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*)
imagedir = "../IMAGES/";(*directory to save figures in*)
datadir = "SIM_DATA/";(*directory with simulation data*)
```

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)

$$fs[s\_, so\_, \lambda\_, n\_] := \frac{2}{\lambda} \text{PDF}\left[\text{NoncentralChiSquareDistribution}\left[n, \frac{2\,so}{\lambda}\right], \frac{2}{\lambda}(so - s)\right] \text{HeavisideTheta}[so - s]$$

```
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]
```

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

```
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]]
```

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

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

```
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}]
```

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

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

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

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

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

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

```
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}];
```

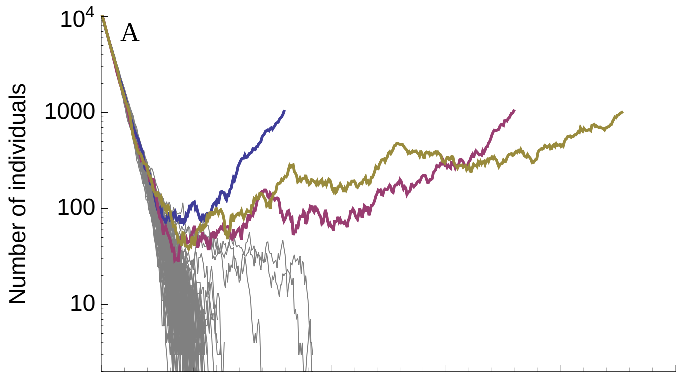
Example simulations

1-step rescue (figure 1)

Population size dynamics

Total population size for many replicates

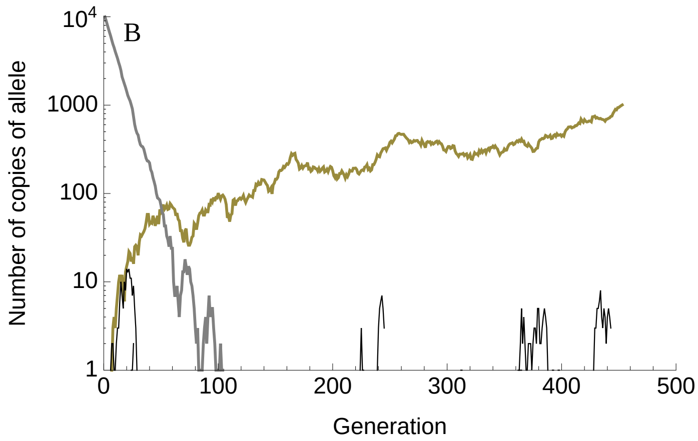
```
n0 = "10000";
n = "4";
U = "0.000100";
Es = "0.01000";
mmax = "0.50";
mwt = "-0.10";
mutmax = "2";
nreps = 100;

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;

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], Scaled@{0.05, 0.95}]
 ],
 ListLogPlot[
  rescued,
  Joined → True,
  PlotStyle → Thickness[0.005]
 ],
 PlotRange → {{0, genmax}, Log@{2, 10^4}}
]
Export[imagedir <> "Vshape.pdf", %];

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



Mutation dynamics

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];

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], 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]}
 ]
]
Export[imagedir <> "VshapeMutations.pdf", %];

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

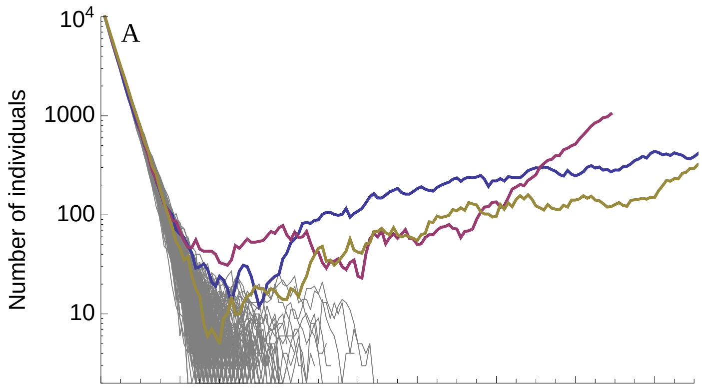


B
Number of copies of allele
10^4
1000
100
10
1
0
100
200
300
400
500
Generation

2-step rescue (figure 2)

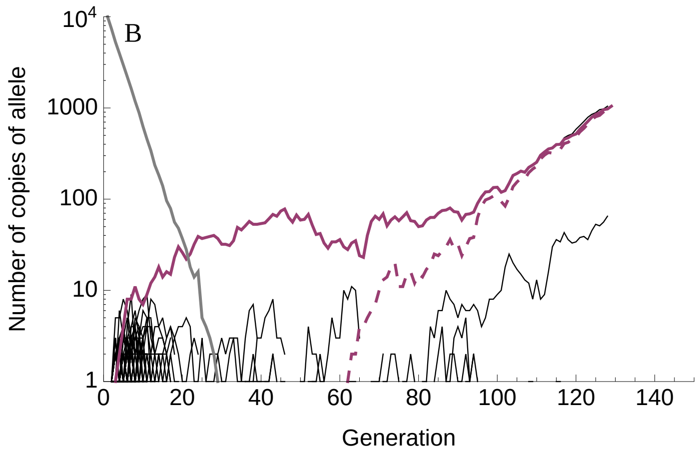
Population size dynamics

```
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;

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], Scaled@{0.05, 0.95}]],
 ListLogPlot[rescued, Joined → True, PlotStyle → Thickness[0.005]
 ],
 PlotRange → {{0, genmax}, Log@{2, 10^4}}
]
Export[imagedir <> "Ushape.pdf", %];

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


Number of individuals
10^4
1000
100
10
A

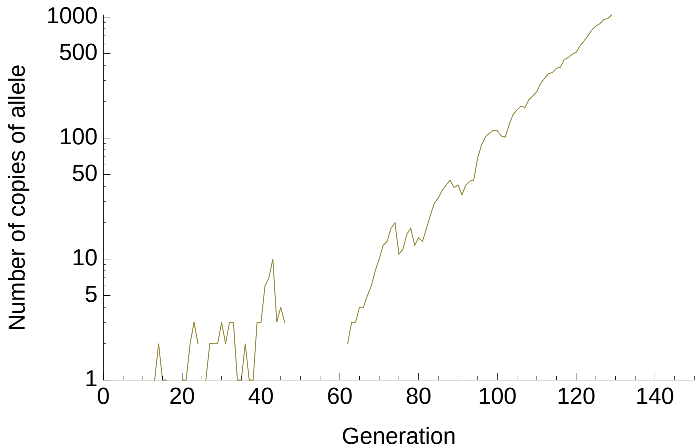
Mutation dynamics

```
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];

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], 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]}]
]
(*Export[imagedir<>"UshapeMutations.pdf",%];*)

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



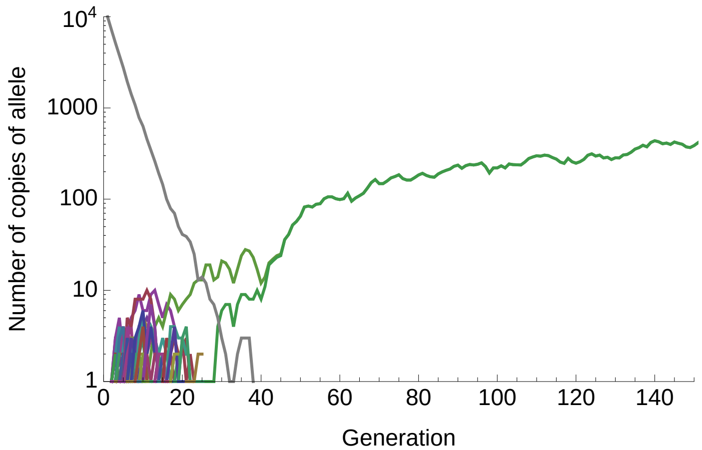
Note that the first mutation is subcritical, but the second mutation makes the double mutant supercritical (we can see this because we keep track of what is supercritical in the sims):

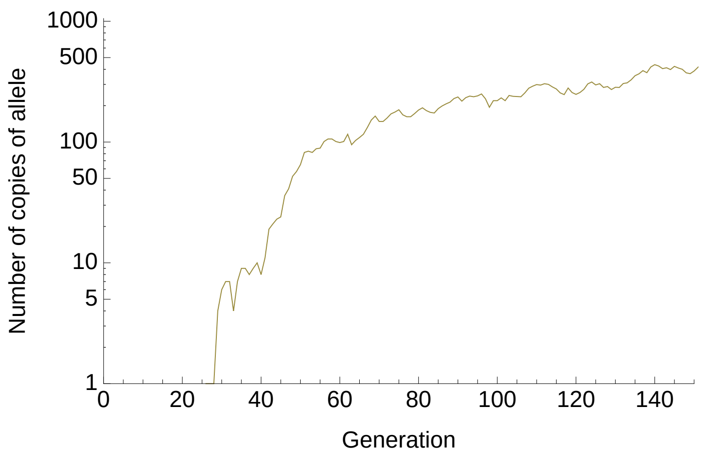
```
n0 = "10000";
n = "4";
U = "0.010000";
Es = "0.01000";
mmax = "0.50";
mwt = "-0.30";
mutmax = "2";
rep = "675";

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

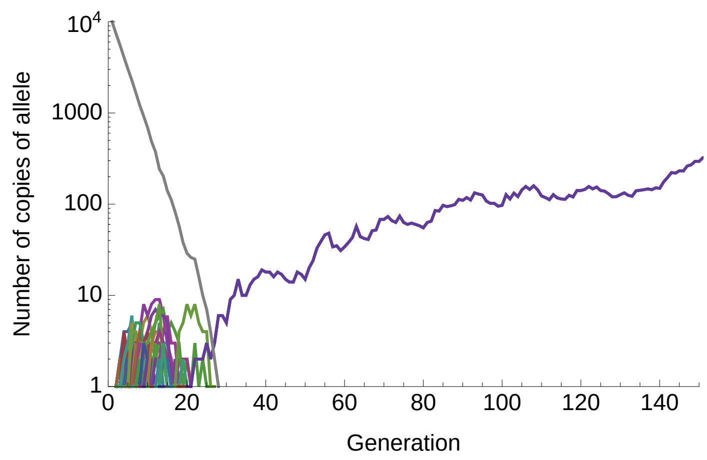
```
n0 = "10000";
n = "4";
U = "0.010000";
Es = "0.01000";
mmax = "0.50";
mwt = "-0.30";
mutmax = "2";
rep = "629";

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]
```

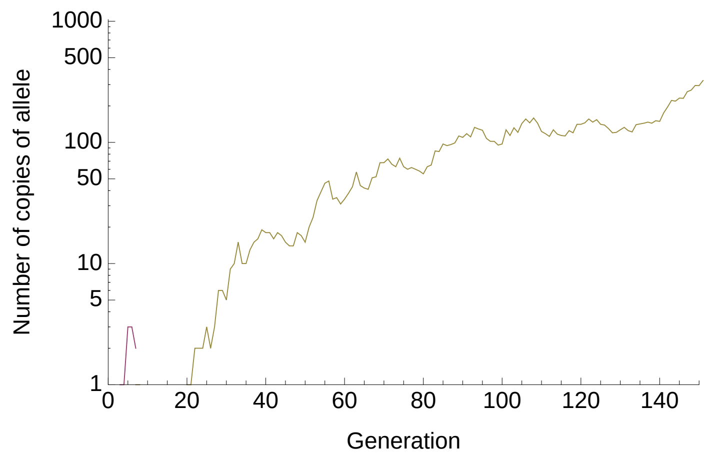




but the yellow replicate is 1-step

```
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]
```





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

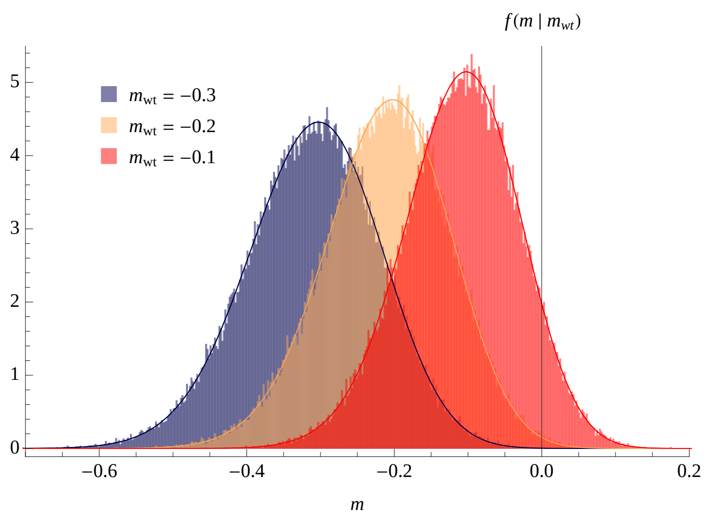
```
n = 4; η = n / 2;(*phenotypic dimensions*)
Es = 0.01;(*mean mutational selective efffect*)
λ = 2 Es / n;(*mutational variance, i.e., scaled size*)
uo = 0 UnitVector[n, 1];(*mean mutational size; set to all zeros*)

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]
```

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

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 é PoissonDistribution[Exp[m]]]
```

$-1 + e^m$

and σ is

```
Expectation[(X - 1)^2, X é PoissonDistribution[Exp[m]]] -
   Expectation[X - 1, X é 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 $\left(F[s, 0] == s^{N0}\right)$ 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
```

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

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, $\lambda>\mu$ 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 A4)

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
```

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

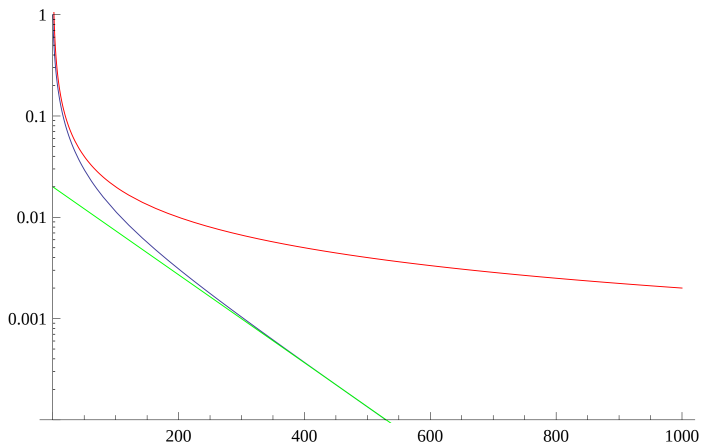
And when -m t >>1, ie -m >> 1/t (that is, when the mutant is effectively subcritical) we have roughly

```
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
```

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

three

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

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

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)
```

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

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 A5)

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
```

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

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
```

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

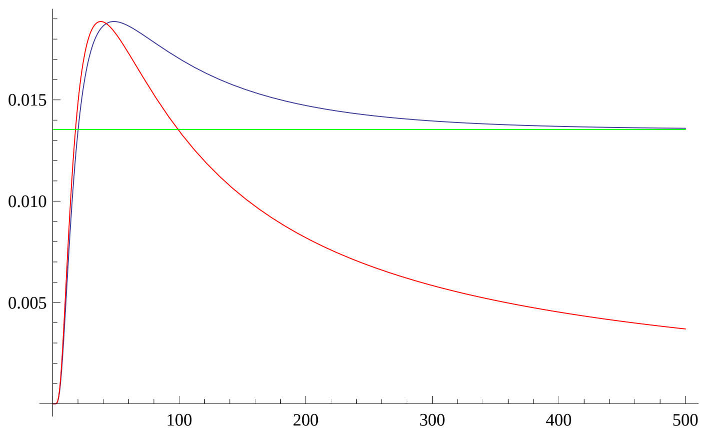
with expectation

```
Sum[n pntgtapp2, {n, 0, ∞}]
```

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

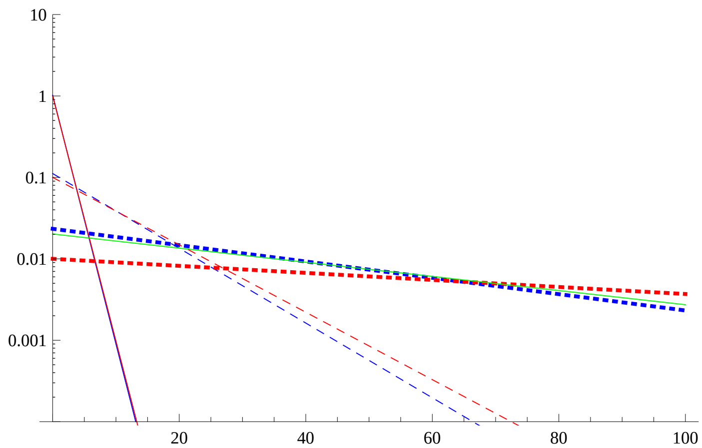
Visually check critical (red) and subcritical (green) approximations against true solution (blue) for n=20 across time

```
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 $f[m \mid m_{\text{wt}}]$ $p_{\text{est}}[m]$ 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

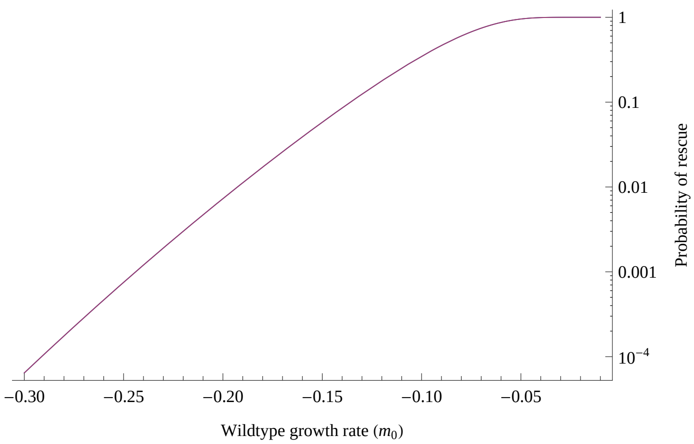
```
PR1[m0_?NumericQ] := prescue /. p0 → prescuem[m0, Λ1[m0, mmax, λ, n, U]]
```

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]
```



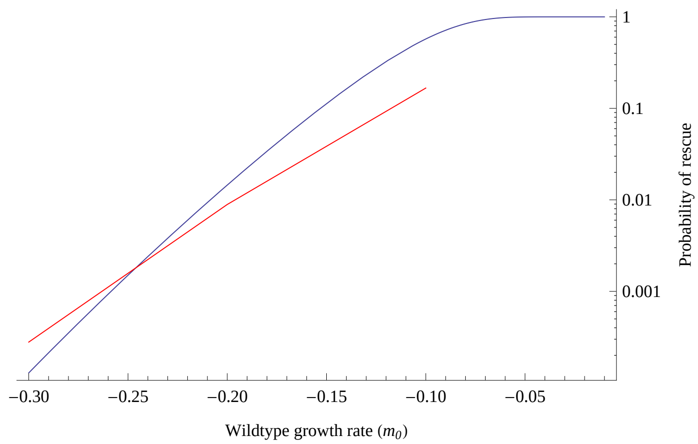
2-step rescue (equation 6)

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, Δ2[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

```
Δ3[m0_?NumericQ, mmax_, λ_, n_, U_] := U NIntegrate[
    fm[m, m0, mmax, λ, n] (1 - pest[m]) prescuem[m, Δ2[m, mmax, λ, n, U]], {m, -∞, mmax}]
```

and 4-step is

```
Δ4[m0_?NumericQ, mmax_, λ_, n_, U_] := U NIntegrate[
    fm[m, m0, mmax, λ, n] (1 - pest[m]) prescuem[m, Δ3[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

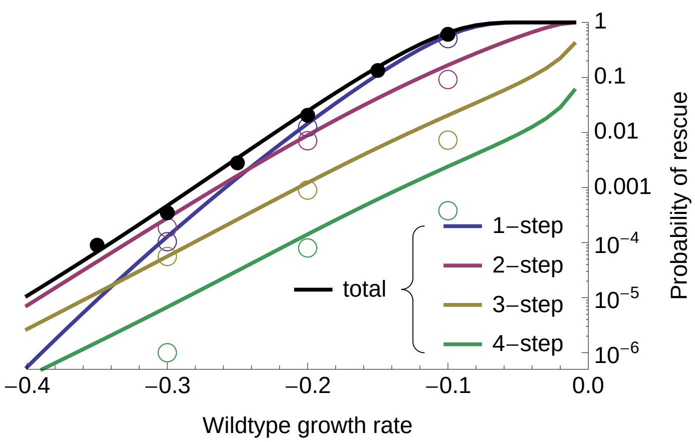
```
N0 = 10^4;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
U = 2 * 10^-3;

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]
```

Plot

```
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 = 100000;
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 = 100000;
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 = 1000000;
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]]
]

Export[imagedir <> "4stepNormalU_sims.pdf", %];

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

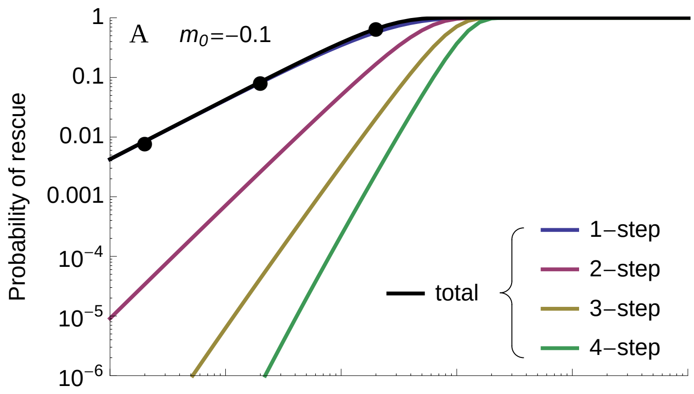
```
Umin = -5;
Umax = 1;
Ustep = 0.1;
mmin = -0.4;

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 = 2 Es / 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]
```

Plot panel A

```
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;

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], 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]]
  }
]

Export[imagedir <> "4step_lowm0.pdf", %];

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

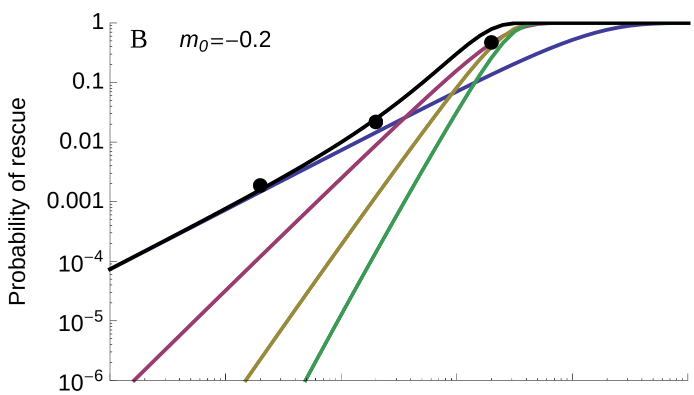


Numerical data for panel B

```
N0 = 10^4;
m0 = -0.2;
mmax = 0.5;
λ = 2 Es / 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]
```

Plot panel B

```
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;

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], 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]
]

Export[imagedir <> "4step_medm0.pdf", %];

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

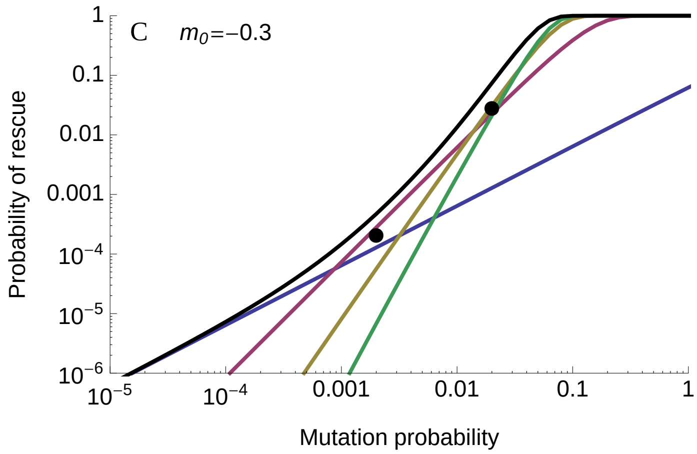


Numerical data for panel C

```
N0 = 10^4;
m0 = -0.3;
mmax = 0.5;
λ = 2 Es / 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]
```

Plot panel C

```
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;

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], 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]
]

Export[imagedir <> "4step_highm0.pdf", %];

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



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)
    Hypergeometric0F1Regularized[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]:

```
Hypergeometric0F1Regularized[θ, z];
Hypergeometric0F1[θ, z] / Gamma[θ];
FullSimplify[% / %%]
```

```
1
```

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

```
Hypergeometric0F1[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 $\frac{1}{(\sqrt{z})^{\theta-1}}$ BesselI$[\theta-1, 2\sqrt{z}]$:

```
Hypergeometric0F1Regularized[θ, z];
```

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

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

1

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

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

where the k^{th} term added to “1” is obtained by taking the previous term and multiplying by $-\frac{(\mu-(2k-1)^{2})}{k\,(8z)}$. For large z, the Bessel function will be dominated by the leading term:

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

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

This allows us to conclude that $\mathtt{Hypergeometric0F1Regularized}[\theta,\ z]=\frac{1}{\left(\sqrt{z}\right)^{\theta-1}}\ \mathtt{BesselI}\left[\theta-1,\ 2\sqrt{z}\right]$ 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

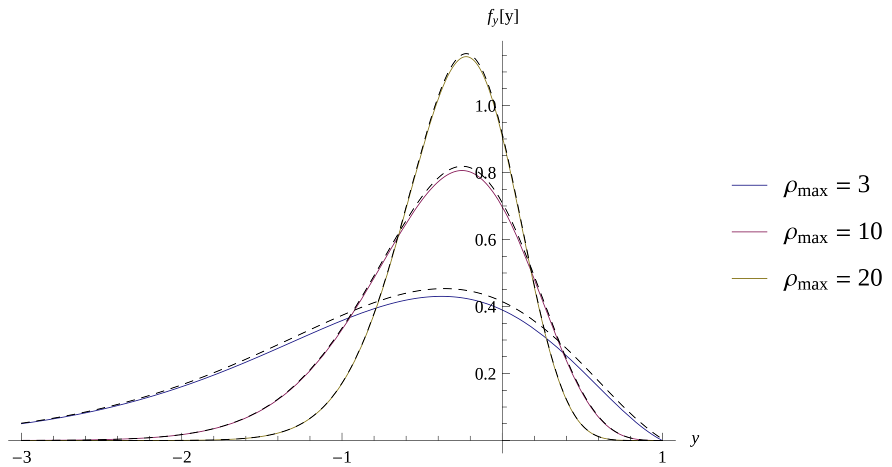
```
fya = FullSimplify[
  fy /. Hypergeometric0F1Regularized → Function[{θ, z}, 1/(2 Sqrt[π]) z^((1-2θ)/4) E^(2 Sqrt[z])] //
   PowerExpand, 0 < y < 1 && ρmax > 0 && ywt < 0 && θ ≥ 1/2]
FullSimplify[% == (E^(-v[y]) (1 - y)^(θ/2 - 3/4) (1 - ywt)^(1/4 - θ/2) Sqrt[ρmax])/(2 Sqrt[π]) /.
  v[y] → (2 - ywt - 2 Sqrt[(1 - ywt) (1 - y)] - y) ρmax,
 {ρmax > 0, ywt < 0, 0 < y < 1, θ ≥ 1/2}] (*compare to eqn A9*)
```

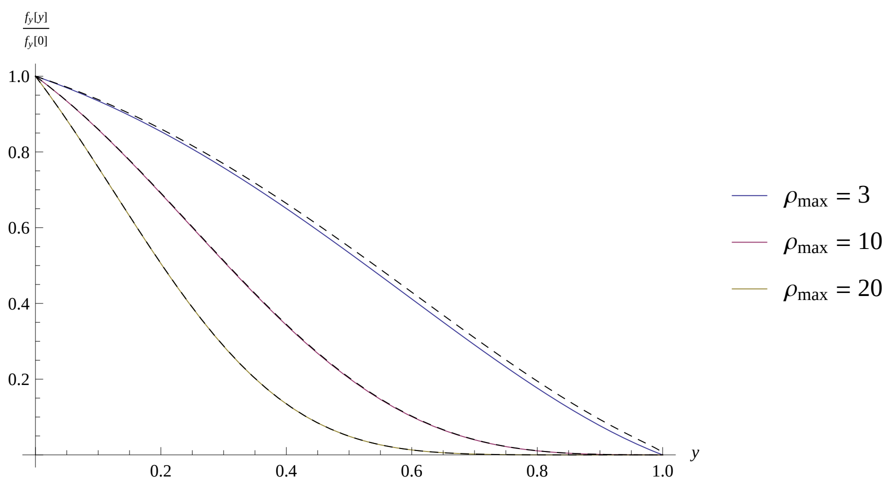
$$-\frac{e^{\left(-2+y+2\sqrt{(-1+y)(-1+ywt)}+ywt\right)\rho max}\left(\frac{-1+y}{-1+ywt}\right)^{\theta/2}(-1+ywt)\sqrt{\rho max}}{2\sqrt{\pi}\,((-1+y)(-1+ywt))^{3/4}}$$

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

$$\frac{U}{-mwt}\,\mathrm{pest}[m]\ \mathrm{fy}\ /.\ m \to \mathrm{mmax}\ y$$

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

which, using the approximation in equation A9, is nearly

$$\frac{U}{-mwt}\,\mathrm{pest}[m]\ \mathrm{fya}\ /.\ m \to \mathrm{mmax}\ y$$

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

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

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

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

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

$$\mathbf{h}[\psi\_] := \left(\frac{1-\psi/2}{1-\psi wt/2}\right)^{\theta-\frac{1}{2}} \left(1-e^{-2\,mmax\,y}\right) \text{ /. } y \to \psi\,(1-\psi/4)$$

$$\mathbf{q}[\psi\_] := \frac{1}{4}\,(\psi-\psi wt)^2$$

$$\frac{U}{-mwt}\,\frac{\sqrt{\rho max}}{2\sqrt{\pi}}\,h[\psi]\;\mathrm{Exp}[-\rho max\; q[\psi]]$$

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

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)

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

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

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

$$\mathbf{h0} = \mathrm{Normal}[\mathrm{Series}[h[\psi],\ \{\psi,\ 0,\ 1\}]]$$

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

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

$$\mathrm{Integrate}\left[\frac{U}{-mwt}\,\frac{\sqrt{\rho max}}{2\sqrt{\pi}}\,h0\;\mathrm{Exp}[-\rho max\; q[\psi]],\ \{\psi,\ 0,\ \infty\},\ \mathrm{Assumptions} \to \{\rho max > 0,\ \psi wt < 0\}\right] \text{ /. } mwt \to \psi wt\,(1-\psi wt/4)\,mmax;$$

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

True

```
AnciauxEqnA12 = U ((1 - ψwt/2)^(1/2 - θ) / (1 - ψwt/4)) (Exp[-α]/Sqrt[π α] - Erfc[Sqrt[α]]);
```

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]
```

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

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

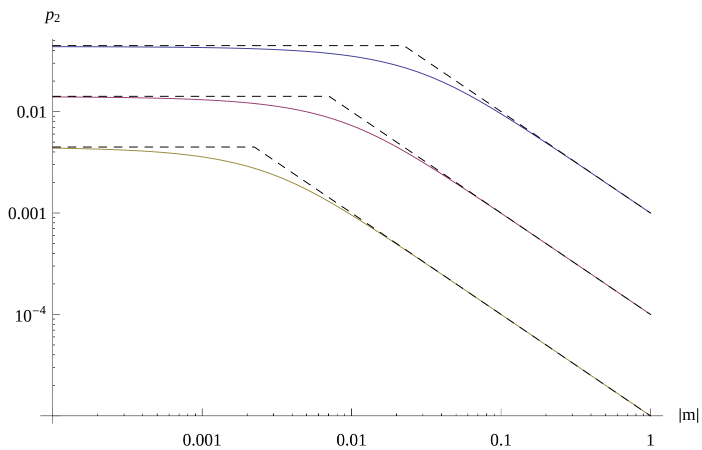
So we should transition from one approx to the other at

```
Solve[√(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 < √(#/2), √(2 #), #/Abs[m]] & /@ {10^-3, 10^-4, 10^-5},
  {m, 0.0001, 1}, PlotStyle → {Dashed, Black}], AxesLabel → {"|m|", "p2"}]
```



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

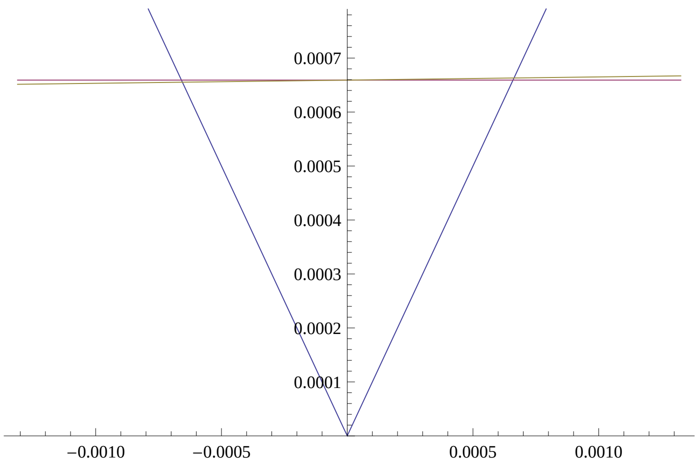
```
U Integrate[fm[0, m0, mmax, λ, n] √(2 Λ0), {m, -√(Λ0/2), √(Λ0/2)}];
% == 2 U fm[0, m0, mmax, λ, n] Λ0
True
```

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

Check integration bounds:

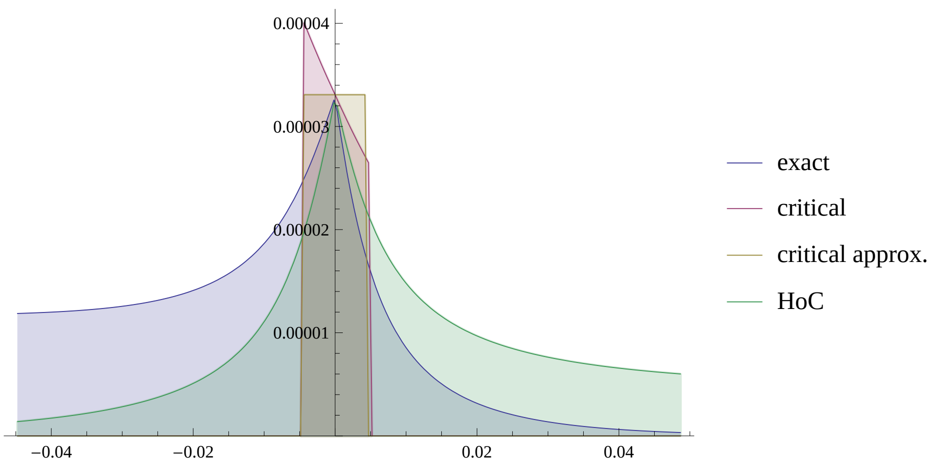
```
U = 2 * 10^-5;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;

{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}}



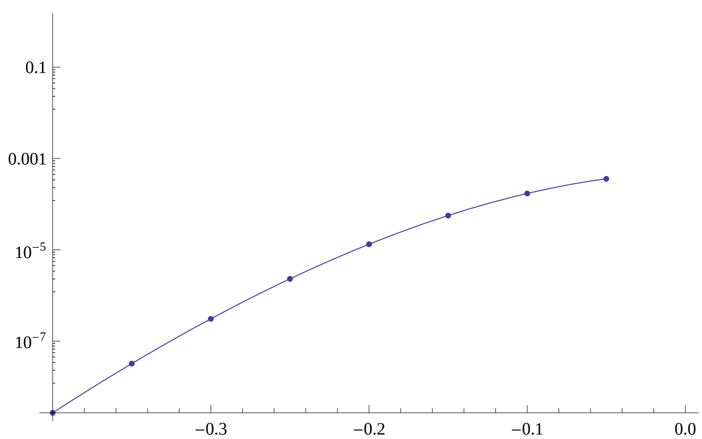
Now check the contribution of single mutant growth rates to 2-step sufficiently critical rescue

```
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, $\Lambda0 = U \int f(m \mid 0)\, p_{est}(m)\, dm$ 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 ψ(1-ψ/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 AnciauxEqnA12 /. ψwt → ψ /. m → mmax ψ (1 - ψ / 4) /. α → ρmax ψ^2/4;
Limit[%, ψ → 0];
Simplify[% /. ρmax → mmax / λ, {mmax > 0, λ > 0}]
```

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

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

```
4 U^2 fm[0, m0, mmax, λ, n] Sqrt[mmax λ / π];
```

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

```
Simplify[
  4 U^2 Sqrt[mmax λ / π] (D[2 (1 - Sqrt[1 - m / mmax]), m] fψ /. ψ → 0) /. mmax → ρmax λ /. m → 0,
  {λ > 0, θ > 1 / 2, ψwt < 0}] /. -ρmax ψwt^2/4 → -α(*/.θ→n/2*) /. ψwt → ψ0 // Simplify
FullSimplify[U^2 (1 - ψ0/2)^(1/2-θ) e^-α 2/π == %]
```

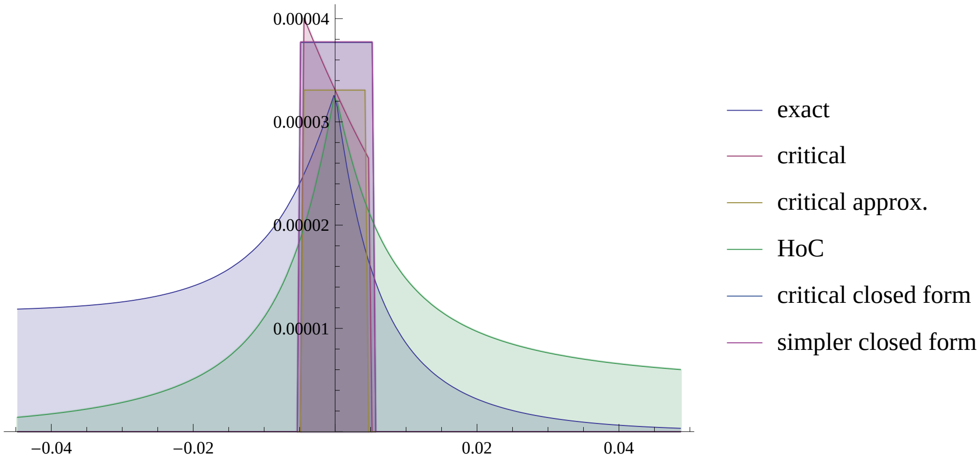
$$\frac{2^{\frac{1}{2}+\theta}\,e^{-\alpha}\,U^2\,(2-\psi_0)^{\frac{1}{2}-\theta}}{\pi}$$

```
True
```

Check contributions across m

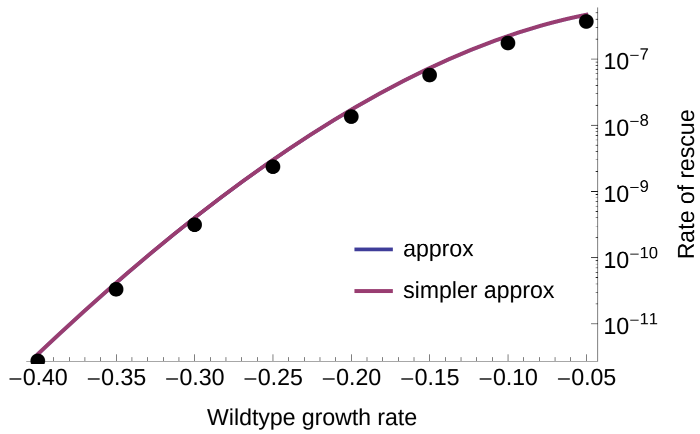
```
Clear[m0]
```

```
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

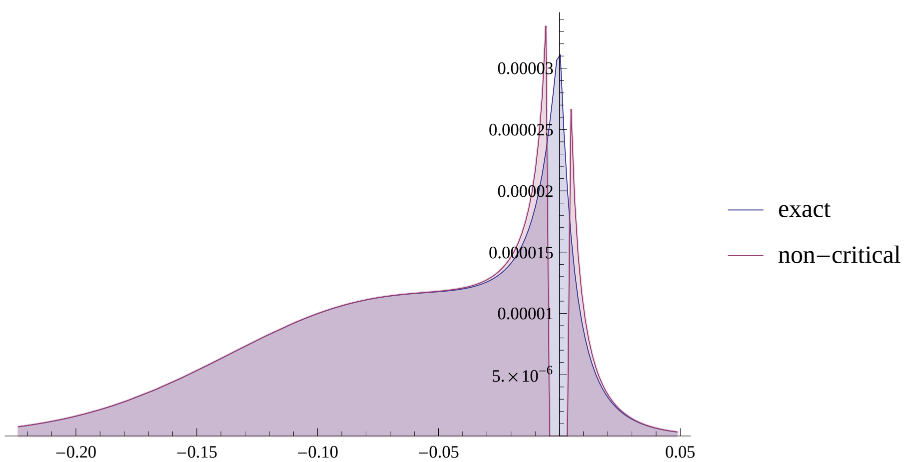
Approximation 1

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 $m = \pm\sqrt{\Lambda[0]/2}$.

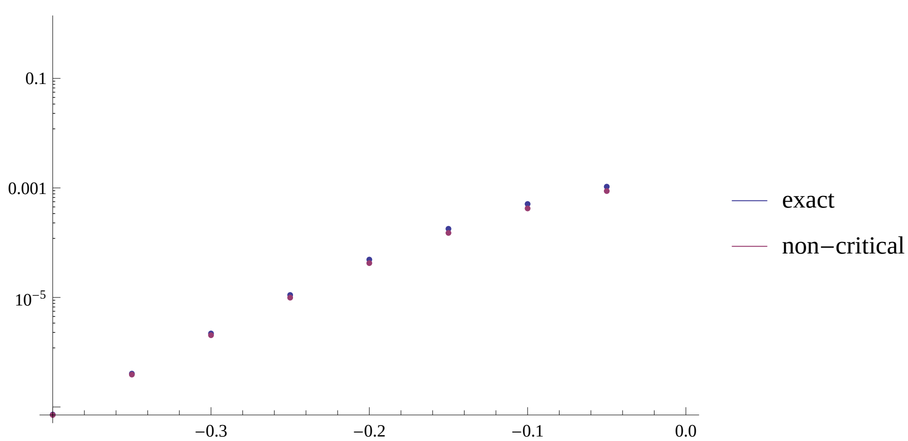
Check the contribution of single mutant growth rates to 2-step sufficiently critical rescue

```
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

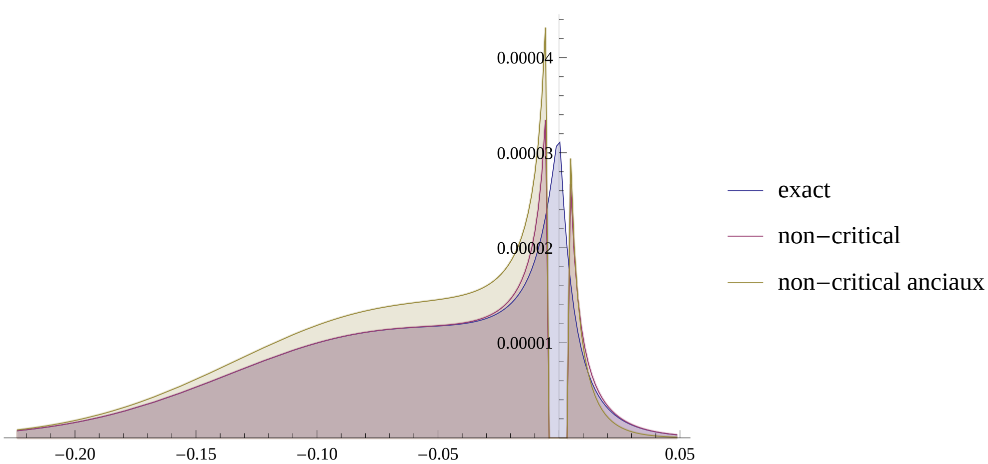
We can next borrow the approximation of $\Lambda 1$ from Anciaux et al. (their eqn A12 without the 1/mwt term)

Abs[mwt] AnciauxEqnA12

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

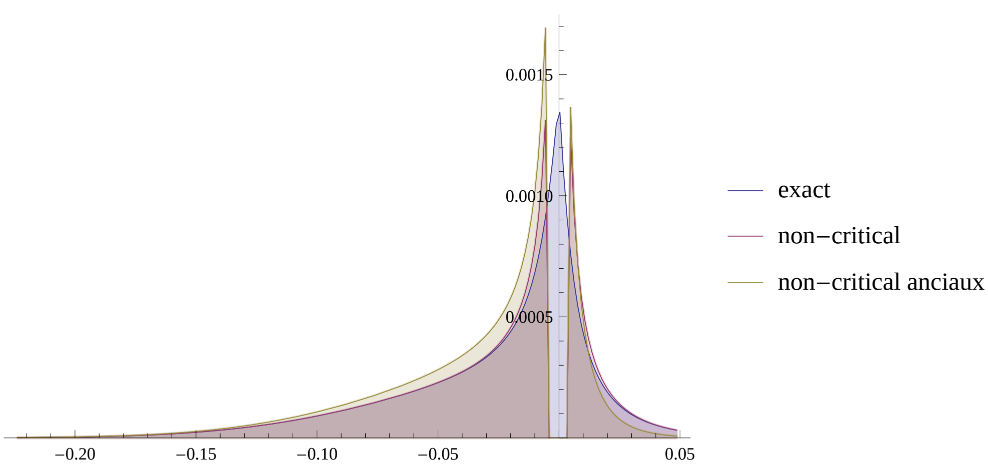
Check contributions of m1

```
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

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

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

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

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

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

True

over ψ between -∞ and ψ*

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

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

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

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

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

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
```

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

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;
```

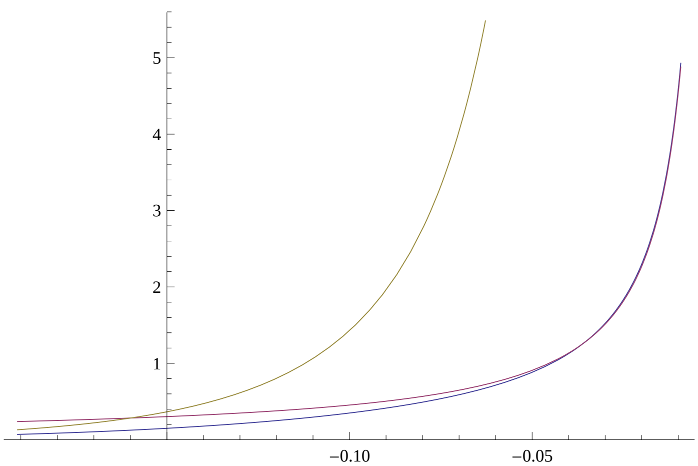
$$m^* = \sqrt{\Lambda 1[0, \text{mmax}, \lambda, n, U] / 2};$$

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

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

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

```
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

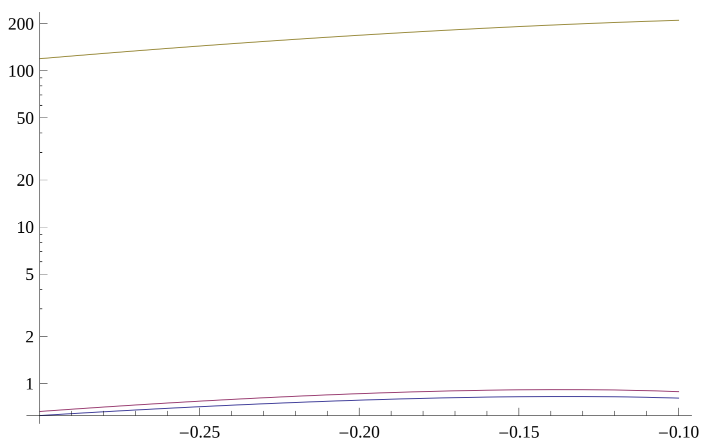
```
U = 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.1;
n = 4;
m* = Sqrt[Λ1[0, mmax, λ, n, U] / 2];
mmax / λ
```

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

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

```
ListLogPlot[%, Joined → True]

Clear[mmax, λ, Es, n, U, mwt]
```

10.



For ρmax=100

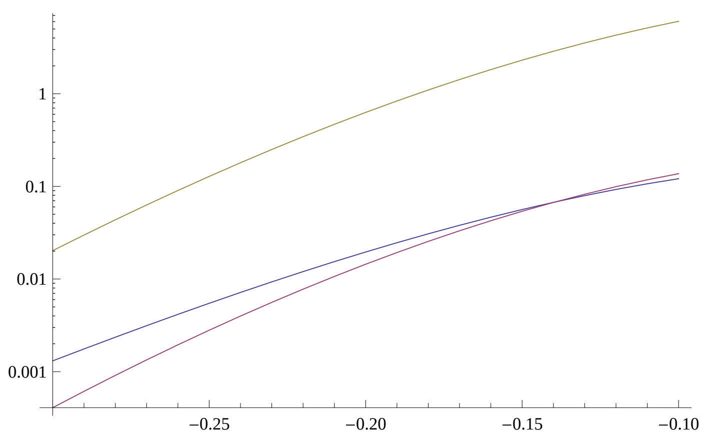
```
U = 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
m* = Sqrt[Λ1[0, mmax, λ, n, U] / 2];
mmax / λ
```

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

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

```
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
```

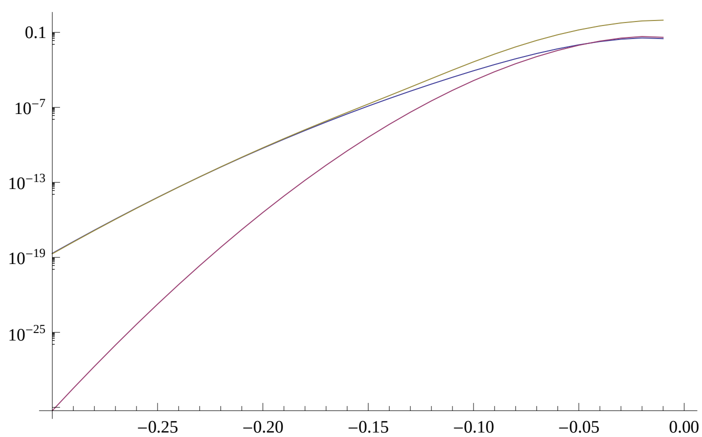
$$\left\{\psi\text{term},\ -\frac{2\,e^{-\frac{\rho\text{max}\,\psi\text{wt}^2}{4}}}{\sqrt{\pi}\,\sqrt{\rho\text{max}}\,\psi},\ -\frac{4\,e^{-\frac{1}{4}\rho\text{max}\left(\psi^2+(\psi-\psi\text{wt})^2\right)}}{\sqrt{\pi}\,\rho\text{max}^{3/2}\,\psi^3}\right\}\ /.\ \rho\text{max}\to\text{mmax}/\lambda\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

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

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

```
Clear[mmax, λ, Es, n, U, mwt]
```

1000.



and for ρmax=10000

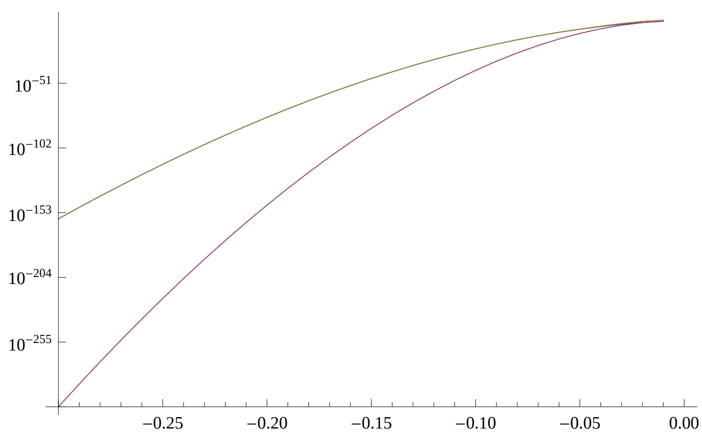
```
U = 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.0001;
n = 4;
m* = Sqrt[Λ1[0, mmax, λ, n, U] / 2];
mmax / λ
```

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

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

```
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

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

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

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

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

And for the large ρmax we need to integrate

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

here we can again use the Laplace approx with

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

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

and we know that q is peaked at

```
Solve[D[q[ψ], ψ] == 0, ψ]
```

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

where h equals

```
h[ψwt / 2]
```

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

giving

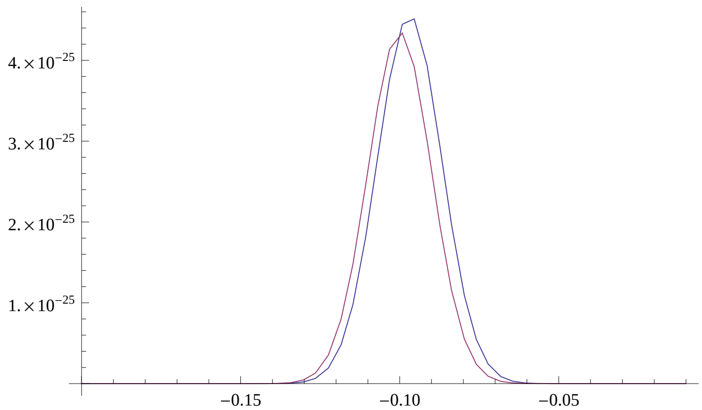
```
h[ψwt / 2] Exp[q[ψ]]
```

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

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

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}]
```

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

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 → 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])
```

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

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

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

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

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

Check formula for text

Simplify$\left[\text{small}\psi\text{approxRescue}\psi == U \frac{\left(1-\frac{\psi\text{wt}}{2}\right)^{1-2\theta}}{\left(1-\frac{\psi\text{wt}}{4}\right)} e^{-\alpha} \frac{\text{Log}\left[\frac{a}{b}\right]}{\pi}\ /.\ \alpha \to \rho\text{max}\,\psi\text{wt}^2 / 4,\ \{a < b < 0\}\right]$

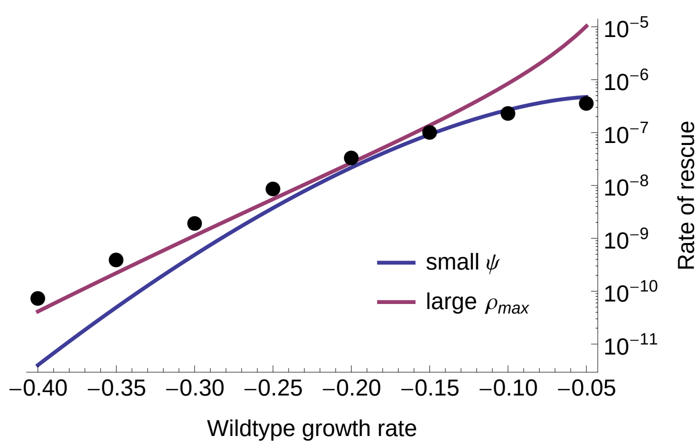
Simplify$\left[\text{verylarge}\rho\text{approxRescue}\psi == \left(-U \frac{\left(1-\frac{\psi\text{wt}}{2}\right)^{1-2\theta}}{\left(1-\frac{\psi\text{wt}}{4}\right)} \left(e^{-\alpha} \frac{1}{(\alpha/2)^3 \pi}\right)^{1/2}\ /.\ \alpha \to \rho\text{max}\,\psi\text{wt}^2 / 4\right),\ \{\rho\text{max} > 0,\ \psi\text{wt} > 0\}\right]$

```
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
```

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

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

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

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

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

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

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

```
True
```

over ψ between ψ^* and 2

```
Clear[m]
```

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

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

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 = $\psi \frac{mmax}{\lambda} = \psi \frac{mmax * n}{2\,Es}$ are really small, giving

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

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

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

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

which has a simple expression

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

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

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 =
```

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

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

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

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.

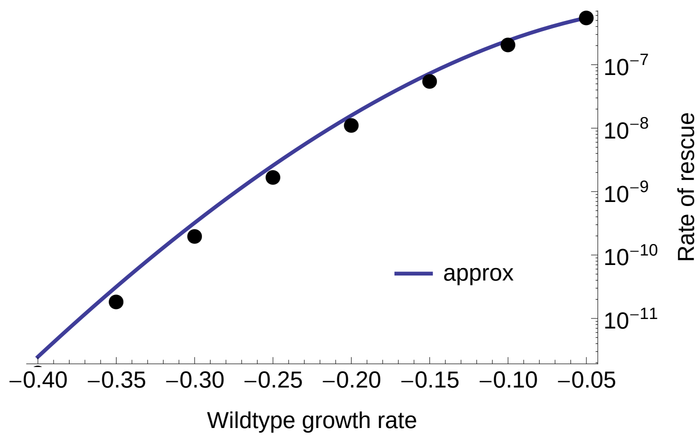
Check formula in text

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

```
True
```

Compare to better approximation

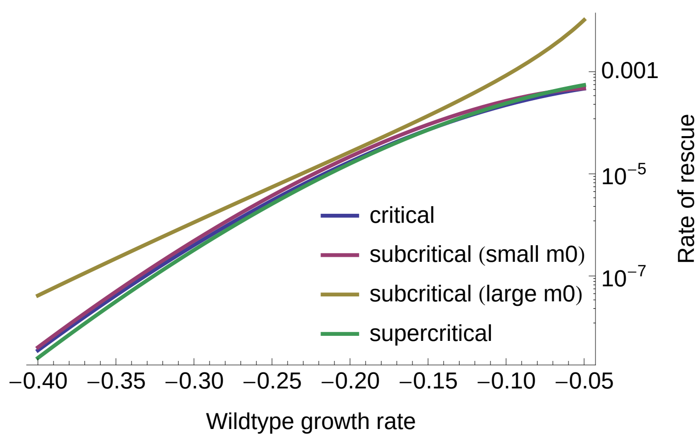
```
n0 = 10^4;
U = 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;

{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\[Psi]approxRescueSuper}, {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)

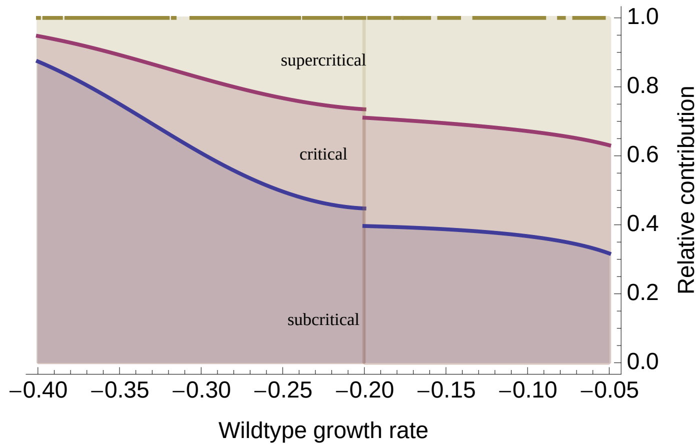
We can now quickly compare the (approximate) rates through each type of 2-step rescue

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

Show[
 LogPlot[
  { 2 Λ0approx fm[0, mwt, mmax, λ, n], smallψapproxRescue,
   verylargeρapproxRescue, smallψapproxRescueSuper}, {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"] & /@
      {"critical", "subcritical (small m0)", "subcritical (large m0)",
       "supercritical"}], Scaled@{3 / 4, 1 / 4}]
 ]
]

Clear[mmax, λ, Es, n, U, n0]
```



or in terms of relative contributions

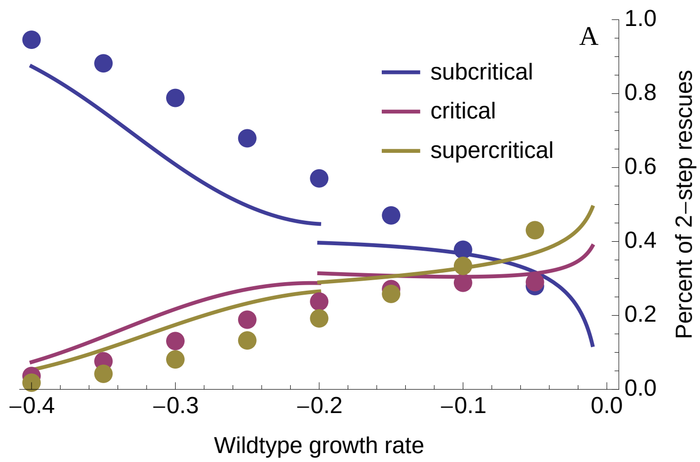
```
n0 = 10^4;
U = 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;

{verylargeρapproxRescue, 2 Λ0approx fm[0, mwt, mmax, λ, n], smallψapproxRescueSuper};
%/Total[%];
Accumulate[%];
largem0plot =
  Plot[
   %, {mwt, -0.8 mmax, -0.2},
   PlotRange → {0, 1},
   PlotStyle → Thick,
   Filling → Bottom,
   Frame → {True, False, False, True},
   FrameLabel → {"Wildtype growth rate", , , "Relative contribution"},
   FrameTicks → {True, False, False, All},
   LabelStyle → labelstyle
  ];

{smallψapproxRescue, 2 Λ0approx fm[0, mwt, mmax, λ, n], smallψapproxRescueSuper};
%/Total[%];
Accumulate[%];
smallm0plot =
  Plot[
   %, {mwt, -0.2, -0.1 mmax},
   PlotRange → {0, 1},
   PlotStyle → Thick,
   Filling → Bottom,
   Frame → {True, False, False, True},
   FrameLabel → {"Wildtype growth rate", , , "Relative contribution"},
   FrameTicks → {True, False, False, All},
   LabelStyle → labelstyle
  ];

Show[largem0plot, smallm0plot, PlotRange → All,
 Epilog → {
   Text["subcritical", Scaled@{0.5, 0.15}],
   Text["critical", Scaled@{0.5, 0.6}],
   Text["supercritical", Scaled@{0.5, 0.85}]
  }
]

Clear[mmax, λ, Es, n, U, n0]
```



Compare with better approximations

```
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];

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

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

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

```
  %
------- ;
Total[%]

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

Export[imagedir <> "p2RelContrGrowth.pdf", %];

Clear[mmax, λ, Es, n, U, n0]
```

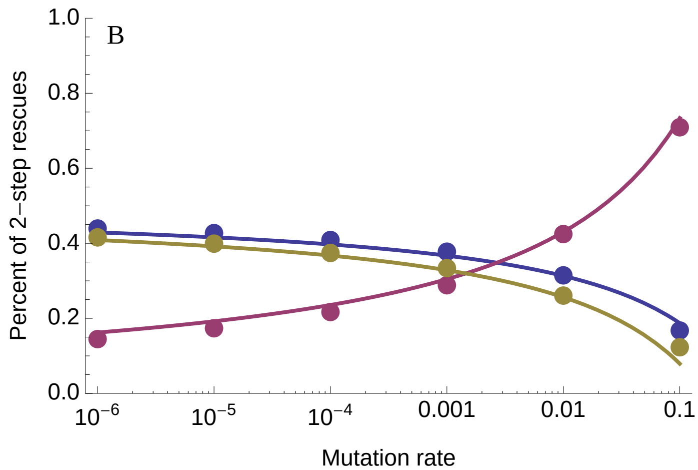


or across mutation rate for a given m0

```
n0 = 10^4;
mwt = -0.1;
```

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

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

temptab2 = Table[
   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];
   {
    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[2 Λ1[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[%];
(*Accumulate[%]*)
data = Table[Transpose[Join[{xs}, {%[[i]]}, 1]], {i, Length[%]}];

Clear[U]
{smallψapproxRescue(*verylargeρapproxRescue*),
  2 Λ0approx fm[0, mwt, mmax, λ, n] , smallψapproxRescueSuper};
% / Total[%];
(*Accumulate[%];*)
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], Scaled@{0.05, 0.95}]
```

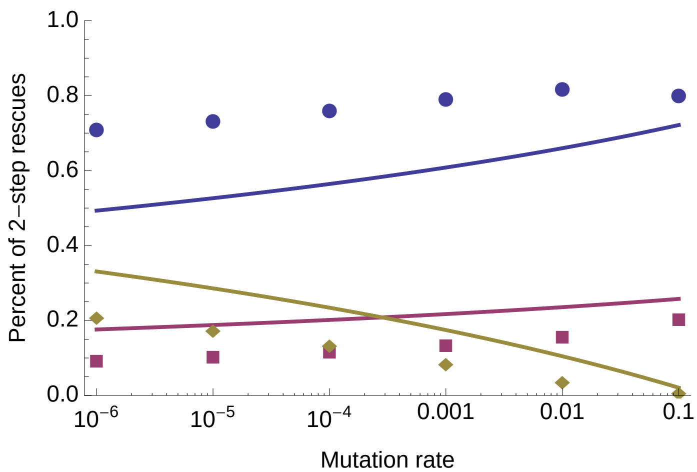
```
 ],
 ListLogLinearPlot[data,
  PlotMarkers → {Graphics[{defaultcolors[[1]], Disk[]}, ImageSize → 10],
    Graphics[{defaultcolors[[2]], Disk[]}, ImageSize → 10],
    Graphics[{defaultcolors[[3]], Disk[]}, ImageSize → 10]}, PlotRange → {0, 1}]
]

Export[imagedir <> "p2RelContrMutationSlow.pdf", %];

Clear[mmax, λ, Es, n, mwt, n0, U]
```



and with a more negative m0 we use the other subcritical approximation

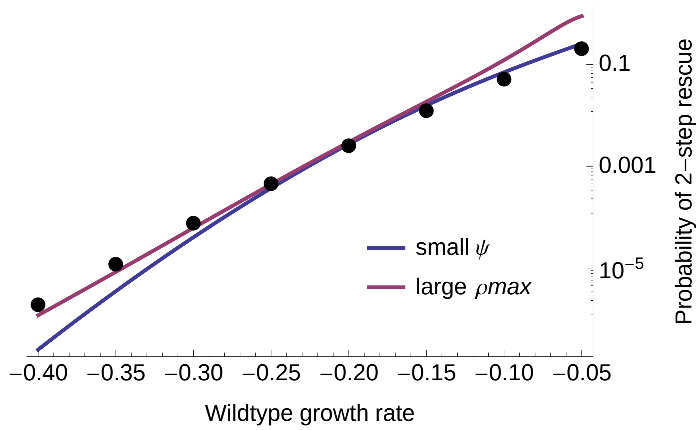
```
n0 = 10^4;
mwt = -0.3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
U = 10^x;

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

temptab3 = Table[
   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];
   {
    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[2 Λ1[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}];
temptab3;
Table[%[[i]] / Total[%[[i]]], {i, Length[%]}];
test = Transpose[%];
(*Accumulate[%]*)
data = Table[Transpose[Join[{xs}, {%[[i]]}, 1]], {i, Length[%]}];

Clear[U]
{verylargeρapproxRescue,
  2 Λ0approx fm[0, mwt, mmax, λ, n] , smallψapproxRescueSuper};
   %
--------;
Total[%]
(*Accumulate[%];*)
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
 ],
 ListLogLinearPlot[data, PlotMarkers → {Automatic, Medium}, PlotRange → {0, 1}]
]

Clear[mmax, λ, Es, n, mwt, n0, U]
```



And we can sum the rates to get the total probability of rescue

```
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];

tab = {
   Table[{
     mwt,
     prescue /. p0 → prescuem[mwt, U NIntegrate[fm[m1, mwt, mmax, λ, n]
            (1 - pest[m1]) prescuem[m1, Λ1[m1, mmax, λ, n, U]], {m1, -∞, mmax}]]
    }, {mwt, -0.8 mmax, -0.1 mmax, 0.1 mmax}]
  };

{
  prescue /. p0 → prescuem[mwt, U Total[{ 2 Λ0approx fm[0, mwt, mmax, λ, n],
        smallψapproxRescue, smallψapproxRescueSuper}]],
  prescue /. p0 → prescuem[mwt, U Total[{ 2 Λ0approx fm[0, mwt, mmax, λ, n],
        verylargeρapproxRescue, smallψapproxRescueSuper}]]
 };
Show[
 LogPlot[
  {%,}, {mwt, -0.8 mmax, -0.1 mmax},
  PlotStyle → Thick,
  Frame → {True, False, False, True},
  FrameLabel → {"Wildtype growth rate", , , "Probability of 2-step 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[tab, PlotMarkers → {Automatic, Medium}, PlotStyle → Black]
]

Clear[mmax, λ, Es, n, U, N0]
```



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

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

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

$$\text{h}[\psi\_] := \left(\frac{1-\psi/2}{1-\psi\text{wt}/2}\right)^{\theta-\frac{1}{2}} \left(1-e^{-2\,\text{mmax}\,y}\right) \text{ /. } y \to \psi\,(1-\psi/4)$$

$$\text{q}[\psi\_] := \frac{1}{4}(\psi-\psi\text{wt})^2$$

h0 = Normal[Series[h[ψ], {ψ, 0, 1}]];

$$\text{g1mapprox} = \text{Simplify}\left[\frac{\frac{\text{U}}{-\text{mwt}}\,\frac{\sqrt{\rho\text{max}}}{2\sqrt{\pi}}\,\text{h0 Exp}[-\rho\text{max q}[\psi]]}{\text{AnciauxEqnA12}} \text{ /. mwt} \to \text{mmax }(4-\psi\text{wt})\,\psi\text{wt}/4,\ \{\psi\text{wt}<0,\ \alpha>0,\ \rho\text{max}>0\}\right]$$

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

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

$$\text{scaleg1approx} = \text{D}\left[2\left(1-\sqrt{1-\frac{\text{m}}{\text{mmax}}}\right), \text{m}\right]$$

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

giving

```
g1mApp = scaleg1approx g1mapprox;
```

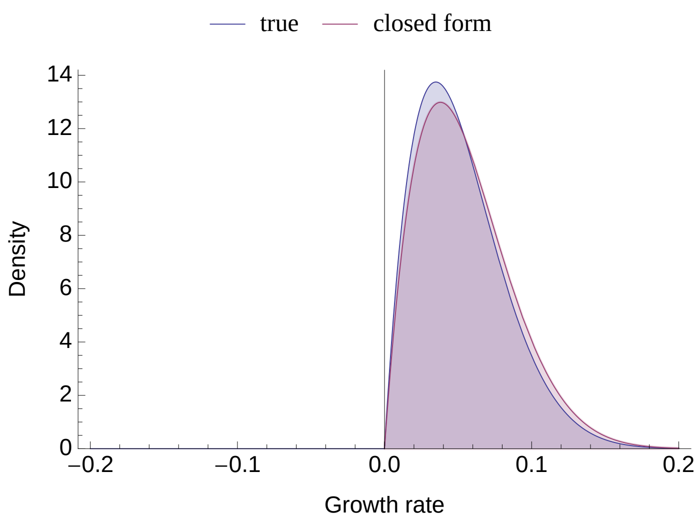
Numerically compare

```
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]);
```

$$\} \;/.\; \alpha \to \psi wt^2\, \rho max / 4 \;/.\; \rho max \to mmax / \lambda \;/.\; \theta \to n/2 \;/.\; \psi wt \to 2\left(1 - \sqrt{1 - \frac{mwt}{mmax}}\right) \;/.\; \psi \to 2\left(1 - \sqrt{1 - \frac{m}{mmax}}\right);$$

```
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,

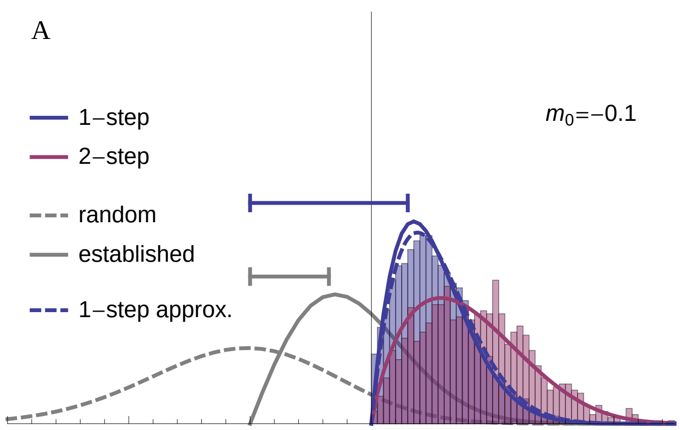
```
g2denominator[m0_?NumericQ] := NIntegrate[U fm[m, m0, mmax, λ, n] (1 - pest[m])
    prescuem[m, U fm[m2, m, mmax, λ, n] pest[m2]], {m, -∞, mmax}, {m2, 0, mmax}];
```

Plot growth rates of rescue genotypes (figure 6)

```
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}];

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], 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}}]}
  }
]

Export[imagedir <> "2step_m2_smallm0_sims.pdf", %];

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. ≫

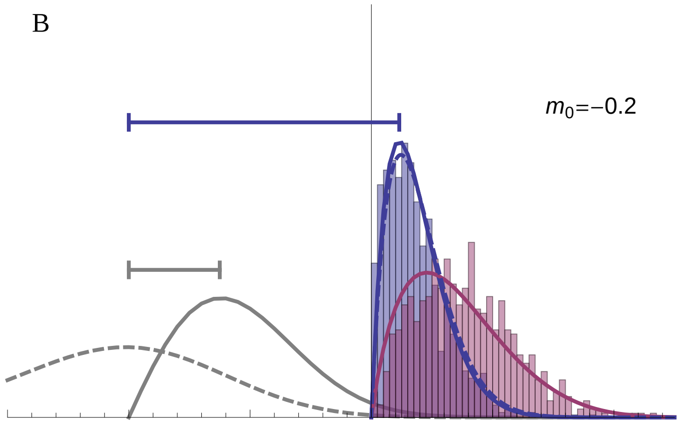



```
U = 2 * 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
mwt = -0.2;
```

```
{
  (*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}];

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], 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}}]}
  }
]

Export[imagedir <> "2step_m2_medm0_sims.pdf", %];

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}]
```

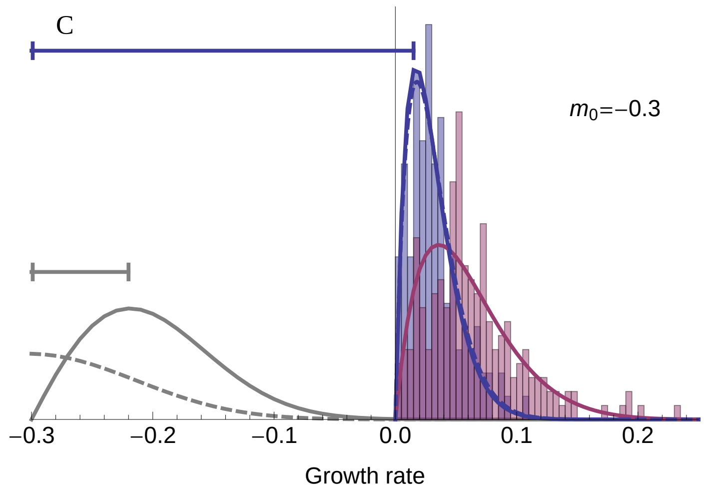
```
 };
theory = ListPlot[%, PlotRange → All,
   Joined → True, PlotStyle → Thick, PerformanceGoal → "Speed"];
```

$$\text{g1mApp /. } \alpha \to \psi\text{wt}^2\,\rho\text{max} / 4 \text{ /. } \rho\text{max} \to \text{mmax} / \lambda \text{ /. } \theta \to \text{n} / 2 \text{ /. } \psi\text{wt} \to 2\left(1 - \sqrt{1 - \frac{\text{mwt}}{\text{mmax}}}\right) \text{ /.}$$

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

```
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}];

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], 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}}]}
  }
]

Export[imagedir <> "2step_m2_largem0_sims.pdf", %];

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]
```

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

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

$$\text{Integrate}[\text{small}\psi\text{approx}, \{\psi, a, b\}, \text{Assumptions} \to \{a < b < 0\}];$$

$$\frac{\text{small}\psi\text{approx}}{\%}$$

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

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

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

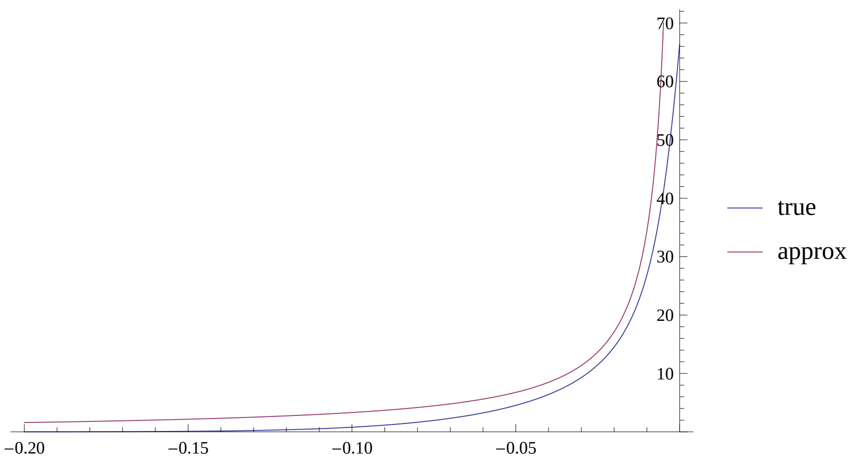
$$\frac{1}{\psi\,\text{Log}\left[\frac{b}{a}\right]}$$

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

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, Δ1[m, mmax, λ, n, U]], {m, -∞, 0}];

Show[
 Plot[1/total U fm[m, mwt, mmax, λ, n] (1 - pest[m]) prescuem[m, Δ1[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]
```

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



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}]
```

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

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

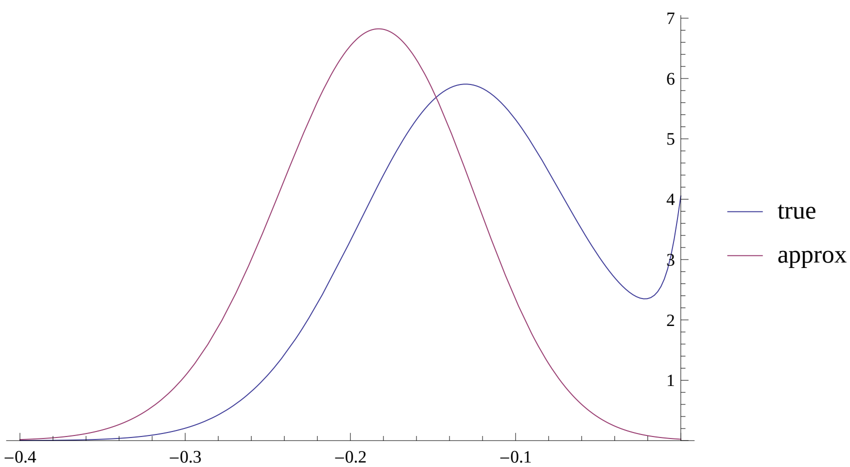
Compare distribution of subcriticals

$$
\begin{aligned}
&\mathbf{U} = \mathbf{10}^{-3};\\
&\mathbf{mmax} = \mathbf{0.5};\\
&\lambda = \mathbf{2\,Es} / \mathbf{n};\\
&\mathbf{Es} = \mathbf{0.01};\\
&\mathbf{n} = \mathbf{4};\\
&\mathbf{mwt} = -\mathbf{0.4};
\end{aligned}
$$

$$
\begin{aligned}
&\mathbf{total} = \mathbf{U\ NIntegrate}[\\
&\quad \mathbf{fm}[\mathrm{m}, \mathrm{mwt}, \mathrm{mmax}, \lambda, \mathrm{n}]\ (1 - \mathbf{pest}[\mathrm{m}])\ \mathbf{prescuem}[\mathrm{m}, \Delta 1[\mathrm{m}, \mathrm{mmax}, \lambda, \mathrm{n}, \mathrm{U}]], \{\mathrm{m}, -\infty, 0\}];
\end{aligned}
$$

$$
\begin{aligned}
&\mathbf{Show}\Big[\\
&\ \mathbf{Plot}\Big[\frac{1}{\mathrm{total}}\mathrm{U}\ \mathrm{fm}[\mathrm{m}, \mathrm{mwt}, \mathrm{mmax}, \lambda, \mathrm{n}]\ (1 - \mathrm{pest}[\mathrm{m}])\ \mathrm{prescuem}[\mathrm{m}, \Delta 1[\mathrm{m}, \mathrm{mmax}, \lambda, \mathrm{n}, \mathrm{U}]],\\
&\quad \{\mathrm{m}, -0.4, 0\}, \mathrm{PerformanceGoal} \to \text{"Speed"}, \mathrm{PlotRange} \to \{0, \mathrm{All}\}\Big],\\
&\ \mathbf{Plot}\Big[\Big\{, \frac{1}{\sqrt{1 - \frac{\mathrm{m}}{\mathrm{mmax}}}\ \mathrm{mmax}}\left(e^{\frac{4\,\mathrm{m} + \mathrm{mwt} + \mathrm{mmax}\left(-6 + 4\sqrt{1 - \frac{\mathrm{m}}{\mathrm{mmax}}} - 2\sqrt{1 - \frac{\mathrm{mwt}}{\mathrm{mmax}}} + 4\sqrt{1 - \frac{\mathrm{m}}{\mathrm{mmax}}}\ \sqrt{1 - \frac{\mathrm{mwt}}{\mathrm{mmax}}}\right)}{2\,\lambda}}\sqrt{\frac{2}{\pi}}\ \sqrt{\frac{\mathrm{mmax}}{\lambda}}\right)\Big/\\
&\qquad \mathrm{Erfc}\left[\frac{\left(1 - \sqrt{1 - \frac{\mathrm{mwt}}{\mathrm{mmax}}}\right)\sqrt{\frac{\mathrm{mmax}}{\lambda}}}{\sqrt{2}}\right]\Big\}, \{\mathrm{m}, -0.4, 0\},\\
&\quad \mathrm{PlotRange} \to \{0, 70\}, \mathrm{PlotLegends} \to \{\text{"true"}, \text{"approx"}\}\Big]\\
&\Big]
\end{aligned}
$$

$$
\mathbf{Clear}[\mathrm{mmax}, \lambda, \mathrm{Es}, \mathrm{n}, \mathrm{U}, \mathrm{mwt}]
$$



Our sufficiently critical approximation is

```
fm[0, m0, mmax, λ, n] /. n -> Sqrt[2 (2 U Sqrt[mmax λ])/Sqrt[π]];
```

$$\texttt{fm[0, m0, mmax, }\lambda\texttt{, n]}\ \sqrt{2\,\frac{2\,U\,\sqrt{\text{mmax}\,\lambda}}{\sqrt{\pi}}}\ ;$$

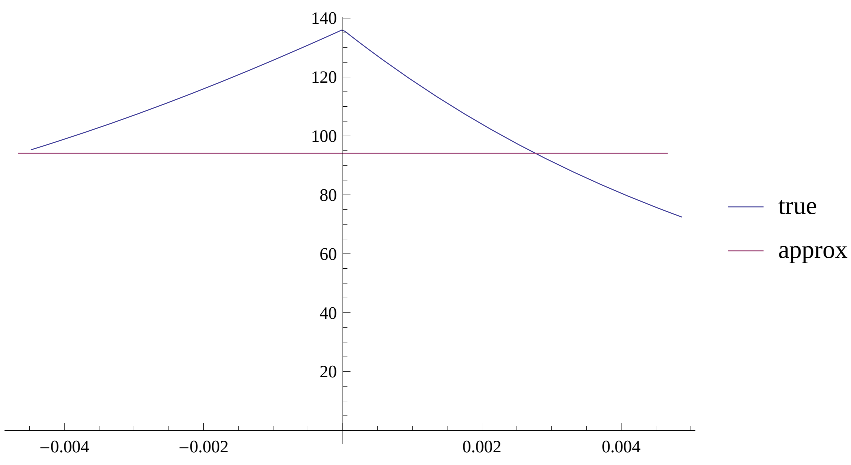
$$\texttt{Integrate}\left[\%,\ \left\{m,\ -\sqrt{\frac{U\,\sqrt{\text{mmax}\,\lambda}}{\sqrt{\pi}}},\ \sqrt{\frac{U\,\sqrt{\text{mmax}\,\lambda}}{\sqrt{\pi}}}\right\}\right];$$

```
Simplify[%% / %, {mmax > 0, λ > 0}]
```

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

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

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

$$\texttt{Integrate}[\texttt{small}\psi\texttt{approx}, \{\psi, a, b\}, \texttt{Assumptions} \to \{0 < a < b\}];$$

$$\frac{\texttt{small}\psi\texttt{approx}}{\%}$$

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

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

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

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

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

Note this is good only to

$$\texttt{Solve}\left[\frac{\sqrt{2}}{\sqrt{\rho\texttt{max}}} == 2\left(1-\sqrt{1-\frac{m}{\texttt{mmax}}}\right), m\right] \texttt{ /. } \rho\texttt{max} \to \texttt{mmax}/\lambda \texttt{ // Simplify}$$

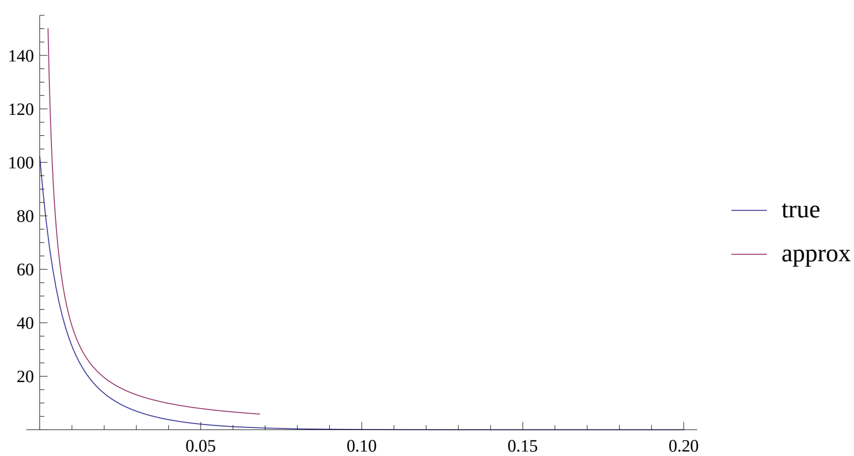
$$\left\{\left\{m \to \left(-\frac{1}{2}+\sqrt{2}\,\sqrt{\frac{\texttt{mmax}}{\lambda}}\right)\lambda\right\}\right\}$$

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, Δ1[m, mmax, λ, n, U]], {m, 0, mmax}];

Show[
 Plot[1/total U fm[m, mwt, mmax, λ, n] (1 - pest[m]) prescuem[m, Δ1[m, mmax, λ, n, U]],
  {m, 0, 0.2}, PerformanceGoal → "Speed", PlotRange → {0, All}],
```

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

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

Clear[mmax, λ, Es, n, U, mwt]
```

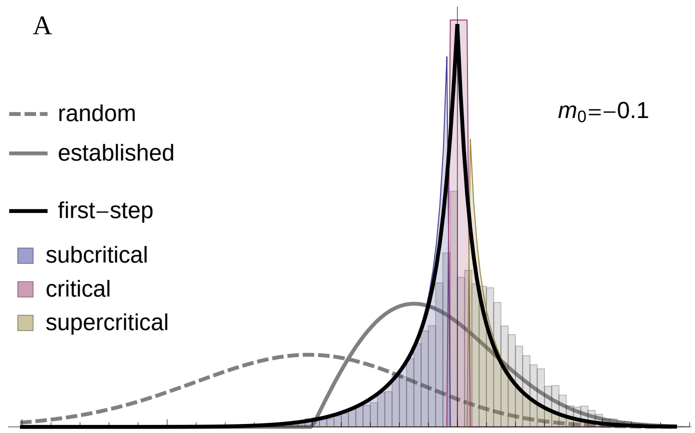


Plot growth rates of rescue intermediates

As function of wildtype growth rate (figure 7)

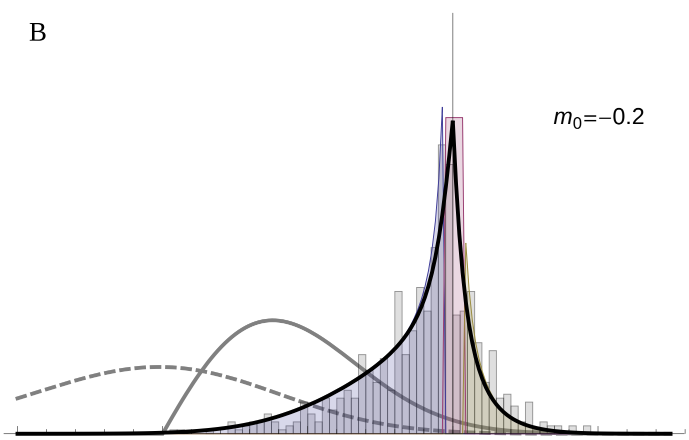
```
xmin = -0.3;
xmax = 0.15;
ymax = 30;

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]]];

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], Scaled@{0.05, 0.95}]}
]

Export[imagedir <> "firststep_smallm0_regimes.pdf", %];

Clear[mmax, λ, Es, n, U, mwt]
```



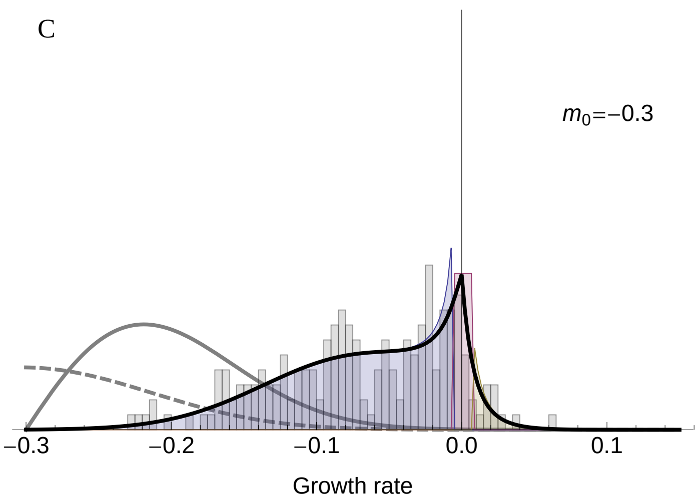

```
U = 2 * 10^-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
mwt = -0.2;

{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]]];

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], Scaled@{0.05, 0.95}]}
]

Export[imagedir <> "firststep_medm0_regimes.pdf", %];

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]]];

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], Scaled@{0.05, 0.95}]}
]

Export[imagedir <> "firststep_largem0_regimes.pdf", %];

Clear[mmax, λ, Es, n, U, mwt]
```

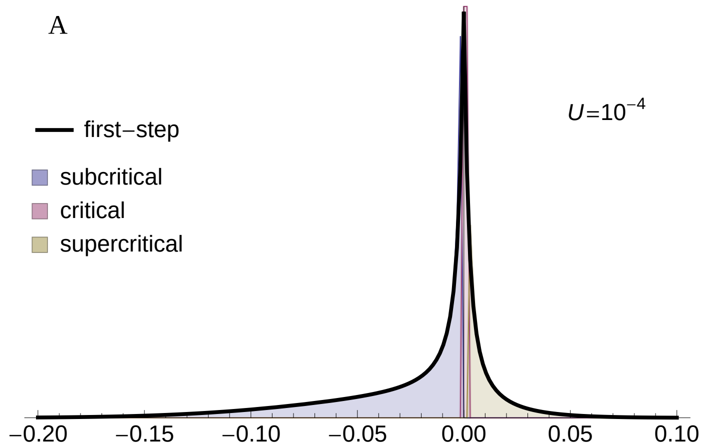



```
Clear[ymax, xmin, xmax]
```

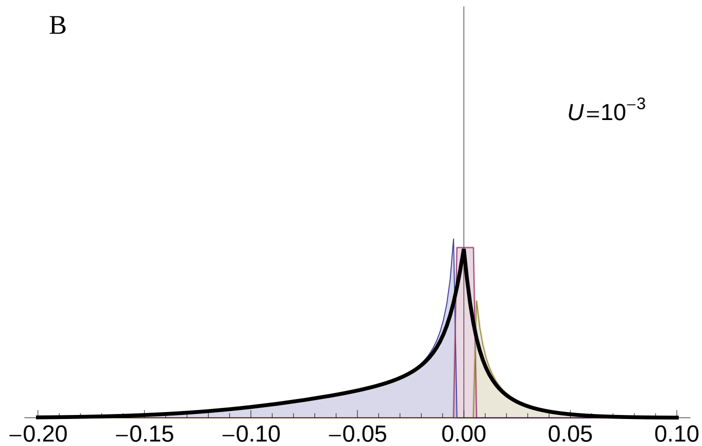
As function of mutation (figure S2)

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

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

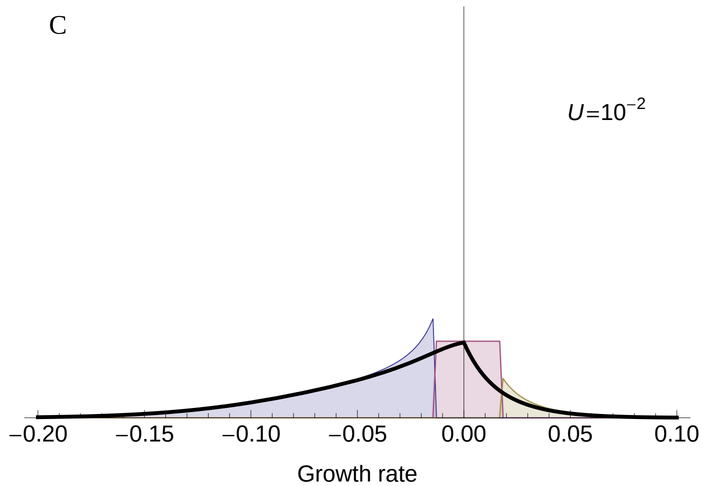
```
mwt = -0.2;

{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}];

Show[
 Plot[
  {subcritical / total, critical / total, supercritical / total},
  {m1, xmin, xmax},
  PlotRange → {0, All},
  (*PlotStyle→Thick,*)
  Filling → Bottom,
  Frame → {True, False, False, False},
  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], 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}}
]

Export[imagedir <> "firststep_smallU.pdf", %];

Clear[mmax, λ, Es, n, U, mwt]
```


A
first−step
subcritical
critical
supercritical
U=10^−4
−0.20
−0.15
−0.10
−0.05
0.00
0.05
0.10

```
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}];

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

Export[imagedir <> "firststep_medU.pdf", %];

Clear[mmax, λ, Es, n, U, mwt]
```


B
U=10^{-3}
–0.20
–0.15
–0.10
–0.05
0.00
0.05
0.10

```
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}];

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], 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}}
]

Export[imagedir <> "firststep_largeU.pdf", %];

Clear[mmax, λ, Es, n, U, mwt]
```



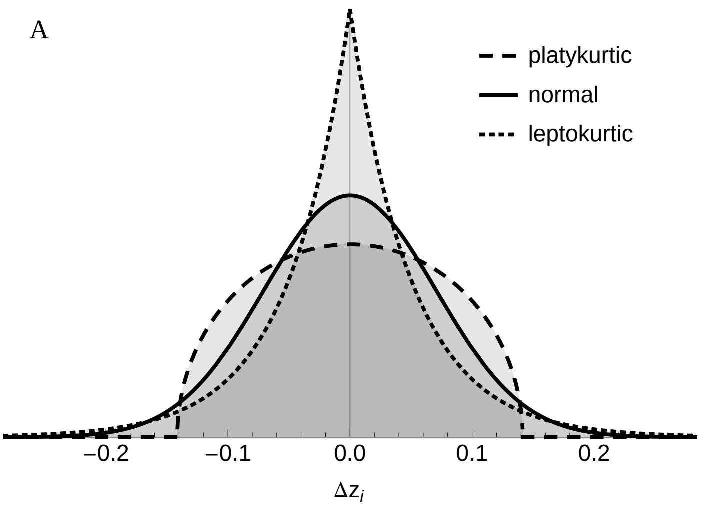

```
Clear[ymax, xmin, xmax]
```

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]};
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 → {"Δzi"},
 FrameStyle → labelstyle,
 PlotRangePadding → None,
 Epilog → {Text[Style["A", 14, Bold], Scaled@{0.05, 0.95}]}
]

Export[imagedir <> "mutational_distns.pdf", %];

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)

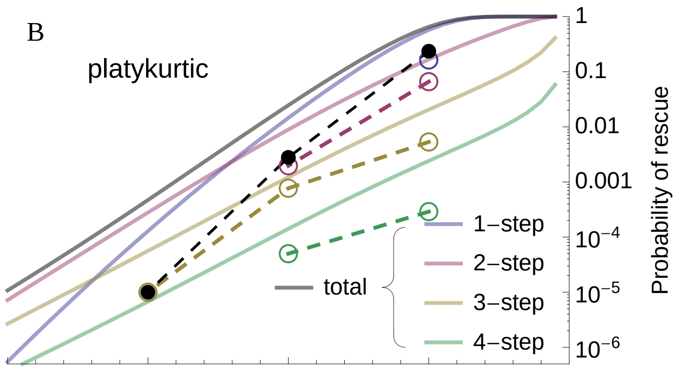
```
N0 = 10^4;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
U = 2 * 10^-3;

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]
```

Platykurtic (semicircle)

```
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]
     }
   ];

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], Scaled@{0.05, 0.95}],
```

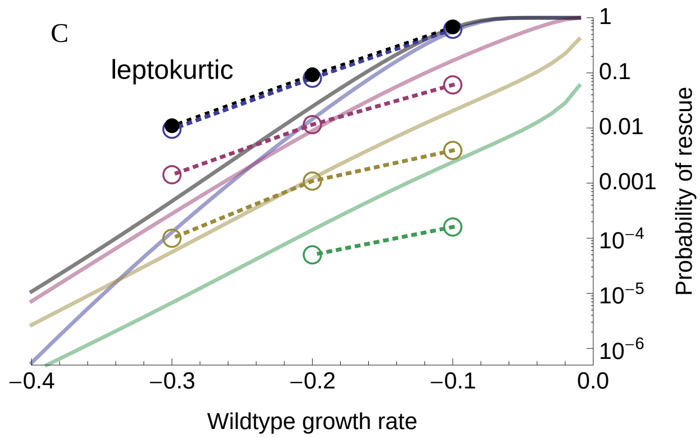
```
    Text[Style["platykurtic", 14, FontFamily → "Helvetica"],
     Scaled@{0.25, 0.85}], {Opacity[0.5],
     braceLabel[{{-0.125, Log@10^-6}, {-0.125, Log@(1.5 * 10^-4)}}, Style["", Larger]]}
   }
]

Export[imagedir <> "platy_prob.pdf", %];

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



Leptokurtic (Laplace)

```
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]
     }
   ];

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], Scaled@{0.05, 0.95}],
   Text[Style["leptokurtic", 14, FontFamily → "Helvetica"], Scaled@{0.25, 0.85}]
  }
]

Export[imagedir <> "lepto_prob.pdf", %];

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



Rescue genotype growth rate (figure S4)

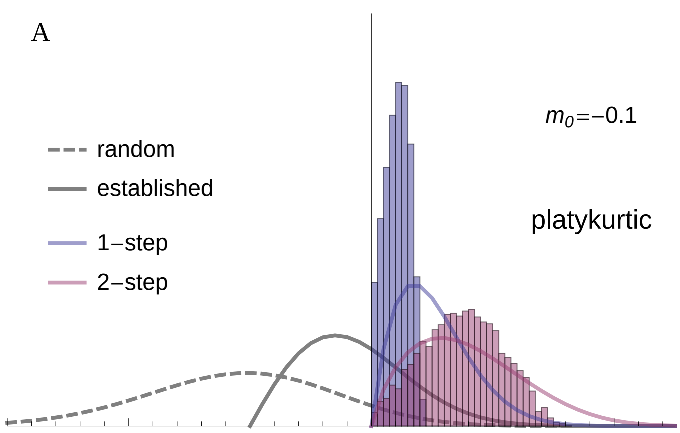
Platykurtic (semicircle)

```
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}];

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], Scaled@{0.05, 0.95}],
   Text[Style["platykurtic", 14, FontFamily → "Helvetica"], Scaled@{7 / 8, 1 / 2}]
  }
]

Export[imagedir <> "dfe_platy_mild.pdf", %];

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. ≫

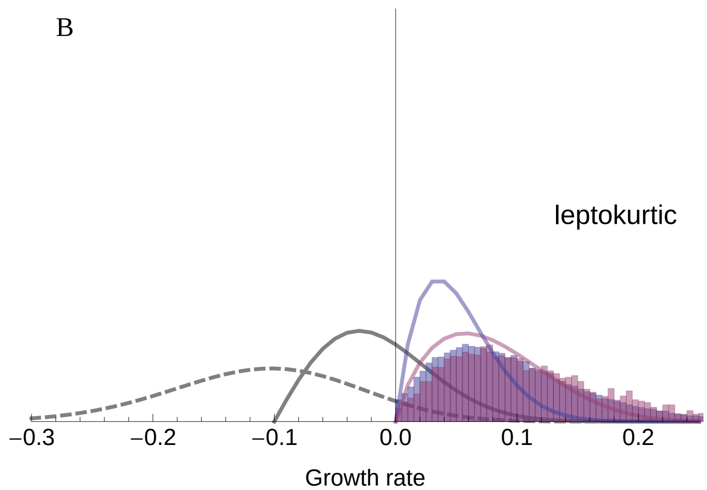


Leptokurtic (Laplace)

```
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}];

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], Scaled@{0.05, 0.95}],
   Text[Style["leptokurtic", 14, FontFamily → "Helvetica"], Scaled@{7 / 8, 1 / 2}]
  }
]

Export[imagedir <> "dfe_lepto_mild.pdf", %];

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. ≫



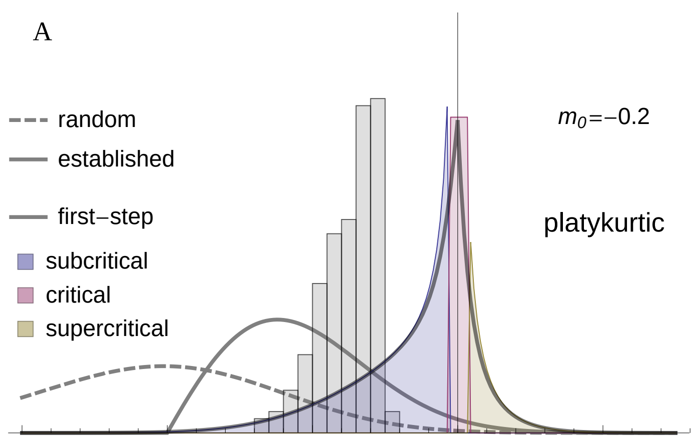
2-step intermediate growth rate (figure S5)

Platykurtic (semicircle)

```
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]]];

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], Scaled@{0.05, 0.95}],
    Text[Style["platykurtic", 14, FontFamily → "Helvetica"], Scaled@{7 / 8, 1 / 2}]
  }
]

Export[imagedir <> "dfe_platy_med_int.pdf", %];

Clear[mmax, λ, Es, n, U, mwt]
```

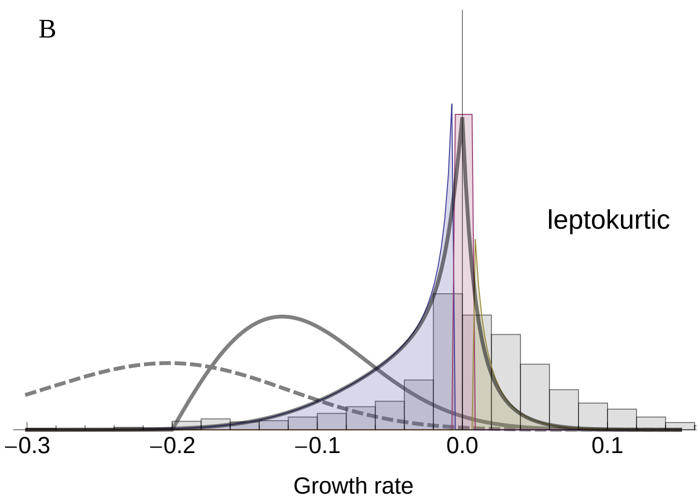


Leptokurtic (Laplace)

```
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]]];

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], Scaled@{0.05, 0.95}],
   Text[Style["leptokurtic", 14, FontFamily → "Helvetica"], Scaled@{7 / 8, 1 / 2}]
  }
]

Export[imagedir <> "dfe_lepto_med_int.pdf", %];

Clear[mmax, λ, Es, n, U, mwt]
```



Dimensionality, n

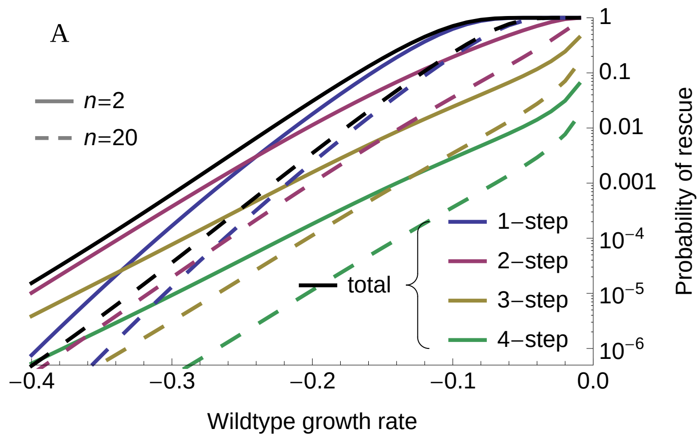
Probability of rescue (figure S6A)

Numerical data

```
N0 = 10^4;
mmax = 0.5;
λ = 2 Es / 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, Δ4Interpolated[m0, mmax, λ, n, U]}, {m0, m0min, m0max, mstep}];
rate3 = Table[{m0, Δ3Interpolated[m0, mmax, λ, n, U]}, {m0, m0min, m0max, mstep}];
rate2 = Table[{m0, Δ2Interpolated[m0, mmax, λ, n, U]}, {m0, m0min, m0max, mstep}];
rate1 = Table[{m0, Δ1Interpolated[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, Δ4Interpolated[m0, mmax, λ, n, U]}, {m0, m0min, m0max, mstep}];
rate3 = Table[{m0, Δ3Interpolated[m0, mmax, λ, n, U]}, {m0, m0min, m0max, mstep}];
rate2 = Table[{m0, Δ2Interpolated[m0, mmax, λ, n, U]}, {m0, m0min, m0max, mstep}];
rate1 = Table[{m0, Δ1Interpolated[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]
```

Plot

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

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], Scaled@{0.05, 0.95}],
   braceLabel[{{-0.125, Log@10^-6}, {-0.125, Log@(2 * 10^-4)}}, Style["", Larger]]
  }
]

Export[imagedir <> "prob_diffn.pdf", %];

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



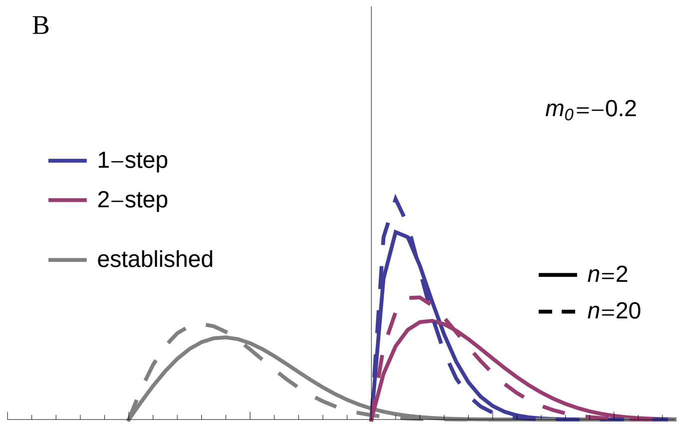
Rescue genotype growth rate (figure S6B)

```
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}]];

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}]
  }
]

Export[imagedir <> "dfe_diffn.pdf", %];

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. ≫

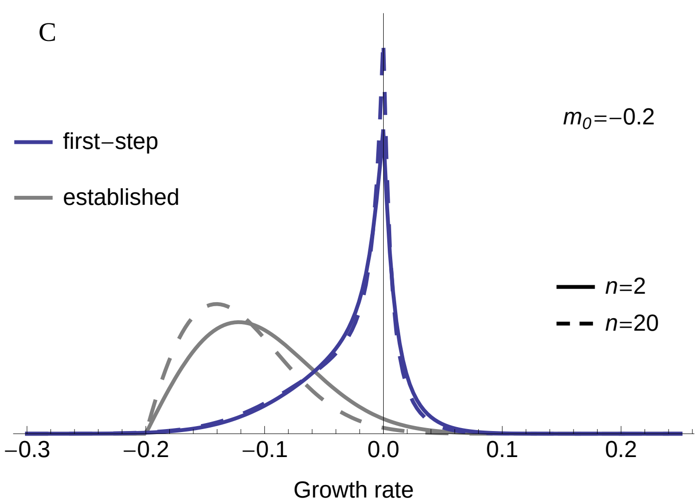
NIntegrate::izero :
Integral and error estimates are 0 on all integration subregions. Try increasing the value of the MinRecursion option. If value of integral may be 0, specify a finite value for the AccuracyGoal option. ≫



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, Δ1[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, Δ1[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"] & /@ {"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], Scaled@{0.05, 0.95}]
   }
]

Export[imagedir <> "dfe_int_diffn.pdf", %];

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



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. ≫

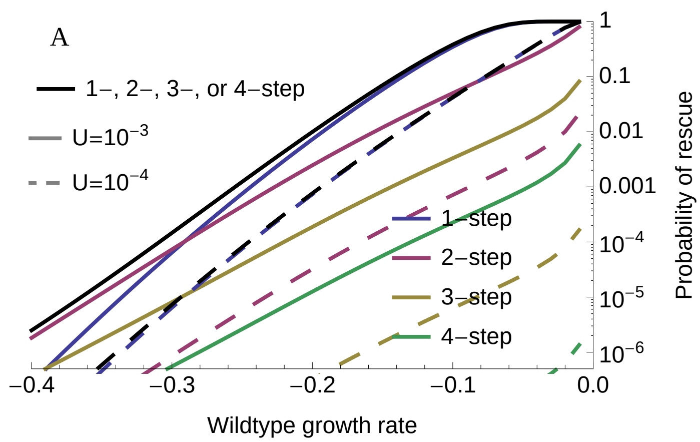
General::stop : Further output of NIntegrate::ncvb will be suppressed during this calculation. ≫

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*)
```

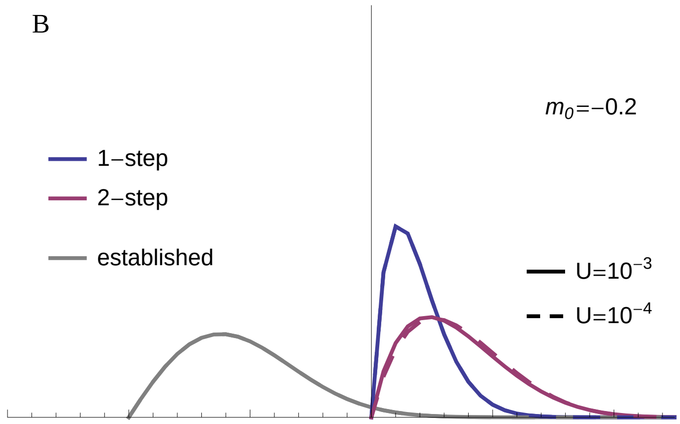
```
  Table[{m2, (fm[m2, mwt, mmax, λ, n] pest[m2 - mwt]) / NIntegrate[
      fm[m2, mwt, mmax, λ, n] pest[m2 - mwt], {m2, mwt, mmax}]}, {m2, mwt, xmax, xint}]
 };
oldtheory2 = ListPlot[%, PlotRange → All, Joined → True,
   PlotStyle → Directive[Thick, Gray], PerformanceGoal → "Speed", PlotLegends →
    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. ≫

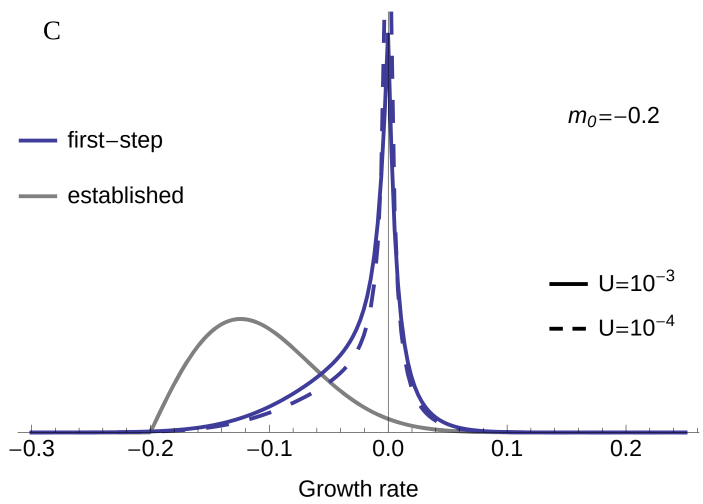
NIntegrate::izero :
Integral and error estimates are 0 on all integration subregions. Try increasing the value of the MinRecursion option. If value of integral may be 0, specify a finite value for the AccuracyGoal option. ≫



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. ≫

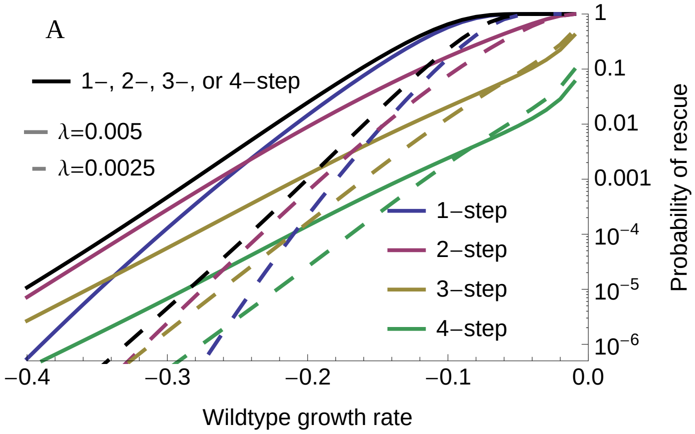
General::stop : Further output of NIntegrate::ncvb will be suppressed during this calculation. ≫

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;
```

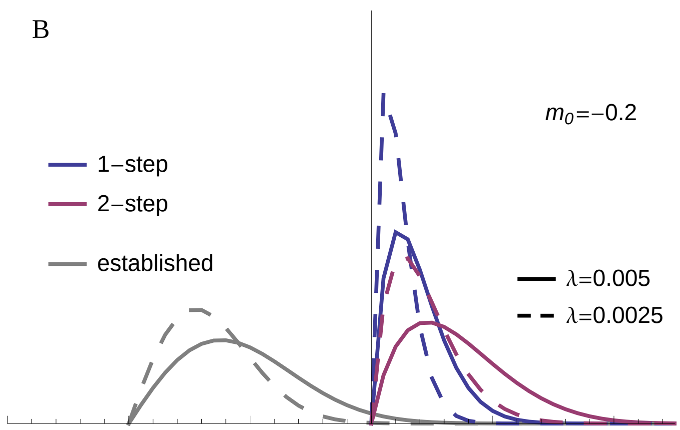
```
ymax = 40;
xint = 0.01;

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, Δ1[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, Δ1[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]
```