \psi wt^2}{4}}}{\sqrt{\pi}\ \sqrt{\rho max}\ \psi},\ -\frac{4\, e^{-\frac{1}{4}\rho max\left(\psi^2+(\psi-\psi wt)^2\right)}}{\sqrt{\pi}\ \rho max^{3/2}\ \psi^3}\right\}\ /.\ \rho max \to mmax / \lambda\ /.\ \theta \to n / 2\ /.$$

$$\psi wt \to 2\left(1-\sqrt{1-\frac{mwt}{mmax}}\right);$$

$$Table\left[Table\left[\left\{mwt,\ NIntegrate\left[\%[[i]],\ \left\{\psi,\ 2\left(1-\sqrt{1-\frac{mwt}{mmax}}\right),\ 2-2\sqrt{\frac{mmax+m^*}{mmax}}\right\}\right]\right\},\ \{mwt,\ -0.3,\ -0.01,\ 0.01\}\right],\ \{i,\ Length[\%]\}\right];$$

```
ListLogPlot[%, Joined → True, PlotRange → All]

Clear[mmax, λ, Es, n, U, mwt]
```

1000.

and for ρmax=10000

```
U = 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.0001;
n = 4;
m* = Sqrt[Λ1[0, mmax, λ, n, U] / 2];
mmax / λ
```

$$\left\{\psi term,\ -\frac{2\, e^{-\frac{\rho max\, \psi wt^2}{4}}}{\sqrt{\pi}\ \sqrt{\rho max}\ \psi},\ -\frac{4\, e^{-\frac{1}{4}\rho max\left(\psi^2+(\psi-\psi wt)^2\right)}}{\sqrt{\pi}\ \rho max^{3/2}\ \psi^3}\right\} /.\ \rho max \to mmax / \lambda\ /.\ \theta \to n / 2\ /.$$

$$\psi wt \to 2\left(1-\sqrt{1-\frac{mwt}{mmax}}\right);$$

$$\text{Table}\left[\text{Table}\left[\left\{mwt,\ \text{NIntegrate}\left[\%[[i]],\ \left\{\psi,\ 2\left(1-\sqrt{1-\frac{mwt}{mmax}}\right),\ 2-2\sqrt{\frac{mmax+m^*}{mmax}}\right\}\right]\right\},\right.\right.$$

$$\left.\left.\{mwt,\ -0.3,\ -0.01,\ 0.01\}\right],\ \{i,\ \text{Length}[\%]\}\right];$$

```
ListLogPlot[%, Joined → True, PlotRange → All]
```

```
Clear[mmax, λ, Es, n, U, mwt]
```

10 000.

Right, so for the small ψ approx we need to integrate

$$small\psi approx = -\frac{2\, e^{-\frac{\rho max\, \psi wt^2}{4}}}{\sqrt{\pi}\ \sqrt{\rho max}\ \psi};$$

which has a simple expression if we do not integrate all the way back to -∞

```
Integrate[smallψapprox, {ψ, a, b}, Assumptions → {a < b < 0}]
```

$$-\frac{2\, e^{-\frac{\rho max\, \psi wt^2}{4}}\, \mathrm{Log}\left[\frac{b}{a}\right]}{\sqrt{\pi}\, \sqrt{\rho max}}$$

And for the large ρmax we need to integrate

$$\mathbf{large\rho approx} = -\frac{4\, e^{-\frac{1}{4}\rho max\left(\psi^2+(\psi-\psi wt)^2\right)}}{\sqrt{\pi}\, \rho max^{3/2}\, \psi^3};$$

here we can again use the Laplace approx with

$$q[\psi_] := -\frac{1}{4}\rho max\left(\psi^2 + (\psi - \psi wt)^2\right)$$

$$h[\psi_] := -\frac{4}{\sqrt{\pi}\, \rho max^{3/2}\, \psi^3}$$

and we know that q is peaked at

```
Solve[D[q[ψ], ψ] == 0, ψ]
```

$$\left\{\left\{\psi \to \frac{\psi wt}{2}\right\}\right\}$$

where h equals

```
h[ψwt / 2]
```

$$-\frac{32}{\sqrt{\pi}\, \rho max^{3/2}\, \psi wt^3}$$

giving

```
h[ψwt / 2] Exp[q[ψ]]
```

$$\mathbf{verylarge\rho approx} = -\frac{32\, e^{-\frac{1}{4}\rho max\left(\psi^2+(\psi-\psi wt)^2\right)}}{\sqrt{\pi}\, \rho max^{3/2}\, \psi wt^3};$$

$$-\frac{32\, e^{-\frac{1}{4}\rho max\left(\psi^2+(\psi-\psi wt)^2\right)}}{\sqrt{\pi}\, \rho max^{3/2}\, \psi wt^3}$$

Numerical check

```
{largeρapprox, verylargeρapprox} /. ρmax → 10 000 /. ψwt → -0.2;
Plot[%, {ψ, -0.2, -0.01}, PlotRange → All]
```

which we can integrate over all ψ with little error (because exponential tails)

```
Integrate[verylargeρapprox, {ψ, -∞, ∞}, Assumptions → {ρmax > 0, ψwt < 0}]
```

$$-\frac{32\sqrt{2}\, e^{-\frac{\rho max\, \psi wt^2}{8}}}{\rho max^2\, \psi wt^3}$$

OK, so our small ρmax approx for the probability of 2-step subcritical rescue is

```
smallψapproxRescueψ =
 constant Integrate[smallψapprox, {ψ, a, b}, Assumptions → {a < b < 0}]
smallψapproxRescue =
```

$$\% \;/.\; a \to 2\left(1-\sqrt{1-\frac{mwt}{mmax}}\right) \;/.\; b \to 2\left(1-\sqrt{1+\frac{mstar}{mmax}}\right) \;/.\; mstar \to \sqrt{\Lambda 0approx/2} \;/.$$

$$\rho max \to mmax/\lambda \;/.\; \theta \to n/2 \;/.\; \psi wt \to 2\left(1-\sqrt{1-\frac{mwt}{mmax}}\right)$$

$$-\frac{e^{-\frac{\rho max\, \psi wt^2}{4}}\, U\left(1-\frac{\psi wt}{2}\right)^{1-2\theta} \mathrm{Log}\left[\frac{b}{a}\right]}{\pi\left(1-\frac{\psi wt}{4}\right)}$$

$$-\left(e^{-\frac{mmax\left(1-\sqrt{1-\frac{mwt}{mmax}}\right)^2}{\lambda}}\left(1-\frac{mwt}{mmax}\right)^{\frac{1-n}{2}} U\, \mathrm{Log}\left[\frac{1-\sqrt{1+\frac{\sqrt{U\sqrt{mmax\,\lambda}}}{mmax\,\pi^{1/4}}}}{1-\sqrt{1-\frac{mwt}{mmax}}}\right]\right) \Big/ \left(\left(1+\frac{1}{2}\left(-1+\sqrt{1-\frac{mwt}{mmax}}\right)\right)\pi\right)$$

and our very large ρmax approx for the probability of 2-step subcritical rescue is

```
verylargeρapproxRescueψ =
 constant Integrate[verylargeρapprox, {ψ, -∞, ∞}, Assumptions → {ρmax > 0, ψwt < 0}]
```

```
verylargeρapproxRescue = % /. ρmax → mmax / λ /. θ → n / 2 /. ψwt → 2 (1 - Sqrt[1 - mwt/mmax])
```

$$-\frac{16\, e^{-\frac{\rho max\, \psi wt^2}{8}} \sqrt{\frac{2}{\pi}}\; U \left(1-\frac{\psi wt}{2}\right)^{1-2\theta}}{\rho max^{3/2} \left(1-\frac{\psi wt}{4}\right) \psi wt^3}$$

$$-\left(2\, e^{-\frac{mmax \left(1-\sqrt{1-\frac{mwt}{mmax}}\right)^2}{2\lambda}} \left(1-\frac{mwt}{mmax}\right)^{\frac{1-n}{2}} \sqrt{\frac{2}{\pi}}\; U\right) \Big/ \left(\left(1-\sqrt{1-\frac{mwt}{mmax}}\right)^3 \left(1+\frac{1}{2}\left(-1+\sqrt{1-\frac{mwt}{mmax}}\right)\right) \left(\frac{mmax}{\lambda}\right)^{3/2}\right)$$

Check formula for text

```
Simplify[
 small ψapproxRescueψ == U ((1 - ψwt/2)^(1-2 θ)/(1 - ψwt/4)) e^(-α) (Log[a/b]/π) /. α → ρmax ψwt^2 / 4, {a < b < 0}]
```

```
Simplify[verylargeρapproxRescueψ ==
 (-U ((1 - ψwt/2)^(1-2 θ)/(1 - ψwt/4)) (e^(-α) 1/((α / 2 )^3 π))^(1/2) /. α → ρmax ψwt^2 / 4), {ρmax > 0, ψwt > 0}]
```

```
True

True
```

Compare to better approximation

```
n0 = 10^4;
U = 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;

{mneg = FindRoot[2 m1^2 - Λ1[m1, mmax, λ, n, U], {m1, -0.1}],
  mpos = FindRoot[2 m1^2 - Λ1[m1, mmax, λ, n, U], {m1, 0.1}]};
pr0 = Sqrt[Λ1[0, mmax, λ, n, U] / 2];

{
  Table[{mwt, U NIntegrate[fm[m1, mwt, mmax, λ, n] Λ1[m1, mmax, λ, n, U] / Abs[m1]
      , {m1, mwt, -pr0}]}, {mwt, -0.8 mmax, -0.1 mmax, 0.1 mmax}]
 };

Show[
 LogPlot[
  {U smallψapproxRescue, U verylargeρapproxRescue}, {mwt, -0.8 mmax, -0.1 mmax},
  PlotStyle → Thick,
  Frame → {True, False, False, True},
  FrameLabel → {"Wildtype growth rate", , , "Rate of rescue"},
  FrameTicks → {True, False, False, True},
  LabelStyle → labelstyle,
  PlotLegends → Placed[
    LineLegend[Style[#, 12, FontFamily → "Helvetica"] & /@ {"small ψ", "large ρmax"}],
    Scaled@{3 / 4, 1 / 4}]
 ],
 ListLogPlot[%, PlotMarkers → {Automatic, Medium}, PlotStyle → Black]
]

Clear[mmax, λ, Es, n, U, n0]
```

Closed form approximation - supercriticals (equation 14)

For the supercriticals our approximation for $\Lambda 2$ is now the integral of

```
fm[m, mwt, mmax, λ, n] (1 - pest[m]) AnciauxEqnA12
```

$$-\frac{1}{(m-\text{mmax})\left(1-\frac{\psi\text{wt}}{4}\right)} e^{\frac{m-2\,\text{mmax}+\text{mwt}}{\lambda}} U \left(\frac{-m+\text{mmax}}{\lambda}\right)^{n/2} \left(1-\frac{\psi\text{wt}}{2}\right)^{\frac{1}{2}-\theta} \left(\frac{e^{-\alpha}}{\sqrt{\pi}\sqrt{\alpha}} - \text{Erfc}\left[\sqrt{\alpha}\right]\right) \left(1-\left(1-e^{-2m}\right)\text{HeavisideTheta}[m]\right) \text{Hypergeometric0F1Regularized}\left[\frac{n}{2}, \frac{(-m+\text{mmax})(\text{mmax}-\text{mwt})}{\lambda^2}\right]$$

over m from m^* to m_{max}, with α dependent on m.

As before we can approximately write fm in the ψ scale, leaving us with the integral of

$$f\psi\ (1-\text{pest}[m])\ \text{AnciauxEqnA12}\ /.\ \alpha \to \frac{\rho\text{max}\,\psi^2}{4}\ /.\ m \to \text{mmax}\,(1-\psi/4)\,\psi$$

$$\text{constant} = \frac{U\sqrt{\rho\text{max}}}{2\sqrt{\pi}\,(1-\psi\text{wt}/4)\,(1-\psi\text{wt}/2)^{-1+2\theta}};$$

$$\psi\text{term} = e^{-2\,\text{mmax}\left(1-\frac{\psi}{4}\right)\psi-\frac{1}{4}\rho\text{max}\,(\psi-\psi\text{wt})^2}\,(1-\psi/2)^{-\frac{1}{2}+\theta}\left(\frac{2\,e^{-\frac{\rho\text{max}\,\psi^2}{4}}}{\sqrt{\pi}\sqrt{\rho\text{max}\,\psi^2}} - \text{Erfc}\left[\frac{\sqrt{\rho\text{max}\,\psi^2}}{2}\right]\right);$$

$$\text{Simplify}\left[\left(f\psi\ (1-\text{pest}[m])\ \text{AnciauxEqnA12}\ /.\ \alpha \to \frac{\rho\text{max}\,\psi^2}{4}\ /.\ m \to \text{mmax}\,(1-\psi/4)\,\psi\right) == \text{constant}\,\psi\text{term},\ \{\psi\text{wt} < 0,\ 2 > \psi > 0,\ \text{mmax} > 0\}\right]$$

$$\frac{1}{2\sqrt{\pi}\left(1-\frac{\psi\text{wt}}{4}\right)} e^{-\frac{1}{4}\rho\text{max}\,(\psi-\psi\text{wt})^2}\,U\sqrt{\rho\text{max}}\left(\frac{2-\psi}{2-\psi\text{wt}}\right)^{-\frac{1}{2}+\theta}\left(1-\frac{\psi\text{wt}}{2}\right)^{\frac{1}{2}-\theta}\left(\frac{2\,e^{-\frac{\rho\text{max}\,\psi^2}{4}}}{\sqrt{\pi}\sqrt{\rho\text{max}\,\psi^2}} - \text{Erfc}\left[\frac{\sqrt{\rho\text{max}\,\psi^2}}{2}\right]\right) \left(1-\left(1-e^{-2\,\text{mmax}\left(1-\frac{\psi}{4}\right)\psi}\right)\text{HeavisideTheta}\left[\text{mmax}\left(1-\frac{\psi}{4}\right)\psi\right]\right)$$

```
True
```

over ψ between ψ^* and 2

```
Clear[m]
Simplify[2 (1 - Sqrt[1 - m/mmax]) /. m → {mstar, mmax}, mmax > 0]
```

$$\left\{2 - 2\sqrt{1 - \frac{\text{mstar}}{\text{mmax}}}, 2\right\}$$

Here we only need one approximation as large m single mutants will establish themselves and are unlikely to rescue. So we just look at when ψ-ψwt and ψ ρmax = ψ $\frac{\text{mmax}}{\lambda} = \psi$ $\frac{\text{mmax}*n}{2\,\text{Es}}$ are really small, giving

```
ψterm /. ψ → ψ ϵ;
Simplify[Normal[Series[%, {ϵ, 0, -1}]] /. ϵ → 1, {ψ > 0}]
```

$$\frac{2\, e^{-\frac{\rho\text{max}\,\psi\text{wt}^2}{4}}}{\sqrt{\pi}\,\sqrt{\rho\text{max}}\,\psi}$$

Right, so for the small ψ approx we need to integrate

$$\text{small}\psi\text{approx} = \frac{2\, e^{-\frac{\rho\text{max}\,\psi\text{wt}^2}{4}}}{\sqrt{\pi}\,\sqrt{\rho\text{max}}\,\psi};$$

which has a simple expression

```
Integrate[smallψapprox, {ψ, a, b}, Assumptions → {0 < a < b < 2}]
```

$$\frac{2\, e^{-\frac{\rho\text{max}\,\psi\text{wt}^2}{4}}\,\text{Log}\left[\frac{b}{a}\right]}{\sqrt{\pi}\,\sqrt{\rho\text{max}}}$$

OK, so our small ρmax approx for the probability of 2-step supercritical rescue is

```
smallψapproxRescueSuperψ =
 constant Integrate[smallψapprox, {ψ, a, b}, Assumptions → {0 < a < b}]
smallψapproxRescueSuper =
```

$$\% \;/.\; a \to 2\left(1-\sqrt{1-\frac{\text{mstar}}{\text{mmax}}}\right) \;/.\; b \to \frac{\sqrt{2}}{\sqrt{\rho\text{max}}} \;/.\; \text{mstar} \to \sqrt{\Lambda 0\text{approx}/2} \;/.\; \rho\text{max} \to \text{mmax}/\lambda \;/.$$

$$\theta \to n/2 \;/.\; \psi\text{wt} \to 2\left(1-\sqrt{1-\frac{\text{mwt}}{\text{mmax}}}\right)$$

$$\frac{e^{-\frac{\rho\text{max}\,\psi\text{wt}^2}{4}}\,U\left(1-\frac{\psi\text{wt}}{2}\right)^{1-2\theta}\text{Log}\left[\frac{b}{a}\right]}{\pi\left(1-\frac{\psi\text{wt}}{4}\right)}$$

$$\left(e^{-\frac{\text{mmax}\left(1-\sqrt{1-\frac{\text{mwt}}{\text{mmax}}}\right)^2}{\lambda}}\left(1-\frac{\text{mwt}}{\text{mmax}}\right)^{\frac{1-n}{2}}U\,\text{Log}\left[\frac{1}{\sqrt{2}\sqrt{\frac{\text{mmax}}{\lambda}}\left(1-\sqrt{1-\frac{\sqrt{U\sqrt{\text{mmax}\,\lambda}}}{\text{mmax}\,\pi^{1/4}}}\right)}\right]\right)\Big/$$

$$\left(\left(1+\frac{1}{2}\left(-1+\sqrt{1-\frac{\text{mwt}}{\text{mmax}}}\right)\right)\pi\right)$$

where we've used our rough cut-off of $\sqrt{2/\rho\text{max}}$, after which the rate of rescue declines very very quickly and therefore is negligible.

Check formula in text

$$\text{Simplify}\left[\frac{U\left(1-\frac{\psi\text{wt}}{2}\right)^{1-2\theta}}{\left(1-\frac{\psi\text{wt}}{4}\right)}e^{-\alpha}\,\text{Log}\left[\frac{b}{a}\right]\Big/\pi == \text{smallψapproxRescueSuperψ} \;/.\; \alpha \to \frac{\rho\text{max}\,\psi\text{wt}^2}{4}\right]$$

```
True
```

Compare to better approximation

```
n0 = 10^4;
U = 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;

{mneg = FindRoot[2 m1^2 - Λ1[m1, mmax, λ, n, U], {m1, -0.1}],
  mpos = FindRoot[2 m1^2 - Λ1[m1, mmax, λ, n, U], {m1, 0.1}]};
pr0 = Sqrt[Λ1[0, mmax, λ, n, U] / 2];

{
  Table[{mwt, U NIntegrate[fm[m1, mwt, mmax, λ, n] (1 - pest[m1]) Λ1[m1, mmax, λ, n, U] / Abs[m1]
      , {m1, pr0, mmax}]}, {mwt, -0.8 mmax, -0.1 mmax, 0.1 mmax}]
 };

Show[
 LogPlot[
  {U small$ψapproxRescueSuper}, {mwt, -0.8 mmax, -0.1 mmax},
  PlotStyle → Thick,
  Frame → {True, False, False, True},
  FrameLabel → {"Wildtype growth rate", , , "Rate of rescue"},
  FrameTicks → {True, False, False, True},
  LabelStyle → labelstyle,
  PlotLegends → Placed[LineLegend[
     Style[#, 12, FontFamily → "Helvetica"] & /@ {"approx"}], Scaled@{3 / 4, 1 / 4}]
 ],
 ListLogPlot[%, PlotMarkers → {Automatic, Medium}, PlotStyle → Black]
]

Clear[mmax, λ, Es, n, U, n0]
```

Plot approximations (figure 5)

Panel A data

```
(*n0=10^4;
U=10^-3;
mmax=0.5;
λ=2Es/n;
Es=0.01;
n=4;

{mneg=FindRoot[2m1^2-Λ1[m1,mmax,λ,n,U],{m1,-0.1}],
 mpos=FindRoot[2m1^2-Λ1[m1,mmax,λ,n,U],{m1,0.1}]};
pr0=Sqrt[Λ1[0,mmax,λ,n,U]/2];

xs=Table[mwt,{mwt,-0.8mmax,-0.1mmax,0.1mmax}];

temptab={
  Table[ NIntegrate[fm[m1,mwt,mmax,λ,n] Λ1[m1,mmax,λ,n,U]/Abs[m1]
    ,{m1,mwt,-pr0}],{mwt,-0.8mmax,-0.1mmax,0.1mmax}],
  Table[NIntegrate[ fm[m1,mwt,mmax,λ,n](1-pest[m1])Sqrt[2Λ1[m1,mmax,λ,n,U]],
    {m1,m1/.mneg,m1/.mpos}],{mwt,-0.8mmax,-0.1mmax,0.1mmax}],
  Table[NIntegrate[fm[m1,mwt,mmax,λ,n](1-pest[m1]) Λ1[m1,mmax,λ,n,U]/Abs[m1]
    ,{m1,pr0,mmax}],{mwt,-0.8mmax,-0.1mmax,0.1mmax}]
 };
Transpose[temptab];
Table[%[[i]]/Total[%[[i]]],{i,Length[%]}];
test=Transpose[%];
data=Table[Transpose[Join[{xs},{%[[i]]},1]],{i,Length[%]}];

Clear[mmax,λ,Es,n,U,n0]*)
```

```
data = {{{-0.4`, 0.9456638573208591`}, {-0.35000000000000003`, 0.8818894810731134`},
    {-0.30000000000000004`, 0.7882778363153661`}, {-0.25`, 0.6791421962065166`},
    {-0.2`, 0.5706393639682957`}, {-0.15000000000000002`, 0.4705197731917115`},
    {-0.09999999999999998`, 0.3776908923323233`},
    {-0.04999999999999999`, 0.2793108104800298`}},
   {{-0.4`, 0.03623085604695413`}, {-0.35000000000000003`, 0.07601020185743679`},
    {-0.30000000000000004`, 0.13070865247937516`}, {-0.25`, 0.1885039970593472`},
    {-0.2`, 0.23742270239875216`}, {-0.15000000000000002`, 0.2712516380984508`},
    {-0.09999999999999998`, 0.2883094661397107`},
    {-0.04999999999999999`, 0.2901562484218649`}},
   {{-0.4`, 0.018105286632186777`}, {-0.35000000000000003`, 0.04210031706944998 6`},
    {-0.30000000000000004`, 0.08101351120525872`}, {-0.25`, 0.13235380673413624`},
    {-0.2`, 0.1919379336329521`}, {-0.15000000000000002`, 0.2582285887098376`},
    {-0.09999999999999998`, 0.3339996415279661`},
    {-0.04999999999999999`, 0.4305329410981054`}}};
```

Panel A

```
n0 = 10^4;
U = 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;

{smallψapproxRescue, 2 Λ0approx fm[0, mwt, mmax, λ, n] , smallψapproxRescueSuper};
    %
 ---------;
Total[%]

{verylargeρapproxRescue, 2 Λ0approx fm[0, mwt, mmax, λ, n] , smallψapproxRescueSuper};
    %
 ---------;
Total[%]

fig5a = Show[
  Plot[
   %, {mwt, -0.4, -0.2},
   PlotRange → {0, 1},
   PlotStyle → Thick,
   Frame → {True, False, False, True},
   FrameLabel → {"Wildtype growth rate", , , "Percent of 2-step rescues"},
   FrameTicks → {True, False, False, All},
   LabelStyle → labelstyle,
   PlotLegends → Placed[LineLegend[Style[#, 12, FontFamily → "Helvetica"] & /@
       {"subcritical", "critical", "supercritical"}], Scaled@{3 / 4, 3 / 4}],
   Epilog → Text[Style["A", 14, Bold, FontFamily → "Helvetica"],
     Scaled@{0.95, 0.95}]
  ],
  Plot[
   %%%, {mwt, -0.2, -0.01},
   PlotRange → {0, 1},
   PlotStyle → Thick
  ],
  ListPlot[data,
   PlotMarkers → {Graphics[{defaultcolors[[1]], Disk[]}, ImageSize → 10],
     Graphics[{defaultcolors[[2]], Disk[]}, ImageSize → 10],
     Graphics[{defaultcolors[[3]], Disk[]}, ImageSize → 10]}, PlotRange → {0, 1}],
  PlotRange → {{-0.4, 0}, {0, 1}}
 ]

Clear[mmax, λ, Es, n, U, n0]
```

Panel B data

```
(*n0=10^4;
mwt=-0.1;
mmax=0.5;
λ=2Es/n;
Es=0.01;
n=4;
U=10^x;

xs=Table[U,{x,-6,-1,1}];

temptab2=Table[
  mneg=FindRoot[2m1^2-Λ1[m1,mmax,λ,n,U],{m1,-0.1}];
  mpos=FindRoot[2m1^2-Λ1[m1,mmax,λ,n,U],{m1,0.1}];
  pr0=Sqrt[Λ1[0,mmax,λ,n,U]/2];
  {
   NIntegrate[fm[m1,mwt,mmax,λ,n] Λ1[m1,mmax,λ,n,U]/Abs[m1],{m1,mwt,-pr0}],
   NIntegrate[
    fm[m1,mwt,mmax,λ,n](1-pest[m1])Sqrt[2Λ1[m1,mmax,λ,n,U]],{m1,m1/.mneg,m1/.mpos}],
   NIntegrate[fm[m1,mwt,mmax,λ,n](1-pest[m1]) Λ1[m1,mmax,λ,n,U]/Abs[m1],{m1,pr0,mmax}]
  }
  ,{x,-6,-1,1}];

temptab2;
Table[%[[i]]/Total[%[[i]]],{i,Length[%]}];
test=Transpose[%];
data=Table[Transpose[Join[{xs},{%[[i]]},1]],{i,Length[%]}];

Clear[mmax,λ,Es,n,mwt,n0,U]*)
```

```
data = {{{1/1000000, 0.4394221756678203`}, {1/100000, 0.4272522411954631`},
    {1/10000, 0.40885542554335036`}, {1/1000, 0.3776908923323242`},
    {1/100, 0.3146639788436848`}, {1/10, 0.16762056652824764`}},
   {{1/1000000, 0.14473575990819615`}, {1/100000, 0.17364469110334504`},
    {1/10000, 0.2168952147581818`}, {1/1000, 0.2883094661397102`},
    {1/100, 0.4246353608625372`}, {1/10, 0.7093264193395161`}},
   {{1/1000000, 0.4158420644239835`}, {1/100000, 0.39910306770119186`},
    {1/10000, 0.37424935969846795`}, {1/1000, 0.3339996415279655`},
    {1/100, 0.26070066029377786`}, {1/10, 0.1230530141322361`}}};
```

Panel B

```
n0 = 10^4;
mwt = -0.1;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;

{smallψapproxRescue(*verylargeρapproxRescue*),
  2 ∧0approx fm[0, mwt, mmax, λ, n] , smallψapproxRescueSuper};
   %
 ———————;
 Total[%]

fig5b = Show[
  LogLinearPlot[
   %, {U, 10^-6, 10^-1},
   PlotRange → {0, 1},
   PlotStyle → Thick,
   Frame → {True, True, False, False},
   FrameLabel → {"Mutation rate", "Percent of 2-step rescues", ,},
   FrameTicks → {True, True, False, False},
   LabelStyle → labelstyle,
   Epilog →
    Text[Style["B", 14, Bold, FontFamily → "Helvetica"], Scaled@{0.05, 0.95}]
  ],
  ListLogLinearPlot[data,
   PlotMarkers → {Graphics[{defaultcolors[[1]], Disk[]}, ImageSize → 10],
     Graphics[{defaultcolors[[2]], Disk[]}, ImageSize → 10],
     Graphics[{defaultcolors[[3]], Disk[]}, ImageSize → 10]}, PlotRange → {0, 1}]
 ]

Clear[mmax, λ, Es, n, mwt, n0, U]
```

Figure 5

```
GraphicsColumn[{fig5a, fig5b}, Spacings → -30, ImageSize → 350]
Export[figdir <> "Figure5.eps", %];
```

Distribution of growth rates given rescue

Distribution of growth rates among 1-step rescue mutants (equations 15 and 16)

The distribution of growth rates among the rescue mutants in 1-step rescue is simply

$$g1m = \frac{U\ fm[m, mwt, mmax, \lambda, n]\ pest[m]}{\Lambda 1[mwt, mmax, \lambda, n, U]};$$

We can approximate this using our Laplacian approach. In this case we have

```
h[ψ_] := ((1 - ψ / 2)/(1 - ψwt / 2))^(θ - 1/2) (1 - e^(-2 mmax y)) /. y → ψ (1 - ψ / 4)
q[ψ_] := 1/4 (ψ - ψwt)^2
h0 = Normal[Series[h[ψ], {ψ, 0, 1}]];
g1mapprox = Simplify[
  (U/(-mwt) (Sqrt[ρmax]/(2 Sqrt[π])) h0 Exp[-ρmax q[ψ]])/AnciauxEqnA12 /. mwt → mmax (4 - ψwt) ψwt / 4, {ψwt < 0, α > 0, ρmax > 0}]
```

$$\frac{e^{\alpha-\frac{1}{4}\rho\max(\psi-\psi\mathrm{wt})^2}\sqrt{\alpha\,\rho\max}\;\psi}{\psi\mathrm{wt}\left(-1+e^{\alpha}\sqrt{\pi}\sqrt{\alpha}\;\mathrm{Erfc}\left[\sqrt{\alpha}\right]\right)}$$

And if we want to plot on an m scale (and still want a pdf) we need to scale by

```
scaleg1approx = D[2 (1 - Sqrt[1 - m/mmax]), m]
```

$$\frac{1}{\sqrt{1-\frac{m}{\mathrm{mmax}}}\;\mathrm{mmax}}$$

giving

```
g1mApp = scaleg1approx g1mapprox;
```

Numerically compare

```
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
mwt = -0.1;
{
        g1m,
        g1mApp
      } /. α → ψwt^2 ρmax / 4 /. ρmax → mmax / λ /. θ → n / 2 /. ψwt → 2 (1 - Sqrt[1 - mwt/mmax]) /.
  ψ → 2 (1 - Sqrt[1 - m/mmax]);

Plot[%, {m, -0.2, 0.2}, PlotRange → {0, All},
 Frame → {True, True, False, False}, FrameLabel → {"Growth rate", "Density"},
 PlotLegends → Placed[{"true", "closed form"}, Top],
 Filling → Bottom, LabelStyle → labelstyle]

Clear[mmax, λ, Es, n, mwt]
```

Distribution of growth rates among 2-step rescue genotypes (equation 17)

The rate of 2-step rescue through double mutants with growth rate m2 is

```
g2numerator[m0_, m2_?NumericQ] := U NIntegrate[fm[m, m0, mmax, λ, n]
      (1 - pest[m]) prescuem[m, U fm[m2, m, mmax, λ, n] pest[m2]], {m, -∞, mmax}];
```

Integrating this over m2 then provides the correct normalization,

```
g2denominator[m0_?NumericQ] := NIntegrate[U fm[m, m0, mmax, λ, n] (1 - pest[m])
     prescuem[m, U fm[m2, m, mmax, λ, n] pest[m2]], {m, -∞, mmax}, {m2, 0, mmax}];
```

Plot growth rates of rescue genotypes (figure 6)

Panels

```
xmin = -0.3;
xmax = 0.25;
ymax = 28;

U = 2 * 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
mwt = -0.1;

{
  (*random*)
  Table[{m2, fm[m2, mwt, mmax, λ, n]}, {m2, xmin, xmax, 0.01}],
  (*established*)
  Table[{m2, (fm[m2, mwt, mmax, λ, n] pest[m2 - mwt]) / NIntegrate[
      fm[m2, mwt, mmax, λ, n] pest[m2 - mwt], {m2, mwt, mmax}]}, {m2, mwt, xmax, 0.01}]
 };
oldtheory = ListPlot[%, PlotRange → All, Joined → True,
   PlotStyle → {Directive[Thick, Gray, Dashed], Directive[Thick, Gray]},
   PerformanceGoal → "Speed",
   PlotLegends → Placed[LineLegend[Style[#, 12, FontFamily → "Helvetica"] & /@
       {"random", "established"}], Scaled@{1.5 / 8, 1 / 2}]];

{
  (*1 step*)
  Table[{m2, g1m /. m → m2}, {m2, 0, xmax, 0.005}],
  (*2 step*)
  total = Re[g2denominator[mwt]];
  Table[{m2, 1/total g2numerator[mwt, m2]}, {m2, 0, xmax, 0.005}]
 };
theory = ListPlot[%, PlotRange → All,
   Joined → True, PlotStyle → Thick, PerformanceGoal → "Speed",
   PlotLegends → Placed[LineLegend[Style[#, 12, FontFamily → "Helvetica"] & /@
       {"1-step", "2-step"}], Scaled@{1.5 / 8, 1 / 2}]];


g1mApp /. α → ψwt^2 ρmax / 4 /. ρmax → mmax / λ /. θ → n / 2 /. ψwt → 2 (1 - Sqrt[1 - mwt/mmax]) /.
  ψ → 2 (1 - Sqrt[1 - m/mmax]);
onestepapp = Plot[%, {m, 0, xmax}, PlotStyle → {Thick, Dashed},
   PlotLegends → Placed[LineLegend[Style[#, 12, FontFamily → "Helvetica"] & /@
       {"1-step approx."}], Scaled@{1.5 / 8, 1 / 2}]];
```

```
dat = Import[datadir <>
    "dfe_poisson_N10000_n4_U0.00200_Es0.01_mmax0.50_mwt-0.10_mutmax10_nreps10000.
      csv"];
onestep = Select[dat, #[[2]] == 1 &][[All, 1]];
twostep = Select[dat, #[[2]] == 2 &][[All, 1]];
data = Histogram[{onestep, twostep}, 50, "PDF", AxesOrigin → {0, 0}];

fig6a = Show[oldtheory, data, theory, onestepapp,
  PlotRange → {{xmin, xmax}, {0, ymax}},
  Frame → {True, False, False, False},
  LabelStyle → labelstyle,
  FrameTicksStyle → {FontColor → White, Automatic, Automatic, Automatic},
  Epilog → {
    Text[Style["m0=" <> ToString[mwt],
      12, FontFamily → "Helvetica"], Scaled@{7 / 8, 3 / 4}],
    Text[Style["A", 14, Bold, FontFamily → "Helvetica"], Scaled@{0.05, 0.95}],
    {Directive[Gray, Thick], Line[{{mwt, 10}, {-0.035, 10}}]},
    {Directive[Gray, Thick], Line[{{mwt, 9.5}, {mwt, 10.5}}]},
    {Directive[Gray, Thick], Line[{{-0.035, 9.5}, {-0.035, 10.5}}]},
    {Directive[defaultcolors[[1]], Thick], Line[{{mwt, 15}, {0.03, 15}}]},
    {Directive[defaultcolors[[1]], Thick], Line[{{mwt, 14.5}, {mwt, 15.5}}]},
    {Directive[defaultcolors[[1]], Thick], Line[{{0.03, 14.5}, {0.03, 15.5}}]}
   }
 ]

Clear[mmax, λ, Es, n, U, mwt]
```

NIntegrate::izero :
Integral and error estimates are 0 on all integration subregions. Try increasing the value of the MinRecursion option. If value of integral may be 0, specify a finite value for the AccuracyGoal option. ≫

```
U = 2 * 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
mwt = -0.2;

{
  (*random*)
```

```
  Table[{m2, fm[m2, mwt, mmax, λ, n]}, {m2, xmin, xmax, 0.01}],
  (*established*)
  Table[{m2, (fm[m2, mwt, mmax, λ, n] pest[m2 - mwt]) / NIntegrate[
      fm[m2, mwt, mmax, λ, n] pest[m2 - mwt], {m2, mwt, mmax}]}, {m2, mwt, xmax, 0.01}]
 };
oldtheory = ListPlot[%, PlotRange → All, Joined → True,
   PlotStyle → {Directive[Thick, Gray, Dashed], Directive[Thick, Gray]},
   PerformanceGoal → "Speed"];

{
  (*1 step*)
  Table[{m2, g1m /. m → m2}, {m2, 0, xmax, 0.005}],
  (*2 step*)
  total = Re[g2denominator[mwt]];
  Table[{m2, 1/total g2numerator[mwt, m2]}, {m2, 0, xmax, 0.005}]
 };
theory = ListPlot[%, PlotRange → All,
   Joined → True, PlotStyle → Thick, PerformanceGoal → "Speed"];

g1mApp /. α → ψwt^2 ρmax / 4 /. ρmax → mmax / λ /. θ → n / 2 /. ψwt → 2 (1 - Sqrt[1 - mwt/mmax]) /.
  ψ → 2 (1 - Sqrt[1 - m/mmax]);
onestepapp = Plot[%, {m, 0, xmax}, PlotStyle → {Thick, Dashed}];

dat = Import[datadir <>
    "dfe_poisson_N10000_n4_U0.00200_Es0.01_mmax0.50_mwt-0.20_mutmax10_nreps100000
      .csv"];
onestep = Select[dat, #[[2]] == 1 &][[All, 1]];
twostep = Select[dat, #[[2]] == 2 &][[All, 1]];
data = Histogram[{onestep, twostep}, 50, "PDF", AxesOrigin → {0, 0}];

fig6b = Show[oldtheory, data, theory, onestepapp,
  PlotRange → {{xmin, xmax}, {0, ymax}},
  Frame → {True, False, False, False},
  LabelStyle → labelstyle,
  FrameTicksStyle → {FontColor → White, Automatic, Automatic, Automatic},
  Epilog → {
    Text[Style["m0=" <> ToString[mwt],
      12, FontFamily → "Helvetica"], Scaled@{7 / 8, 3 / 4}],
    Text[Style["B", 14, Bold, FontFamily → "Helvetica"], Scaled@{0.05, 0.95}],
    {Directive[Gray, Thick], Line[{{mwt, 10}, {-0.125, 10}}]},
    {Directive[Gray, Thick], Line[{{mwt, 9.5}, {mwt, 10.5}}]},
    {Directive[Gray, Thick], Line[{{-0.125, 9.5}, {-0.125, 10.5}}]},
    {Directive[defaultcolors[[1]], Thick], Line[{{mwt, 20}, {0.023, 20}}]},
    {Directive[defaultcolors[[1]], Thick], Line[{{mwt, 20 - 0.5}, {mwt, 20 + 0.5}}]},
    {Directive[defaultcolors[[1]], Thick],
     Line[{{0.023, 20 - 0.5}, {0.023, 20 + 0.5}}]}
```

```
    }
  ]

Clear[mmax, λ, Es, n, U, mwt]
```

NIntegrate::izero :
Integral and error estimates are 0 on all integration subregions. Try increasing the value of the MinRecursion option. If value of integral may be 0, specify a finite value for the AccuracyGoal option. ≫

```
U = 2 * 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
mwt = -0.3;

{
   (*random*)
   Table[{m2, fm[m2, mwt, mmax, λ, n]}, {m2, xmin, xmax, 0.01}],
   (*established*)
   Table[{m2, (fm[m2, mwt, mmax, λ, n] pest[m2 - mwt]) / NIntegrate[
        fm[m2, mwt, mmax, λ, n] pest[m2 - mwt], {m2, mwt, mmax}]}, {m2, mwt, xmax, 0.01}]
  };
oldtheory = ListPlot[%, PlotRange → All, Joined → True,
    PlotStyle → {Directive[Thick, Gray, Dashed], Directive[Thick, Gray]},
    PerformanceGoal → "Speed"];

{
   (*1 step*)
   Table[{m2, g1m /. m → m2}, {m2, 0, xmax, 0.005}],
   (*2 step*)
   total = Re[g2denominator[mwt]];
   Table[{m2, 1/total g2numerator[mwt, m2]}, {m2, 0, xmax, 0.005}]
  };
theory = ListPlot[%, PlotRange → All,
    Joined → True, PlotStyle → Thick, PerformanceGoal → "Speed"];
```

```
g1mApp /. α → ψwt^2 ρmax / 4 /. ρmax → mmax / λ /. θ → n / 2 /. ψwt → 2 (1 - Sqrt[1 - mwt/mmax]) /.
  ψ → 2 (1 - Sqrt[1 - m/mmax]);
onestepapp = Plot[%, {m, 0, xmax}, PlotStyle → {Thick, Dashed}];

dat = Import[datadir <>
    "dfe_poisson_N10000_n4_U0.00200_Es0.01_mmax0.50_mwt-0.30_mutmax10
      _nreps1000000.csv"];
onestep = Select[dat, #[[2]] == 1 &][[All, 1]];
twostep = Select[dat, #[[2]] == 2 &][[All, 1]];
data = Histogram[{onestep, twostep}, 50, "PDF", AxesOrigin → {0, 0}];

fig6c = Show[oldtheory, data, theory, onestepapp,
  PlotRange → {{xmin, xmax}, {0, ymax}},
  Frame → {True, False, False, False},
  FrameLabel → {"Growth rate"},
  LabelStyle → labelstyle, Epilog → {
    Text[Style["m0=" <> ToString[mwt],
      12, FontFamily → "Helvetica"], Scaled@{7 / 8, 3 / 4}],
    Text[Style["C", 14, Bold, FontFamily → "Helvetica"], Scaled@{0.05, 0.95}],
    {Directive[Gray, Thick], Line[{{mwt, 10}, {-0.22, 10}}]},
    {Directive[Gray, Thick], Line[{{mwt + 0.001, 9.5}, {mwt + 0.001, 10.5}}]},
    {Directive[Gray, Thick], Line[{{-0.22, 9.5}, {-0.22, 10.5}}]},
    {Directive[defaultcolors[[1]], Thick], Line[{{mwt, 25}, {0.015, 25}}]},
    {Directive[defaultcolors[[1]], Thick],
     Line[{{mwt + 0.001, 25 - 0.5}, {mwt + 0.001, 25 + 0.5}}]},
    {Directive[defaultcolors[[1]], Thick],
     Line[{{0.015, 25 - 0.5}, {0.015, 25 + 0.5}}]}
   }
 ]

Clear[mmax, λ, Es, n, U, mwt]
```

NIntegrate::izero :

Integral and error estimates are 0 on all integration subregions. Try increasing the value of the MinRecursion option. If value of integral may be 0, specify a finite value for the AccuracyGoal option. ≫

```
Clear[ymax, xmin, xmax]
```

Figure 6

```
GraphicsColumn[{fig6a, fig6b, fig6c}, Spacings → -30, ImageSize → 350]
Export[figdir <> "Figure6.pdf", %];
```

Distribution of first-step growth rates in 2-step rescue genotypes (equation 18)

As, in the 1-step case, we can use the Λ2 term to write the distribution of growth rates of rescue genotypes

```
h2[m_?NumericQ, m0_] :=
 (U fm[m, m0, mmax, λ, n] (1 - pest[m]) prescuem[m, Λ1[m, mmax, λ, n, U]]) /
  Λ2[m0, mmax, λ, n, U]
```

We can also use our approximations above to get a closed form approximation for this.

For sufficiently subcritical m near -m* we have

$$\text{small}\psi\text{approx} = -\frac{2\, e^{-\frac{\rho\text{max}\,\psi\text{wt}^2}{4}}}{\sqrt{\pi}\,\sqrt{\rho\text{max}}\,\psi};$$

```
Integrate[smallψapprox, {ψ, a, b}, Assumptions → {a < b < 0}];
smallψapprox/%
```

$$D\left[2\left(1-\sqrt{1-\frac{m}{mmax}}\right), m\right] \% \,/.\, a \to 2\left(1-\sqrt{1-\frac{mwt}{mmax}}\right) \,/.\, b \to 2\left(1-\sqrt{1+\frac{mstar}{mmax}}\right) \,/.$$

$$mstar \to \sqrt{\Lambda 0approx / 2} \,/.\, \rho max \to mmax / \lambda \,/.\, \theta \to n / 2 \,/.$$

$$\psi wt \to 2\left(1-\sqrt{1-\frac{mwt}{mmax}}\right) \,/.\, \psi \to 2\left(1-\sqrt{1-\frac{m}{mmax}}\right) \,//\, \text{Simplify}$$

$$\frac{1}{\psi\,\text{Log}\left[\frac{b}{a}\right]}$$

$$-1\Big/\left(2\left(-1+\sqrt{1-\frac{m}{mmax}}\right)\sqrt{1-\frac{m}{mmax}}\;mmax\,\text{Log}\left[\frac{1-\sqrt{1+\frac{\sqrt{U\sqrt{mmax\,\lambda}}}{mmax\,\pi^{1/4}}}}{1-\sqrt{1-\frac{mwt}{mmax}}}\right]\right)$$

Compare distribution of subcriticals

```
U = 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
mwt = -0.1;

total = U NIntegrate[
    fm[m, mwt, mmax, λ, n] (1 - pest[m]) prescuem[m, Λ1[m, mmax, λ, n, U]], {m, -∞, 0}];

Show[
 Plot[1/total U fm[m, mwt, mmax, λ, n] (1 - pest[m]) prescuem[m, Λ1[m, mmax, λ, n, U]],
  {m, -0.2, 0}, PerformanceGoal → "Speed", PlotRange → {0, All}],
 Plot[{, -1/(2 (-1 + Sqrt[1 - m/mmax]) Sqrt[1 - m/mmax] mmax Log[(1 - Sqrt[1 + Sqrt[U Sqrt[mmax λ]]/(mmax π^(1/4))])/(1 - Sqrt[1 - mwt/mmax])])},
  {m, -0.2, 0}, PlotRange → {0, 70}, PlotLegends → {"true", "approx"}]
]

Clear[mmax, λ, Es, n, U, mwt]
```

and for large ρmax we have

```
verylargeρapprox = -(32 e^(-1/4 ρmax (ψ^2 + (ψ - ψwt)^2)))/(Sqrt[π] ρmax^(3/2) ψwt^3);
Integrate[verylargeρapprox, {ψ, -∞, 0}, Assumptions → {ρmax > 0, ψwt < 0}];
verylargeρapprox/%;
Simplify[
 D[2 (1 - Sqrt[1 - m/mmax]), m] % /. a → 2 (1 - Sqrt[1 - mwt/mmax]) /. b → 2 (1 - Sqrt[1 + mstar/mmax]) /. mstar →
    Sqrt[Λ0approx / 2] /. ρmax → mmax / λ /. θ → n / 2 /. ψwt → 2 (1 - Sqrt[1 - mwt/mmax]) /.
  ψ → 2 (1 - Sqrt[1 - m/mmax]), {m < 0, mwt < 0, mmax > 0, λ > 0}]
```

$$\frac{e^{-\frac{1}{4}\rho\max\left(\psi^2+(\psi-\psi\mathrm{wt})^2\right)+\frac{\rho\max\,\psi\mathrm{wt}^2}{8}}\sqrt{\frac{2}{\pi}}\sqrt{\rho\max}}{\mathrm{Erfc}\left[\frac{\sqrt{\rho\max}\,\psi\mathrm{wt}}{2\sqrt{2}}\right]}$$

$$\left(e^{\frac{4\,\mathrm{m}-6\,\mathrm{mmax}+4\sqrt{\mathrm{mmax}\,(-\mathrm{m}+\mathrm{mmax})}-2\sqrt{\mathrm{mmax}\,(\mathrm{mmax}-\mathrm{mwt})}+4\sqrt{(-\mathrm{m}+\mathrm{mmax})\,(\mathrm{mmax}-\mathrm{mwt})}+\mathrm{mwt}}{2\lambda}}\sqrt{\frac{2}{\pi}}\right)\Big/\left(\sqrt{(-\mathrm{m}+\mathrm{mmax})\,\lambda}\;\mathrm{Erfc}\left[\frac{\left(1-\sqrt{1-\frac{\mathrm{mwt}}{\mathrm{mmax}}}\right)\sqrt{\frac{\mathrm{mmax}}{\lambda}}}{\sqrt{2}}\right]\right)$$

Compare distribution of subcriticals

```
U = 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
mwt = -0.4;

total = U NIntegrate[
    fm[m, mwt, mmax, λ, n] (1 - pest[m]) prescuem[m, Λ1[m, mmax, λ, n, U]], {m, -∞, 0}];

Show[
 Plot[1/total U fm[m, mwt, mmax, λ, n] (1 - pest[m]) prescuem[m, Λ1[m, mmax, λ, n, U]],
  {m, -0.4, 0}, PerformanceGoal → "Speed", PlotRange → {0, All}],
 Plot[{, 1/(Sqrt[1 - m/mmax] mmax) (e^((4 m+mwt+mmax (-6+4 Sqrt[1-m/mmax] -2 Sqrt[1-mwt/mmax] +4 Sqrt[1-m/mmax] Sqrt[1-mwt/mmax]))/(2 λ)) Sqrt[2/π] Sqrt[mmax/λ]) /
    Erfc[((1 - Sqrt[1 - mwt/mmax]) Sqrt[mmax/λ])/Sqrt[2]]}, {m, -0.4, 0},
  PlotRange → {0, 70}, PlotLegends → {"true", "approx"}]
]

Clear[mmax, λ, Es, n, U, mwt]
```

Our sufficiently critical approximation is

```
fm[0, m0, mmax, λ, n] Sqrt[2 (2 U Sqrt[mmax λ])/Sqrt[π]];
Integrate[%, {m, -Sqrt[(U Sqrt[mmax λ])/Sqrt[π]], Sqrt[(U Sqrt[mmax λ])/Sqrt[π]]}];
Simplify[%% / %, {mmax > 0, λ > 0}]
```

$$\frac{\pi^{1/4}}{2\sqrt{U}\,(\mathrm{mmax}\,\lambda)^{1/4}}$$

Compare distributions of criticals

```
U = 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
mwt = -0.2;

{mneg = FindRoot[2 m^2 - Λ1[m, mmax, λ, n, U], {m, -0.1}],
  mpos = FindRoot[2 m^2 - Λ1[m, mmax, λ, n, U], {m, 0.1}]};
pr0 = Sqrt[Λ1[0, mmax, λ, n, U] / 2 ];
total = U NIntegrate[fm[m, mwt, mmax, λ, n] (1 - pest[m])
      prescuem[m, Λ1[m, mmax, λ, n, U]], {m, m /. mneg, m /. mpos}];

Show[
 Plot[1/total U fm[m, mwt, mmax, λ, n] (1 - pest[m]) prescuem[m, Λ1[m, mmax, λ, n, U]],
  {m, m /. mneg, m /. mpos}, PerformanceGoal → "Speed", PlotRange → {0, All}],
 Plot[{, π^(1/4)/(2 Sqrt[U] (mmax λ)^(1/4))}, {m, -pr0, pr0}, PlotRange → {0, All},
  PlotLegends → {"true", "approx"}],
 PlotRange → All
]

Clear[mmax, λ, Es, n, U, mwt]
```

And finally our distribution of supercriticals

```
small ψapprox = 2 e^(-ρmax ψwt^2/4) / (√π √ρmax ψ);
Integrate[small ψapprox, {ψ, a, b}, Assumptions → {0 < a < b}];
small ψapprox / %
D[2 (1 - Sqrt[1 - m/mmax]), m] % /. a → 2 (1 - Sqrt[1 - mstar/mmax]) /. b → Sqrt[2]/Sqrt[ρmax] /.
    mstar → Sqrt[Λ0approx / 2] /. ρmax → mmax / λ /. θ → n / 2 /.
  ψwt → 2 (1 - Sqrt[1 - mwt/mmax]) /. ψ → 2 (1 - Sqrt[1 - m/mmax])
```

$$\frac{1}{\psi \operatorname{Log}\left[\frac{b}{a}\right]}$$

$$1 \Big/ \left(2 \left(1 - \sqrt{1 - \frac{m}{mmax}}\right) \sqrt{1 - \frac{m}{mmax}}\; mmax \operatorname{Log}\left[\frac{1}{\sqrt{2}\sqrt{\frac{mmax}{\lambda}}\left(1 - \sqrt{1 - \frac{\sqrt{U\sqrt{mmax\,\lambda}}}{mmax\,\pi^{1/4}}}\right)}\right] \right)$$

Note this is good only to

```
Solve[Sqrt[2]/Sqrt[ρmax] == 2 (1 - Sqrt[1 - m/mmax]), m] /. ρmax → mmax / λ // Simplify
```

$$\left\{\left\{m \to \left(-\frac{1}{2} + \sqrt{2}\sqrt{\frac{mmax}{\lambda}}\right)\lambda\right\}\right\}$$

Compare distn of supercriticals

```
U = 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
mwt = -0.2;

total = U NIntegrate[fm[m, mwt, mmax, λ, n]
      (1 - pest[m]) prescuem[m, Λ1[m, mmax, λ, n, U]], {m, 0, mmax}];

Show[
 Plot[1/total U fm[m, mwt, mmax, λ, n] (1 - pest[m]) prescuem[m, Λ1[m, mmax, λ, n, U]],
  {m, 0, 0.2}, PerformanceGoal → "Speed", PlotRange → {0, All}],
```

$$\text{Plot}\left[\left\{, 1\Big/\left(2\left(1-\sqrt{1-\frac{m}{mmax}}\right)\sqrt{1-\frac{m}{mmax}}\ mmax\ \text{Log}\left[\frac{1}{\sqrt{2}\sqrt{\frac{mmax}{\lambda}}\left(1-\sqrt{1-\frac{\sqrt{U\sqrt{mmax\,\lambda}}}{mmax\,\pi^{1/4}}}\right)}\right]\right)\right\}, \left\{m, 0, \left(-\frac{1}{2}+\sqrt{2}\sqrt{\frac{mmax}{\lambda}}\right)\lambda\right\},\right.$$

```
  PlotRange → {0, 150}, PlotLegends → {"true", "approx"}]
]

Clear[mmax, λ, Es, n, U, mwt]
```

Plot growth rates of rescue intermediates (figures 7 and S2)

As function of wildtype growth rate (figure 7)

```
xmin = -0.3;
xmax = 0.15;
ymax = 30;

U = 2 * 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
mwt = -0.1;

{mneg = FindRoot[2 m1^2 - Λ1[m1, mmax, λ, n, U], {m1, -0.1}],
  mpos = FindRoot[2 m1^2 - Λ1[m1, mmax, λ, n, U], {m1, 0.1}]};
pr0 = Sqrt[Λ1[m1, mmax, λ, n, U] / 2];

exact = fm[m1, mwt, mmax, λ, n] (1 - pest[m1]) prescuem[m1, Λ1[m1, mmax, λ, n, U]];

critical =
  fm[0, mwt, mmax, λ, n] Sqrt[2 Λ1[0, mmax, λ, n, U]] HeavisideTheta[(m1 + pr0) (pr0 - m1)];

subcritical =
  fm[m1, mwt, mmax, λ, n] (Λ1[m1, mmax, λ, n, U]) / Abs[m1] HeavisideTheta[(-m1 - pr0)];
supercritical = fm[m1, mwt, mmax, λ, n] (1 - pest[m1])
    (Λ1[m1, mmax, λ, n, U]) / Abs[m1] HeavisideTheta[(m1 - pr0)];

allexact = NIntegrate[exact, {m1, mwt, 0.1}];

{
  fm[m1, mwt, mmax, λ, n],
  (fm[m1, mwt, mmax, λ, n] pest[m1 - mwt] HeavisideTheta[m1 - mwt]) /
   NIntegrate[fm[m1, mwt, mmax, λ, n] pest[m1 - mwt], {m1, mwt, mmax}]
 };
oldtheory = Plot[
   %,
   {m1, xmin, xmax},
   PlotRange → {0, All},
   (*Filling→Bottom,*)
   PlotStyle → {Directive[Gray, Thick, Dashed], Directive[Gray, Thick]},
   PerformanceGoal → "Speed",
   PlotLegends → Placed[LineLegend[Style[#, 12, FontFamily → "Helvetica"] & /@
       {"random", "established"}], Scaled@{1 / 8, 1.25 / 2}]
  ];
```

```
{subcritical/allexact, critical/allexact, supercritical/allexact};
theory = Plot[
   %,
   {m1, xmin, xmax},
   PlotRange → {0, All},
   Filling → Bottom,
   PerformanceGoal → "Speed",
   PlotLegends → Placed[SwatchLegend[{Directive[defaultcolors[[1]], Opacity[0.5]],
       Directive[defaultcolors[[2]], Opacity[0.5]], Directive[defaultcolors[[3]],
        Opacity[0.5]]}, Style[#, 12, FontFamily → "Helvetica"] & /@
       {"subcritical", "critical", "supercritical"}], Scaled@{1 / 8, 0.65 / 2}]
  ];

exactplot = Plot[
   exact / allexact, {m1, xmin, xmax},
   PlotStyle → Directive[Thick, Black], PerformanceGoal → "Speed", PlotRange → All,
   PlotLegends → Placed[LineLegend[Style[#, 12, FontFamily → "Helvetica"] & /@
       {"first-step"}], Scaled@{1 / 8, 1.25 / 2}]
  ];

dat = Import[datadir <>
    "int_dfe_poisson_N10000_n4_U0.00200_Es0.01_mmax0.50_mwt-0.10_mutmax10
      _nreps100000.csv"];
Select[dat, #[[2]] == 2 &][[All, 3]];
data = Histogram[%, 50, "PDF",
   AxesOrigin → {0, 0}, ChartStyle → Directive[Gray, Opacity[0.25]]];

fig7a = Show[
  oldtheory, data, theory, exactplot,
  Frame → {True, False, False, False},
  FrameTicksStyle → {FontColor → White, Automatic, Automatic, Automatic},
  PlotRange → {{xmin, xmax}, {0, ymax}},
  LabelStyle → labelstyle,
  Epilog → {Text[Style["m0=" <> ToString[mwt],
      12, FontFamily → "Helvetica"], Scaled@{7 / 8, 3 / 4}],
    Text[Style["A", 14, Bold, FontFamily → "Helvetica"], Scaled@{0.05, 0.95}]}
 ]

Clear[mmax, λ, Es, n, U, mwt]
```

```
U = 2 * 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
mwt = -0.2;

{mneg = FindRoot[2 m1^2 - Λ1[m1, mmax, λ, n, U], {m1, -0.1}],
  mpos = FindRoot[2 m1^2 - Λ1[m1, mmax, λ, n, U], {m1, 0.1}]};
pr0 = Sqrt[Λ1[m1, mmax, λ, n, U] / 2];

exact = fm[m1, mwt, mmax, λ, n] (1 - pest[m1]) prescuem[m1, Λ1[m1, mmax, λ, n, U]];

critical =
  fm[0, mwt, mmax, λ, n] Sqrt[2 Λ1[0, mmax, λ, n, U]] HeavisideTheta[(m1 + pr0) (pr0 - m1)];

subcritical =
  fm[m1, mwt, mmax, λ, n] (Λ1[m1, mmax, λ, n, U]) / Abs[m1] HeavisideTheta[(-m1 - pr0)];
supercritical = fm[m1, mwt, mmax, λ, n] (1 - pest[m1])
    (Λ1[m1, mmax, λ, n, U]) / Abs[m1] HeavisideTheta[(m1 - pr0)];

allexact = NIntegrate[exact, {m1, mwt, 0.1}];

{
  fm[m1, mwt, mmax, λ, n],
  (fm[m1, mwt, mmax, λ, n] pest[m1 - mwt] HeavisideTheta[m1 - mwt]) /
   NIntegrate[fm[m1, mwt, mmax, λ, n] pest[m1 - mwt], {m1, mwt, mmax}]
 };
oldtheory = Plot[
   %,
   {m1, xmin, xmax},
   PlotRange → {0, All},
   (*Filling→Bottom,*)
   PlotStyle → {Directive[Gray, Thick, Dashed], Directive[Gray, Thick]},
```

```
    PerformanceGoal → "Speed"
  ];

{subcritical/allexact, critical/allexact, supercritical/allexact};
theory = Plot[
    %,
    {m1, xmin, xmax},
    PlotRange → {0, All},
    Filling → Bottom,
    PerformanceGoal → "Speed"
  ];

exactplot = Plot[
    exact / allexact, {m1, xmin, xmax},
    PlotStyle → Directive[Thick, Black], PerformanceGoal → "Speed", PlotRange → All
  ];

dat = Import[datadir <>
     "int_dfe_poisson_N10000_n4_U0.00200_Es0.01_mmax0.50_mwt-0.20_mutmax10
       _nreps100000.csv"];
Select[dat, #[[2]] == 2 &][[All, 3]];
data = Histogram[%, 50, "PDF",
    AxesOrigin → {0, 0}, ChartStyle → Directive[Gray, Opacity[0.25]]];

fig7b = Show[
  oldtheory, data, theory, exactplot,
  Frame → {True, False, False, False},
  FrameTicksStyle → {FontColor → White, Automatic, Automatic, Automatic},
  PlotRange → {{xmin, xmax}, {0, ymax}},
  LabelStyle → labelstyle,
  Epilog → {Text[Style["m0=" <> ToString[mwt],
      12, FontFamily → "Helvetica"], Scaled@{7 / 8, 3 / 4}],
    Text[Style["B", 14, Bold, FontFamily → "Helvetica"], Scaled@{0.05, 0.95}]}
 ]

Clear[mmax, λ, Es, n, U, mwt]
```

```
U = 2 * 10^-3;
mmax = 0.5;
```

```
λ = 2 Es / n;
Es = 0.01;
n = 4;
mwt = -0.3;

{mneg = FindRoot[2 m1^2 - Λ1[m1, mmax, λ, n, U], {m1, -0.1}],
  mpos = FindRoot[2 m1^2 - Λ1[m1, mmax, λ, n, U], {m1, 0.1}]};
pr0 = Sqrt[Λ1[m1, mmax, λ, n, U] / 2];

exact = fm[m1, mwt, mmax, λ, n] (1 - pest[m1]) prescuem[m1, Λ1[m1, mmax, λ, n, U]];

critical =
  fm[0, mwt, mmax, λ, n] Sqrt[2 Λ1[0, mmax, λ, n, U]] HeavisideTheta[(m1 + pr0) (pr0 - m1)];

subcritical =
  fm[m1, mwt, mmax, λ, n] (Λ1[m1, mmax, λ, n, U]) / Abs[m1] HeavisideTheta[(-m1 - pr0)];
supercritical = fm[m1, mwt, mmax, λ, n] (1 - pest[m1])
    (Λ1[m1, mmax, λ, n, U]) / Abs[m1] HeavisideTheta[(m1 - pr0)];

allexact = NIntegrate[exact, {m1, mwt, 0.1}];

{
  fm[m1, mwt, mmax, λ, n],
  (fm[m1, mwt, mmax, λ, n] pest[m1 - mwt] HeavisideTheta[m1 - mwt]) /
   NIntegrate[fm[m1, mwt, mmax, λ, n] pest[m1 - mwt], {m1, mwt, mmax}]
 };
oldtheory = Plot[
   %,
   {m1, xmin, xmax},
   PlotRange → {0, All},
   (*Filling→Bottom,*)
   PlotStyle → {Directive[Gray, Thick, Dashed], Directive[Gray, Thick]},
   PerformanceGoal → "Speed"
  ];

{subcritical / allexact, critical / allexact, supercritical / allexact};
theory = Plot[
   %,
   {m1, xmin, xmax},
   PlotRange → {0, All},
   Filling → Bottom,
   PerformanceGoal → "Speed"
  ];

exactplot = Plot[
   exact / allexact, {m1, xmin, xmax},
   PlotStyle → Directive[Thick, Black], PerformanceGoal → "Speed", PlotRange → All
  ];
```

```
dat = Import[datadir <>
    "int_dfe_poisson_N10000_n4_U0.00200_Es0.01_mmax0.50_mwt-0.30_mutmax10
      _nreps1000000.csv"];
Select[dat, #[[2]] == 2 &][[All, 3]];
data = Histogram[%, 50, "PDF",
   AxesOrigin → {0, 0}, ChartStyle → Directive[Gray, Opacity[0.25]]];

fig7c = Show[
  oldtheory, data, theory, exactplot,
  Frame → {True, False, False, False},
  FrameLabel → {"Growth rate"},
  PlotRange → {{xmin, xmax}, {0, ymax}},
  LabelStyle → labelstyle,
  Epilog → {Text[Style["m0=" <> ToString[mwt],
      12, FontFamily → "Helvetica"], Scaled@{7 / 8, 3 / 4}],
    Text[Style["C", 14, Bold, FontFamily → "Helvetica"], Scaled@{0.05, 0.95}]}
 ]

Clear[mmax, λ, Es, n, U, mwt]
```

```
Clear[ymax, xmin, xmax]
```

```
GraphicsColumn[{fig7a, fig7b, fig7c}, Spacings → -30, ImageSize → 350]
Export[figdir <> "Figure7.pdf", %];
```

As function of mutation (figure S2)

```
xmin = mwt;
xmax = -mwt / 2;
ymax = 70;

U = 10^-4;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
```

```
n = 4;
mwt = -0.2;


{mneg = FindRoot[2 m1^2 - Λ1[m1, mmax, λ, n, U], {m1, -0.1}],
  mpos = FindRoot[2 m1^2 - Λ1[m1, mmax, λ, n, U], {m1, 0.1}]};
pr0 = Sqrt[Λ1[m1, mmax, λ, n, U] / 2 ];

exact = fm[m1, mwt, mmax, λ, n] (1 - pest[m1]) prescuem[m1, Λ1[m1, mmax, λ, n, U]];

critical =
  fm[0, mwt, mmax, λ, n] Sqrt[2 Λ1[0, mmax, λ, n, U]] HeavisideTheta[(m1 + pr0) (pr0 - m1)];

subcritical =
  fm[m1, mwt, mmax, λ, n] (Λ1[m1, mmax, λ, n, U]) / Abs[m1] HeavisideTheta[(-m1 - pr0)];
supercritical = fm[m1, mwt, mmax, λ, n] (1 - pest[m1])
    (Λ1[m1, mmax, λ, n, U]) / Abs[m1] HeavisideTheta[(m1 - pr0)];
total = NIntegrate[exact, {m1, mwt, 0.1}];

figS2a = Show[
  Plot[
   {subcritical / total, critical / total, supercritical / total},
   {m1, xmin, xmax},
   PlotRange → {0, All},
   (*PlotStyle→Thick,*)
   Filling → Bottom,
   Frame → {True, False, False, False},
   FrameTicksStyle → {FontColor → White, Automatic, Automatic, Automatic},
   PlotLegends →
    Placed[SwatchLegend[{Directive[defaultcolors[[1]], Opacity[0.5]],
       Directive[defaultcolors[[2]], Opacity[0.5]], Directive[defaultcolors[[3]],
        Opacity[0.5]]}, Style[#, 12, FontFamily → "Helvetica"] & /@
       {"subcritical", "critical", "supercritical"}], Scaled@{1 / 8, 0.5}],
   LabelStyle → labelstyle,
   Epilog →
    {Text[Style["U=10^-4", 12, FontFamily → "Helvetica"], Scaled@{7 / 8, 3 / 4}],
     Text[Style["A", 14, Bold, FontFamily → "Helvetica"], Scaled@{0.05, 0.95}]},
   PerformanceGoal → "Speed"
  ],
  Plot[exact / total, {m1, xmin, xmax},
   PlotStyle → Directive[Thick, Black], PerformanceGoal → "Speed", PlotRange → All,
   PlotLegends → Placed[Style[#, 12, FontFamily → "Helvetica"] & /@ {"first-step"},
     Scaled@{1 / 8, 0.7}]
  ],
  PlotRange → {{xmin, xmax}, {0, ymax}}
 ]

Clear[mmax, λ, Es, n, U, mwt]
```

A
first−step
subcritical
critical
supercritical
U=10^−4

```
U = 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
mwt = -0.2;

{mneg = FindRoot[2 m1^2 - Λ1[m1, mmax, λ, n, U], {m1, -0.1}],
  mpos = FindRoot[2 m1^2 - Λ1[m1, mmax, λ, n, U], {m1, 0.1}]};
pr0 = Sqrt[Λ1[m1, mmax, λ, n, U] / 2];

exact = fm[m1, mwt, mmax, λ, n] (1 - pest[m1]) prescuem[m1, Λ1[m1, mmax, λ, n, U]];

critical =
  fm[0, mwt, mmax, λ, n] Sqrt[2 Λ1[0, mmax, λ, n, U]] HeavisideTheta[(m1 + pr0) (pr0 - m1)];

subcritical =
  fm[m1, mwt, mmax, λ, n] (Λ1[m1, mmax, λ, n, U]) / Abs[m1] HeavisideTheta[(-m1 - pr0)];
supercritical = fm[m1, mwt, mmax, λ, n] (1 - pest[m1])
    (Λ1[m1, mmax, λ, n, U]) / Abs[m1] HeavisideTheta[(m1 - pr0)];

total = NIntegrate[exact, {m1, mwt, 0.1}];

figS2b = Show[
  Plot[
   {subcritical / total, critical / total, supercritical / total},
   {m1, xmin, xmax},
   PlotRange → {0, All},
   (*PlotStyle→Thick,*)
   Filling → Bottom,
   Frame → {True, False, False, False},
   FrameTicksStyle → {FontColor → White, Automatic, Automatic, Automatic},
   LabelStyle → labelstyle,
   Epilog →
    {Text[Style["U=10^-3", 12, FontFamily → "Helvetica"], Scaled@{7 / 8, 3 / 4}],
     Text[Style["B", 14, Bold, FontFamily → "Helvetica"], Scaled@{0.05, 0.95}]},
   PerformanceGoal → "Speed"
  ],
  Plot[{exact / total}, {m1, xmin, xmax}, PlotStyle → Directive[Thick, Black],
   PerformanceGoal → "Speed", PlotRange → All(*,Filling→Bottom*)],
  PlotRange → {{xmin, xmax}, {0, ymax}}
 ]

Clear[mmax, λ, Es, n, U, mwt]
```

B
U=10^-3

```
U = 10^-2;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
mwt = -0.2;

{mneg = FindRoot[2 m1^2 - Λ1[m1, mmax, λ, n, U], {m1, -0.1}],
  mpos = FindRoot[2 m1^2 - Λ1[m1, mmax, λ, n, U], {m1, 0.1}]};
pr0 = Sqrt[Λ1[m1, mmax, λ, n, U] / 2];

exact = fm[m1, mwt, mmax, λ, n] (1 - pest[m1]) prescuem[m1, Λ1[m1, mmax, λ, n, U]];

critical =
  fm[0, mwt, mmax, λ, n] Sqrt[2 Λ1[0, mmax, λ, n, U]] HeavisideTheta[(m1 + pr0) (pr0 - m1)];

subcritical =
  fm[m1, mwt, mmax, λ, n] (Λ1[m1, mmax, λ, n, U]) / Abs[m1] HeavisideTheta[(-m1 - pr0)];
supercritical = fm[m1, mwt, mmax, λ, n] (1 - pest[m1])
    (Λ1[m1, mmax, λ, n, U]) / Abs[m1] HeavisideTheta[(m1 - pr0)];
total = NIntegrate[exact, {m1, mwt, 0.1}];

figS2c = Show[
  Plot[
   {subcritical / total, critical / total, supercritical / total},
   {m1, xmin, xmax},
   PlotRange → {0, All},
   Filling → Bottom,
   Frame → {True, False, False, False},
   FrameLabel → {"Growth rate", ""},
   LabelStyle → labelstyle,
   Epilog →
    {Text[Style["U=10^-2", 12, FontFamily → "Helvetica"], Scaled@{7 / 8, 3 / 4}],
     Text[Style["C", 14, Bold, FontFamily → "Helvetica"], Scaled@{0.05, 0.95}]},
   PerformanceGoal → "Speed"
  ],
  Plot[{exact / total}, {m1, xmin, xmax},
   PlotStyle → Directive[Thick, Black], PerformanceGoal → "Speed", PlotRange → All],
  PlotRange → {{xmin, xmax}, {0, ymax}}
 ]

Clear[mmax, λ, Es, n, U, mwt]
```

```
Clear[ymax, xmin, xmax]
```

```
GraphicsColumn[{figS2a, figS2b, figS2c}, Spacings → -30, ImageSize → 350]
Export[supfigdir <> "FigureS2.eps", %];
```

Kurtosis

Mutational distributions (figure S3A)

Let's compare our results when we take mutational distributions of phenotypic changes with the same mean (0), variance (λ), and skewness (0), but different kurtosis.

```
n = 4;(*phenotypic dimensions*)
Es = 0.01;(*mean mutational selective effect*)
λ = 2 Es / n;(*mutational variance per trait*)
styl = {FontFamily → "Times", FontSize → 10};(*styles of axes and legend*)

{PDF[WignerSemicircleDistribution[√(4 λ)], z],
  PDF[NormalDistribution[0, √λ], z], PDF[LaplaceDistribution[0, √(λ / 2)], z]};
figS3a = Plot[%, {z, -4 √λ, 4 √λ},
  PlotStyle → {Directive[Thick, Dashing[Medium], Black], Directive[Thick, Black],
    Directive[Thick, Dotted, Black]}, PlotRange → {0, All},
  Filling → Bottom, FillingStyle → Directive[Black, Opacity[0.1]],
  PlotLegends → Placed[LineLegend[Style[#, labelstyle] & /@
      {"platykurtic", "normal", "leptokurtic"}], Scaled@{0.8, 0.8}],
  Frame → {True, False, False, False},
  FrameLabel → {"Δz_i"},
  FrameStyle → labelstyle,
  PlotRangePadding → None,
  Epilog →
   {Text[Style["A", 14, Bold, FontFamily → "Helvetica"], Scaled@{0.05, 0.95}]}
 ]

Clear[n, Es, λ, styl, platy, meso, lepto]
```

Probability of rescue (figure S3B,C)

Interpolation function

The probability of rescue by k steps involves k integrals, and so with even small k (e.g, k=3) they are very slow to compute in their exact form. We can, however, combine an approximation (don't integrate below mmin) with interpolation functions to greatly speed things up (with some loss of accuaracy)

```
mTempmin = -0.4;
mTempmax = -0.01;
step = 0.01;
mmin = mTempmin;

Clear[Λ1Interpolated, Λ2Interpolated, Λ3Interpolated, Λ4Interpolated]

Λ1Interpolated[m0_, mmax_, λ_, n_, U_] :=
 Λ1Interpolated[m0, mmax, λ, n, U] = Block[{},
   f = Interpolation[Table[{mTemp, U NIntegrate[fm[m, mTemp, mmax, λ, n] pest[m],
          {m, 0, mmax}, Method → {Automatic, "SymbolicProcessing" → 0}]},
       {mTemp, mTempmin, mTempmax, step}]];
   f[m0]
  ]

Λ2Interpolated[m0_, mmax_, λ_, n_, U_] :=
 Λ2Interpolated[m0, mmax, λ, n, U] = Block[{},
   f = Interpolation[Table[{mTemp, U NIntegrate[fm[m, mTemp, mmax, λ, n]
           (1 - pest[m]) prescuem[m, Λ1Interpolated[m, mmax, λ, n, U]],
          {m, mmin, mmax}, Method → {Automatic, "SymbolicProcessing" → 0}]},
       {mTemp, mTempmin, mTempmax, step}]];
   f[m0]
  ]

Λ3Interpolated[m0_, mmax_, λ_, n_, U_] :=
 Λ3Interpolated[m0, mmax, λ, n, U] = Block[{},
   f = Interpolation[Table[{mTemp, U NIntegrate[fm[m, mTemp, mmax, λ, n]
           (1 - pest[m]) prescuem[m, Λ2Interpolated[m, mmax, λ, n, U]],
          {m, mmin, mmax}, Method → {Automatic, "SymbolicProcessing" → 0}]},
       {mTemp, mTempmin, mTempmax, step}]];
   f[m0]
  ]

Λ4Interpolated[m0_, mmax_, λ_, n_, U_] :=
 Λ4Interpolated[m0, mmax, λ, n, U] = Block[{},
   f = Interpolation[Table[{mTemp, U NIntegrate[fm[m, mTemp, mmax, λ, n]
           (1 - pest[m]) prescuem[m, Λ3Interpolated[m, mmax, λ, n, U]],
          {m, mmin, mmax}, Method → {Automatic, "SymbolicProcessing" → 0}]},
       {mTemp, mTempmin, mTempmax, step}]];
   f[m0]
  ]
```

Numerical data (for normal distribution)

```
(*N0=10^4;
mmax=0.5;
λ=2Es/n;
Es=0.01;
n=4;
U=2*10^-3;

m0min=mTempmin;
m0max=mTempmax;
mstep=step;
rate4=Table[{m0,Λ4Interpolated[m0,mmax,λ,n,U]},{m0,m0min,m0max,mstep}];
rate3=Table[{m0,Λ3Interpolated[m0,mmax,λ,n,U]},{m0,m0min,m0max,mstep}];
rate2=Table[{m0,Λ2Interpolated[m0,mmax,λ,n,U]},{m0,m0min,m0max,mstep}];
rate1=Table[{m0,Λ1Interpolated[m0,mmax,λ,n,U]},{m0,m0min,m0max,mstep}];
m0list=Table[m0,{m0,m0min,m0max,mstep}];
theory={
  Table[{m0list[[i]],prescue/.p0→prescuem[m0list[[i]],rate1[[i,2]]]},
   {i,Length[m0list]}],
  Table[{m0list[[i]],prescue/.p0→prescuem[m0list[[i]],rate2[[i,2]]]},
   {i,Length[m0list]}],
  Table[{m0list[[i]],prescue/.p0→prescuem[m0list[[i]],rate3[[i,2]]]},
   {i,Length[m0list]}],
  Table[{m0list[[i]],prescue/.p0→prescuem[m0list[[i]],rate4[[i,2]]]},
   {i,Length[m0list]}]
 };
alltheory=
 Table[{m0list[[i]],prescue/.p0→prescuem[m0list[[i]],rate1[[i,2]]+rate2[[i,2]]+
       rate3[[i,2]]+rate4[[i,2]]]},{i,Length[m0list]}];

Clear[N0,mmax,λ,Es,n,U,m0min,m0max]*)
```

```
theory = {{{-0.4`, 5.472398814099222`*^-7}, {-0.39`, 9.745688406281872`*^-7},
    {-0.38`, 1.7238895513305152`*^-6}, {-0.37`, 3.0285772651961196`*^-6},
    {-0.36000000000000004`, 5.2841014319682245`*^-6}, {-0.35000000000000003`,
     9.155420059081543`*^-6}, {-0.34`, 0.00001575188019520279 4`},
    {-0.33`, 0.00002690955788409166`}, {-0.32`, 0.00004564308357801749 6`},
    {-0.31000000000000005`, 0.0000768622102641503`},
    {-0.30000000000000004`, 0.00012849810996373723`},
    {-0.29000000000000004`, 0.0002132574731799064`},
    {-0.28`, 0.0003513291377449379`}, {-0.27`, 0.00057452097472376 9`},
    {-0.26`, 0.0009325213318174264`}, {-0.25`, 0.0015022797840921198`},
    {-0.24000000000000002`, 0.0024019086800984857`},
    {-0.23`, 0.0038110379258926574`}, {-0.22000000000000003`,
     0.00600020901304088`}, {-0.21000000000000002`, 0.00937261491044139`},
    {-0.2`, 0.014522096798011974`}, {-0.19000000000000003`, 0.022311337733202485`},
    {-0.18000000000000002`, 0.03397263148001661`},
    {-0.17`, 0.0512283883233019`}, {-0.16000000000000003`, 0.07641581098977057`},
    {-0.15000000000000002`, 0.11257347217569635`},
    {-0.14`, 0.16339795924448708`}, {-0.13`, 0.23289952993154328`},
    {-0.12`, 0.3244893834485655`}, {-0.11000000000000004`, 0.43919411790398366`},
    {-0.10000000000000003`, 0.5729341370203966`},
    {-0.09000000000000002`, 0.7137213876566558`},
```

```
 {-0.08000000000000002`, 0.8414602539868381`}, {-0.07`, 0.9344415307620567`},
 {-0.06`, 0.9829032755970813`}, {-0.04999999999999999`, 0.9979187459679042`},
 {-0.040000000000000036`, 0.9999341480370483`},
 {-0.030000000000000027`, 0.9999998505645212`},
 {-0.020000000000000018`, 0.9999999999991431`}, {-0.010000000000000009`, 1.`}},
{{-0.4`, 7.1817194564616216`*^-6}, {-0.39`, 0.00001038286843568769 8`},
 {-0.38`, 0.000015004899198478583`}, {-0.37`, 0.000021674932411452907`},
 {-0.36000000000000004`, 0.000031295722740964926`},
 {-0.35000000000000003`, 0.00004516336475557381`},
 {-0.34`, 0.00006513527103491068`}, {-0.33`, 0.00009386674884392932`},
 {-0.32`, 0.00013514257904490012`}, {-0.31000000000000005`,
  0.0001943394640103735`}, {-0.30000000000000004`, 0.00027906144855771586`},
 {-0.29000000000000004`, 0.0004000224444989930 5`},
 {-0.28`, 0.0005722318522486392`}, {-0.27`, 0.0008166042269467377`},
 {-0.26`, 0.0011621019720312598`}, {-0.25`, 0.0016485639043937184`},
 {-0.24000000000000002`, 0.002330394186973561`},
 {-0.23`, 0.0032813120522319217`}, {-0.22000000000000003`,
  0.0046003825714453495`}, {-0.21000000000000002`, 0.006419557828723499`},
 {-0.2`, 0.008912948912746632`}, {-0.19000000000000003`, 0.012308013245967753`},
 {-0.18000000000000002`, 0.01689876878901897`}, {-0.17`, 0.02306102686962941`},
 {-0.16000000000000003`, 0.031269462419949656`},
 {-0.15000000000000002`, 0.042116115688766054`}, {-0.14`, 0.05632965853148175`},
 {-0.13`, 0.07479449506069946`}, {-0.12`, 0.09856854888921651`},
 {-0.11000000000000004`, 0.12889844527072303`}, {-0.10000000000000003`,
  0.1672306176682965`}, {-0.09000000000000002`, 0.21521607762716344`},
 {-0.08000000000000002`, 0.2747032194313106`}, {-0.07`, 0.3477011299288638`},
 {-0.06`, 0.4362577296013713`}, {-0.04999999999999999`, 0.5420788502184701`},
 {-0.040000000000000036`, 0.6653477290582192`},
 {-0.030000000000000027`, 0.8010818232849237`}, {-0.020000000000000018`,
  0.9286233811012167`}, {-0.010000000000000009`, 0.9962496646879948`}},
{{-0.4`, 2.672518644497579`*^-6}, {-0.39`, 3.6200066483305093`*^-6},
 {-0.38`, 4.9024286813414975`*^-6}, {-0.37`, 6.639033992561494`*^-6},
 {-0.36000000000000004`, 8.99229424278225`*^-6}, {-0.35000000000000003`,
  0.000012183830842893428`}, {-0.34`, 0.000016516674993138913`},
 {-0.33`, 0.00002240514549411987`}, {-0.32`, 0.00003041648537960295 3`},
 {-0.31000000000000005`, 0.000041327352556463914`},
 {-0.30000000000000004`, 0.00005620069935863281`},
 {-0.29000000000000004`, 0.00007648968361839703`},
 {-0.28`, 0.0001041772194614321`}, {-0.27`, 0.00014196192976223543`},
 {-0.26`, 0.00019350379587734778`}, {-0.25`, 0.0002637455775598152`},
 {-0.24000000000000002`, 0.0003593290092440693`},
 {-0.23`, 0.0004891277868906974`},
 {-0.22000000000000003`, 0.0006649222935298793`}, {-0.21000000000000002`,
  0.0009022438378168962`}, {-0.2`, 0.0012214190541605108`},
 {-0.19000000000000003`, 0.0016488487049626244`}, {-0.18000000000000002`,
  0.0022185608705778126`}, {-0.17`, 0.0029740895246452848`},
 {-0.16000000000000003`, 0.003970751527472172`}, {-0.15000000000000002`,
  0.005278436334274735`}, {-0.14`, 0.006985125056896413`},
 {-0.13`, 0.009201449505447323`}, {-0.12`, 0.012067026227695399`},
 {-0.11000000000000004`, 0.015759693621743676`}, {-0.10000000000000003`,
  0.020509966391728862`}, {-0.09000000000000002`, 0.02662504581244618`},
 {-0.08000000000000002`, 0.03453108060938248`}, {-0.07`, 0.04485200223554198`},
 {-0.06`, 0.0585665300648599`}, {-0.04999999999999999`, 0.0773474840786541`},
 {-0.040000000000000036`, 0.10438028623999529`},
 {-0.030000000000000027`, 0.14667096966766024`},
```

```
 {-0.020000000000000018`, 0.2233073280524227`},
 {-0.010000000000000009`, 0.4098900908454398`}},
{{-0.4`, 3.665400664099039`*^-7}, {-0.39`, 4.882948413387211`*^-7},
 {-0.38`, 6.507825516255394`*^-7}, {-0.37`, 8.679175866888045`*^-7},
 {-0.36000000000000004`, 1.1585392625246271`*^-6}, {-0.35000000000000003`,
  1.548213704460899`*^-6}, {-0.34`, 2.071738417153135`*^-6},
 {-0.33`, 2.776581790708832`*^-6}, {-0.32`, 3.727611290194055`*^-6},
 {-0.31000000000000005`, 5.013589215119296`*^-6},
 {-0.30000000000000004`, 6.756030736299046`*^-6},
 {-0.29000000000000004`, 9.12124881535803`*^-6},
 {-0.28`, 0.00001233658455390696`}, {-0.27`, 0.000016712145389896627`},
 {-0.26`, 0.00002266963795427568`}, {-0.25`, 0.000030780242171069006`},
 {-0.24000000000000002`, 0.00004181381972367948`},
 {-0.23`, 0.000056802136495281985`},
 {-0.22000000000000003`, 0.00007711911056884624`}, {-0.21000000000000002`,
  0.00010458146610448082`}, {-0.2`, 0.0001415735100674942`},
 {-0.19000000000000003`, 0.00019120021529694942`}, {-0.18000000000000002`,
  0.0002574735404686779`}, {-0.17`, 0.00034553832838446485`},
 {-0.16000000000000003`, 0.0004619470399811476`}, {-0.15000000000000002`,
  0.0006149981944676419`}, {-0.14`, 0.0008151642974213447`},
 {-0.13`, 0.0010756555359718867`}, {-0.12`, 0.0014132038091301258`},
 {-0.11000000000000004`, 0.0018492239194836113`},
 {-0.10000000000000003`, 0.002411647781310755`},
 {-0.09000000000000002`, 0.003138005818001832`},
 {-0.08000000000000002`, 0.004080917925158634`},
 {-0.07`, 0.005318491045821605`}, {-0.06`, 0.006975434272220693`},
 {-0.04999999999999999`, 0.009269923451119766`},
 {-0.040000000000000036`, 0.012631023980203326`},
 {-0.030000000000000027`, 0.01804961542287531`},
 {-0.020000000000000018`, 0.0284671089107692`},
 {-0.010000000000000009`, 0.05823795851907776`}}};
```

```
alltheory = {{-0.4`, 0.000010767989638504893`}, {-0.39`, 0.000015465680252679803`},
   {-0.38`, 0.000022281877958607588`}, {-0.37`, 0.00003221020658283891`},
   {-0.36000000000000004`, 0.00004673011156652862`}, {-0.35000000000000003`,
    0.00006804965109896699`}, {-0.34`, 0.00009947299961354794`},
   {-0.33`, 0.0001459524027258574`}, {-0.32`, 0.00021491729975098295`},
   {-0.31000000000000005`, 0.00031751489398534893`},
   {-0.30000000000000004`, 0.0004704543728014654`},
   {-0.29000000000000004`, 0.0006987523028609832`},
   {-0.28`, 0.0010397647754660788`}, {-0.27`, 0.0015491068347829318`},
   {-0.26`, 0.0023092555158806816`}, {-0.25`, 0.0034419561736643844`},
   {-0.24000000000000002`, 0.005125934145003619`},
   {-0.23`, 0.007621874910163862`}, {-0.22000000000000003`, 0.011307117362613917`},
   {-0.21000000000000002`, 0.01672286182842886`},
   {-0.2`, 0.024636589665609887`}, {-0.19000000000000003`, 0.03612111665412221`},
   {-0.18000000000000002`, 0.0526478810505413`}, {-0.17`, 0.07618321541025108`},
   {-0.16000000000000003`, 0.10925842311524103`},
   {-0.15000000000000002`, 0.154951959045035`}, {-0.14`, 0.21667029213726385`},
   {-0.13`, 0.29754827077524637`}, {-0.12`, 0.39924782631433087`},
   {-0.11000000000000004`, 0.5200288215021587`},
   {-0.10000000000000003`, 0.6524246688522214`},
   {-0.09000000000000002`, 0.7819169338181124`},
   {-0.08000000000000002`, 0.8893420776854711`}, {-0.07`, 0.9592948833994817`},
   {-0.06`, 0.9909501188644341`}, {-0.04999999999999999`, 0.9991194054587093`},
   {-0.040000000000000036`, 0.9999799413255674`},
   {-0.030000000000000027`, 0.999999972757273`},
   {-0.020000000000000018`, 0.9999999999999342`}, {-0.010000000000000009`, 1.`}};
```

Platykurtic (semicircle, panel B)

```
N0 = 10 000;
U = 2 * 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
mwts = {-0.1, -0.2, -0.3};
type = "platy";
nreps = 100 000;

data = Table[
   file = StringForm[datadir <> "dfe_``_N``_n``_U``_Es``_mmax``_mwt``_nreps``.csv",
     type, N0, n, NumberForm[U // N, {6, 5}], NumberForm[Es, {3, 2}],
     NumberForm[mmax, {3, 2}], mwts[[i]], nreps];
   dat = Import[ToString[file]];
   onestep = Length[Select[dat, #[[2]] == 1 &]] / nreps;
   twostep = Length[Select[dat, #[[2]] == 2 &]] / nreps;
   threestep = Length[Select[dat, #[[2]] == 3 &]] / nreps;
   fourstep = Length[Select[dat, #[[2]] == 4 &]] / nreps;
   total = onestep + twostep + threestep + fourstep;
   {onestep, twostep, threestep, fourstep, total} // N,
   {i, Length[mwts]}
  ];

Table[Table[{mwts[[i]], data[[i, j]]}, {i, Length[mwts]}], {j, Length[data[[1]]]}];
```

```
dataplot = ListLogPlot[%,
   PlotRange → {{-0.4, 0}, {10^-6, 1}},
   Frame → {True, False, False, True},
   Joined → True,
   PlotStyle → {
     Directive[defaultcolors[[1]], Thick, Dashing[Medium]],
     Directive[defaultcolors[[2]], Thick, Dashing[Medium]],
     Directive[defaultcolors[[3]], Thick, Dashing[Medium]],
     Directive[defaultcolors[[4]], Thick, Dashing[Medium]],
     Directive[Black, Thickness[0.005], Dashing[Medium]]
    },
   PlotMarkers → {
     Graphics[{Dashing[None], Thickness[Medium],
       defaultcolors[[1]], Circle[]}, ImageSize → 10],
     Graphics[{Dashing[None], Thickness[Medium], Circle[], defaultcolors[[2]]},
      ImageSize → 10], Graphics[{Dashing[None], Thickness[Medium],
       Circle[], defaultcolors[[3]]}, ImageSize → 10],
     Graphics[{Dashing[None], Thickness[Medium], Circle[],
       defaultcolors[[4]]}, ImageSize → 10],
     Graphics[{Black, Disk[]}, ImageSize → 8]
    }
  ];

figS3b = Show[
  ListLogPlot[
   theory,
   Joined → True,
   PlotStyle → Directive[Thick, Opacity[0.5]],
   PlotRange → {{-0.4, 0}, {5 * 10^-7, 1}},
   Frame → {True, False, False, True},
   FrameLabel → {(*"Wildtype growth rate"*), , , "Probability of rescue"},
   FrameTicks → {True, False, False, True},
   FrameTicksStyle → {FontColor → White, Automatic, Automatic, Automatic},
   LabelStyle → labelstyle,
   PlotLegends → Placed[LineLegend[Style[#, 12, FontFamily → "Helvetica"] & /@
       {"1-step", "2-step", "3-step", "4-step"}], Scaled@{0.85, 0.22}]
  ],
  ListLogPlot[alltheory, Joined → True, PlotStyle → {Black, Thick, Opacity[0.5]},
   PlotLegends → Placed[LineLegend[
      Style[#, 12, FontFamily → "Helvetica"] & /@ {"total"}], Scaled@{0.56, 0.22}]
  ],
  dataplot,
  PlotRangePadding → 0,
  (*ImagePadding→probpadding,*)
  Epilog → {
    Text[Style["B", 14, Bold, FontFamily → "Helvetica"], Scaled@{0.05, 0.95}],
    Text[Style["platykurtic", 14, FontFamily → "Helvetica"], Scaled@{0.25, 0.85}],
    {Opacity[0.5], braceLabel[
      {{-0.125, Log@10^-6}, {-0.125, Log@(1.5 * 10^-4)}}, Style["", Larger]]}
   }
 ]
```

```
Clear[N0, mmax, λ, Es, n, U, mwts, type, nreps]
```

Leptokurtic (Laplace, panel C)

```
N0 = 10 000;
U = 2 * 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
mwts = {-0.1, -0.2, -0.3};
type = "lepto";
nreps = 100 000;

data = Table[
   file = StringForm[datadir <> "dfe_``_N``_n``_U``_Es``_mmax``_mwt``_nreps``.csv",
     type, N0, n, NumberForm[U // N, {6, 5}], NumberForm[Es, {3, 2}],
     NumberForm[mmax, {3, 2}], mwts[[i]], nreps];
   dat = Import[ToString[file]];
   onestep = Length[Select[dat, #[[2]] == 1 &]] / nreps;
   twostep = Length[Select[dat, #[[2]] == 2 &]] / nreps;
   threestep = Length[Select[dat, #[[2]] == 3 &]] / nreps;
   fourstep = Length[Select[dat, #[[2]] == 4 &]] / nreps;
   total = onestep + twostep + threestep + fourstep;
   {onestep, twostep, threestep, fourstep, total} // N,
   {i, Length[mwts]}
  ];

Table[Table[{mwts[[i]], data[[i, j]]}, {i, Length[mwts]}], {j, Length[data[[1]]]}];
dataplot = ListLogPlot[%,
   PlotRange → {{-0.4, 0}, {10^-6, 1}},
   Frame → {True, False, False, True},
   Joined → True,
   PlotStyle → {
     Directive[defaultcolors[[1]], Thick, Dotted],
     Directive[defaultcolors[[2]], Thick, Dotted],
     Directive[defaultcolors[[3]], Thick, Dotted],
     Directive[defaultcolors[[4]], Thick, Dotted],
```

```
      Directive[Black, Thickness[0.005], Dotted]
     },
    PlotMarkers → {
      Graphics[{Dashing[None], Thickness[Medium],
        defaultcolors[[1]], Circle[]}, ImageSize → 10],
      Graphics[{Dashing[None], Thickness[Medium], Circle[], defaultcolors[[2]]},
       ImageSize → 10], Graphics[{Dashing[None], Thickness[Medium],
        Circle[], defaultcolors[[3]]}, ImageSize → 10],
      Graphics[{Dashing[None], Thickness[Medium], Circle[],
        defaultcolors[[4]]}, ImageSize → 10],
      Graphics[{Black, Disk[]}, ImageSize → 8]
     }
   ];

figS3c = Show[
  ListLogPlot[
   theory,
   Joined → True,
   PlotStyle → Directive[Thick, Opacity[0.5]],
   PlotRange → {{-0.4, 0}, {5 * 10^-7, 1}},
   Frame → {True, False, False, True},
   FrameLabel → {"Wildtype growth rate", , , "Probability of rescue"},
   FrameTicks → {True, False, False, True},
   LabelStyle → labelstyle(*,
   PlotLegends→Placed[LineLegend[Style[#,12,FontFamily→"Helvetica"]&/@
       {"1-step","2-step","3-step","4-step"}],Scaled@{7/8,1/4}]*)
  ],
  ListLogPlot[alltheory, Joined → True, PlotStyle → {Black, Thick, Opacity[0.5]}(*,
   PlotLegends→Placed[LineLegend[Style[#,12,FontFamily→"Helvetica"]&/@
       {"1-, 2-, 3-, or 4-step"}],Scaled@{1/4,7/8}]*)
  ],
  dataplot,
  PlotRangePadding → 0,
  (*ImagePadding→probpadding,*)
  Epilog → {
    Text[Style["C", 14, Bold, FontFamily → "Helvetica"], Scaled@{0.05, 0.95}],
    Text[Style["leptokurtic", 14, FontFamily → "Helvetica"], Scaled@{0.25, 0.85}]
   }
 ]

Clear[N0, mmax, λ, Es, n, U, mwts, type, nreps]
```

c
leptokurtic
1
0.1
0.01
0.001
10^{-4}
10^{-5}
10^{-6}
Probability of rescue
−0.4
−0.3
−0.2
−0.1
0.0
Wildtype growth rate

Figure S3

```
GraphicsColumn[{figS3a, figS3b, figS3c}, Spacings → -70, ImageSize → 375]
Export[supfigdir <> "FigureS3.eps", %];
```

Rescue genotype growth rate (figure S4)

Platykurtic (semicircle, panel A)

```
xmin = -0.3;
xmax = 0.25;
ymax = 40;

N0 = 10 000;
U = 2 * 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
mwt = -0.1;
xint = 0.01;
type = "platy";

{
  (*random*)
  Table[{m2, fm[m2, mwt, mmax, λ, n]}, {m2, xmin, xmax, xint}],
  (*established*)
  Table[{m2, (fm[m2, mwt, mmax, λ, n] pest[m2 - mwt]) / NIntegrate[
      fm[m2, mwt, mmax, λ, n] pest[m2 - mwt], {m2, mwt, mmax}]}, {m2, mwt, xmax, xint}]
 };
oldtheory = ListPlot[%, PlotRange → All, Joined → True,
   PlotStyle → {Directive[Thick, Gray, Dashed], Directive[Thick, Gray]},
   PerformanceGoal → "Speed",
   PlotLegends → Placed[LineLegend[Style[#, 12, FontFamily → "Helvetica"] & /@
       {"random", "established"}], Scaled@{1.5 / 8, 1 / 2}]];

{
  (*1 step*)
  Table[{m2, g1m /. m → m2}, {m2, 0, xmax, xint}],
  (*2 step*)
  total = Re[g2denominator[mwt]];
  Table[{m2, 1/total g2numerator[mwt, m2]}, {m2, 0, xmax, xint}]
 };
theory = ListPlot[%, PlotRange → All, Joined → True,
   PlotStyle → Directive[Thick, Opacity[0.5]], PerformanceGoal → "Speed",
   PlotLegends → Placed[LineLegend[Style[#, 12, FontFamily → "Helvetica"] & /@
       {"1-step", "2-step"}], Scaled@{1.5 / 8, 1 / 2}]];

StringForm[datadir <> "dfe_``_N``_n``_U``_Es``_mmax``_mwt``_nreps100000.csv",
  type, N0, n, NumberForm[U // N, {6, 5}],
  NumberForm[Es, {3, 2}], NumberForm[mmax, {3, 2}], mwt];
dat = Import[ToString[%]];
onestep = Select[dat, #[[2]] == 1 &][[All, 1]];
twostep = Select[dat, #[[2]] == 2 &][[All, 1]];
data = Histogram[{onestep, twostep}, Automatic, "PDF", AxesOrigin → {0, 0}];
```

```
figS4a = Show[
  {oldtheory, data, theory},
  PlotRange → {{xmin, xmax}, {0, ymax}},
  Frame → {True, False, False, False},
  LabelStyle → labelstyle,
  FrameTicksStyle → {FontColor → White, Automatic, Automatic, Automatic},
  Epilog → {
    Text[Style["m0=" <> ToString[mwt],
      12, FontFamily → "Helvetica"], Scaled@{7 / 8, 3 / 4}],
    Text[Style["A", 14, Bold, FontFamily → "Helvetica"], Scaled@{0.05, 0.95}],
    Text[Style["platykurtic", 14, FontFamily → "Helvetica"], Scaled@{7 / 8, 1 / 2}]
   }
 ]

Clear[mmax, λ, Es, n, U, mwt]
```

NIntegrate::izero :
Integral and error estimates are 0 on all integration subregions. Try increasing the value of the MinRecursion option. If value of integral may be 0, specify a finite value for the AccuracyGoal option. ≫

Leptokurtic (Laplace, panel B)

```
xmin = -0.3;
xmax = 0.25;
ymax = 40;

N0 = 10 000;
U = 2 * 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
mwt = -0.1;
xint = 0.01;
type = "lepto";

{
  (*random*)
  Table[{m2, fm[m2, mwt, mmax, λ, n]}, {m2, xmin, xmax, xint}],
```

```
  (*established*)
  Table[{m2, (fm[m2, mwt, mmax, λ, n] pest[m2 - mwt]) / NIntegrate[
      fm[m2, mwt, mmax, λ, n] pest[m2 - mwt], {m2, mwt, mmax}]}, {m2, mwt, xmax, xint}]
 };
oldtheory = ListPlot[%, PlotRange → All, Joined → True,
   PlotStyle → {Directive[Thick, Gray, Dashed], Directive[Thick, Gray]},
   PerformanceGoal → "Speed"(*,
   PlotLegends→Placed[LineLegend[Style[#,12,FontFamily→"Helvetica"]&/@
       {"random","established"}],Scaled@{1.5/8,1/2}]*)];

{
  (*1 step*)
  Table[{m2, g1m /. m → m2}, {m2, 0, xmax, xint}],
  (*2 step*)
  total = Re[g2denominator[mwt]];
  Table[{m2, 1/total g2numerator[mwt, m2]}, {m2, 0, xmax, xint}]
 };
theory = ListPlot[%, PlotRange → All, Joined → True,
   PlotStyle → Directive[Thick, Opacity[0.5]], PerformanceGoal → "Speed"(*,
   PlotLegends→Placed[LineLegend[Style[#,12,FontFamily→"Helvetica"]&/@
       {"1-step","2-step"}],Scaled@{1.5/8,1/2}]*)];

StringForm[datadir <> "dfe_``_N``_n``_U``_Es``_mmax``_mwt``_nreps100000.csv",
  type, N0, n, NumberForm[U // N, {6, 5}],
  NumberForm[Es, {3, 2}], NumberForm[mmax, {3, 2}], mwt];
dat = Import[ToString[%]];
onestep = Select[dat, #[[2]] == 1 &][[All, 1]];
twostep = Select[dat, #[[2]] == 2 &][[All, 1]];
data = Histogram[{onestep, twostep}, Automatic, "PDF", AxesOrigin → {0, 0}];

figS4b = Show[
  {oldtheory, data, theory},
  PlotRange → {{xmin, xmax}, {0, ymax}},
  Frame → {True, False, False, False},
  LabelStyle → labelstyle,
  FrameTicksStyle → {Automatic, Automatic, Automatic, Automatic},
  FrameLabel → {"Growth rate"},
  Epilog → {
    (*Text[
     Style["m0="<>ToString[mwt],12,FontFamily→"Helvetica"],Scaled@{7/8,3/4}],*)
    Text[Style["B", 14, Bold, FontFamily → "Helvetica"], Scaled@{0.05, 0.95}],
    Text[Style["leptokurtic", 14, FontFamily → "Helvetica"], Scaled@{7 / 8, 1 / 2}]
   }
 ]

Clear[mmax, λ, Es, n, U, mwt]
```

NIntegrate::izero :

Integral and error estimates are 0 on all integration subregions. Try increasing the value of the MinRecursion option. If value of integral may be 0, specify a finite value for the AccuracyGoal option. ≫

Figure S4

```
GraphicsColumn[{figS4a, figS4b}, Spacings → -50, ImageSize → 350]
Export[supfigdir <> "FigureS4.pdf", %];
```

2-step intermediate growth rate (figure S5)

Platykurtic (semicircle, panel A)

```
xmin = -0.3;
xmax = 0.15;
ymax = 30;

N0 = 10 000;
U = 2 * 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
mwt = -0.2;
type = "platy";

{mneg = FindRoot[2 m1^2 - Λ1[m1, mmax, λ, n, U], {m1, -0.1}],
  mpos = FindRoot[2 m1^2 - Λ1[m1, mmax, λ, n, U], {m1, 0.1}]};
pr0 = Sqrt[Λ1[m1, mmax, λ, n, U] / 2];

exact = fm[m1, mwt, mmax, λ, n] (1 - pest[m1]) prescuem[m1, Λ1[m1, mmax, λ, n, U]];

critical =
  fm[0, mwt, mmax, λ, n] Sqrt[2 Λ1[0, mmax, λ, n, U]] HeavisideTheta[(m1 + pr0) (pr0 - m1)];

subcritical =
  fm[m1, mwt, mmax, λ, n] (Λ1[m1, mmax, λ, n, U]) / Abs[m1] HeavisideTheta[(-m1 - pr0)];
supercritical = fm[m1, mwt, mmax, λ, n] (1 - pest[m1])
    (Λ1[m1, mmax, λ, n, U]) / Abs[m1] HeavisideTheta[(m1 - pr0)];

allexact = NIntegrate[exact, {m1, mwt, 0.1}];

{
  fm[m1, mwt, mmax, λ, n],
  (fm[m1, mwt, mmax, λ, n] pest[m1 - mwt] HeavisideTheta[m1 - mwt]) /
   NIntegrate[fm[m1, mwt, mmax, λ, n] pest[m1 - mwt], {m1, mwt, mmax}]
 };
oldtheory = Plot[
   %,
   {m1, xmin, xmax},
   PlotRange → {0, All},
   (*Filling→Bottom,*)
   PlotStyle → {Directive[Gray, Thick, Dashed], Directive[Gray, Thick]},
   PerformanceGoal → "Speed",
   PlotLegends → Placed[LineLegend[Style[#, 12, FontFamily → "Helvetica"] & /@
       {"random", "established"}], Scaled@{1 / 8, 1.25 / 2}]
  ];
```

```
{subcritical/allexact, critical/allexact, supercritical/allexact};
theory = Plot[
   %,
   {m1, xmin, xmax},
   PlotRange → {0, All},
   Filling → Bottom,
   PerformanceGoal → "Speed",
   PlotLegends → Placed[SwatchLegend[{Directive[defaultcolors[[1]], Opacity[0.5]],
       Directive[defaultcolors[[2]], Opacity[0.5]], Directive[defaultcolors[[3]],
        Opacity[0.5]]}, Style[#, 12, FontFamily → "Helvetica"] & /@
       {"subcritical", "critical", "supercritical"}], Scaled@{1 / 8, 0.65 / 2}]
  ];

exactplot = Plot[
   exact / allexact, {m1, xmin, xmax},
   PlotStyle → Directive[Thick, Black, Opacity[0.5]],
   PerformanceGoal → "Speed", PlotRange → All,
   PlotLegends → Placed[LineLegend[Style[#, 12, FontFamily → "Helvetica"] & /@
       {"first-step"}], Scaled@{1 / 8, 1.25 / 2}]
  ];

StringForm[datadir <> "dfe_``_N``_n``_U``_Es``_mmax``_mwt``_nreps100000.csv",
  type, N0, n, NumberForm[U // N, {6, 5}],
  NumberForm[Es, {3, 2}], NumberForm[mmax, {3, 2}], mwt];
dat = Import[ToString[%]];
Select[dat, #[[2]] == 2 &][[All, 3]];
data = Histogram[%, Automatic, "PDF",
   AxesOrigin → {0, 0}, ChartStyle → Directive[Gray, Opacity[0.25]]];

figS5a = Show[
  oldtheory, data, theory, exactplot,
  Frame → {True, False, False, False},
  FrameTicksStyle → {FontColor → White, Automatic, Automatic, Automatic},
  PlotRange → {{xmin, xmax}, {0, ymax}},
  LabelStyle → labelstyle,
  Epilog → {
    Text[Style["m0=" <> ToString[mwt],
      12, FontFamily → "Helvetica"], Scaled@{7 / 8, 3 / 4}],
    Text[Style["A", 14, Bold, FontFamily → "Helvetica"], Scaled@{0.05, 0.95}],
    Text[Style["platykurtic", 14, FontFamily → "Helvetica"], Scaled@{7 / 8, 1 / 2}]
   }
 ]

Clear[mmax, λ, Es, n, U, mwt]
```

Leptokurtic (Laplace, panel B)

```
N0 = 10 000;
U = 2 * 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
mwt = -0.2;
type = "lepto";

{mneg = FindRoot[2 m1^2 - Λ1[m1, mmax, λ, n, U], {m1, -0.1}],
  mpos = FindRoot[2 m1^2 - Λ1[m1, mmax, λ, n, U], {m1, 0.1}]};
pr0 = Sqrt[Λ1[m1, mmax, λ, n, U] / 2];

exact = fm[m1, mwt, mmax, λ, n] (1 - pest[m1]) prescuem[m1, Λ1[m1, mmax, λ, n, U]];

critical =
  fm[0, mwt, mmax, λ, n] Sqrt[2 Λ1[0, mmax, λ, n, U]] HeavisideTheta[(m1 + pr0) (pr0 - m1)];

subcritical =
  fm[m1, mwt, mmax, λ, n] (Λ1[m1, mmax, λ, n, U]) / Abs[m1] HeavisideTheta[(-m1 - pr0)];
supercritical = fm[m1, mwt, mmax, λ, n] (1 - pest[m1])
    (Λ1[m1, mmax, λ, n, U]) / Abs[m1] HeavisideTheta[(m1 - pr0)];

allexact = NIntegrate[exact, {m1, mwt, 0.1}];

{
  fm[m1, mwt, mmax, λ, n],
  (fm[m1, mwt, mmax, λ, n] pest[m1 - mwt] HeavisideTheta[m1 - mwt]) /
   NIntegrate[fm[m1, mwt, mmax, λ, n] pest[m1 - mwt], {m1, mwt, mmax}]
 };
oldtheory = Plot[
```

```
    %,
    {m1, xmin, xmax},
    PlotRange → {0, All},
    (*Filling→Bottom,*)
    PlotStyle → {Directive[Gray, Thick, Dashed], Directive[Gray, Thick]},
    PerformanceGoal → "Speed"(*,
    PlotLegends→Placed[LineLegend[Style[#,12,FontFamily→"Helvetica"]&/@
        {"random","established"}],Scaled@{1/8,1.25/2}]*)
  ];

{subcritical/allexact, critical/allexact, supercritical/allexact};
theory = Plot[
    %,
    {m1, xmin, xmax},
    PlotRange → {0, All},
    Filling → Bottom,
    PerformanceGoal → "Speed"(*,
    PlotLegends→Placed[SwatchLegend[{Directive[defaultcolors[[1]],Opacity[0.5]],
        Directive[defaultcolors[[2]],Opacity[0.5]],Directive[defaultcolors[[3]],
         Opacity[0.5]]},Style[#,12,FontFamily→"Helvetica"]&/@
        {"subcritical","critical","supercritical"}],Scaled@{1/8,0.65/2}]*)
  ];

exactplot = Plot[
    exact / allexact, {m1, xmin, xmax},
    PlotStyle → Directive[Thick, Black, Opacity[0.5]],
    PerformanceGoal → "Speed", PlotRange → All(*,
    PlotLegends→Placed[LineLegend[Style[#,12,FontFamily→"Helvetica"]&/@
        {"first-step"}],Scaled@{1/8,1.25/2}]*)
  ];

StringForm[datadir <> "dfe_``_N``_n``_U``_Es``_mmax``_mwt``_nreps100000.csv",
  type, N0, n, NumberForm[U // N, {6, 5}],
  NumberForm[Es, {3, 2}], NumberForm[mmax, {3, 2}], mwt];
dat = Import[ToString[%]];
Select[dat, #[[2]] == 2 &][[All, 3]];
data = Histogram[%, Automatic, "PDF",
    AxesOrigin → {0, 0}, ChartStyle → Directive[Gray, Opacity[0.25]]];

figS5b = Show[
  oldtheory, data, theory, exactplot,
  Frame → {True, False, False, False},
  FrameTicksStyle → {Automatic, Automatic, Automatic, Automatic},
  FrameLabel → {"Growth rate"},
  PlotRange → {{xmin, xmax}, {0, ymax}},
  LabelStyle → labelstyle,
  Epilog → {
    (*Text[
     Style["m0="<>ToString[mwt],12,FontFamily→"Helvetica"],Scaled@{7/8,3/4}],*)
    Text[Style["B", 14, Bold, FontFamily → "Helvetica"], Scaled@{0.05, 0.95}],
    Text[Style["leptokurtic", 14, FontFamily → "Helvetica"], Scaled@{7 / 8, 1 / 2}]
    }
 ]
```

```
Clear[mmax, λ, Es, n, U, mwt]
```

Figure S5

```
GraphicsColumn[{figS5a, figS5b}, Spacings → -50, ImageSize → 350]
Export[supfigdir <> "FigureS5.pdf", %];
```

Dimensionality, n

Probability of rescue (figure S6A)

Numerical data

```
(*N0=10^4;
mmax=0.5;
λ=2Es/4;
Es=0.01;
U=2*10^-3;

m0min=mTempmin;
m0max=mTempmax;
mstep=step;
m0list=Table[m0,{m0,m0min,m0max,mstep}];

n=2;

rate4=Table[{m0,Λ4Interpolated[m0,mmax,λ,n,U]},{m0,m0min,m0max,mstep}];
rate3=Table[{m0,Λ3Interpolated[m0,mmax,λ,n,U]},{m0,m0min,m0max,mstep}];
rate2=Table[{m0,Λ2Interpolated[m0,mmax,λ,n,U]},{m0,m0min,m0max,mstep}];
rate1=Table[{m0,Λ1Interpolated[m0,mmax,λ,n,U]},{m0,m0min,m0max,mstep}];
theory2={
  Table[{m0list[[i]],prescue/.p0→prescuem[m0list[[i]],rate1[[i,2]]]},
   {i,Length[m0list]}],
  Table[{m0list[[i]],prescue/.p0→prescuem[m0list[[i]],rate2[[i,2]]]},
   {i,Length[m0list]}],
  Table[{m0list[[i]],prescue/.p0→prescuem[m0list[[i]],rate3[[i,2]]]},
   {i,Length[m0list]}],
  Table[{m0list[[i]],prescue/.p0→prescuem[m0list[[i]],rate4[[i,2]]]},
   {i,Length[m0list]}]
 };
alltheory2=
 Table[{m0list[[i]],prescue/.p0→prescuem[m0list[[i]],rate1[[i,2]]+rate2[[i,2]]+
       rate3[[i,2]]+rate4[[i,2]]]},{i,Length[m0list]}];

n=20;

rate4=Table[{m0,Λ4Interpolated[m0,mmax,λ,n,U]},{m0,m0min,m0max,mstep}];
rate3=Table[{m0,Λ3Interpolated[m0,mmax,λ,n,U]},{m0,m0min,m0max,mstep}];
rate2=Table[{m0,Λ2Interpolated[m0,mmax,λ,n,U]},{m0,m0min,m0max,mstep}];
rate1=Table[{m0,Λ1Interpolated[m0,mmax,λ,n,U]},{m0,m0min,m0max,mstep}];
theory20={
  Table[{m0list[[i]],prescue/.p0→prescuem[m0list[[i]],rate1[[i,2]]]},
   {i,Length[m0list]}],
  Table[{m0list[[i]],prescue/.p0→prescuem[m0list[[i]],rate2[[i,2]]]},
   {i,Length[m0list]}],
  Table[{m0list[[i]],prescue/.p0→prescuem[m0list[[i]],rate3[[i,2]]]},
   {i,Length[m0list]}],
  Table[{m0list[[i]],prescue/.p0→prescuem[m0list[[i]],rate4[[i,2]]]},
   {i,Length[m0list]}]
 };
alltheory20=
 Table[{m0list[[i]],prescue/.p0→prescuem[m0list[[i]],rate1[[i,2]]+rate2[[i,2]]+
       rate3[[i,2]]+rate4[[i,2]]]},{i,Length[m0list]}];

Clear[N0,mmax,λ,Es,n,U,m0min,m0max,mstep]*)
```

```
theory2 = {{{-0.4`, 7.550146599033525`*^-7}, {-0.39`, 1.3377479120002533`*^-6},
    {-0.38`, 2.3541607676591525`*^-6}, {-0.37`, 4.114440329328062`*^-6},
```

```
 {-0.36000000000000004`, 7.141165515145431`*^-6}, {-0.35000000000000003`,
  0.000012307857882642992`}, {-0.34`, 0.00002106313373739787 7`},
 {-0.33`, 0.00003579015229548954`}, {-0.32`, 0.00006037791098467693`},
 {-0.31000000000000005`, 0.00010112104250870058`},
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 {-0.29000000000000004`, 0.00027747271956068964`},
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 {-0.23`, 0.004789432638810376`}, {-0.22000000000000003`,
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 {-0.18000000000000002`, 0.0413097839349571`},
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 {-0.13`, 0.2694211954092305`}, {-0.12`, 0.36973364252078456`},
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 {-0.10000000000000003`, 0.6280170641956851`},
 {-0.09000000000000002`, 0.7642175408782299`},
 {-0.08000000000000002`, 0.8792912943690248`}, {-0.07`, 0.9553462152859784`},
 {-0.06`, 0.9900819921225776`}, {-0.04999999999999999`, 0.9990479451974486`},
 {-0.040000000000000036`, 0.9999791099242765`},
 {-0.030000000000000027`, 0.999999973930803`},
 {-0.020000000000000018`, 0.9999999999999477`}, {-0.010000000000000009`, 1.`}},
{{-0.4`, 0.00001019935603518 9844`}, {-0.39`, 0.00001467716287217868 4`},
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 {-0.33`, 0.00012883241729277906`}, {-0.32`, 0.00018451270537933606`},
 {-0.31000000000000005`, 0.00026391758906829654`},
 {-0.30000000000000004`, 0.0003769004573965784`},
 {-0.29000000000000004`, 0.0005372530345478799`},
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 {-0.24000000000000002`, 0.0030374086953640633`},
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 {-0.06`, 0.4820455848517148`}, {-0.04999999999999999`, 0.5892003916766011`},
 {-0.040000000000000036`, 0.709836933580263`},
 {-0.030000000000000027`, 0.8365501253166521`}, {-0.020000000000000018`,
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 {-0.33`, 0.00003118061729001642`}, {-0.32`, 0.00004209066999139033`},
 {-0.31000000000000005`, 0.00005686144346772615`},
```

```
 {-0.30000000000000004`, 0.00007687529434197149`},
 {-0.29000000000000004`, 0.00010400918245812019`},
 {-0.28`, 0.00014080627657486744`}, {-0.27`, 0.00019070236208684754`},
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 {-0.10000000000000003`, 0.024337817579831333`},
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 {-0.040000000000000036`, 0.11700327307874947`},
 {-0.030000000000000027`, 0.16254620716433155`},
 {-0.020000000000000018`, 0.24419952262430733`},
 {-0.010000000000000009`, 0.43935473836510974`}},
{{-0.4`, 5.338328372683776`*^-7}, {-0.39`, 7.072562302479213`*^-7},
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 {-0.33`, 3.8841721338167545`*^-6}, {-0.32`, 5.1827130552739575`*^-6},
 {-0.31000000000000005`, 6.927380244214909`*^-6},
 {-0.30000000000000004`, 9.275985834444889`*^-6},
 {-0.29000000000000004`, 0.00001244297924640758 2`},
 {-0.28`, 0.00001671937282088365`}, {-0.27`, 0.00002249911711860175 2`},
 {-0.26`, 0.00003031375183593088`}, {-0.25`, 0.00004087737876667940 6`},
 {-0.24000000000000002`, 0.00005514440657494735`},
 {-0.23`, 0.00007438275838622666`},
 {-0.22000000000000003`, 0.00010026550102237852`}, {-0.21000000000000002`,
  0.00013498406279732755`}, {-0.2`, 0.00018138631638997538`},
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  0.00032494753038614377`}, {-0.17`, 0.0004327518267689401`},
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 {-0.08000000000000002`, 0.0047436536786403805`},
 {-0.07`, 0.006126667221285187`}, {-0.06`, 0.007961666583326976`},
 {-0.04999999999999999`, 0.01048121505556654`},
 {-0.040000000000000036`, 0.014143839155673521`},
 {-0.030000000000000027`, 0.02001029300962276`},
 {-0.020000000000000018`, 0.03123097614317294`},
 {-0.010000000000000009`, 0.06315917180894381`}}};
```

```
alltheory2 = {{-0.4`, 0.00001535020218101923 5`}, {-0.39`, 0.00002192622029173474 4`},
   {-0.38`, 0.00003141319399246889`}, {-0.37`, 0.00004515085310408118`},
   {-0.36000000000000004`, 0.00006512135528791152`}, {-0.35000000000000003`,
    0.00009426393931810662`}, {-0.34`, 0.0001369477559153287`},
   {-0.33`, 0.00019967684960509047`}, {-0.32`, 0.0002921410564045157`},
   {-0.31000000000000005`, 0.0004287770736822738`},
   {-0.30000000000000004`, 0.0006310647602509878`},
   {-0.29000000000000004`, 0.0009309326073357882`},
   {-0.28`, 0.0013756940254245897`}, {-0.27`, 0.0020352456926138185`},
   {-0.26`, 0.0030124200353386366`}, {-0.25`, 0.004457757273886531`},
   {-0.24000000000000002`, 0.006590343936563103`},
   {-0.23`, 0.009726798586397578`}, {-0.22000000000000003`, 0.014320858948354664`},
   {-0.21000000000000002`, 0.02101611059527131`},
   {-0.2`, 0.030713710195301225`}, {-0.19000000000000003`, 0.0446545404194304`},
   {-0.18000000000000002`, 0.06450934056844149`},
   {-0.17`, 0.09245805644330285`}, {-0.16000000000000003`, 0.131216670813028`},
   {-0.15000000000000002`, 0.18393152366588073`},
   {-0.14`, 0.2538073877249182`}, {-0.13`, 0.34328369492122546`},
   {-0.12`, 0.45258605307953326`}, {-0.11000000000000004`, 0.5777030417626707`},
   {-0.10000000000000003`, 0.7084886985816767`},
   {-0.09000000000000002`, 0.8287134862581917`},
   {-0.08000000000000002`, 0.9206113607139523`}, {-0.07`, 0.974263154496821`},
   {-0.06`, 0.9952181649470924`}, {-0.04999999999999999`, 0.9996420086675802`},
   {-0.040000000000000036`, 0.9999945277896636`},
   {-0.030000000000000027`, 0.9999999960926514`},
   {-0.020000000000000018`, 0.9999999999999969`}, {-0.010000000000000009`, 1.`}};

theory20 = {{{-0.4`, 3.6721736207390165`*^-8}, {-0.39`, 6.809108610283943`*^-8},
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    {-0.36000000000000004`, 4.176091951135774`*^-7}, {-0.35000000000000003`,
     7.544562181660552`*^-7}, {-0.34`, 1.3539615881796863`*^-6},
    {-0.33`, 2.413573102710842`*^-6}, {-0.32`, 4.2733913914183574`*^-6},
    {-0.31000000000000005`, 7.514843870071175`*^-6},
    {-0.30000000000000004`, 0.00001312444652046274`},
    {-0.29000000000000004`, 0.00002276335086792702 4`},
    {-0.28`, 0.000039207417075748374`}, {-0.27`, 0.00006705980661603217`},
    {-0.26`, 0.00011389547082241158`}, {-0.25`, 0.00019208432406314646`},
    {-0.24000000000000002`, 0.00032167205540878374`},
    {-0.23`, 0.0005348952348056546`}, {-0.22000000000000003`,
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    {-0.17`, 0.009752194976848538`}, {-0.16000000000000003`,
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    {-0.12`, 0.08924118251846858`}, {-0.11000000000000004`, 0.1348578732623491`},
    {-0.10000000000000003`, 0.20069983428605798`},
    {-0.09000000000000002`, 0.2926736492678442`},
    {-0.08000000000000002`, 0.415007688928513 8`}, {-0.07`, 0.5658189827878293`},
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    {-0.040000000000000036`, 0.9680381655938813`},
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    {-0.020000000000000018`, 0.9999877420421525`},
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```

```
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 {-0.38`, 2.1102008918028048`*^-8}, {-0.37`, 2.939870547002954`*^-8},
 {-0.36000000000000004`, 4.1023850316790345`*^-8}, {-0.35000000000000003`,
  5.7350789561816384`*^-8}, {-0.34`, 8.034572707149579`*^-8},
 {-0.33`, 1.1282418876934486`*^-7}, {-0.32`, 1.5883404491656705`*^-7},
 {-0.31000000000000005`, 2.2421284684437381`*^-7},
 {-0.30000000000000004`, 3.173871782058413`*^-7},
 {-0.29000000000000004`, 4.50536176255234`*^-7},
 {-0.28`, 6.412768283059478`*^-7}, {-0.27`, 9.15076491470046`*^-7},
 {-0.26`, 1.3086989646415859`*^-6}, {-0.25`, 1.8751116518389566`*^-6},
 {-0.24000000000000002`, 2.6904020712370524`*^-6},
 {-0.23`, 3.863469882126047`*^-6},
 {-0.22000000000000003`, 5.549512137048573`*^-6}, {-0.21000000000000002`,
  7.968629597288057`*^-6}, {-0.2`, 0.00001143132724257264`},
 {-0.19000000000000003`, 0.00001637322207959091`}, {-0.18000000000000002`,
  0.00002340201637718308`}, {-0.17`, 0.00003336083728600059`},
 {-0.16000000000000003`, 0.00004741354938231357`}, {-0.15000000000000002`,
  0.00006715998630013598`}, {-0.14`, 0.00009479288612268544`},
 {-0.13`, 0.00013331480113920602`}, {-0.12`, 0.00018684503949184528`},
 {-0.11000000000000004`, 0.00026106844205453505`},
 {-0.10000000000000003`, 0.0003639201714409346`},
 {-0.09000000000000002`, 0.0005066865483106531`},
 {-0.08000000000000002`, 0.0007058861356389334`},
 {-0.07`, 0.0009867178388376363`}, {-0.06`, 0.0013899202861142879`},
 {-0.04999999999999999`, 0.0019868453399276564`},
 {-0.04000000000000036`, 0.0029171473631195433`},
 {-0.03000000000000027`, 0.0045017862748640836`},
 {-0.02000000000000018`, 0.0076938147012420854`},
 {-0.01000000000000009`, 0.017208482985485385`}}};
```

```
alltheory20 = {{-0.4`, 4.834442790535576`*^-7}, {-0.39`, 7.280806675336038`*^-7},
   {-0.38`, 1.1013550670346817`*^-6}, {-0.37`, 1.6739418127187378`*^-6},
   {-0.36000000000000004`, 2.5571145922942407`*^-6}, {-0.35000000000000003`,
    3.926711245827441`*^-6}, {-0.34`, 6.0616106480892995`*^-6},
   {-0.33`, 9.405275660845369`*^-6}, {-0.32`, 0.00001466408464945168`},
   {-0.31000000000000005`, 0.00002296397914403059`},
   {-0.30000000000000004`, 0.00003609994775854996`},
   {-0.29000000000000004`, 0.00005692977382387720`},
   {-0.28`, 0.00008999608544957294`}, {-0.27`, 0.00014250026368112234`},
   {-0.26`, 0.00022582428462614157`}, {-0.25`, 0.0003578891368045678`},
   {-0.24000000000000002`, 0.0005667927225286862`},
   {-0.23`, 0.0008963839013724773`}, {-0.22000000000000003`,
    0.0014147467761264076`}, {-0.21000000000000002`, 0.0022270230475007757`},
   {-0.2`, 0.003494639623003337`}, {-0.19000000000000003`, 0.005463884823775689`},
   {-0.18000000000000002`, 0.008507921962300657`},
   {-0.17`, 0.013187701890287507`}, {-0.16000000000000003`, 0.020338576198859037`},
   {-0.15000000000000002`, 0.031189923818135568`},
   {-0.14`, 0.04752275577813281`}, {-0.13`, 0.07186039463277039`},
   {-0.12`, 0.10766009539364907`}, {-0.11000000000000004`, 0.15941014043993607`},
   {-0.10000000000000003`, 0.23240769609962075`},
   {-0.09000000000000002`, 0.33176964127173436`},
   {-0.08000000000000002`, 0.4599591492094549`}, {-0.07`, 0.6121606584397329`},
   {-0.06`, 0.7703936794609902`}, {-0.04999999999999999`, 0.9023396525261022`},
   {-0.040000000000000036`, 0.9773439970496514`},
   {-0.030000000000000027`, 0.9984758621156562`},
   {-0.020000000000000018`, 0.9999949973318434`},
   {-0.010000000000000009`, 0.999999999999264`}};
```

Plot

```
N0 = 10^4;
mmax = 0.5;
λ = 2 Es / 4;
Es = 0.01;
U = 2 * 10^-3;
letter = "A";

figS6a = Show[
  ListLogPlot[theory2,
   Joined → True,
   PlotStyle → Thick,
   PlotRange → {{-0.4, 0}, {5 * 10^-7, 1}},
   Frame → {True, False, False, True},
   FrameLabel → {"Wildtype growth rate", , , "Probability of rescue"},
   FrameTicks → {True, False, False, True},
   LabelStyle → labelstyle,
   PlotLegends → Placed[LineLegend[Style[#, 12, FontFamily → "Helvetica"] & /@
        {"1-step", "2-step", "3-step", "4-step"}], Scaled@{0.85, 0.23}]
  ],
  ListLogPlot[alltheory2, Joined → True, PlotStyle → {Black, Thick},
   PlotLegends → Placed[LineLegend[
       Style[#, 12, FontFamily → "Helvetica"] & /@ {"total"}], Scaled@{0.56, 0.23}]
  ],
  ListLogPlot[theory20,
   Joined → True,
   PlotStyle → Directive[Thick, Dashing[Large]]
  ],
  ListLogPlot[alltheory20,
   Joined → True, PlotStyle → {Black, Thick, Dashing[Large]},
   PlotLegends → Placed[LineLegend[
       {Directive[Thick, Gray], Directive[Thick, Gray, Dashing[Medium]]},
       Style[#, 12, FontFamily → "Helvetica"] & /@ {"n=2", "n=20"}],
      Scaled@{1 / 10, 7 / 10}]
  ],
  Epilog → {
    Text[Style[letter, Bold, 14, FontFamily → "Helvetica"], Scaled@{0.05, 0.95}],
    braceLabel[{{-0.125, Log@10^-6}, {-0.125, Log@(2 * 10^-4)}}, Style["", Larger]]
   }
 ]

Clear[N0, mmax, λ, Es, n, U, m0min, m0max, mstep, letter]
```

Rescue genotype growth rate (figure S6B)

```
xmin = -0.3;
xmax = 0.25;
ymax = 40;

N0 = 10 000;
U = 2 * 10^-3;
mmax = 0.5;
λ = 2 Es / 4;
Es = 0.01;
mwt = -0.2;
xint = 0.01;

n = 2;

{
  (*established*)
  Table[{m2, (fm[m2, mwt, mmax, λ, n] pest[m2 - mwt]) / NIntegrate[
      fm[m2, mwt, mmax, λ, n] pest[m2 - mwt], {m2, mwt, mmax}]}, {m2, mwt, xmax, xint}]
 };
oldtheory2 = ListPlot[%, PlotRange → All, Joined → True,
   PlotStyle → Directive[Thick, Gray], PerformanceGoal → "Speed", PlotLegends →
    Placed[LineLegend[Style[#, 12, FontFamily → "Helvetica"] & /@ {"established"}],
     Scaled@{1.5 / 8, 1 / 2}]];

{
  (*1 step*)
  Table[{m2, g1m /. m → m2}, {m2, 0, xmax, xint}],
  (*2 step*)
  total = Re[g2denominator[mwt]];
  Table[{m2, 1/total g2numerator[mwt, m2]}, {m2, 0, xmax, xint}]
 };
theory2 = ListPlot[%, PlotRange → All, Joined → True,
   PlotStyle → Directive[Thick], PerformanceGoal → "Speed",
   PlotLegends → Placed[LineLegend[Style[#, 12, FontFamily → "Helvetica"] & /@
```

```
        {"1-step", "2-step"}], Scaled@{1.5 / 8, 1 / 2}]];

n = 20;

{
  (*established*)
  Table[{m2, (fm[m2, mwt, mmax, λ, n] pest[m2 - mwt]) / NIntegrate[
      fm[m2, mwt, mmax, λ, n] pest[m2 - mwt], {m2, mwt, mmax}]}, {m2, mwt, xmax, xint}]
 };
oldtheory4 = ListPlot[%, PlotRange → All, Joined → True,
   PlotStyle → Directive[Thick, Gray, Dashing[Large]], PerformanceGoal → "Speed"];

{
  (*1 step*)
  Table[{m2, g1m /. m → m2}, {m2, 0, xmax, xint}],
  (*2 step*)
  total = Re[g2denominator[mwt]];
  Table[{m2, 1/total g2numerator[mwt, m2]}, {m2, 0, xmax, xint}]
 };
theory4 = ListPlot[%, PlotRange → All,
   Joined → True, PlotStyle → Directive[Thick, Dashing[Large]],
   PerformanceGoal → "Speed", PlotLegends → Placed[LineLegend[
      {Directive[Thick, Black], Directive[Thick, Black, Dashing[Medium]]}, Style[#,
         12, FontFamily → "Helvetica"] & /@ {"n=2", "n=20"}], Scaled@{7 / 8, 3 / 10}]];

figS6b = Show[
  {oldtheory2, theory2, oldtheory4, theory4},
  PlotRange → {{xmin, xmax}, {0, ymax}},
  Frame → {True, False, False, False},
  LabelStyle → labelstyle,
  FrameTicksStyle → {FontColor → White, Automatic, Automatic, Automatic},
  Epilog → {
    Text[Style["m0=" <> ToString[mwt],
      12, FontFamily → "Helvetica"], Scaled@{7 / 8, 3 / 4}],
    Text[Style["B", 14, Bold, FontFamily → "Helvetica"], Scaled@{0.05, 0.95}]
   }
 ]

Clear[mmax, λ, Es, n, U, mwt, xmin, xmax, ymax, xint]
```

NIntegrate::izero :
  Integral and error estimates are 0 on all integration subregions. Try increasing the value of the MinRecursion option. If value of integral may be 0, specify a finite value for the AccuracyGoal option. ≫

NIntegrate::izero :
  Integral and error estimates are 0 on all integration subregions. Try increasing the value of the MinRecursion option. If value of integral may be 0, specify a finite value for the AccuracyGoal option. ≫

2-step intermediate growth rate (figure S6C)

```
xmin = -0.3;
xmax = 0.25;
ymax = 30;

N0 = 10 000;
U = 2 * 10^-3;
mmax = 0.5;
λ = 2 Es / 4;
Es = 0.01;
mwt = -0.2;

n = 2;

exact2 = fm[m1, mwt, mmax, λ, n] (1 - pest[m1]) prescuem[m1, Λ1[m1, mmax, λ, n, U]];
allexact2 = NIntegrate[exact2, {m1, mwt, 0.1}];
oldtheory2 = (fm[m1, mwt, mmax, λ, n] pest[m1 - mwt] HeavisideTheta[m1 - mwt]) /
   NIntegrate[fm[m1, mwt, mmax, λ, n] pest[m1 - mwt], {m1, mwt, mmax}];

n = 20;

exact4 = fm[m1, mwt, mmax, λ, n] (1 - pest[m1]) prescuem[m1, Λ1[m1, mmax, λ, n, U]];
allexact4 = NIntegrate[exact4, {m1, mwt, 0.1}];
oldtheory4 = (fm[m1, mwt, mmax, λ, n] pest[m1 - mwt] HeavisideTheta[m1 - mwt]) /
   NIntegrate[fm[m1, mwt, mmax, λ, n] pest[m1 - mwt], {m1, mwt, mmax}];

figS6c = Show[
  Plot[
   {oldtheory2, oldtheory4},
   {m1, xmin, xmax},
   PlotRange → {0, All},
   PlotStyle → {Directive[Gray, Thick], Directive[Gray, Thick, Dashing[Large]]},
   PerformanceGoal → "Speed",
   PlotLegends →
    Placed[LineLegend[Style[#, 12, FontFamily → "Helvetica"] & /@ {"established"}],
     Scaled@{1 / 8, 1.25 / 2}]
  ],
  Plot[
```

```
    exact2 / allexact2,
    {m1, xmin, xmax},
    PlotRange → {0, All},
    PlotStyle → Directive[Thick],
    PerformanceGoal → "Speed",
    PlotLegends →
     Placed[LineLegend[Style[#, 12, FontFamily → "Helvetica"] & /@ {"first-step"}],
      Scaled@{1 / 8, 1.25 / 2}]
   ],
   Plot[
    exact4 / allexact4,
    {m1, xmin, xmax},
    PlotRange → {0, All},
    PlotStyle → Directive[Thick, Dashing[Large]],
    PerformanceGoal → "Speed",
    PlotLegends → Placed[LineLegend[
        {Directive[Thick, Black], Directive[Thick, Black, Dashing[Medium]]},
        Style[#, 12, FontFamily → "Helvetica"] & /@
         {"n=2", "n=20"}], Scaled@{7 / 8, 3 / 10}]
   ],
   Frame → {True, False, False, False},
   FrameTicksStyle → {Automatic, Automatic, Automatic, Automatic},
   FrameLabel → {"Growth rate"},
   PlotRange → {{xmin, xmax}, {0, ymax}},
   LabelStyle → labelstyle,
   Epilog → {
     Text[Style["m0=" <> ToString[mwt],
       12, FontFamily → "Helvetica"], Scaled@{7 / 8, 3 / 4}],
     Text[Style["C", 14, Bold, FontFamily → "Helvetica"], Scaled@{0.05, 0.95}]
    }
  ]

Clear[mmax, λ, Es, n, U, mwt, xmin, xmax, ymax, N0]
```

Figure S6

```
GraphicsColumn[{figS6a, figS6b, figS6c}, Spacings → -110, ImageSize → 350]
Export[supfigdir <> "FigureS6.eps", %];
```

Mutation rate U vs mutational variance λ

Rate, U

Probability of rescue

```
N0 = 10^4;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;

m0min = mTempmin;
m0max = mTempmax;
mstep = step;
m0list = Table[m0, {m0, m0min, m0max, mstep}];

U = 10^-3;

rate4 = Table[{m0, Λ4Interpolated[m0, mmax, λ, n, U]}, {m0, m0min, m0max, mstep}];
rate3 = Table[{m0, Λ3Interpolated[m0, mmax, λ, n, U]}, {m0, m0min, m0max, mstep}];
rate2 = Table[{m0, Λ2Interpolated[m0, mmax, λ, n, U]}, {m0, m0min, m0max, mstep}];
rate1 = Table[{m0, Λ1Interpolated[m0, mmax, λ, n, U]}, {m0, m0min, m0max, mstep}];
theory2 = {
   Table[{m0list[[i]], prescue /. p0 → prescuem[m0list[[i]], rate1[[i, 2]]]},
    {i, Length[m0list]}],
   Table[{m0list[[i]], prescue /. p0 → prescuem[m0list[[i]], rate2[[i, 2]]]},
    {i, Length[m0list]}],
   Table[{m0list[[i]], prescue /. p0 → prescuem[m0list[[i]], rate3[[i, 2]]]},
    {i, Length[m0list]}],
   Table[{m0list[[i]], prescue /. p0 → prescuem[m0list[[i]], rate4[[i, 2]]]},
    {i, Length[m0list]}]
  };
alltheory2 = Table[
   {m0list[[i]], prescue /. p0 → prescuem[m0list[[i]], rate1[[i, 2]] + rate2[[i, 2]] +
        rate3[[i, 2]] + rate4[[i, 2]]]}, {i, Length[m0list]}];

U = 10^-4;

rate4 = Table[{m0, Λ4Interpolated[m0, mmax, λ, n, U]}, {m0, m0min, m0max, mstep}];
rate3 = Table[{m0, Λ3Interpolated[m0, mmax, λ, n, U]}, {m0, m0min, m0max, mstep}];
rate2 = Table[{m0, Λ2Interpolated[m0, mmax, λ, n, U]}, {m0, m0min, m0max, mstep}];
rate1 = Table[{m0, Λ1Interpolated[m0, mmax, λ, n, U]}, {m0, m0min, m0max, mstep}];
theory4 = {
   Table[{m0list[[i]], prescue /. p0 → prescuem[m0list[[i]], rate1[[i, 2]]]},
    {i, Length[m0list]}],
   Table[{m0list[[i]], prescue /. p0 → prescuem[m0list[[i]], rate2[[i, 2]]]},
    {i, Length[m0list]}],
   Table[{m0list[[i]], prescue /. p0 → prescuem[m0list[[i]], rate3[[i, 2]]]},
    {i, Length[m0list]}],
```

```
    Table[{m0list[[i]], prescue /. p0 → prescuem[m0list[[i]], rate4[[i, 2]]]},
     {i, Length[m0list]}]
   };
alltheory4 = Table[
    {m0list[[i]], prescue /. p0 → prescuem[m0list[[i]], rate1[[i, 2]] + rate2[[i, 2]] +
          rate3[[i, 2]] + rate4[[i, 2]]]}, {i, Length[m0list]}];

Show[
 ListLogPlot[theory2,
  Joined → True,
  PlotStyle → Thick,
  PlotRange → {{-0.4, 0}, {5 * 10^-7, 1}},
  Frame → {True, False, False, True},
  FrameLabel → {"Wildtype growth rate", , , "Probability of rescue"},
  FrameTicks → {True, False, False, True},
  LabelStyle → labelstyle,
  PlotLegends → Placed[LineLegend[Style[#, 12, FontFamily → "Helvetica"] & /@
       {"1-step", "2-step", "3-step", "4-step"}], Scaled@{3 / 4, 1 / 4}]
 ],
 ListLogPlot[alltheory2, Joined → True, PlotStyle → {Black, Thick},
  PlotLegends → Placed[LineLegend[Style[#, 12, FontFamily → "Helvetica"] & /@
       {"1-, 2-, 3-, or 4-step"}], Scaled@{1 / 4, 8 / 10}]
 ],
 ListLogPlot[theory4,
  Joined → True,
  PlotStyle → Directive[Thick, Dashing[Large]]
 ],
 ListLogPlot[alltheory4, Joined → True, PlotStyle → {Black, Thick, Dashing[Large]},
  PlotLegends → Placed[
    LineLegend[{Directive[Thick, Gray], Directive[Thick, Gray, Dashing[Medium]]},
     Style[#, 12, FontFamily → "Helvetica"] & /@
      {"U=10^-3", "U=10^-4"}], Scaled@{1 / 10, 6 / 10}]
 ],
 Epilog → Text[Style["A", Bold, 14], Scaled@{0.05, 0.95}]
]

Clear[N0, mmax, λ, Es, n, U, m0min, m0max, mstep]
```

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
NIntegrate obtained 7.279705329608732`*^-8 and
8.761530263711027`*^-13 for the integral and error estimates. ≫

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
NIntegrate obtained 1.0286191497588282`*^-7 and
1.124360034010241`*^-12 for the integral and error estimates. ≫

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
NIntegrate obtained 1.4522794837384644`*^-7 and
2.2232504361922817`*^-12 for the integral and error estimates. ≫

General::stop : Further output of NIntegrate::ncvb will be suppressed during this calculation. ≫

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
NIntegrate obtained 1.4807240285122168`*^-8 and
7.012035920314079`*^-13 for the integral and error estimates. ≫

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
NIntegrate obtained 1.961272248188249`*^-8 and
1.2926522573741938`*^-12 for the integral and error estimates. ≫

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
NIntegrate obtained 2.5960369823117813`*^-8 and
2.0146265215810807`*^-12 for the integral and error estimates. ≫

General::stop : Further output of NIntegrate::ncvb will be suppressed during this calculation. ≫

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
NIntegrate obtained 7.279705329608732`*^-8 and
8.761530263711027`*^-13 for the integral and error estimates. ≫

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
NIntegrate obtained 1.0286191497588282`*^-7 and
1.124360034010241`*^-12 for the integral and error estimates. ≫

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
NIntegrate obtained 1.4522794837384644`*^-7 and
2.2232504361922817`*^-12 for the integral and error estimates. ≫

General::stop : Further output of NIntegrate::ncvb will be suppressed during this calculation. ≫

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
NIntegrate obtained 7.594589776123759`*^-9 and
4.002636289199166`*^-13 for the integral and error estimates. ≫

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
NIntegrate obtained 1.0811191772406686`*^-8 and
6.179494725282621`*^-13 for the integral and error estimates. ≫

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
NIntegrate obtained 1.539096864690094`*^-8 and
1.0371883643828802`*^-12 for the integral and error estimates. ≫

General::stop : Further output of NIntegrate::ncvb will be suppressed during this calculation. ≫

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
NIntegrate obtained 1.9750026573164113`*^-10 and
1.9587973588764628`*^-13 for the integral and error estimates. ≫

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
NIntegrate obtained 2.6362598419413893`*^-10 and
3.2561917484902713`*^-13 for the integral and error estimates. ≫

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
NIntegrate obtained 3.518449596971985`*^-10 and
5.369851615725374`*^-13 for the integral and error estimates. ≫

General::stop : Further output of NIntegrate::ncvb will be suppressed during this calculation. ≫

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
NIntegrate obtained 7.594589776123759`*^-9 and
4.002636289199166`*^-13 for the integral and error estimates. ≫

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
NIntegrate obtained 1.0811191772406686`*^-8 and
6.179494725282621`*^-13 for the integral and error estimates. ≫

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
NIntegrate obtained 1.539096864690094`*^-8 and
1.0371883643828802`*^-12 for the integral and error estimates. ≫

General::stop : Further output of NIntegrate::ncvb will be suppressed during this calculation. ≫

Rescue genotype growth rate

```
xmin = -0.3;
xmax = 0.25;
ymax = 40;
xint = 0.01;

N0 = 10 000;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
mwt = -0.2;

U = 10^-3;

{
  (*established*)
```

```
  Table[{m2, (fm[m2, mwt, mmax, λ, n] pest[m2 - mwt]) / NIntegrate[
      fm[m2, mwt, mmax, λ, n] pest[m2 - mwt], {m2, mwt, mmax}]}, {m2, mwt, xmax, xint}]
 };
oldtheory2 = ListPlot[%, PlotRange → All, Joined → True,
   PlotStyle → Directive[Thick, Gray], PerformanceGoal → "Speed", PlotLegends →
    Placed[LineLegend[Style[#, 12, FontFamily → "Helvetica"] & /@ {"established"}],
     Scaled@{1.5 / 8, 1 / 2}]];

{
  (*1 step*)
  Table[{m2, g1m /. m → m2}, {m2, 0, xmax, xint}],
  (*2 step*)
  total = Re[g2denominator[mwt]];
  Table[{m2, 1/total g2numerator[mwt, m2]}, {m2, 0, xmax, xint}]
 };
theory2 = ListPlot[%, PlotRange → All, Joined → True,
   PlotStyle → Directive[Thick], PerformanceGoal → "Speed",
   PlotLegends → Placed[LineLegend[Style[#, 12, FontFamily → "Helvetica"] & /@
       {"1-step", "2-step"}], Scaled@{1.5 / 8, 1 / 2}]];

U = 10^-4;

{
  (*established*)
  Table[{m2, (fm[m2, mwt, mmax, λ, n] pest[m2 - mwt]) / NIntegrate[
      fm[m2, mwt, mmax, λ, n] pest[m2 - mwt], {m2, mwt, mmax}]}, {m2, mwt, xmax, xint}]
 };
oldtheory4 = ListPlot[%, PlotRange → All, Joined → True,
   PlotStyle → Directive[Thick, Gray, Dashing[Large]], PerformanceGoal → "Speed"];

{
  (*1 step*)
  Table[{m2, g1m /. m → m2}, {m2, 0, xmax, xint}],
  (*2 step*)
  total = Re[g2denominator[mwt]];
  Table[{m2, 1/total g2numerator[mwt, m2]}, {m2, 0, xmax, xint}]
 };
theory4 = ListPlot[%, PlotRange → All,
   Joined → True, PlotStyle → Directive[Thick, Dashing[Large]],
   PerformanceGoal → "Speed", PlotLegends → Placed[LineLegend[
      {Directive[Thick, Black], Directive[Thick, Black, Dashing[Medium]]},
      Style[#, 12, FontFamily → "Helvetica"] & /@ {"U=10^-3", "U=10^-4"}],
     Scaled@{7 / 8, 3 / 10}]];

Show[
 {oldtheory2, theory2, oldtheory4, theory4},
 PlotRange → {{xmin, xmax}, {0, ymax}},
 Frame → {True, False, False, False},
```

```
 LabelStyle → labelstyle,
 FrameTicksStyle → {FontColor → White, Automatic, Automatic, Automatic},
 Epilog → {
   Text[Style["m0=" <> ToString[mwt], 12, FontFamily → "Helvetica"],
    Scaled@{7 / 8, 3 / 4}],
   Text[Style["B", 14, Bold], Scaled@{0.05, 0.95}]
  }
]

Clear[mmax, λ, Es, n, U, mwt, xmin, xmax, ymax, xint]
```

NIntegrate::izero :
Integral and error estimates are 0 on all integration subregions. Try increasing the value of the MinRecursion option. If value of integral may be 0, specify a finite value for the AccuracyGoal option. ≫

NIntegrate::izero :
Integral and error estimates are 0 on all integration subregions. Try increasing the value of the MinRecursion option. If value of integral may be 0, specify a finite value for the AccuracyGoal option. ≫

2-step intermediate growth rate

```
xmin = -0.3;
xmax = 0.25;
ymax = 30;

N0 = 10 000;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
mwt = -0.2;
n = 4;

U = 10^-3;

exact2 = fm[m1, mwt, mmax, λ, n] (1 - pest[m1]) prescuem[m1, Λ1[m1, mmax, λ, n, U]];
allexact2 = NIntegrate[exact2, {m1, mwt, 0.1}];
oldtheory2 = (fm[m1, mwt, mmax, λ, n] pest[m1 - mwt] HeavisideTheta[m1 - mwt]) /
   NIntegrate[fm[m1, mwt, mmax, λ, n] pest[m1 - mwt], {m1, mwt, mmax}];

U = 10^-4;
```

```
exact4 = fm[m1, mwt, mmax, λ, n] (1 - pest[m1]) prescuem[m1, Λ1[m1, mmax, λ, n, U]];
allexact4 = NIntegrate[exact4, {m1, mwt, 0.1}];
oldtheory4 = (fm[m1, mwt, mmax, λ, n] pest[m1 - mwt] HeavisideTheta[m1 - mwt]) /
   NIntegrate[fm[m1, mwt, mmax, λ, n] pest[m1 - mwt], {m1, mwt, mmax}];

Show[
 Plot[
  {oldtheory2, oldtheory4},
  {m1, xmin, xmax},
  PlotRange → {0, All},
  PlotStyle → {Directive[Gray, Thick], Directive[Gray, Thick, Dashing[Large]]},
  PerformanceGoal → "Speed",
  PlotLegends →
   Placed[LineLegend[Style[#, 12, FontFamily → "Helvetica"] & /@ {"established"}],
    Scaled@{1 / 8, 1.25 / 2}]
 ],
 Plot[
  exact2 / allexact2,
  {m1, xmin, xmax},
  PlotRange → {0, All},
  PlotStyle → Directive[Thick],
  PerformanceGoal → "Speed",
  PlotLegends →
   Placed[LineLegend[Style[#, 12, FontFamily → "Helvetica"] & /@ {"first-step"}],
    Scaled@{1 / 8, 1.25 / 2}]
 ],
 Plot[
  exact4 / allexact4,
  {m1, xmin, xmax},
  PlotRange → {0, All},
  PlotStyle → Directive[Thick, Dashing[Large]],
  PerformanceGoal → "Speed",
  PlotLegends → Placed[
    LineLegend[{Directive[Thick, Black], Directive[Thick, Black, Dashing[Medium]]},
     Style[#, 12, FontFamily → "Helvetica"] & /@
      {"U=10^-3", "U=10^-4"}], Scaled@{7 / 8, 3 / 10}]
 ],
 Frame → {True, False, False, False},
 FrameTicksStyle → {Automatic, Automatic, Automatic, Automatic},
 FrameLabel → {"Growth rate"},
 PlotRange → {{xmin, xmax}, {0, ymax}},
 LabelStyle → labelstyle,
 Epilog → {
   Text[Style["m0=" <> ToString[mwt], 12, FontFamily → "Helvetica"],
    Scaled@{7 / 8, 3 / 4}],
   Text[Style["C", 14, Bold], Scaled@{0.05, 0.95}]
  }
]

Clear[mmax, λ, Es, n, U, mwt, xmin, xmax, ymax, N0]
```

Variance, λ

Probability of rescue

```
N0 = 10^4;
mmax = 0.5;
Es = 0.01;
n = 4;
U = 2 * 10^-3;

m0min = mTempmin;
m0max = mTempmax;
mstep = step;
m0list = Table[m0, {m0, m0min, m0max, mstep}];

λ = 0.005;

rate4 = Table[{m0, Λ4Interpolated[m0, mmax, λ, n, U]}, {m0, m0min, m0max, mstep}];
rate3 = Table[{m0, Λ3Interpolated[m0, mmax, λ, n, U]}, {m0, m0min, m0max, mstep}];
rate2 = Table[{m0, Λ2Interpolated[m0, mmax, λ, n, U]}, {m0, m0min, m0max, mstep}];
rate1 = Table[{m0, Λ1Interpolated[m0, mmax, λ, n, U]}, {m0, m0min, m0max, mstep}];
theory2 = {
   Table[{m0list[[i]], prescue /. p0 → prescuem[m0list[[i]], rate1[[i, 2]]]},
    {i, Length[m0list]}],
   Table[{m0list[[i]], prescue /. p0 → prescuem[m0list[[i]], rate2[[i, 2]]]},
    {i, Length[m0list]}],
   Table[{m0list[[i]], prescue /. p0 → prescuem[m0list[[i]], rate3[[i, 2]]]},
    {i, Length[m0list]}],
   Table[{m0list[[i]], prescue /. p0 → prescuem[m0list[[i]], rate4[[i, 2]]]},
    {i, Length[m0list]}]
  };
alltheory2 = Table[
   {m0list[[i]], prescue /. p0 → prescuem[m0list[[i]], rate1[[i, 2]] + rate2[[i, 2]] +
        rate3[[i, 2]] + rate4[[i, 2]]]}, {i, Length[m0list]}];
```

```
λ = 0.005/2;

rate4 = Table[{m0, Λ4Interpolated[m0, mmax, λ, n, U]}, {m0, m0min, m0max, mstep}];
rate3 = Table[{m0, Λ3Interpolated[m0, mmax, λ, n, U]}, {m0, m0min, m0max, mstep}];
rate2 = Table[{m0, Λ2Interpolated[m0, mmax, λ, n, U]}, {m0, m0min, m0max, mstep}];
rate1 = Table[{m0, Λ1Interpolated[m0, mmax, λ, n, U]}, {m0, m0min, m0max, mstep}];
theory4 = {
   Table[{m0list[[i]], prescue /. p0 → prescuem[m0list[[i]], rate1[[i, 2]]]},
    {i, Length[m0list]}],
   Table[{m0list[[i]], prescue /. p0 → prescuem[m0list[[i]], rate2[[i, 2]]]},
    {i, Length[m0list]}],
   Table[{m0list[[i]], prescue /. p0 → prescuem[m0list[[i]], rate3[[i, 2]]]},
    {i, Length[m0list]}],
   Table[{m0list[[i]], prescue /. p0 → prescuem[m0list[[i]], rate4[[i, 2]]]},
    {i, Length[m0list]}]
  };
alltheory4 = Table[
   {m0list[[i]], prescue /. p0 → prescuem[m0list[[i]], rate1[[i, 2]] + rate2[[i, 2]] +
        rate3[[i, 2]] + rate4[[i, 2]]]}, {i, Length[m0list]}];

Show[
 ListLogPlot[
  theory2,
  Joined → True,
  PlotStyle → Thick,
  PlotRange → {{-0.4, 0}, {5 * 10^-7, 1}},
  Frame → {True, False, False, True},
  FrameLabel → {"Wildtype growth rate", , , "Probability of rescue"},
  FrameTicks → {True, False, False, True},
  LabelStyle → labelstyle,
  PlotLegends → Placed[LineLegend[Style[#, 12, FontFamily → "Helvetica"] & /@
      {"1-step", "2-step", "3-step", "4-step"}], Scaled@{3 / 4, 1 / 4}]
 ],
 ListLogPlot[alltheory2, Joined → True, PlotStyle → {Black, Thick},
  PlotLegends → Placed[LineLegend[Style[#, 12, FontFamily → "Helvetica"] & /@
      {"1-, 2-, 3-, or 4-step"}], Scaled@{1 / 4, 8 / 10}]
 ],
 ListLogPlot[theory4,
  Joined → True,
  PlotStyle → Directive[Thick, Dashing[Large]]
 ],
 ListLogPlot[alltheory4, Joined → True, PlotStyle → {Black, Thick, Dashing[Large]},
  PlotLegends → Placed[
    LineLegend[{Directive[Thick, Gray], Directive[Thick, Gray, Dashing[Medium]]},
     Style[#, 12, FontFamily → "Helvetica"] & /@
      {"λ=0.005", "λ=0.0025"}], Scaled@{1 / 10, 6 / 10}]
 ],
 Epilog → Text[Style["A", Bold, 14], Scaled@{0.05, 0.95}]
]

Clear[N0, mmax, λ, Es, n, U, m0min, m0max, mstep]
```

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
NIntegrate obtained 1.4363490176861695`*^-7 and
1.034782441470326`*^-12 for the integral and error estimates. ≫

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
NIntegrate obtained 2.0246698484863734`*^-7 and
1.0921054693023465`*^-12 for the integral and error estimates. ≫

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
NIntegrate obtained 2.850952330867838`*^-7 and
2.321744002394699`*^-12 for the integral and error estimates. ≫

General::stop : Further output of NIntegrate::ncvb will be suppressed during this calculation. ≫

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
NIntegrate obtained 5.3450453526009294`*^-8 and
5.951525075263353`*^-13 for the integral and error estimates. ≫

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
NIntegrate obtained 7.059025621526559`*^-8 and
8.588848983658455`*^-13 for the integral and error estimates. ≫

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
NIntegrate obtained 9.314638149255934`*^-8 and
1.711619241364099`*^-12 for the integral and error estimates. ≫

General::stop : Further output of NIntegrate::ncvb will be suppressed during this calculation. ≫

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
NIntegrate obtained 1.4363490176861695`*^-7 and
1.034782441470326`*^-12 for the integral and error estimates. ≫

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
NIntegrate obtained 2.0246698484863734`*^-7 and
1.0921054693023465`*^-12 for the integral and error estimates. ≫

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
NIntegrate obtained 2.850952330867838`*^-7 and
2.321744002394699`*^-12 for the integral and error estimates. ≫

General::stop : Further output of NIntegrate::ncvb will be suppressed during this calculation. ≫

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {-0.199623}.
NIntegrate obtained 1.371611099561599`*^-10 and
3.2533774948230864`*^-16 for the integral and error estimates. ≫

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {-0.199623}.
NIntegrate obtained 2.459129528372128`*^-10 and
5.379711113614932`*^-16 for the integral and error estimates. ≫

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {−0.199623}.
NIntegrate obtained 4.382809860895368`*^−10 and
8.119644899145538`*^−16 for the integral and error estimates. ≫

General::stop : Further output of NIntegrate::ncvb will be suppressed during this calculation. ≫

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
NIntegrate obtained 2.830813641888082`*^−9 and
3.4578366587790035`*^−15 for the integral and error estimates. ≫

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
NIntegrate obtained 4.427814198985973`*^−9 and
8.978439335615778`*^−15 for the integral and error estimates. ≫

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
NIntegrate obtained 6.8986954726390565`*^−9 and
2.174871671811652`*^−14 for the integral and error estimates. ≫

General::stop : Further output of NIntegrate::ncvb will be suppressed during this calculation. ≫

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {−0.199623}.
NIntegrate obtained 1.371611099561599`*^−10 and
3.2533774948230864`*^−16 for the integral and error estimates. ≫

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {−0.199623}.
NIntegrate obtained 2.459129528372128`*^−10 and
5.379711113614932`*^−16 for the integral and error estimates. ≫

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {−0.199623}.
NIntegrate obtained 4.382809860895368`*^−10 and
8.119644899145538`*^−16 for the integral and error estimates. ≫

General::stop : Further output of NIntegrate::ncvb will be suppressed during this calculation. ≫

Rescue genotype growth rate

```
xmin = -0.3;
xmax = 0.25;
```

```
ymax = 40;
xint = 0.01;

N0 = 10 000;
mmax = 0.5;
Es = 0.01;
n = 4;
mwt = -0.2;
U = 2 * 10^-3;

λ = 0.005;

{
  (*established*)
  Table[{m2, (fm[m2, mwt, mmax, λ, n] pest[m2 - mwt]) / NIntegrate[
      fm[m2, mwt, mmax, λ, n] pest[m2 - mwt], {m2, mwt, mmax}]}, {m2, mwt, xmax, xint}]
 };
oldtheory2 = ListPlot[%, PlotRange → All, Joined → True,
   PlotStyle → Directive[Thick, Gray], PerformanceGoal → "Speed", PlotLegends →
    Placed[LineLegend[Style[#, 12, FontFamily → "Helvetica"] & /@ {"established"}],
     Scaled@{1.5 / 8, 1 / 2}]];

{
  (*1 step*)
  Table[{m2, g1m /. m → m2}, {m2, 0, xmax, xint}],
  (*2 step*)
  total = Re[g2denominator[mwt]];
  Table[{m2, 1/total g2numerator[mwt, m2]}, {m2, 0, xmax, xint}]
 };
theory2 = ListPlot[%, PlotRange → All, Joined → True,
   PlotStyle → Directive[Thick], PerformanceGoal → "Speed",
   PlotLegends → Placed[LineLegend[Style[#, 12, FontFamily → "Helvetica"] & /@
       {"1-step", "2-step"}], Scaled@{1.5 / 8, 1 / 2}]];

λ = 0.005 / 2;

{
  (*established*)
  Table[{m2, (fm[m2, mwt, mmax, λ, n] pest[m2 - mwt]) / NIntegrate[
      fm[m2, mwt, mmax, λ, n] pest[m2 - mwt], {m2, mwt, mmax}]}, {m2, mwt, xmax, xint}]
 };
oldtheory4 = ListPlot[%, PlotRange → All, Joined → True,
   PlotStyle → Directive[Thick, Gray, Dashing[Large]], PerformanceGoal → "Speed"];

{
  (*1 step*)
  Table[{m2, g1m /. m → m2}, {m2, 0, xmax, xint}],
  (*2 step*)
  total = Re[g2denominator[mwt]];
  Table[{m2, 1/total g2numerator[mwt, m2]}, {m2, 0, xmax, xint}]
```

```
 };
theory4 = ListPlot[%, PlotRange → All, Joined → True,
   PlotStyle → Directive[Thick, Dashing[Large]], PerformanceGoal → "Speed",
   PlotLegends → Placed[LineLegend[{Directive[Thick, Black], Directive[Thick,
        Black, Dashing[Medium]]}, Style[#, 12, FontFamily → "Helvetica"] & /@
       {"λ=0.005", "λ=0.0025"}], Scaled@{7 / 8, 3 / 10}]];

Show[
 {oldtheory2, theory2, oldtheory4, theory4},
 PlotRange → {{xmin, xmax}, {0, ymax}},
 Frame → {True, False, False, False},
 LabelStyle → labelstyle,
 FrameTicksStyle → {FontColor → White, Automatic, Automatic, Automatic},
 Epilog → {
   Text[Style["m0=" <> ToString[mwt], 12, FontFamily → "Helvetica"],
    Scaled@{7 / 8, 3 / 4}],
   Text[Style["B", 14, Bold], Scaled@{0.05, 0.95}]
  }
]

Clear[mmax, λ, Es, n, U, mwt, xmin, xmax, ymax, xint]
```

NIntegrate::izero :
Integral and error estimates are 0 on all integration subregions. Try increasing the value of the MinRecursion option. If value of integral may be 0, specify a finite value for the AccuracyGoal option. ≫

NIntegrate::izero :
Integral and error estimates are 0 on all integration subregions. Try increasing the value of the MinRecursion option. If value of integral may be 0, specify a finite value for the AccuracyGoal option. ≫

NIntegrate::slwcon :
Numerical integration converging too slowly; suspect one of the following: singularity, value of the integration is 0, highly oscillatory integrand, or WorkingPrecision too small. ≫

2-step intermediate growth rate

```
xmin = -0.3;
xmax = 0.25;
ymax = 30;
```

```
N0 = 10 000;
mmax = 0.5;
Es = 0.01;
mwt = -0.2;
n = 4;
U = 2 * 10^-3;

λ = 0.005;

exact2 = fm[m1, mwt, mmax, λ, n] (1 - pest[m1]) prescuem[m1, Λ1[m1, mmax, λ, n, U]];
allexact2 = NIntegrate[exact2, {m1, mwt, 0.1}];
oldtheory2 = (fm[m1, mwt, mmax, λ, n] pest[m1 - mwt] HeavisideTheta[m1 - mwt]) /
   NIntegrate[fm[m1, mwt, mmax, λ, n] pest[m1 - mwt], {m1, mwt, mmax}];

λ = 0.005 / 2;

exact4 = fm[m1, mwt, mmax, λ, n] (1 - pest[m1]) prescuem[m1, Λ1[m1, mmax, λ, n, U]];
allexact4 = NIntegrate[exact4, {m1, mwt, 0.1}];
oldtheory4 = (fm[m1, mwt, mmax, λ, n] pest[m1 - mwt] HeavisideTheta[m1 - mwt]) /
   NIntegrate[fm[m1, mwt, mmax, λ, n] pest[m1 - mwt], {m1, mwt, mmax}];

Show[
 Plot[
  {oldtheory2, oldtheory4},
  {m1, xmin, xmax},
  PlotRange → {0, All},
  PlotStyle → {Directive[Gray, Thick], Directive[Gray, Thick, Dashing[Large]]},
  PerformanceGoal → "Speed",
  PlotLegends →
   Placed[LineLegend[Style[#, 12, FontFamily → "Helvetica"] & /@ {"established"}],
    Scaled@{1 / 8, 1.25 / 2}]
 ],
 Plot[
  exact2 / allexact2,
  {m1, xmin, xmax},
  PlotRange → {0, All},
  PlotStyle → Directive[Thick],
  PerformanceGoal → "Speed",
  PlotLegends →
   Placed[LineLegend[Style[#, 12, FontFamily → "Helvetica"] & /@ {"first-step"}],
    Scaled@{1 / 8, 1.25 / 2}]
 ],
 Plot[
  exact4 / allexact4,
  {m1, xmin, xmax},
  PlotRange → {0, All},
  PlotStyle → Directive[Thick, Dashing[Large]],
  PerformanceGoal → "Speed",
  PlotLegends → Placed[
    LineLegend[{Directive[Thick, Black], Directive[Thick, Black, Dashing[Medium]]},
     Style[#, 12, FontFamily → "Helvetica"] & /@
      {"λ=0.005", "λ=0.0025"}], Scaled@{7 / 8, 3 / 10}]
 ],
 Frame → {True, False, False, False},
 FrameTicksStyle → {Automatic, Automatic, Automatic, Automatic},
```

```
  FrameLabel → {"Growth rate"},
  PlotRange → {{xmin, xmax}, {0, ymax}},
  LabelStyle → labelstyle,
  Epilog → {
    Text[Style["m0=" <> ToString[mwt], 12, FontFamily → "Helvetica"],
     Scaled@{7 / 8, 3 / 4}],
    Text[Style["C", 14, Bold], Scaled@{0.05, 0.95}]
   }
]

Clear[mmax, λ, Es, n, U, mwt, xmin, xmax, ymax, N0]
```