

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

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Dependencies

Directories

```
In[1]:= SetDirectory[NotebookDirectory[]];
(*sets current directory to be location of this file*)
imagedir = "../IMAGES/";(*directory to save figures in*)
datadir = "../SOM/SIM_DATA/";(*directory with simulation data*)
```

Plot styles

```
In[4]:= labelstyle = Directive[12, FontFamily -> "Helvetica"];
defaultcolors = ColorData[1, "ColorList"];
```

Functions (derived below)

```
In[6]:= fs[s_, so_, λ_, n_] :=
  
$$\frac{2}{\lambda} \text{PDF}\left[\text{NoncentralChiSquareDistribution}\left[n, \frac{2 \text{so}}{\lambda}\right], \frac{2}{\lambda} (\text{so} - s)\right] \text{HeavisideTheta}[\text{so} - s]$$

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

prescue = 1 - (1 - p0)N0;
prescueApp = 1 - e-N0 p0;

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

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

```

 $\Lambda 1[m0\_?NumericQ, mmax_, \lambda_, n_, U_] :=$ 
  UNIntegrate[fm[m, m0, mmax,  $\lambda$ , n] pest[m], {m, 0, mmax}]
PR1[m0_?NumericQ] := prescue /. p0  $\rightarrow$  prescuem[m0,  $\Lambda 1[m0, mmax, \lambda, n, U]$ ]
PR1App[m0_?NumericQ] := prescueApp /. p0  $\rightarrow$  prescuem[m0,  $\Lambda 1[m0, mmax, \lambda, n, U]$ ]

```

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

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

```

 $\Lambda 2[m0\_?NumericQ, mmax_, \lambda_, n_, U_] :=$  UNIntegrate[
  fm[m, m0, mmax,  $\lambda$ , n] (1 - pest[m]) prescuem[m,  $\Lambda 1[m, mmax, \lambda, n, U]$ ], {m, - $\infty$ , mmax}]

```

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

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

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

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

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

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

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

```

g1m =  $\frac{U \text{fm}[m, \text{mwt}, \text{mmax}, \lambda, n] \text{pest}[m]}{\Lambda 1[\text{mwt}, \text{mmax}, \lambda, n, U]}$ ;
g2numerator[m0_, m2_?NumericQ] := UNIntegrate[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}
];

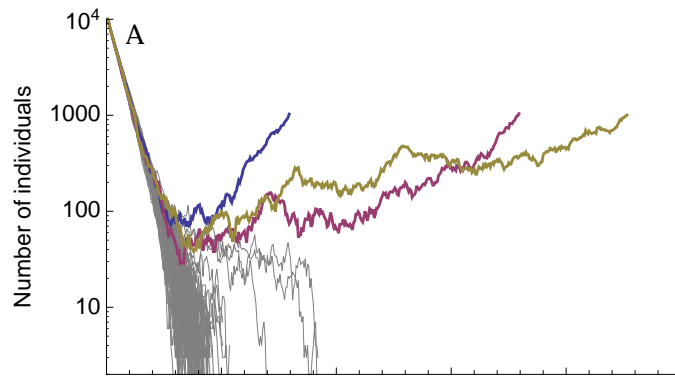
rescued = Select[data, #[[-1]] > 1000 &];
extinct = Select[data, #[[-1]] < 1000 &];

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, 104}}
]
(*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[%]];

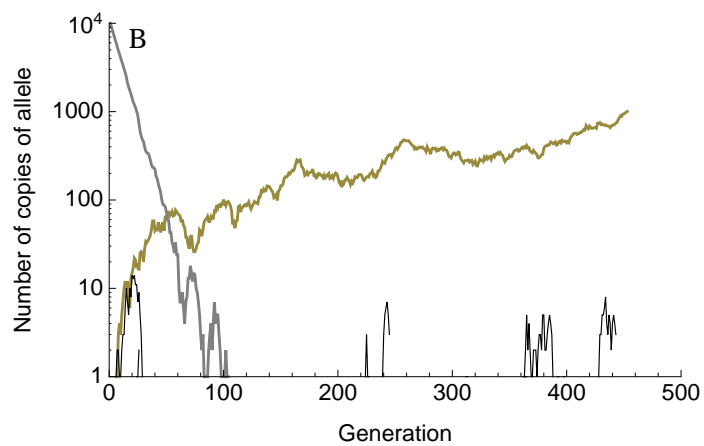
Import[datadir <> "kmuts_N" <> n0 <> "_n" <> n <> "_U" <> U <> "_Es" <> Es <> "_mmax" <>
  mmax <> "_mwt" <> mwt <> "_mutmax" <> mutmax <> "_rep" <> rep <> ".csv"];
allmut = Transpose[PadRight[%]];

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[
    allmut[[1]],
    Joined -> True,
    PlotStyle -> {Gray, Thickness[0.005]}
  ]
]
(*Export[imagedir<>"VshapeMutations.pdf",%];*)

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

```



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}
];

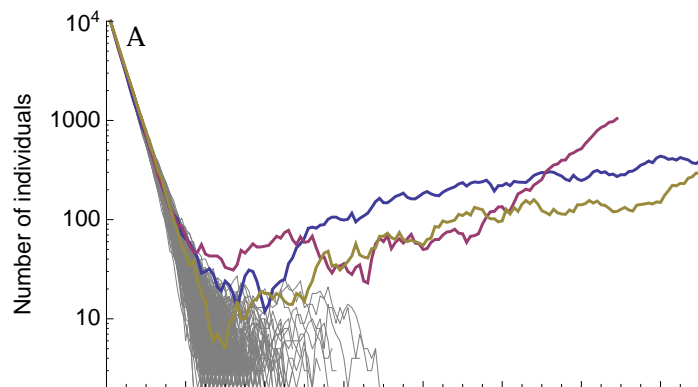
rescued = Select[data, #[[-1]] > 1000 &];
extinct = Select[data, #[[-1]] < 1000 &];

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]

```

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 = 104;

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

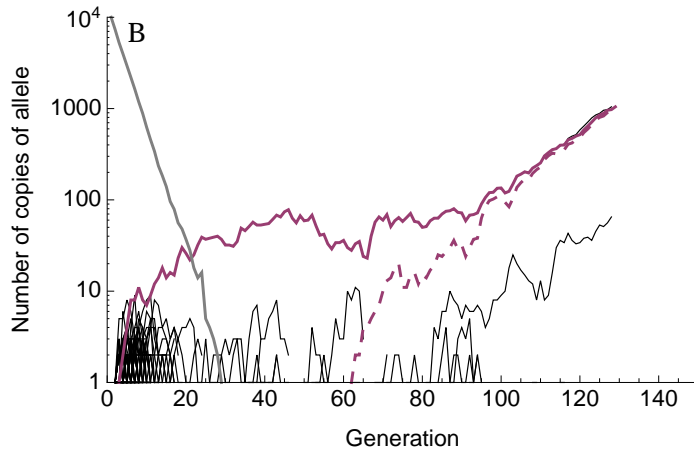
Import[datadir <> "kmuts_N" <> n0 <> "_n" <> n <> "_U" <> U <> "_Es" <> Es <> "_mmax" <>
  mmax <> "_mwt" <> mwt <> "_mutmax" <> mutmax <> "_rep" <> rep <> ".csv"];
allmut = Transpose[PadRight[%]];

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

Show[
  ListLogPlot[Drop[alleles[[2 ;;]], {rescuemut[[1]]}], {rescuemut[[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 ;;]][[rescuemut]],
    Joined → True,
    PlotStyle → {Directive[Thickness[0.005], defaultcolors[[2]], Dashing[Medium]],
      Directive[Thickness[0.005], defaultcolors[[2]]]}
  ],
  ListLogPlot[allmut[[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";

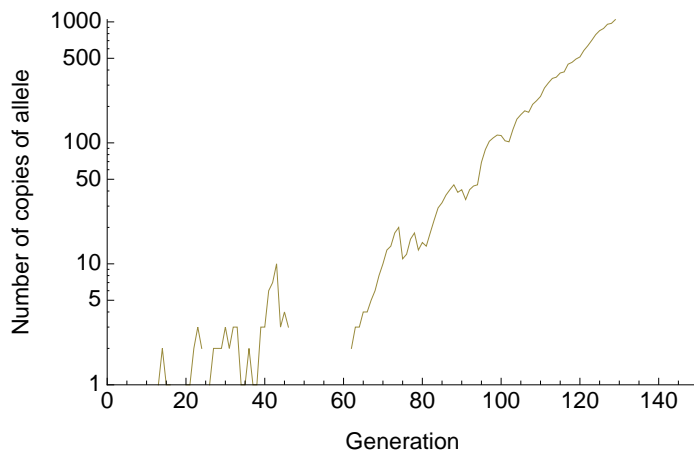
genmax = 150;
nmax = 1000;
ymax = 104;

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

ListLogPlot[supermut, 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 = 104;

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"];
allmut = Transpose[PadRight[%]];

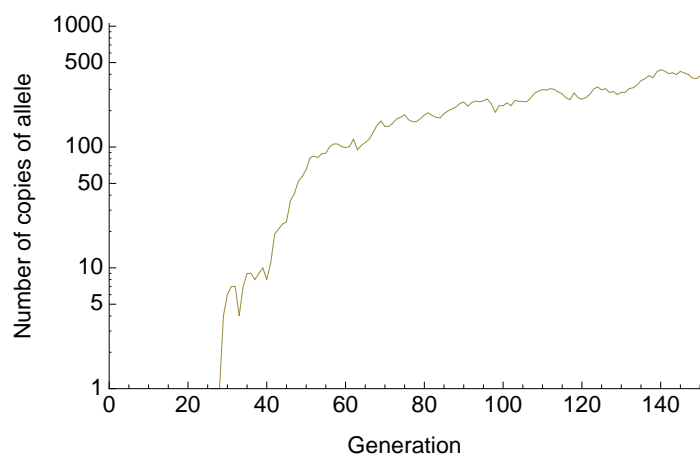
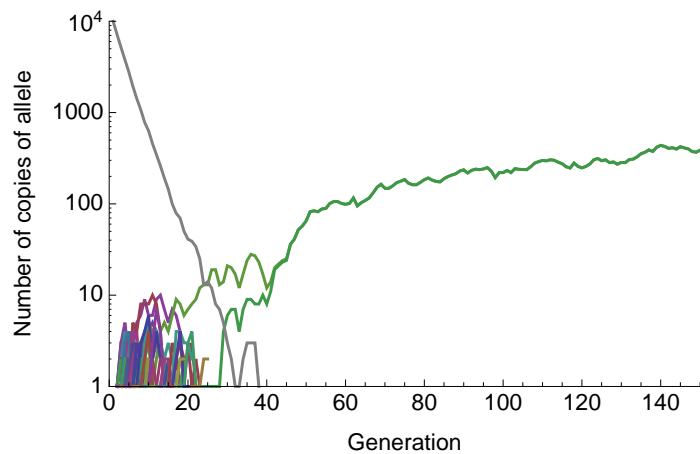
Show[
  ListLogPlot[alleles[[2 ;;]], Joined -> True,
    PlotRange -> {{0, genmax}, {1, ymax}}, Frame -> {True, True, False, False},
    FrameLabel -> {"Generation", "Number of copies of allele"}, LabelStyle ->
      labelstyle, (*Epilog->Text[Style["B", 14, Bold], Scaled@{0.05, 0.95}], *)
    PlotStyle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

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

ListLogPlot[supermut, 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 = 104;

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"];
allmut = Transpose[PadRight[%]];

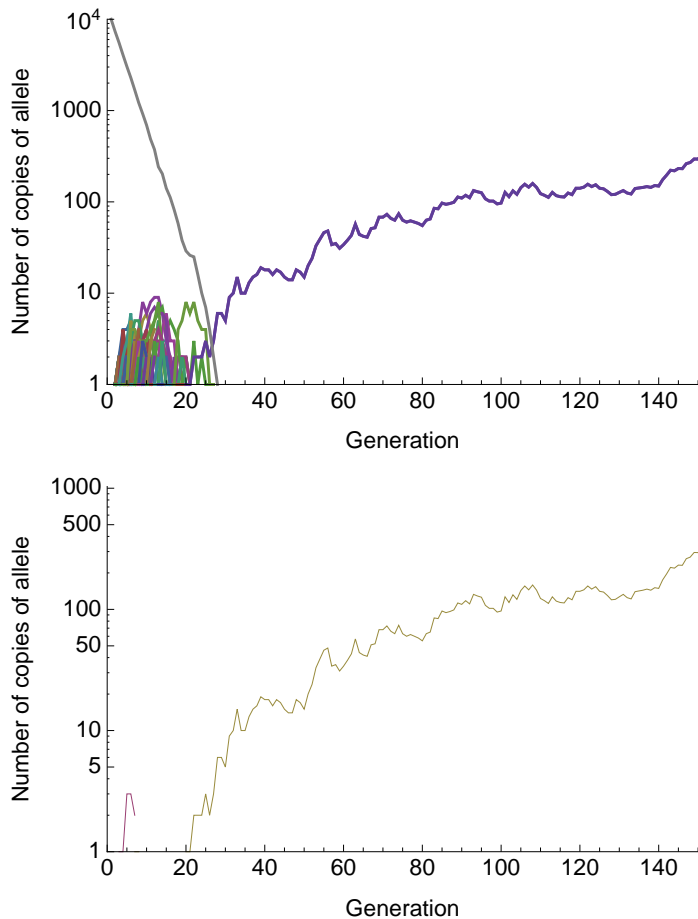
Show[
  ListLogPlot[alleles[[2 ;;]], Joined -> True,
    PlotRange -> {{0, genmax}, {1, ymax}}, Frame -> {True, True, False, False},
    FrameLabel -> {"Generation", "Number of copies of allele"}, LabelStyle ->
      labelstyle, (*Epilog->Text[Style["B", 14, Bold], Scaled@{0.05, 0.95}], *)
    PlotStyle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

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

ListLogPlot[supermut, 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]

```



General

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)

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

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)

$$fm[m_, mwt_, mmax_, \lambda_, n_] := \text{Simplify}[fs[s, so, \lambda, n] /. s \rightarrow m - mwt /. so \rightarrow mmax - mwt, \{mmax > m, \lambda > 0\}]$$

Simulate some mutants


```

n = 4;  $\eta$  = n / 2; (*phenotypic dimensions*)
Es = 0.01; (*mean mutational selective effect*)
 $\lambda$  = 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 = 105; (*number of mutants to create*)
dz = RandomReal[MultinormalDistribution[uo,  $\lambda$  Idn], NT];

Clear[ $\lambda$ , n, Es,  $\eta$ , uo, Idn, NT]
Calculate selection coefficient given mutant vectors dz and vector to optimum zopt

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

Check distributions with simulated mutants:

```

```

n = 4;  $\eta$  = n / 2; (*phenotypic dimensions*)
Es = 0.01; (*mean mutational selective effect*)
 $\lambda$  = 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*)

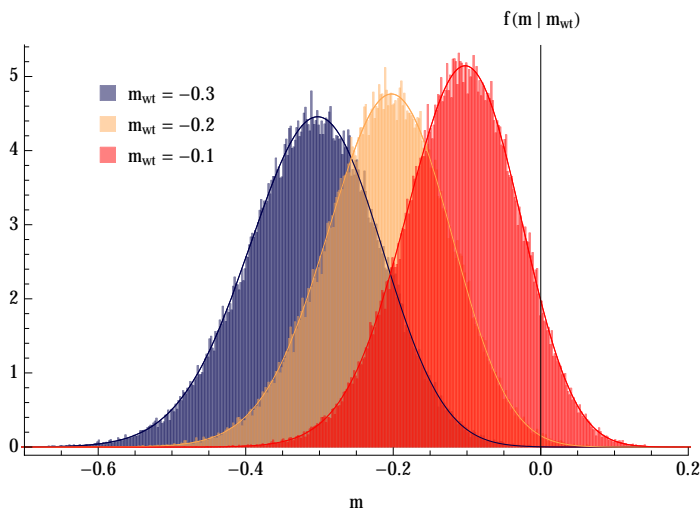
legends = Table[StringForm["mwt = `", NumberForm[mwts[[i]], 3]], {i, nmwts}];
simuls = Histogram[Table[mwts[[i]] + ss[dz, zis[[i]]], {i, nmwts}], 500,
  "PDF", ChartStyle -> color, PlotRange -> {{-2, 0.5}, All}, Axes -> False,
  ChartLegends -> Placed[legends, {0.2, 0.8}]]; (*simulation results*)

Table[fm[m, mwts[[i]], mmax,  $\lambda$ , 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 | mwt)"}]
(*Export[imagedir<"fmmwt.pdf",%];*)

Clear[ $\lambda$ , n,  $\eta$ , Es, mmax, mwts, nmwts, zis, color, styl, legends, simuls, theory]

```



Probability of rescue (equations 2 and 3)

Let p_0 be the probability a wildtype individual has descendants that rescue the population. If we start with N_0 wildtypes the probability of rescue is then

$$p_{\text{rescue}} = 1 - (1 - p_0)^{N_0};$$

which with small p_0 and large N_0 is approximately

```
prescueApp = Series[1 - (1 - p0)^N0 /. p0 -> p0 e /. N0 -> N0 / e, {e, 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]
```

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

Let an individual with growth rate m produce rescue mutants at rate $\Lambda(m)$. The probability its lineage rescues the population is then $1 - \mathbb{E}_Y[e^{-Y(m) \Lambda(m)}] = 1 - M_Y[-\Lambda(m)]$ 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 A1)

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]
```

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

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

In our discrete generation Poisson process, r is

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

$$-1 + e^m$$

and σ is

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

When m is small these are roughly

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

$$m$$

and

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

$$1$$

Then the probability of establishment for $m > 0$ is roughly

$$1 - \text{Exp}[-2r/\sigma] \text{ /. } r \rightarrow m \text{ /. } \sigma \rightarrow 1$$

and this is zero when $m < 0$.

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

$$\text{Normal}[\text{Series}[1 - \text{Exp}[-2m], \{m, 0, 1\}]] \text{ /. } m \rightarrow m_{wt} + s \text{ /. } m_{wt} \rightarrow 0$$

$$2s$$

$$\text{Normal}[\text{Series}[1 - \text{Exp}[-2m], \{m, 0, 1\}]] \text{ /. } m \rightarrow m_{wt} + s$$

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

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 $m = \lambda - \mu$ and, as discussed in Uecker & Hermisson 2016 Genetics and Uecker et al 2014 Am Nat, $\lambda + \mu = 1$. 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 $\lambda = (1 + m)/2$ and $\mu = (1 - m)/2$. Note that this is only valid for $|m| < 1$.

For a continuous-time birth death process starting from N_0 individuals ($F[s, 0] = s^{N_0}$) the PGF for the number of individuals at time t can be solved for explicitly

$$\text{fst} = \text{DSolve}[\{D[F[s, t], t] == D[F[s, t], s] (\lambda s^2 - (\lambda + \mu) s + \mu), F[s, 0] == s^{N_0}\}, F[s, t], \{s, t\}] // \text{Flatten}$$

$$\left\{ F[s, t] \rightarrow \left(\left(e^{\frac{\mu (t \lambda - t \mu + \text{Log}[-1+s] - \text{Log}[s \lambda - \mu])}{\lambda - \mu}} - e^{\frac{\lambda (t \lambda - t \mu + \text{Log}[-1+s] - \text{Log}[s \lambda - \mu])}{\lambda - \mu}} \right) \mu \right) / \left(e^{\frac{\mu (t \lambda - t \mu + \text{Log}[-1+s] - \text{Log}[s \lambda - \mu])}{\lambda - \mu}} - e^{\frac{\lambda (t \lambda - t \mu + \text{Log}[-1+s] - \text{Log}[s \lambda - \mu])}{\lambda - \mu}} \right) \lambda \right)^{N_0} \right\}$$

Probability of persistence

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

$$\text{pextt} = F[s, t] \text{ /. } \text{fst} \text{ /. } s \rightarrow 0 // \text{Factor} // \text{FullSimplify}$$

$$\left(1 + \frac{-\lambda + \mu}{\lambda - e^{t(-\lambda + \mu)} \mu} \right)^{N_0}$$

Evaluating at $s=0$ as t goes to infinity gives the probability 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}]
```

$$\left(\frac{\mu}{\lambda}\right)^{N_0}$$

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

(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

```
pest = 1 - pextt
```

$$1 - \left(1 + \frac{-\lambda + \mu}{\lambda - e^{t(-\lambda + \mu)}}\right)^{N_0}$$

Distribution of extinction times (equation A4)

When $|m| \ll 1/t \ll 1$, ie $|1/m| \gg t \gg 1$ (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[
  pest /. λ -> (1 + m)/2 /. μ -> (1 - m)/2 /. N0 -> 1 /. m -> m ε^2 /. t -> t / ε, {ε, 0, 1}]] /. ε -> 1
```

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

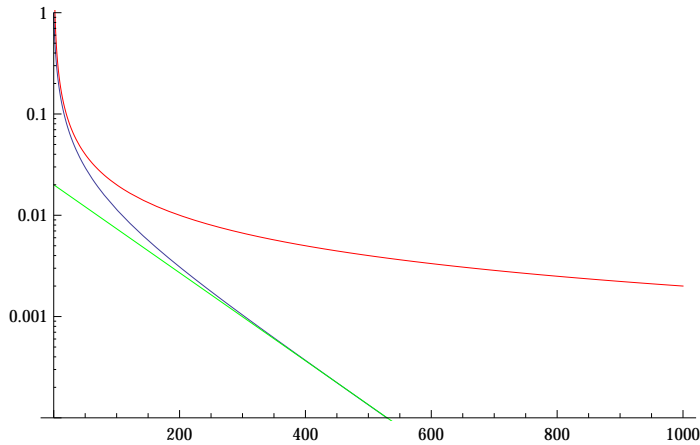
And when $-m t \gg 1$, ie $-m \gg 1/t$ (that is, when the mutant is effectively subcritical) we have roughly

```
pestapp2 = Simplify[pest /. 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[pest /. λ →  $\frac{1+m}{2}$  /. μ →  $\frac{1-m}{2}$  /. 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

$$\text{pn1} = \text{D}[\text{F}[s, t] /. \text{fst}, \{s, n\}] / n! /. n \rightarrow 1 /. s \rightarrow 0 /. \lambda \rightarrow \frac{1+m}{2} /. \mu \rightarrow \frac{1-m}{2} /. N0 \rightarrow 1 //$$

Simplify

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

and two individuals

$$\text{pn2} = \text{D}[\text{F}[s, t] /. \text{fst}, \{s, n\}] / n! /. n \rightarrow 2 /. s \rightarrow 0 /. \lambda \rightarrow \frac{1+m}{2} /. \mu \rightarrow \frac{1-m}{2} /. N0 \rightarrow 1 //$$

Simplify

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

three

$$\begin{aligned} & \text{D}[F[s, t] /. \text{fst}, \{s, n\}] / n! /. n \rightarrow 3 /. s \rightarrow 0 /. \lambda \rightarrow \frac{1+m}{2} /. \mu \rightarrow \frac{1-m}{2} /. N0 \rightarrow 1 // \text{Simplify} \\ & \frac{4 e^{m t} (-1 + e^{m t})^2 m^2 (1+m)^2}{(-1+m+e^{m t} (1+m))^4} \end{aligned}$$

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

$$\begin{aligned} & \text{pnt} = \text{pn1} (\text{pn2} / \text{pn1})^{n-1} \\ & \frac{4 e^{m t} m^2 \left(\frac{(-1+e^{m t}) (1+m)}{-1+m+e^{m t} (1+m)} \right)^{-1+n}}{(-1+m+e^{m t} (1+m))^2} \end{aligned}$$

Check for n=4:

$$\begin{aligned} & \text{pnt} / (\text{D}[F[s, t] /. \text{fst}, \{s, n\}] / n!) /. n \rightarrow 4 /. s \rightarrow 0 /. \lambda \rightarrow \frac{1+m}{2} /. \mu \rightarrow \frac{1-m}{2} /. N0 \rightarrow 1 // \\ & \text{Simplify} \\ & 1 \end{aligned}$$

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

$$\begin{aligned} & \text{pntgt} = \text{pnt} / \text{pest} /. \lambda \rightarrow \frac{1+m}{2} /. \mu \rightarrow \frac{1-m}{2} /. N0 \rightarrow 1 // \text{FullSimplify} \\ & \frac{2 m \left(1 - \frac{2 m}{-1+m+e^{m t} (1+m)} \right)^n}{(-1+e^{m t}) (1+m)} \end{aligned}$$

When $t \ll |1/m|$ (effectively critical) this is approximately

$$\begin{aligned} & \text{pntgtapp1} = \text{Normal}[\text{Series}[\text{pntgt} /. m \rightarrow m \epsilon, \{\epsilon, 0, 0\}]] /. \epsilon \rightarrow 1 // \text{FullSimplify} \\ & \text{simplify}\left[\% == 2 \left(\frac{1}{t} \right) \left(1 + \frac{2}{t} \right)^{-n}, \{t > 0, n > 0\}\right] \\ & 2 t^{-1+n} (2+t)^{-n} \\ & \text{True} \end{aligned}$$

with expectation

$$\begin{aligned} & \text{Sum}[n \text{ pntgtapp1}, \{n, 0, \infty\}] \\ & \frac{2+t}{2} \end{aligned}$$

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

$$\begin{aligned} & \text{Sum}[t/2, \{t, 0, T\}] \\ & \frac{1}{4} T (1+T) \end{aligned}$$

Or when $-1/m \ll t$ (ie subcritical mutants) we have approximately

```
pntgtapp2 = pntgt /. -1 + m + em t (1 + m) → -1 + m /. -1 + em t → -1 // Simplify;
% /. 1 - m → 1
- 2 m (1 + m)-1+n
```

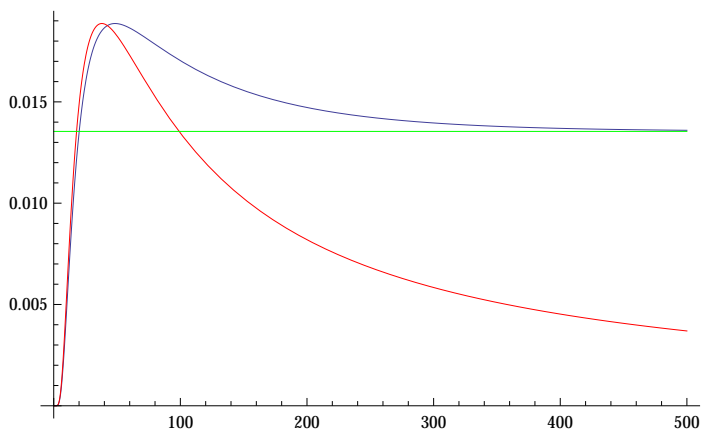
with expectation

```
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]
]
```

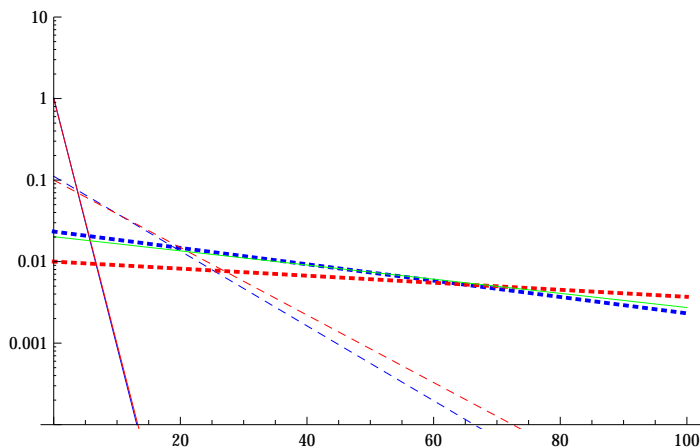


Check distribution of n at 3 different times


```

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 ($t \ll |1/m|$ and $t \gg -1/m$), 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 4)

The probability that a mutant with growth rate in $[m, m+dm]$ rescues the population is $f[m | m_{wt}] p_{\text{est}}[m] dm$. Integrating over all $m > 0$ gives the probability of 1-step rescue from an individual with growth rate m_0

```

Clear[Δ1]
Δ1[m0_?NumericQ, mmax_, λ_, n_, U_] :=
  UNIntegrate[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,  $\Lambda$ 1[m0, mmax,  $\lambda$ , n, U]]
```

And we can approximate this as

```
PR1App[m0_?NumericQ] := prescueApp /. p0 → prescuem[m0,  $\Lambda$ 1[m0, mmax,  $\lambda$ , n, U]]
```

Numerical example

```
N0 = 104;
```

```
U = 10-3;
```

```
mmax = 0.5;
```

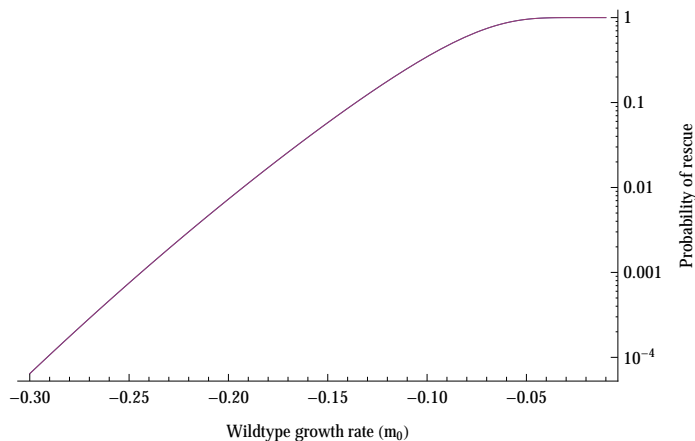
```
 $\lambda$  = 2 Es / n;
```

```
Es = 0.01;
```

```
n = 4;
```

```
LogPlot[
  {PR1[m0], PR1App[m0]},
  {m0, -0.3, -0.01},
  Frame → {True, False, False, True},
  FrameLabel → {"Wildtype growth rate ( $m_0$ )", "", "", "Probability of rescue"},
  FrameTicks → {True, False, False, True}
]
```

```
Clear[N0, U, mmax,  $\lambda$ , Es, n, mwt]
```



2-step rescue (equation 5)

The rate of 2-step rescue from a single individual with growth rate m_0 is the probability of a mutation to growth rate m , which does not establish, but then creates a second mutation that does

```
 $\Lambda$ 2[m0_?NumericQ, mmax_,  $\lambda$ _, n_, U_] := UNIntegrate[
  fm[m, m0, mmax,  $\lambda$ , n] (1 - pest[m]) prescuem[m,  $\Lambda$ 1[m, mmax,  $\lambda$ , n, U]], {m, - $\infty$ , mmax}]
```

Numerical comparison with probability of 1-step rescue

```

N0 = 104;
U = 2 * 10-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;

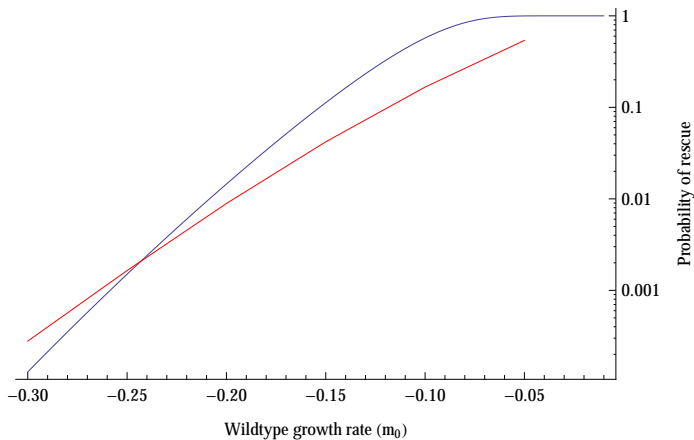
Table[{m0, prescue /. p0 → prescuem[m0, λ2[m0, mmax, λ, n, U]]},
  {m0, -0.3, -0.01, 0.05}];
plot1 = ListLogPlot[%, Joined → True, PlotStyle → Red];

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}];

Show[plot2, plot1]

Clear[mmax, λ, Es, n, N0, U]

```



k-step rescue (equation 6)

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

```

λ3[m0_?NumericQ, mmax_, λ_, n_, U_] := UNIntegrate[
  fm[m, m0, mmax, λ, n] (1 - pest[m]) prescuem[m, λ2[m, mmax, λ, n, U]], {m, -∞, mmax}]

```

and 4-step is

```

λ4[m0_?NumericQ, mmax_, λ_, n_, U_] := UNIntegrate[
  fm[m, m0, mmax, λ, n] (1 - pest[m]) prescuem[m, λ3[m, mmax, λ, n, U]], {m, -∞, mmax}]

```

etc

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

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 accuracy)

```

In[162]:= 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},
  f = Interpolation[Table[{mTemp, UNIntegrate[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},
  f = Interpolation[Table[{mTemp, UNIntegrate[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},
  f = Interpolation[Table[{mTemp, UNIntegrate[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},
  f = Interpolation[Table[{mTemp, UNIntegrate[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]
]

```

Use this to plot the probability of rescue as a function of wildtype decline rate

```

N0 = 104;
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}];

m0min = mTempmin;
m0max = mTempmax;
mstep = step;
rate4 = Table[{m0, A4Interpolated[m0, mmax,  $\lambda$ , n, U]}, {m0, m0min, m0max, mstep}];
rate3 = Table[{m0, A3Interpolated[m0, mmax,  $\lambda$ , n, U]}, {m0, m0min, m0max, mstep}];
rate2 = Table[{m0, A2Interpolated[m0, mmax,  $\lambda$ , n, U]}, {m0, m0min, m0max, mstep}];
rate1 = Table[{m0, A1Interpolated[m0, mmax,  $\lambda$ , n, U]}, {m0, m0min, m0max, mstep}];
m0list = Table[m0, {m0, m0min, m0max, mstep}];
theory = {
  Table[{m0list[[i]], prescue /. p0  $\rightarrow$  prescuem[m0list[[i]], rate1[[i, 2]]}],
    {i, Length[m0list]}],
  Table[{m0list[[i]], prescue /. p0  $\rightarrow$  prescuem[m0list[[i]], rate2[[i, 2]]}],
    {i, Length[m0list]}],
  Table[{m0list[[i]], prescue /. p0  $\rightarrow$  prescuem[m0list[[i]], rate3[[i, 2]]}],
    {i, Length[m0list]}],
  Table[{m0list[[i]], prescue /. p0  $\rightarrow$  prescuem[m0list[[i]], rate4[[i, 2]]}],
    {i, Length[m0list]}]
};
alltheory = Table[
  {m0list[[i]], prescue /. p0  $\rightarrow$  prescuem[m0list[[i]], rate1[[i, 2]] + rate2[[i, 2]] +
    rate3[[i, 2]] + rate4[[i, 2]]}], {i, Length[m0list]};

Show[
  ListLogPlot[theory,
    Joined  $\rightarrow$  True,
    PlotStyle  $\rightarrow$  Thick,
    PlotRange  $\rightarrow$  {{m0min, 0}, {5 * 10-7, 1}},
    Frame  $\rightarrow$  {True, False, False, True},
    FrameLabel  $\rightarrow$  {"Wildtype growth rate", , , "Probability of rescue"},
    FrameTicks  $\rightarrow$  {True, False, False, True},
    LabelStyle  $\rightarrow$  labelstyle,
    PlotLegends  $\rightarrow$  Placed[LineLegend[Style[#, 12, FontFamily  $\rightarrow$  "Helvetica"] & /@
      {"1-step", "2-step", "3-step", "4-step"}], Scaled@{3 / 4, 1 / 4}]
  ],
  ListLogPlot[alltheory, Joined  $\rightarrow$  True, PlotStyle  $\rightarrow$  {Black, Thick},
    PlotLegends  $\rightarrow$  Placed[LineLegend[Style[#, 12, FontFamily  $\rightarrow$  "Helvetica"] & /@
      {"1-", "2-", "3-", "4-step"}], Scaled@{1 / 4, 7 / 8}]
  ],
  ListLogPlot[alldat, PlotMarkers  $\rightarrow$  {Automatic, Medium}, PlotStyle  $\rightarrow$  Black
]
]

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

Clear[N0, mmax,  $\lambda$ , Es, n, U, m0min, m0max]

```

NIntegrate::ncvb :

NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
 NIntegrate obtained $1.4363490176861695 \times 10^{-7}$ and
 $1.034782441470326 \times 10^{-12}$ 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 $2.0246698484863734 \times 10^{-7}$ and
 $1.0921054693023465 \times 10^{-12}$ 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 $2.850952330867838 \times 10^{-7}$ and
 $2.321744002394699 \times 10^{-12}$ 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 $5.3450453526009294 \times 10^{-8}$ and
 $5.951525075263353 \times 10^{-13}$ 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 $7.059025621526559 \times 10^{-8}$ and
 $8.588848983658455 \times 10^{-13}$ 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 $9.314638149255934 \times 10^{-8}$ and
 $1.711619241364099 \times 10^{-12}$ 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 $1.4363490176861695 \times 10^{-7}$ and
 $1.034782441470326 \times 10^{-12}$ for the integral and error estimates. >>

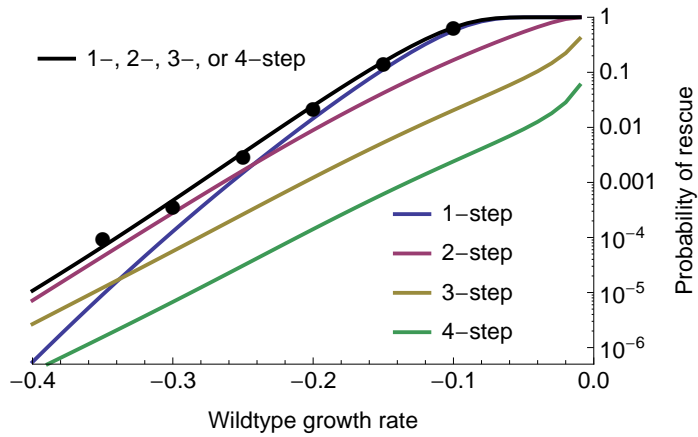
NIntegrate::ncvb :

NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
 NIntegrate obtained $2.0246698484863734 \times 10^{-7}$ and
 $1.0921054693023465 \times 10^{-12}$ 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 $2.850952330867838 \times 10^{-7}$ and
 $2.321744002394699 \times 10^{-12}$ for the integral and error estimates. >>

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



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

We again use interpolation functions to speed things up, this time across U instead of m_0

```

In[171]:= 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, 10xtemp 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, 10xtemp NIntegrate[fm[m, m0, mmax, λ, n] (1 - pest[m]) prescuem[
        m, Λ1Interpolated[m, mmax, λ, n, 10xtemp]], {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, 10xtemp NIntegrate[fm[m, m0, mmax, λ, n] (1 - pest[m]) prescuem[
        m, Λ2Interpolated[m, mmax, λ, n, 10xtemp]], {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, 10xtemp NIntegrate[fm[m, m0, mmax, λ, n] (1 - pest[m]) prescuem[
        m, Λ3Interpolated[m, mmax, λ, n, 10xtemp]], {m, mmin, mmax}, Method →
        {Automatic, "SymbolicProcessing" → 0}]}, {xtemp, Umin, Umax, Ustep}]]];
    f[x]
  ]

```

with slow decline


```

N0 = 104;
m0 = -0.1;
mmax = 0.5;
 $\lambda = 2 \text{ Es} / n$ ;
Es = 0.01;
n = 4;

rate4 = Table[ $\Lambda 4$ InterpolatedU[m0, mmax,  $\lambda$ , n, x], {x, Umin, Umax, Ustep}];
rate3 = Table[ $\Lambda 3$ InterpolatedU[m0, mmax,  $\lambda$ , n, x], {x, Umin, Umax, Ustep}];
rate2 = Table[ $\Lambda 2$ InterpolatedU[m0, mmax,  $\lambda$ , n, x], {x, Umin, Umax, Ustep}];
rate1 = Table[ $\Lambda 1$ InterpolatedU[m0, mmax,  $\lambda$ , n, x], {x, Umin, Umax, Ustep}];
Ulist = Table[10x, {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]}}];

dat = Import[datadir <>
  "prescue_poisson_N10000_n4_Es0.01_mmax0.50_mwt-0.10_nreps10000.csv"];
dat[[All, {1}]] = dat[[All, {1}]] * Uc /. Uc → n2  $\lambda$  / 4 /.  $\lambda$  → 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["A", 14, Bold], Scaled@{0.05, 0.95}],
      Text[Style["m0 = -0.1", 12, FontFamily → "Helvetica"], Scaled@{2 / 10, 9.5 / 10}]}],
    PlotLegends → Placed[LineLegend[Style[#, 12, FontFamily → "Helvetica"] & /@
      {"1-step", "2-step", "3-step", "4-step"}], Scaled@{3 / 4, 2 / 4}]
  ],
  ListLogLogPlot[Re[alltheory], Joined → True, PlotStyle → {Thick, Black},
    PlotLegends → Placed[LineLegend[Style[#, 12, FontFamily → "Helvetica"] & /@
      {"1-", "2-", "3-", "4-step"}], Scaled@{3 / 4, 1 / 8}]
  ],
  ListLogLogPlot[dat, PlotMarkers → {Automatic, Medium}, PlotStyle → Black]
]

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

Clear[mmax,  $\lambda$ , Es, n, m0, N0, U]

```

NIntegrate::ncvb :

NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
 NIntegrate obtained $7.903638159610268 \times 10^{-10}$ and
 $3.5726477013409734 \times 10^{-13}$ 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 $1.132748210984352 \times 10^{-9}$ and
 $5.950875139485354 \times 10^{-13}$ 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 $1.6246334730600223 \times 10^{-9}$ and
 $9.929455600565392 \times 10^{-13}$ 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 $8.753307496629023 \times 10^{-9}$ and
 $4.750302433350434 \times 10^{-10}$ 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 $1.3575488239636588 \times 10^{-8}$ and
 $7.25858306184013 \times 10^{-10}$ 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 $2.1026854190828714 \times 10^{-8}$ and
 $1.0992553380604717 \times 10^{-9}$ 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 $9.089503232603941 \times 10^{-6}$ and
 $2.113297006455717 \times 10^{-8}$ for the integral and error estimates. >>

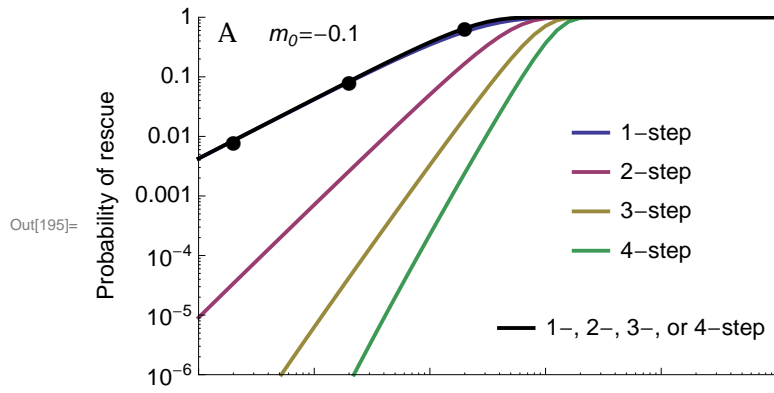
NIntegrate::ncvb :

NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
 NIntegrate obtained 0.000011196431231312265 and
 $2.2364339692500994 \times 10^{-8}$ 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 0.000013784490184224995 and
 $2.390798329394519 \times 10^{-8}$ for the integral and error estimates. >>

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



medium decline

```

N0 = 104;
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[10x, {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]}];

Import[datadir<>
  "prescue_poisson_N10000_n4_Es0.01_mmax0.50_mwt-0.20_mutmax10_nreps10000.csv"];
dat[[All, {1}]] = dat[[All, {1}]] * Uc /. Uc → n2 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["B", 14, Bold], Scaled@{0.05, 0.95}],
      Text[Style["m0 = -0.2", 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]

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
NIntegrate obtained 7.689945886277756`*^-13 and
3.1458541548910146`*^-14 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 $1.5018132795465648 \times 10^{-12}$ and
 $6.142801595515576 \times 10^{-14}$ 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 $2.9290281019524058 \times 10^{-12}$ and
 $1.1980244212352876 \times 10^{-13}$ 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 $8.845565356724366 \times 10^{-10}$ and
 $3.685681109184114 \times 10^{-11}$ 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 $1.3718713944242797 \times 10^{-9}$ and
 $5.6320692478365926 \times 10^{-11}$ 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 $2.125282151926249 \times 10^{-9}$ and
 $8.529847969923773 \times 10^{-11}$ 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 $7.956241203818995 \times 10^{-7}$ and
 $1.8562455321306012 \times 10^{-9}$ for the integral and error estimates. >>

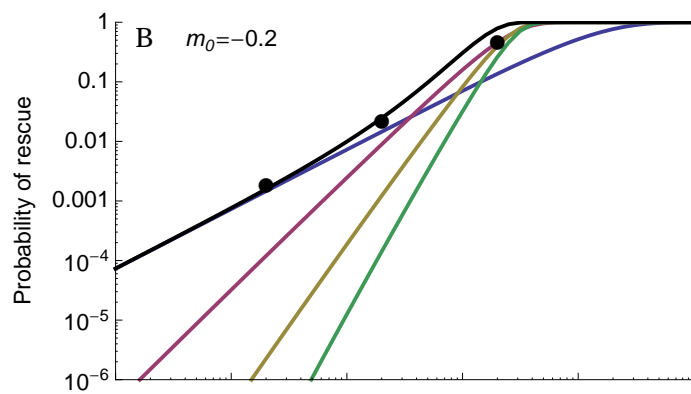
NIntegrate::ncvb :

NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
 NIntegrate obtained $9.825981217373451 \times 10^{-7}$ and
 $2.006510765409658 \times 10^{-9}$ 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 $1.2130137702122066 \times 10^{-6}$ and
 $2.1950038123030257 \times 10^{-9}$ for the integral and error estimates. >>

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



fast decline

```

N0 = 104;
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[10x, {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]}];

Import[datadir<>
  "prescue_poisson_N10000_n4_Es0.01_mmax0.50_mwt-0.30_mutmax10_nreps10000.csv"];
dat[[All, {1}]] = dat[[All, {1}]] * Uc /. Uc → n2 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["C", 14, Bold], Scaled@{0.05, 0.95}],
      Text[Style["m0 = -0.3", 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]

NIntegrate::ncvb :
NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
NIntegrate obtained 4.4872125010643695`*^-14 and
7.452858931215058`*^-16 for the integral and error estimates. >>

```

NIntegrate::ncvb :

NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
 NIntegrate obtained $8.76424641221469 \times 10^{-14}$ and
 $1.4426107999370389 \times 10^{-15}$ 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 $1.7091266720072494 \times 10^{-13}$ and
 $2.7938862711702696 \times 10^{-15}$ 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 $4.711755302324864 \times 10^{-11}$ and
 $8.595567431789738 \times 10^{-13}$ 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 $7.31130866505538 \times 10^{-11}$ and
 $1.313507119224805 \times 10^{-12}$ 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 $1.1336497554230762 \times 10^{-10}$ and
 $1.9892851056999597 \times 10^{-12}$ 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 $2.908470076125397 \times 10^{-8}$ and
 $4.2461541157965886 \times 10^{-11}$ for the integral and error estimates. >>

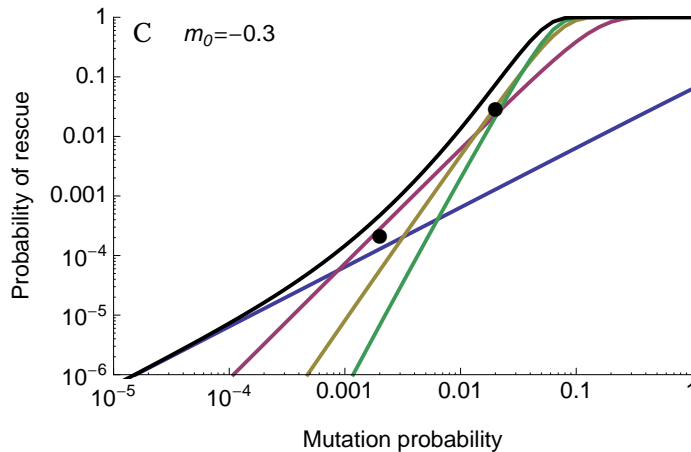
NIntegrate::ncvb :

NIntegrate failed to converge to prescribed accuracy after 9 recursive bisections in m near {m} = {0.000767263}.
 NIntegrate obtained $3.6172582841345096 \times 10^{-8}$ and
 $4.570705224988314 \times 10^{-11}$ 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 $4.4979987722070854 \times 10^{-8}$ and
 $4.9773275558549576 \times 10^{-11}$ for the integral and error estimates. >>

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



Approximating the probability of 1-step rescue

Replicating Anciaux et al 2018, Genetics

Change of variables

We first introduce the variables $y = m/m_{\max}$, $ywt = mwt/m_{\max}$, $\rho_{\max} = m_{\max}/\lambda$, $\theta = n/2$. The distribution of y among new mutations is then

$$f_y = e^{-(2-y-ywt)\rho_{\max}} \rho_{\max}^{\theta} (1-y)^{\theta-1} \text{Hypergeometric0F1Regularized}[\theta, (1-y)(1-ywt)\rho_{\max}^2]$$

$$\text{Simplify}\left[f_y == \frac{1}{D\left[\frac{m}{m_{\max}}, m\right]} f_m[y m_{\max}, ywt m_{\max}, m_{\max}, m_{\max}/\rho_{\max}, 2\theta], \right.$$

$$\left. \{\rho_{\max} > 0, 0 < y < 1\} \right]$$

$$f_y /. y \rightarrow m/m_{\max} /. ywt \rightarrow mwt/m_{\max} /. \rho_{\max} \rightarrow m_{\max}/\lambda /. \theta \rightarrow n/2;$$

$$\text{Simplify}[\% D[m/m_{\max}, m] == f_m[m, mwt, m_{\max}, \lambda, n], \{m_{\max} > 0, \lambda > 0\}]$$

$$e^{(-2+y+ywt)\rho_{\max}} (1-y)^{-1+\theta} \rho_{\max}^{\theta} \text{Hypergeometric0F1Regularized}[\theta, (1-y)(1-ywt)\rho_{\max}^2]$$

True

True

Approximate hypergeometric function

We next want to approximate the hypergeometric function in f_y .

Note first that $\text{Hypergeometric0F1Regularized}[\theta, z]$ is defined in *Mathematica* as $\text{Hypergeometric0F1}[\theta, z]/\Gamma[\theta]$:

$$\text{Hypergeometric0F1Regularized}[\theta, z];$$

$$\text{Hypergeometric0F1}[\theta, z] / \Gamma[\theta];$$

$$\text{FullSimplify}[\% / \%]$$

1

Next note that $\text{Hypergeometric0F1}[\theta, z]$ can be written as $\frac{\Gamma[\theta]}{(\sqrt{z})^{\theta-1}} \text{BesselI}[\theta-1, 2\sqrt{z}]$ using

9.6.47 of Abramowitz and Stegun (1964):

```
Hypergeometric0F1[θ, z];
Gamma[θ]
(√z)^(θ-1) BesselI[θ-1, 2√z];
FullSimplify[% / %]
1
```

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

```
Hypergeometric0F1Regularized[θ, z];
1
(√z)^(θ-1) BesselI[θ-1, 2√z];
FullSimplify[% / %]
1
```

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

```
BesselI[θ-1, 2 Sqrt[z]] /. BesselI → Function[{v, x},
  e^x / (√(2 π x)) (1 - (μ-1)/(8 x) + ((μ-1)(μ-9))/(2! (8 x)^2) - ((μ-1)(μ-9)(μ-25))/(3! (8 x)^3) + added) /. μ → 4 v^2];
```

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:

```
BesselI[θ-1, 2 Sqrt[z]] /. BesselI → Function[{v, x}, e^x / (√(2 π x))];
e^(2√z) / (2√π z^(1/4))
```

This allows us to conclude that

$\text{Hypergeometric0F1Regularized}[\theta, z] = \frac{1}{(\sqrt{z})^{\theta-1}} \text{BesselI}[\theta-1, 2\sqrt{z}]$ can be approxi-

mated for z large as $\frac{1}{(\sqrt{z})^{\theta-1}} \frac{e^{2\sqrt{z}}}{2\sqrt{\pi} z^{1/4}}$, 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 $\rho_{\text{max}} = m_{\text{max}}/\lambda$ goes to infinity, i.e., mutant growth rates are much less than maximal

```

fya = FullSimplify[
  fy /. Hypergeometric0F1Regularized -> Function[{θ, z},  $\frac{1}{2\sqrt{\pi}} z^{\frac{1-2\theta}{4}} e^{2\sqrt{z}}$ ] //
  PowerExpand, 0 < y < 1 && ρmax > 0 && ywt < 0 && θ ≥ 1/2]
FullSimplify[% ==  $\frac{e^{-v[y]} (1-y)^{\frac{\theta}{2}-\frac{3}{4}} (1-ywt)^{\frac{1}{4}-\frac{\theta}{2}} \sqrt{\rho_{\max}}}{2\sqrt{\pi}}$  /.
  v[y] ->  $\left(2 - ywt - 2\sqrt{(1-ywt)(1-y)} - y\right) \rho_{\max}$ ,
  {ρmax > 0, ywt < 0, 0 < y < 1, θ ≥ 1/2}] (*compare to eqn A9*)
-  $\left( e^{\left(-2+y+2\sqrt{(-1+y)(-1+ywt)}+ywt\right)\rho_{\max}} \left(\frac{-1+y}{-1+ywt}\right)^{\theta/2} (-1+ywt)\sqrt{\rho_{\max}} \right) /$ 
 $\left(2\sqrt{\pi}((-1+y)(-1+ywt))^{3/4}\right)$ 
True

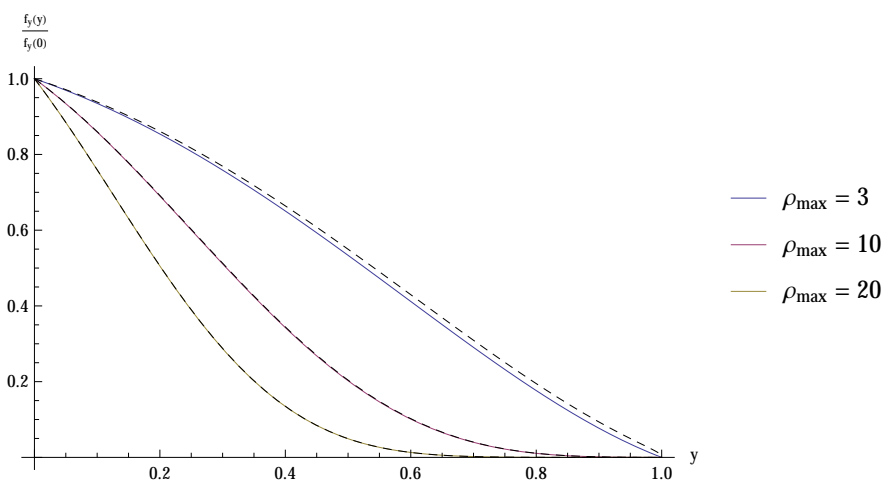
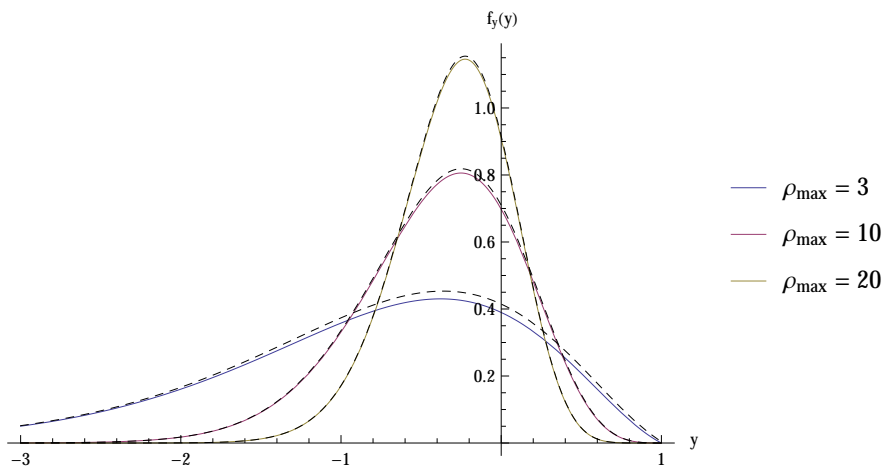
```

This does great for large ρ_{\max} , especially at the tails

```

 $\theta = 2$ ;  $ywt = -0.2$ ;  $\rho_{max} = \{3, 10, 20\}$ ;  $f_y$ ;
Plot[%, {y, -3, 1}, PlotRange -> All, PlotLegends -> LineLegend[
  Table[StringForm[" $\rho_{max} = \text{``}$ ", Round[ $\rho_{max}[[i]]$ ]], {i, Length[ $\rho_{max}$ ]}]]];
 $f_y a$ ;
Plot[%, {y, -3, 1}, PlotRange -> All, PlotStyle -> {{Dashed, Black}}];
Show[%%, %, AxesLabel -> {y,  $f_y[y]$ }]
 $\frac{f_y}{f_y[0]}$ ;
 $f_y / . y \rightarrow 0$ ;
Plot[%, {y, 0, 1}, PlotRange -> All, PlotLegends -> LineLegend[
  Table[StringForm[" $\rho_{max} = \text{``}$ ", Round[ $\rho_{max}[[i]]$ ]], {i, Length[ $\rho_{max}$ ]}]]];
 $f_y a$ ;
 $\frac{f_y a}{f_y a / . y \rightarrow 0}$ ;
 $f_y a / . y \rightarrow 0$ ;
Plot[%, {y, 0, 1}, PlotRange -> All, PlotStyle -> {{Dashed, Black}}];
Show[%%, %, AxesLabel -> {y,  $\frac{f_y[y]}{f_y[0]}$ }]
 $\theta = .$ ;  $ywt = .$ ;  $\rho_{max} = .$ ;

```



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

$$2 \left(\sqrt{1 - y} - 1 \right) /. y \rightarrow \frac{m}{m_{\max}} // \text{Expand}$$

FullSimplify[

$$2 \frac{x_0 - x_c}{x_c} == \% /. \text{Flatten} \left[\text{Solve} \left[\left\{ \sqrt{2 (m_{\max} - m)} = x_0, \sqrt{2 m_{\max}} = x_c \right\}, \{m_{\max}, m\} \right] \right] //$$

$$\text{Expand}, x_0 > 0 \ \&\& \ x_c > 0]$$

$$-2 + 2 \sqrt{1 - \frac{m}{m_{\max}}}$$

True

The pdf of ψ is then approximately

$$\text{Solve} \left[\left\{ 2 \left(1 - \sqrt{1 - y} \right) = \psi, 2 \left(1 - \sqrt{1 - y_{wt}} \right) = \psi_{wt} \right\}, \{y, y_{wt}\} \right] // \text{Flatten}$$

$$\text{Simplify}[\text{Abs}[D[y /. \%, \psi]] \text{ fya} /. \%, \{0 < \psi < 2, \psi_{wt} < 0, \rho_{\max} > 0, \theta \geq 1/2\}]$$

$$\text{FullSimplify}[\% == \frac{e^{-\frac{1}{4} \rho_{\max} (\psi - \psi_{wt})^2} \sqrt{\rho_{\max}} \left(\frac{2 - \psi}{2 - \psi_{wt}} \right)^{-\frac{1}{2} + \theta}}{2 \sqrt{\pi}}, \{0 < \psi < 2, \psi_{wt} < 0, \rho_{\max} > 0, \theta \geq 1/2\}]$$

(*compare to eqn A10*)

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

$$\left\{ y \rightarrow \frac{1}{4} (4 \psi - \psi^2), y_{wt} \rightarrow \frac{1}{4} (4 \psi_{wt} - \psi_{wt}^2) \right\}$$

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

True

Note that this is a normal distribution, with mean ψ_{wt} and variance $\frac{2}{\rho_{\max}}$, as $\left(\frac{-2 + \psi}{-2 + \psi_{wt}} \right)^{-\frac{1}{2} + \theta} \rightarrow 1$ (which is reasonable when the absolute values of ψ and ψ_{wt} 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).

$$f\psi /. \left(\frac{2-\psi}{2-\psi_{wt}} \right)^{-\frac{1}{2}+\theta} \rightarrow 1;$$

```
Simplify[% == Simplify[PDF[NormalDistribution[\psi_{wt}, \sqrt{\frac{2}{\rho_{max}}}], \psi], \rho_{max} > 0],
{0 < \psi < 2, \psi_{wt} < 0, \rho_{max} > 0, \theta > 1/2}]
True
```

Laplace approximation and compact form (equation A2)

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

$$\frac{U}{-mwt} \text{pest}[m] \text{fy} /. m \rightarrow m_{\max} y$$

$$- \frac{1}{mwt} e^{(-2+y+ywt) \rho_{\max}} (1 - e^{-2 m_{\max} y}) U (1-y)^{-1+\theta}$$

$$\rho_{\max}^{\theta} \text{Hypergeometric0F1Regularized}[\theta, (1-y) (1-ywt) \rho_{\max}^2]$$

which, using the approximation in equation A9, is nearly

$$\frac{U}{-mwt} \text{pest}[m] \text{fya} /. m \rightarrow m_{\max} y$$

$$\left(e^{(-2+y+2\sqrt{(-1+y)(-1+ywt)}+ywt) \rho_{\max}} (1 - e^{-2 m_{\max} y}) U \left(\frac{-1+y}{-1+ywt} \right)^{\theta/2} (-1+ywt) \sqrt{\rho_{\max}} \right) /$$

$$(2 mwt \sqrt{\pi} ((-1+y)(-1+ywt))^{3/4})$$

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

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

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

$$h[\psi_] := \left(\frac{1-\psi/2}{1-\psi_{wt}/2} \right)^{\theta-\frac{1}{2}} (1 - e^{-2 m_{\max} y}) /. y \rightarrow \psi (1-\psi/4)$$

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

$$\frac{U}{-mwt} \frac{\sqrt{\rho_{\max}}}{2 \sqrt{\pi}} h[\psi] \text{Exp}[-\rho_{\max} q[\psi]]$$

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

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)

$$\text{Simplify}\left[\left(-\frac{1}{2 \text{mwt} \sqrt{\pi}} e^{-\frac{1}{4} \rho_{\text{max}} (\psi - \psi_{\text{wt}})^2} \left(1 - e^{-2 \text{mmax} \left(1 - \frac{\psi}{4}\right) \psi}\right) \sqrt{\rho_{\text{max}}} \left(\frac{1 - \frac{\psi}{2}}{1 - \frac{\psi_{\text{wt}}}{2}}\right)^{-\frac{1}{2} + \theta}\right) \right. \\ \left. \left(\frac{\text{U}}{-\text{mwt}} \frac{e^{-\frac{1}{4} \rho_{\text{max}} (\psi - \psi_{\text{wt}})^2} \sqrt{\rho_{\text{max}}} \left(\frac{2 - \psi}{2 - \psi_{\text{wt}}}\right)^{-\frac{1}{2} + \theta}}{2 \sqrt{\pi}}\right)\right] \\ 1 - e^{\frac{1}{2} \text{mmax} (-4 + \psi) \psi}$$

As $\rho_{\text{max}} = \text{mmax}/\lambda$ goes to ∞ the Exp term dominates and we take the leading order of h

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

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

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

$$\text{Integrate}\left[\frac{\text{U}}{-\text{mwt}} \frac{\sqrt{\rho_{\text{max}}}}{2 \sqrt{\pi}} h0 \text{Exp}[-\rho_{\text{max}} \text{q}[\psi]], \{\psi, 0, \infty\}, \right. \\ \left. \text{Assumptions} \rightarrow \{\rho_{\text{max}} > 0, \psi_{\text{wt}} < 0\}\right] /. \text{mwt} \rightarrow \psi_{\text{wt}} (1 - \psi_{\text{wt}}/4) \text{mmax}; \\ \text{FullSimplify}\left[\% == \text{U} \frac{\left(1 - \frac{\psi_{\text{wt}}}{2}\right)^{\frac{1}{2} - \theta}}{1 - \frac{\psi_{\text{wt}}}{4}} \left(\frac{\text{Exp}[-\alpha]}{\sqrt{\pi \alpha}} - \text{Erfc}[\sqrt{\alpha}]\right) /. \alpha \rightarrow \frac{\rho_{\text{max}} \psi_{\text{wt}}^2}{4}, \right. \\ \left. \{\psi_{\text{wt}} < 0, \rho_{\text{max}} > 0, \text{U} > 0\}\right] \\ \text{True}$$

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

Approximating the probability of 2-step rescue

Defining “sufficiently critical” and “sufficiently non-critical” regimes (equation 7)

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

`prescuem[m, Λ]`

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

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

$$\text{Normal}\left[\text{Series}\left[\text{prescuem}[m, \Lambda] /. \Lambda \rightarrow \epsilon \text{Abs}[m]^2, \{\epsilon, 0, 1\}\right] /. \epsilon \rightarrow \frac{\Lambda}{\text{Abs}[m]^2}\right]$$

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

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

$$\text{Limit}[\text{prescuem}[m, \Lambda], m \rightarrow 0]$$

$$\text{Normal}\left[\text{Series}\left[\% /. \Lambda \rightarrow x^2, \{x, 0, 1\}\right] /. x \rightarrow \sqrt{\Lambda}\right]$$

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

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

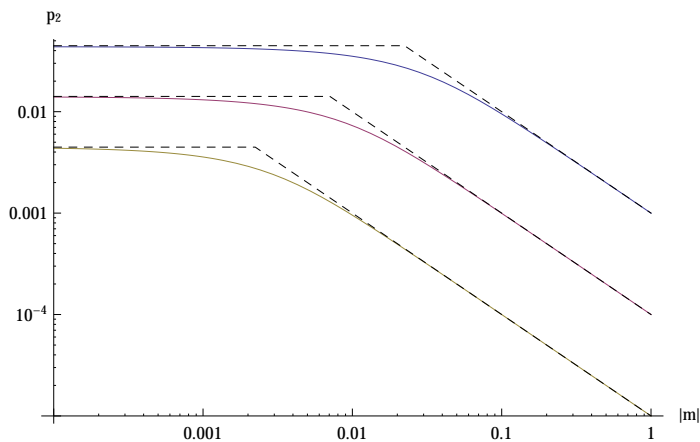
So we should transition from one approx to the other at

$$\text{Solve}\left[\sqrt{2\Lambda} = \Lambda / m, m\right] // \text{Flatten}$$

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

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[{"UR = 10-3", "UR = 10-4", "UR = 10-5"}] *),
  LogLogPlot[If[m < Sqrt[#/2], Sqrt[2 #], #/Abs[m]] & /@ {10-3, 10-4, 10-5},
    {m, 0.0001, 1}, PlotStyle → {Dashed, Black}], AxesLabel → {"|m|", "p2"}]
```



Approximate probability of rescue: sufficiently critical single mutants

Approximation (equation 7 and 8)

When $m \ll \sqrt{\Lambda/2}$ 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 $\Lambda[m] \sim \Lambda[0]$, $f(m|m_0) \sim f(0|m_0)$, and $\text{pest}(m) \sim 0$. So the rate of 2-step “sufficiently critical” rescue from single mutants is roughly

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

with $\Lambda_0 = \Lambda[0, mmax, \lambda, n, U]$.

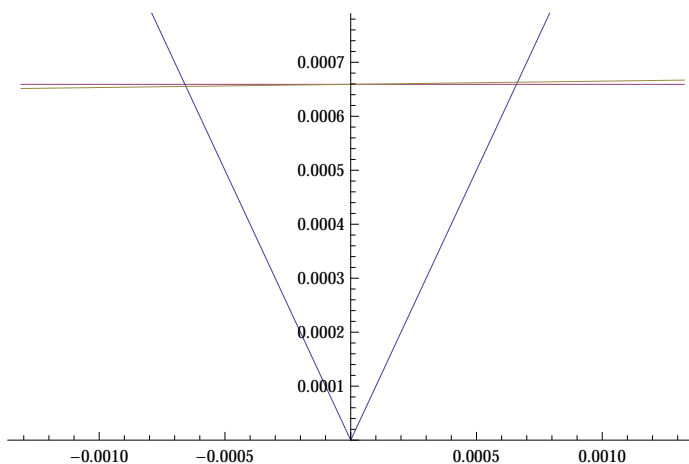
Check integration bounds:

```
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}]

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;

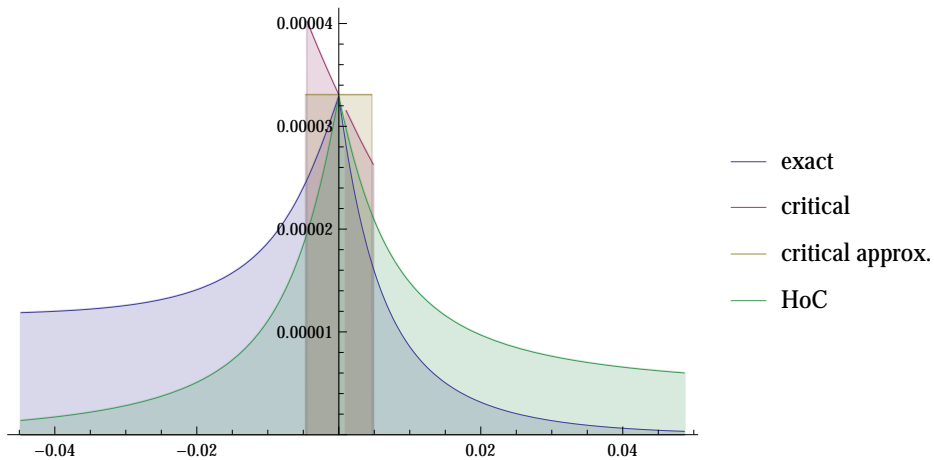
{mneg = FindRoot[2 m2 - λ1[m, mmax, λ, n, U], {m, -0.1}],
 mpos = FindRoot[2 m2 - λ1[m, mmax, λ, n, U], {m, 0.1}]}];
pr0 = √(λ1[0, mmax, λ, n, U] / 2);

{
  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]) √(2 λ1[m, mmax, λ, n, U])
  HeavisideTheta[(m - (m /. mneg)) ((m /. mpos) - m)],
  fm[0, m0, mmax, λ, n] √(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"}]]

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 m2 - Λ1[m, mmax, λ, n, U], {m, -0.1}],
 mpos = FindRoot[2 m2 - Λ1[m, mmax, λ, n, U], {m, 0.1}]}];
pr0 =  $\sqrt{\Lambda 1[0, mmax, \lambda, n, U] / 2}$ ;

{

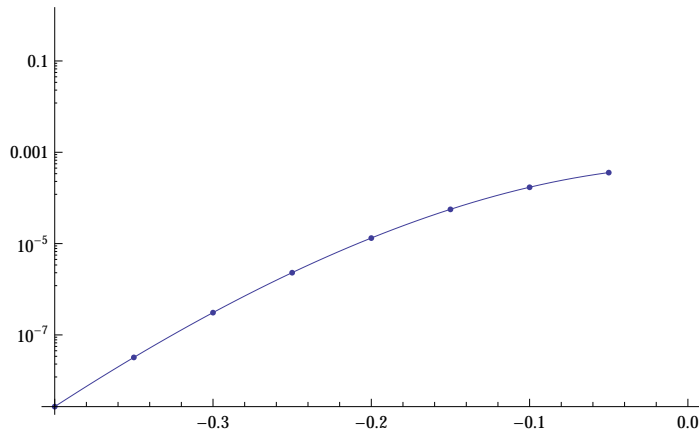
Table[{m0, NIntegrate[fm[m, m0, mmax, λ, n] (1 - pest[m])  $\sqrt{2 \Lambda 1[m, mmax, \lambda, n, U]}$  ,
 {m, m /. mneg, m /. mpos}]}], {m0, -0.8 mmax, -0.1 mmax, 0.1 mmax}]

};

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

Clear[mmax, λ, Es, n, U, n0]

```



Closed form approximation (equation 9 / equation A3)

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

$$2 \Lambda 0 \text{ fm}[0, m0, mmax, \lambda, n];$$

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

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

AnciauxEqnA12

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

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

$$m \text{ AnciauxEqnA12} /. \psi \text{wt} \rightarrow \psi /. m \rightarrow m_{\text{max}} \psi (1 - \psi / 4) /. \alpha \rightarrow \frac{\rho_{\text{max}} \psi^2}{4};$$

Limit[%, $\psi \rightarrow 0$];

Simplify[% /. $\rho_{\text{max}} \rightarrow m_{\text{max}} / \lambda$, { $m_{\text{max}} > 0$, $\lambda > 0$ }]

$$\frac{2 U \sqrt{m_{\text{max}} \lambda}}{\sqrt{\pi}}$$

Check contributions across m

```

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

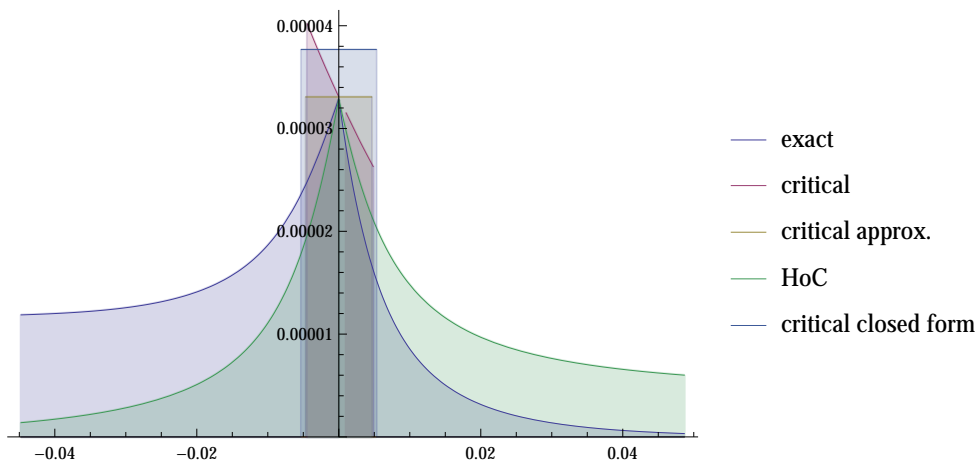
{mneg = FindRoot[2 m2 - Λ1[m, mmax, λ, n, U], {m, -0.1}],
 mpos = FindRoot[2 m2 - Λ1[m, mmax, λ, n, U], {m, 0.1}]}];
pr0 = √Λ1[0, mmax, λ, n, U] / 2 ;

{
  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]) √2 Λ1[m, mmax, λ, n, U]
  HeavisideTheta[(m - (m /. mneg)) ((m /. mpos) - m)],
  fm[0, m0, mmax, λ, n] √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] √2  $\frac{U \sqrt{mmax} \lambda}{\sqrt{\pi}}$ 
  HeavisideTheta $\left[ \left( m + \sqrt{\frac{U \sqrt{mmax} \lambda}{\sqrt{\pi}}} \right) \left( \sqrt{\frac{U \sqrt{mmax} \lambda}{\sqrt{\pi}}} - m \right) \right]$ 
};

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

Clear[mmax, λ, Es, n, U, mwt]

```



And check total rate

```

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

{mneg = FindRoot[2 m2 - Λ1[m, mmax, λ, n, U], {m, -0.1}],
 mpos = FindRoot[2 m2 - Λ1[m, mmax, λ, n, U], {m, 0.1}]};
pr0 = √Λ1[0, mmax, λ, n, U] / 2 ;

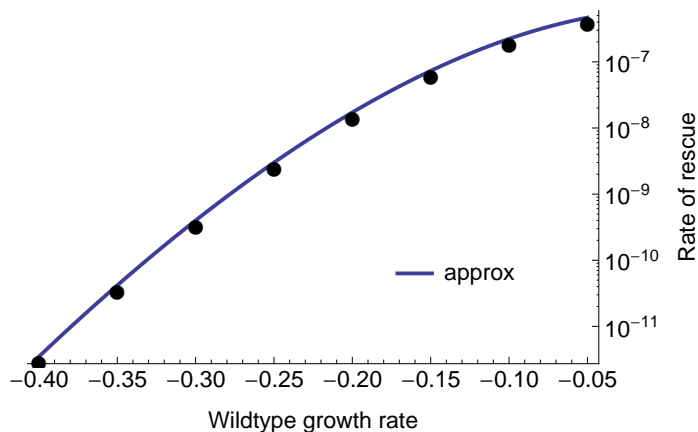
{
  Table[{m0, NIntegrate[U fm[m, m0, mmax, λ, n] (1 - pest[m]) √2 Λ1[m, mmax, λ, n, U] ,
    {m, m /. mneg, m /. mpos}]}], {m0, -0.8 mmax, -0.1 mmax, 0.1 mmax}]
};

Show[
  LogPlot[
    {U 2 Λ0approx fm[0, m0, mmax, λ, n]}, {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"}], Scaled@{3 / 4, 1 / 4}]
    ],
  ListLogPlot[%, PlotMarkers → {Automatic, Medium}, PlotStyle → Black]
]

(*Export[imagedir<>"p2CritApprox.pdf", %];*)

Clear[mmax, λ, Es, n, U, mwt]

```



Approximate probability of rescue: sufficiently non-critical single mutants

Approximation 1 (equation 7)

When $m \gg \sqrt{\Lambda/2}$ 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;

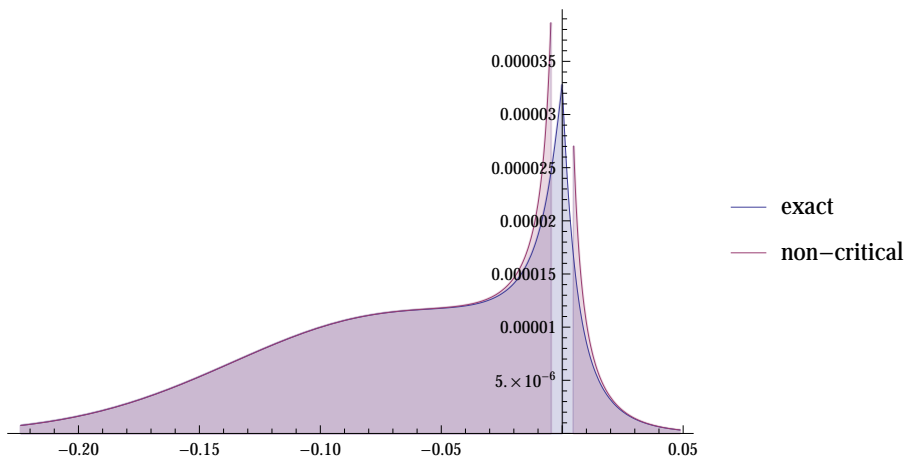
{mneg = FindRoot[2 m12 - Λ1[m1, mmax, λ, n, U], {m1, -0.1}],
 mpos = FindRoot[2 m12 - Λ1[m1, mmax, λ, n, U], {m1, 0.1}]}];
pr0 =  $\sqrt{\Lambda1[0, mmax, \lambda, n, U] / 2}$ ;

{
  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])
   $\frac{\Lambda1[m1, mmax, \lambda, n, U]}{\text{Abs}[m1]}$  HeavisideTheta[(-pr0 - m1) (pr0 - m1)]
};

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

Clear[mmax, λ, Es, n, U, mwt]

```



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


```

n0 = 104;
U = 10-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;

{mneg = FindRoot[2 m12 - Λ1[m1, mmax, λ, n, U], {m1, -0.1}],
 mpos = FindRoot[2 m12 - Λ1[m1, mmax, λ, n, U], {m1, 0.1}]}];
pr0 = √Λ1[0, mmax, λ, n, U] / 2 ;

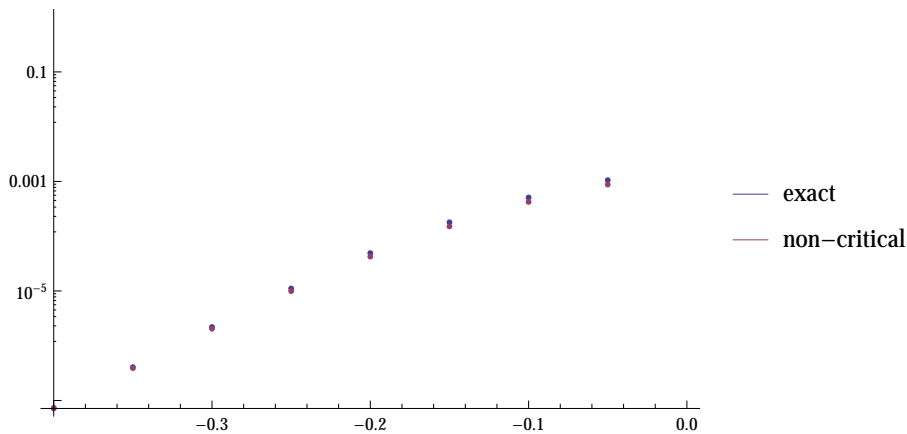
{
  Table[{mwt, NIntegrate[
    fm[m1, mwt, mmax, λ, n] (1 - pest[m1]) prescuem[m1, Λ1[m1, mmax, λ, n, U]],
    {m1, mwt, mmax}]}], {mwt, -0.8 mmax, -0.1 mmax, 0.1 mmax}],
  Table[{mwt, NIntegrate[fm[m1, mwt, mmax, λ, n]  $\frac{\Lambda1[m1, mmax, \lambda, n, U]}{\text{Abs}[m1]}$ 
    , {m1, mwt, -pr0}]}] +
    NIntegrate[fm[m1, mwt, mmax, λ, n] (1 - pest[m1])  $\frac{\Lambda1[m1, mmax, \lambda, n, U]}{\text{Abs}[m1]}$ 
    , {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 (approximate Λ_1 using equation A2)

We can next borrow the approximation of Λ_1 from Anciaux et al. (their eqn A12 without the $1/mwt$ term)

Abs[mwt] AnciauxEqnA12

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

Check contributions of m1

```

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

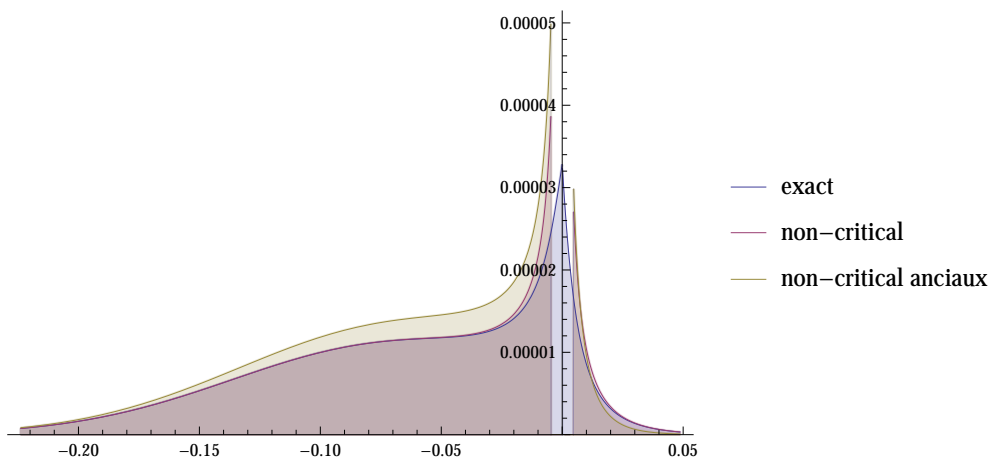
{mneg = FindRoot[2 m12 - λ1[m1, mmax, λ, n, U], {m1, -0.1}],
 mpos = FindRoot[2 m12 - λ1[m1, mmax, λ, n, U], {m1, 0.1}]}];
pr0 =  $\sqrt{\lambda1[0, mmax, \lambda, n, U] / 2}$ ;

{
  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])
   $\frac{\lambda1[m1, mmax, \lambda, n, U]}{\text{Abs}[m1]} \text{HeavisideTheta}[(-pr0 - m1) (pr0 - m1)]$ ,
  (
    fm[m1, mwt, mmax, λ, n] (1 - pest[m1])  $\frac{\text{Abs}[m1] \text{AnciauxEqnA12}}{\text{Abs}[m1]}$  /. ψwt → ψ /.
    m → mmax ψ (1 - ψ / 4) /. α →  $\frac{\rho_{\text{max}} \psi^2}{4}$  /. ψ →  $2 \left(1 - \sqrt{1 - \frac{m}{mmax}}\right)$  /.
    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"}]]

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 m12 - Λ1[m1, mmax, λ, n, U], {m1, -0.1}],
 mpos = FindRoot[2 m12 - Λ1[m1, mmax, λ, n, U], {m1, 0.1}]}];

pr0 = √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])
  
$$\frac{\Lambda1[m1, mmax, \lambda, n, U]}{\text{Abs}[m1]} \text{HeavisideTheta}[(-pr0 - m1) (pr0 - m1)],$$

  (
    fm[m1, mwt, mmax, λ, n] (1 - pest[m1])  $\frac{\text{Abs}[m1] \text{AnciauxEqnA12}}{\text{Abs}[m1]}$  /. ψwt → ψ /.
    
$$m \rightarrow mmax \psi (1 - \psi / 4) /. \alpha \rightarrow \frac{\rho_{max} \psi^2}{4} /. \psi \rightarrow 2 \left( 1 - \sqrt{1 - \frac{m}{mmax}} \right) /.$$

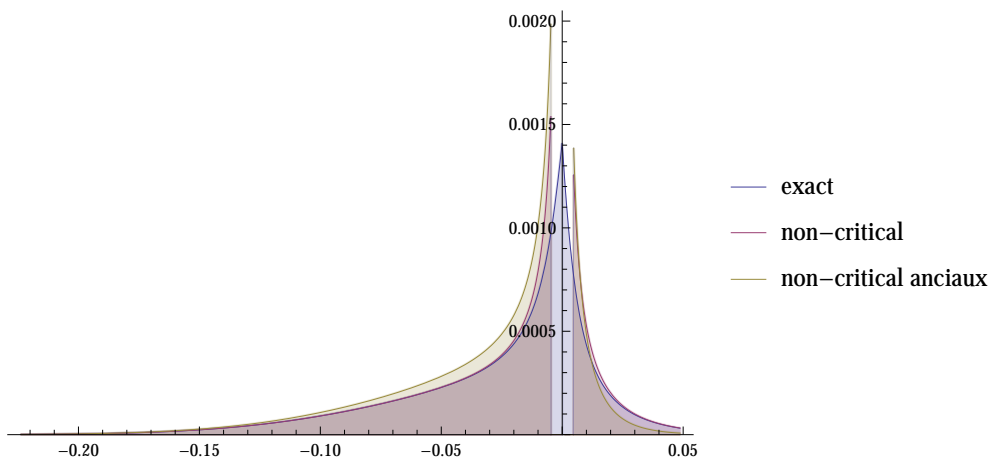
    
$$\rho_{max} \rightarrow mmax / \lambda /. \theta \rightarrow n / 2 /. m \rightarrow m1$$

  ) 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"}]]

Clear[mmax, λ, Es, n, U, mwt]

```



Closed form approximation - subcriticals (equations 10 and 11)

For the subcriticals our approximation for Λ_2 is now the integral of

fm[m, mwt, mmax, λ, n] AnciauxEqnA12

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

over m from $-\infty$ to $-m^*$, with α dependent on m .

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

$$f\psi \text{ AnciauxEqnA12} /. \alpha \rightarrow \frac{\rho_{\text{max}} \psi^2}{4}$$

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

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

Simplify[

$$\left(e^{-\frac{1}{4} \rho_{\text{max}} (\psi - \psi w t)^2} U \sqrt{\rho_{\text{max}}} \left(\frac{2 - \psi}{2 - \psi w t} \right)^{-\frac{1}{2}+\theta} \left(1 - \frac{\psi w t}{2} \right)^{\frac{1}{2}-\theta} \left(\frac{2 e^{-\frac{\rho_{\text{max}} \psi^2}{4}}}{\sqrt{\pi} \sqrt{\rho_{\text{max}} \psi^2}} - \text{Erfc}\left[\frac{\sqrt{\rho_{\text{max}} \psi^2}}{2}\right] \right) \right) / \\ \left(2 \sqrt{\pi} \left(1 - \frac{\psi w t}{4} \right) \right) == \text{constant} \psi \text{term}, \{\psi w t < 0\} \\ \left(e^{-\frac{1}{4} \rho_{\text{max}} (\psi - \psi w t)^2} U \sqrt{\rho_{\text{max}}} \left(\frac{2 - \psi}{2 - \psi w t} \right)^{-\frac{1}{2}+\theta} \left(1 - \frac{\psi w t}{2} \right)^{\frac{1}{2}-\theta} \left(\frac{2 e^{-\frac{\rho_{\text{max}} \psi^2}{4}}}{\sqrt{\pi} \sqrt{\rho_{\text{max}} \psi^2}} - \text{Erfc}\left[\frac{\sqrt{\rho_{\text{max}} \psi^2}}{2}\right] \right) \right) / \\ \left(2 \sqrt{\pi} \left(1 - \frac{\psi w t}{4} \right) \right)$$

True

over ψ between $-\infty$ and ψ^*

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

$$\left\{-\infty, 2 - 2 \sqrt{\frac{0.00466097 + \text{mmax}}{\text{mmax}}}\right\}$$

We make 2 different approximations. When $\psi - \psi w t$ and $\psi \rho_{\text{max}} = \psi \frac{\text{mmax}}{\lambda} = \psi \frac{\text{mmax} * n}{2 E s}$ are really small we

have

```
 $\psi_{\text{term}} /. \psi - \psi_{\text{wt}} \rightarrow \psi_{\text{wt}} + d\psi \epsilon /. \psi \rightarrow \psi \epsilon;$   
Simplify[Normal[Series[%, { $\epsilon$ , 0, -1}]] /.  $\epsilon \rightarrow 1$ , { $\psi < 0$ }]
```

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

And when ψ is small but ρ_{\max} is really large we have

```
 $\psi_{\text{term}} /. \rho_{\max} \rightarrow \rho_{\max} / \epsilon;$ 
```

```
Simplify[Normal[Series[%, { $\epsilon$ , 0, 2}]] /.  $\epsilon \rightarrow 1$ , { $\psi < 0$ }] /.  $\left(1 - \frac{\psi}{2}\right)^{\theta} \rightarrow 1 /.$ 
```

```
 $2 \pi - \pi \psi \rightarrow 2 \pi$ 
```

$$-\frac{4 e^{-\frac{1}{4} \rho_{\max} (\psi^2 + (\psi - \psi_{\text{wt}})^2)}}{\sqrt{\pi} \rho_{\max}^{3/2}} \psi^3$$

Compare numerically over m (from ψ_{wt} to ψ^*)

```

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

```

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

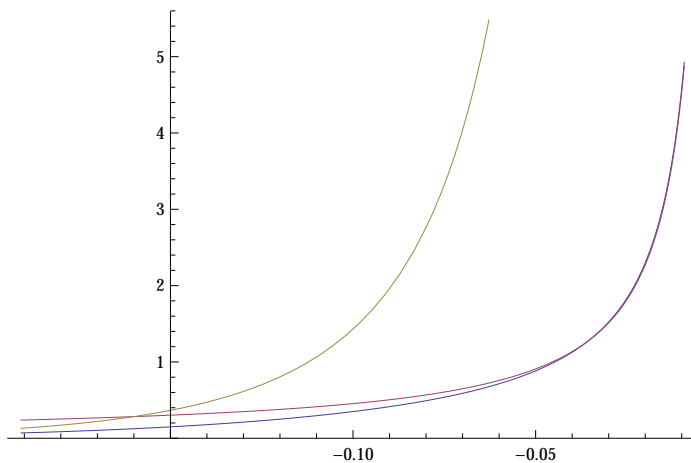
$$\psi_{\text{wt}} \rightarrow 2 \left(1 - \sqrt{1 - \frac{\text{mwt}}{\text{mmax}}} \right);$$

```

Plot[%, {ψ, 2 (1 - √[1 - mwt/mmax]), 2 - 2 √[(mmax + m*)/mmax]}, PlotRange → {0, Automatic}]

```

```
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 ρ_{max} approx as we increase ρ_{max} :

For $\rho_{\text{max}} = 10$

```

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

```

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

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

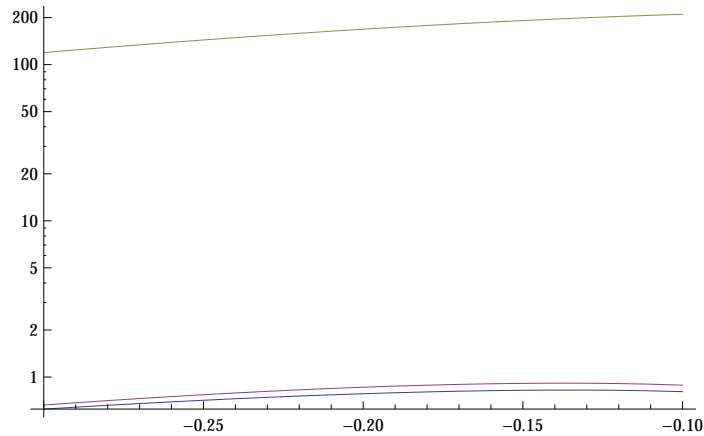
```

Table[Table[{mwt, NIntegrate[%[[i]], {ψ, 2 (1 - √(1 - mwt/mmax))}, 2 - 2 √(mmax + m*)/mmax}]}],
  {mwt, -0.3, -0.1, 0.01}], {i, Length[%]}];
ListLogPlot[%, Joined → True]

```

```
Clear[mmax, λ, Es, n, U, mwt]
```

```
10.
```



For $\rho_{\text{max}}=100$


```

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

```

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

$$\psi_{\text{wt}} \rightarrow 2 \left(1 - \sqrt{1 - \frac{m_{\text{wt}}}{m_{\text{max}}}} \right);$$

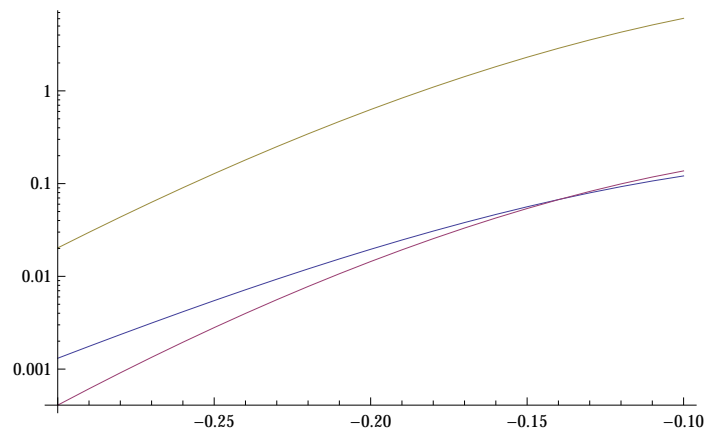
```

Table[Table[{mwt, NIntegrate[%[[i]], {ψ, 2 (1 - √(1 - mwt/mmax)) , 2 - 2 √(mmax + m*)/mmax }]}],
  {mwt, -0.3, -0.1, 0.01}], {i, Length[%]}];
ListLogPlot[%, Joined → True]

```

```
Clear[mmax, λ, Es, n, U, mwt]
```

```
100.
```



for $\rho_{\text{max}}=1000$

```

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

```

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

$$\psi_{\text{wt}} \rightarrow 2 \left(1 - \sqrt{1 - \frac{\text{mwt}}{m_{\text{max}}}} \right);$$

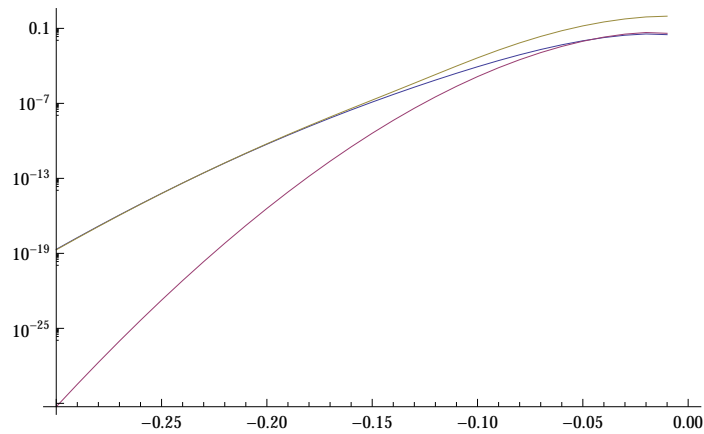
```

Table[Table[{mwt, NIntegrate[%[[i]], {ψ, 2 (1 - √(1 - mwt/mmax))}, 2 - 2 √(mmax + m*)/mmax}]}],
  {mwt, -0.3, -0.01, 0.01}], {i, Length[%]}];
ListLogPlot[%, Joined → True, PlotRange → All]

```

```
Clear[mmax, λ, Es, n, U, mwt]
```

```
1000.
```



and for $\rho_{\text{max}}=10000$

```

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

```

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

$$\psi_{\text{wt}} \rightarrow 2 \left(1 - \sqrt{1 - \frac{m_{\text{wt}}}{m_{\text{max}}}} \right);$$

```

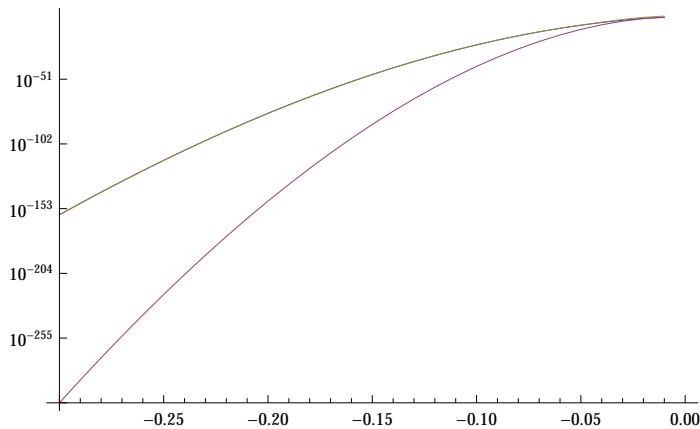
Table[Table[{mwt, NIntegrate[%[[i]], {ψ, 2 (1 - √(1 - mwt/mmax)) , 2 - 2 √(mmax + m*)/mmax }]}],
  {mwt, -0.3, -0.01, 0.01}], {i, Length[%]}];
ListLogPlot[%, Joined → True, PlotRange → All]

```

```

Clear[mmax, λ, Es, n, U, mwt]
10 000.

```



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

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

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

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

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

And for the large ρ_{\max} we need to integrate

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

here we can again use the Laplace approx with

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

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

and we know that q is peaked at

`Solve[D[q[ψ], ψ] == 0, ψ]`

$$\left\{ \left\{ \psi \rightarrow \frac{\psi_{\text{wt}}}{2} \right\} \right\}$$

where h equals

$$h[\psi_{\text{wt}} / 2] \\ -\frac{32}{\sqrt{\pi} \rho_{\max}^{3/2} \psi_{\text{wt}}^3}$$

giving

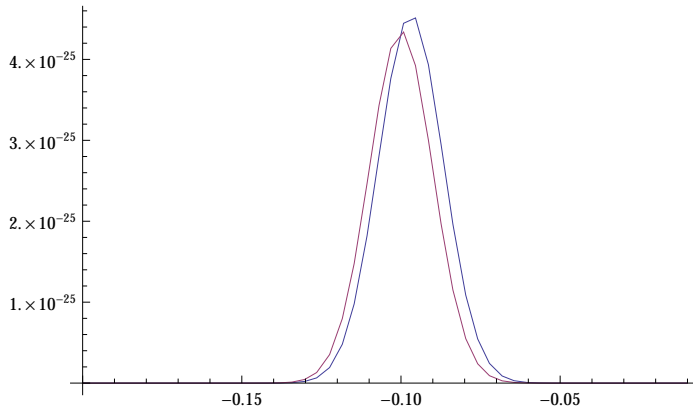
`h[ψwt / 2] Exp[q[ψ]]`

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

$$-\frac{32 e^{-\frac{1}{4} \rho_{\max} (\psi^2 + (\psi - \psi_{\text{wt}})^2)}}{\sqrt{\pi} \rho_{\max}^{3/2} \psi_{\text{wt}}^3}$$

Numerical check

```
{largeapprox, verylargeapprox} /. rho_max -> 10 000 /. psiwt -> -0.2;
Plot[%, {psi, -0.2, -0.01}, PlotRange -> All]
```



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

```
Integrate[verylargeapprox, {psi, -infinity, infinity}, Assumptions -> {rho_max > 0, psiwt < 0}]
```

$$-\frac{32\sqrt{2}e^{-\frac{\rho_{\max}\psi_{\text{wt}}^2}{8}}}{\rho_{\max}^2\psi_{\text{wt}}^3}$$

OK, so our small ρ_{\max} approx for the probability of 2-step subcritical rescue is

```
smallpsiapproxRescuepsi =
```

```
constant Integrate[smallpsiapprox, {psi, a, b}, Assumptions -> {a < b < 0}]
```

```
smallpsiapproxRescue =
```

$$\% /. a \rightarrow 2 \left(1 - \sqrt{1 - \frac{\text{mwt}}{\text{mmax}}} \right) /. b \rightarrow 2 \left(1 - \sqrt{1 + \frac{\text{mstar}}{\text{mmax}}} \right) /. \text{mstar} \rightarrow \sqrt{\Lambda_0 \text{approx} / 2} /.$$

$$\rho_{\max} \rightarrow \text{mmax} / \lambda /. \theta \rightarrow n / 2 /. \psi_{\text{wt}} \rightarrow 2 \left(1 - \sqrt{1 - \frac{\text{mwt}}{\text{mmax}}} \right)$$

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

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

and our very large ρ_{\max} approx for the probability of 2-step subcritical rescue is

```
verylargeapproxRescueψ =
```

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

```
verylargeapproxRescue = % /. ρmax → mmax / λ /. θ → n / 2 /. ψwt → 2  $\left(1 - \sqrt{1 - \frac{\text{mwt}}{\text{mmax}}}\right)$ 
```

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

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

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

Check formula for text

```
Simplify[
```

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

```
Simplify[verylargeapproxRescueψ ==
```

$$\left(-\text{U} \frac{\left(1 - \frac{\psi_{\text{wt}}}{2}\right)^{1-2\theta}}{\left(1 - \frac{\psi_{\text{wt}}}{4}\right)} \left(e^{-\alpha} \frac{1}{(\alpha/2)^3 \pi} \right)^{1/2} /. \alpha \rightarrow \rho_{\max} \psi_{\text{wt}}^2 / 4, \{\rho_{\max} > 0, \psi_{\text{wt}} > 0\} \right)$$

True

True

Compare to better approximation

```

n0 = 104;
U = 10-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;

{mneg = FindRoot[2 m12 - λ1[m1, mmax, λ, n, U], {m1, -0.1}],
 mpos = FindRoot[2 m12 - λ1[m1, mmax, λ, n, U], {m1, 0.1}]}];
pr0 =  $\sqrt{\lambda_1[0, m_{\max}, \lambda, n, U] / 2}$ ;

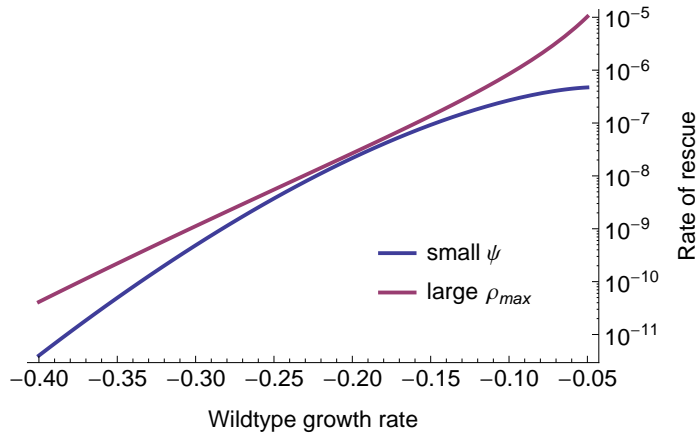
{
  Table[
    {mwt, UNIntegrate[fm[m1, mwt, mmax, λ, n]  $\frac{\lambda_1[m1, mmax, \lambda, n, U]}{\text{Abs}[m1]}$ ],
     {m1, mwt, -pr0}], {mwt, -0.8 mmax, -0.1 mmax, 0.1 mmax}
  ];

Show[
  LogPlot[
    {U small ψ approx Rescue, U very large ρ approx Rescue}, {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] *)
]

(*Export[imagedir<>"p2SubApprox.pdf", %];*)

Clear[mmax, λ, Es, n, U, n0]

```



Closed form approximation - supercriticals (equation 12)

For the supercriticals our approximation for Λ_2 is now the integral of

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

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

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

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

$$f\psi(1 - \text{pest}[m]) \text{AnciauxEqnA12} /. \alpha \rightarrow \frac{\rho_{\max} \psi^2}{4} /. m \rightarrow m_{\max}(1 - \psi/4) \psi$$

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

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

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

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

True

over ψ between ψ^* and 2

Clear[m]

$$\text{Simplify}\left[2 \left(1 - \sqrt{1 - \frac{m}{m_{\max}}}\right) /. m \rightarrow \{m_{\text{star}}, m_{\max}\}, m_{\max} > 0\right]$$

$$\left\{2 - 2 \sqrt{1 - \frac{m_{\text{star}}}{m_{\max}}}, 2\right\}$$

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 $\psi - \psi_{\text{wt}}$ and $\psi \rho_{\max} = \psi \frac{m_{\max}}{\lambda} = \psi \frac{m_{\max} \cdot n}{2 E_s}$ are really small, giving

$$\psi_{\text{term}} /. \psi \rightarrow \psi \epsilon;$$

$$\text{Simplify}[\text{Normal}[\text{Series}[\%, \{\epsilon, 0, -1\}]] /. \epsilon \rightarrow 1, \{\psi > 0\}]$$

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

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

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

which has a simple expression

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

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

OK, so our small ρ_{\max} approx for the probability of 2-step supercritical rescue is

```
smallψapproxRescueSuperψ =
```

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

```
smallψapproxRescueSuper =
```

$$\% /. a \rightarrow 2 \left(1 - \sqrt{1 - \frac{m_{\text{star}}}{m_{\text{max}}}} \right) /. b \rightarrow \frac{\sqrt{2}}{\sqrt{\rho_{\max}}} /. m_{\text{star}} \rightarrow \sqrt{\Lambda 0_{\text{approx}} / 2} /. \rho_{\max} \rightarrow m_{\text{max}} / \lambda /.$$

$$\theta \rightarrow n / 2 /. \psi_{\text{wt}} \rightarrow 2 \left(1 - \sqrt{1 - \frac{m_{\text{wt}}}{m_{\text{max}}}} \right)$$

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

$$\left(e^{-\frac{m_{\text{max}} \left(1 - \sqrt{1 - \frac{m_{\text{wt}}}{m_{\text{max}}}} \right)^2}{\lambda}} \left(1 - \frac{m_{\text{wt}}}{m_{\text{max}}} \right)^{\frac{1-n}{2}} U \text{Log}\left[\frac{1}{\sqrt{2} \sqrt{\frac{m_{\text{max}}}{\lambda}} \left(1 - \sqrt{1 - \frac{\sqrt{U \sqrt{m_{\text{max}} \lambda}}}{m_{\text{max}} \pi^{1/4}}}} \right)} \right] \right) /$$

$$\left(\left(1 + \frac{1}{2} \left(-1 + \sqrt{1 - \frac{m_{\text{wt}}}{m_{\text{max}}}} \right) \right) \right) \pi$$

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

Check formula in text

$$\text{Simplify}\left[\frac{U \left(1 - \frac{\psi_{\text{wt}}}{2} \right)^{1-2\theta}}{\left(1 - \frac{\psi_{\text{wt}}}{4} \right)} e^{-\alpha \text{Log}\left[\frac{b}{a}\right]} / \pi == \text{smallψapproxRescueSuperψ} /. \alpha \rightarrow \frac{\rho_{\max} \psi_{\text{wt}}^2}{4} \right]$$

True

Compare to better approximation

```

n0 = 104;
U = 10-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;

{mneg = FindRoot[2 m12 - Λ1[m1, mmax, λ, n, U], {m1, -0.1}],
 mpos = FindRoot[2 m12 - Λ1[m1, mmax, λ, n, U], {m1, 0.1}]}];
pr0 =  $\sqrt{\Lambda1[0, mmax, \lambda, n, U] / 2}$ ;

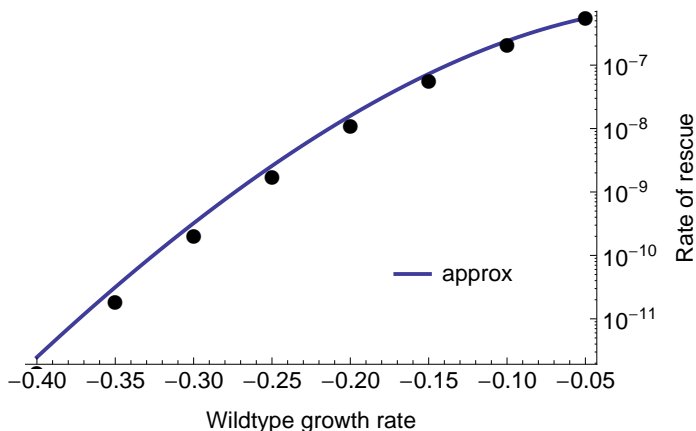
{
  Table[{mwt, UNIntegrate[fm[m1, mwt, mmax, λ, n] (1 - pest[m1])  $\frac{\Lambda1[m1, mmax, \lambda, n, U]}{\text{Abs}[m1]}$ ], {m1, pr0, mmax}]}], {mwt, -0.8 mmax, -0.1 mmax, 0.1 mmax}]}];
};

Show[
  LogPlot[
    {U small#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]
]

(*Export[imagedir<"p2SuperApprox.pdf",%];*)

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

```

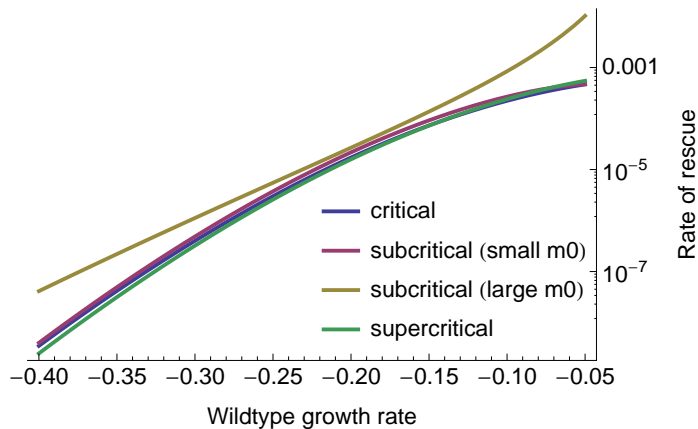
n0 = 104;
U = 10-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;

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}]
  ]
]

(*Export[imagedir<>"p2SuperApprox.pdf",%];*)

Clear[mmax, λ, Es, n, U, n0]

```



or in terms of relative contributions

```

n0 = 104;
U = 10-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;

{verylargeapproxRescue, 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
  ];

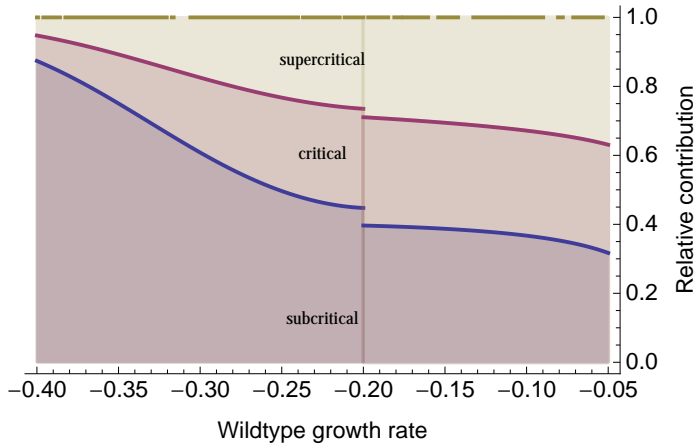
(*Export[imagedir<>"p2SuperApprox.pdf",%];*)

{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 = 104;
U = 10-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;

{mneg = FindRoot[2 m12 - Λ1[m1, mmax, λ, n, U], {m1, -0.1}],
 mpos = FindRoot[2 m12 - Λ1[m1, mmax, λ, n, U], {m1, 0.1}]}];
pr0 = √(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]  $\frac{\Lambda1[m1, mmax, \lambda, n, U]}{\text{Abs}[m1]}$ ,
    {m1, mwt, -pr0}], {mwt, -0.8 mmax, -0.1 mmax, 0.1 mmax}],
  Table[NIntegrate[fm[m1, mwt, mmax, λ, n] (1 - pest[m1])  $\sqrt{2 \Lambda1[m1, mmax, \lambda, n, U]}$ ,
    {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])  $\frac{\Lambda1[m1, mmax, \lambda, n, U]}{\text{Abs}[m1]}$ ,
    {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[%];

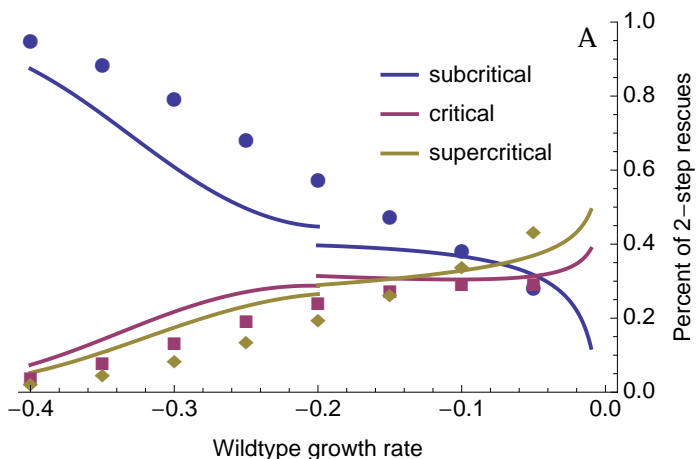
{verylarge $\rho$ approxRescue, 2  $\Delta$ 0approx fm[0, mwt, mmax,  $\lambda$ , n] , small $\psi$ approxRescueSuper};

%
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 -> {Automatic, Medium}, PlotRange -> {0, 1}],
PlotRange -> {{-0.4, 0}, {0, 1}}
]

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

```

```
Clear[mmax,  $\lambda$ , Es, n, U, n0]
```



or across mutation rate for a given m_0

```

n0 = 104;
mwt = -0.1;
mmax = 0.5;
 $\lambda$  = 2 Es / n;
Es = 0.01;

```

```

n = 4;
U = 10x;

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

temptab2 = Table[
  mneg = FindRoot[2 m12 -  $\Lambda$ 1[m1, mmax,  $\lambda$ , n, U], {m1, -0.1}];
  mpos = FindRoot[2 m12 -  $\Lambda$ 1[m1, mmax,  $\lambda$ , n, U], {m1, 0.1}];
  pr0 =  $\sqrt{\Lambda$ 1[0, mmax,  $\lambda$ , n, U] / 2 ;
  {
    NIntegrate[fm[m1, mwt, mmax,  $\lambda$ , n]  $\frac{\Lambda$ 1[m1, mmax,  $\lambda$ , n, U]}{Abs[m1]}, {m1, mwt, -pr0}],
    NIntegrate[fm[m1, mwt, mmax,  $\lambda$ , n] (1 - pest[m1])  $\sqrt{2 \Lambda$ 1[m1, mmax,  $\lambda$ , n, U]},
      {m1, m1 /. mneg, m1 /. mpos}],
    NIntegrate[fm[m1, mwt, mmax,  $\lambda$ , n] (1 - pest[m1])  $\frac{\Lambda$ 1[m1, mmax,  $\lambda$ , 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[%]}];

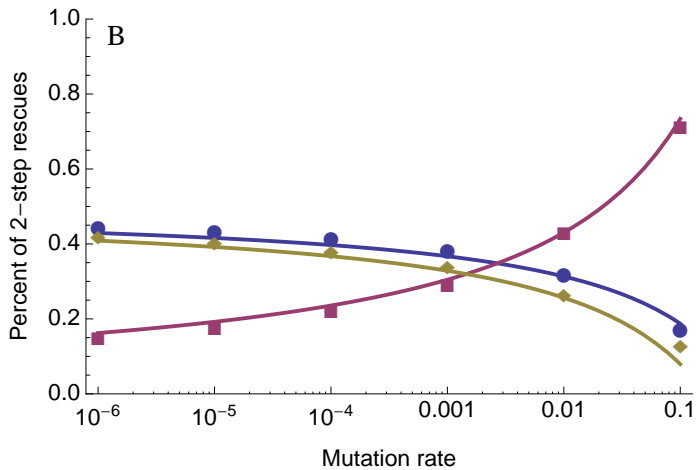
Clear[U]
 $\frac{2 \Lambda$ 0approx fm[0, mwt, mmax,  $\lambda$ , n] , small $\frac{1}{\Lambda$ approxRescueSuper};
Total[%]
(*Accumulate[%];*)
Show[
  LogLinearPlot[
    %, {U, 10-6, 10-1},
    PlotRange → {0, 1},
    PlotStyle → Thick,
    Frame → {True, True, False, False},
    FrameLabel → {"Mutation 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 → {Automatic, Medium}, PlotRange → {0, 1}]
]

```



```
(*Export[imagedir<>"p2RelContrMutationSlow.pdf",%];*)
```

```
Clear[mmax, λ, Es, n, mwt, n0, U]
```



and with a more negative m0

```
n0 = 104;
mwt = -0.3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
U = 10x;
```

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

```
temptab3 = Table[
  mneg = FindRoot[2 m12 - λ1[m1, mmax, λ, n, U], {m1, -0.1}];
  mpos = FindRoot[2 m12 - 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]  $\frac{\lambda1[m1, mmax, \lambda, n, U]}{\text{Abs}[m1]}$ , {m1, mwt, -pr0}],
    NIntegrate[fm[m1, mwt, mmax, λ, n] (1 - pest[m1])  $\sqrt{2 \lambda1[m1, mmax, \lambda, n, U]}$ ,
      {m1, m1 /. mneg, m1 /. mpos}],
    NIntegrate[fm[m1, mwt, mmax, λ, n] (1 - pest[m1])  $\frac{\lambda1[m1, mmax, \lambda, n, U]}{\text{Abs}[m1]}$ ,
      {m1, pr0, mmax}]
  }
, {x, -6, -1, 1}];
temptab3;
```

```

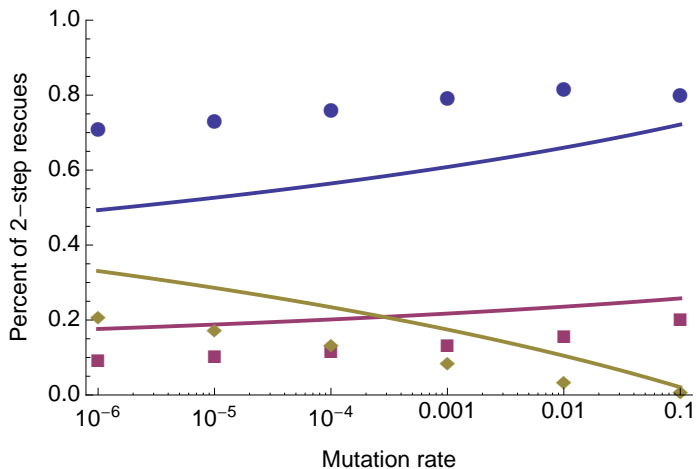
Table[%[[i]] / Total[%[[i]]], {i, Length[%]};
test = Transpose[%];
(*Accumulate[%]*)
data = Table[Transpose[Join[{xs}, {%[[i]]}, 1]], {i, Length[%]};

Clear[U]
{verylargeapproxRescue,
  2  $\wedge$  0approx fm[0, mwt, mmax,  $\lambda$ , n] , small/approxRescueSuper};
%
Total[%];
(*Accumulate[%];*)
Show[
  LogLinearPlot[
    %, {U, 10-6, 10-1},
    PlotRange  $\rightarrow$  {0, 1},
    PlotStyle  $\rightarrow$  Thick,
    Frame  $\rightarrow$  {True, True, False, False},
    FrameLabel  $\rightarrow$  {"Mutation rate", "Percent of 2-step rescues", , },
    FrameTicks  $\rightarrow$  {True, True, False, False},
    LabelStyle  $\rightarrow$  labelstyle
  ],
  ListLogLinearPlot[data, PlotMarkers  $\rightarrow$  {Automatic, Medium}, PlotRange  $\rightarrow$  {0, 1}]
]

(*Export[imagedir<>"p2RelContrMutationFast.pdf",%];*)

```

```
Clear[mmax,  $\lambda$ , Es, n, mwt, n0, U]
```



and sum them to get the total rate of rescue

```

n0 = 104;
U = 10-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;

{mneg = FindRoot[2 m12 - λ1[m1, mmax, λ, n, U], {m1, -0.1}],
 mpos = FindRoot[2 m12 - λ1[m1, mmax, λ, n, U], {m1, 0.1}]}];
pr0 =  $\sqrt{\lambda_1[0, mmax, \lambda, n, U] / 2}$ ;

{
  Table[{mwt, 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}]
};

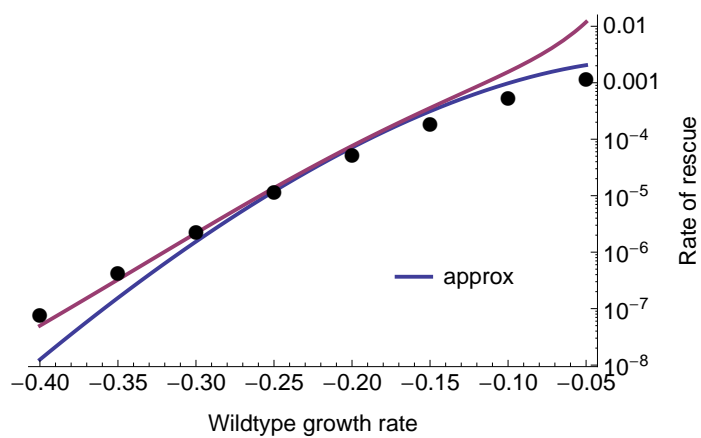
{
  Total[{2 Δ0approx fm[0, mwt, mmax, λ, n],
    smallψapproxRescue, smallψapproxRescueSuper}],
  Total[{2 Δ0approx fm[0, mwt, mmax, λ, n], verylargeψapproxRescue,
    smallψapproxRescueSuper}]
};

Show[
  LogPlot[
    %, {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]
]

(*Export[imagedir<>"p2SuperApprox.pdf",%];*)

Clear[mmax, λ, Es, n, U, n0]

```



or use this rate to get the total probability of rescue

```

N0 = 104;
U = 10-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;

{mneg = FindRoot[2 m12 - λ1[m1, mmax, λ, n, U], {m1, -0.1}],
 mpos = FindRoot[2 m12 - λ1[m1, mmax, λ, n, U], {m1, 0.1}]}];
pr0 =  $\sqrt{\lambda_1[0, mmax, \lambda, n, U] / 2}$ ;

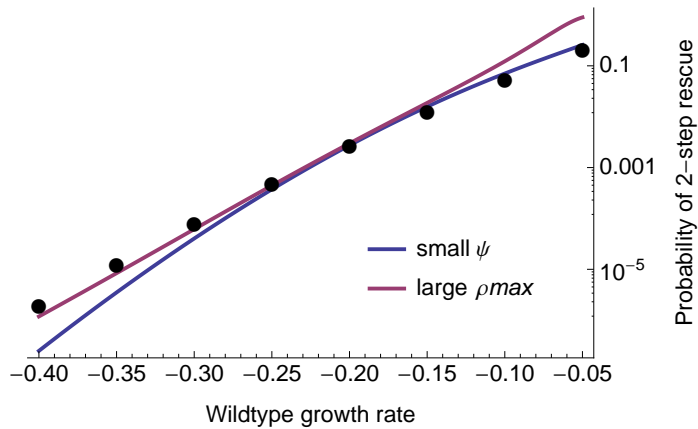
tab = {
  Table[{
    mwt,
    rescue /. p0 → rescuem[mwt, U Integrate[fm[m1, mwt, mmax, λ, n]
      (1 - pest[m1]) rescuem[m1, λ1[m1, mmax, λ, n, U]], {m1, -∞, mmax}]]],
    {mwt, -0.8 mmax, -0.1 mmax, 0.1 mmax}
  ]};

{
  rescue /. p0 → rescuem[mwt, U Total[{2 λ0approx fm[0, mwt, mmax, λ, n],
    smallψapproxRescue, smallψapproxRescueSuper}]],
  rescue /. p0 → rescuem[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]
]

(*Export[imagedir<>"p2TotalApprox.pdf",%];
*)
Clear[mmax, λ, Es, n, U, N0]

```



Distribution of growth rates given rescue

Distribution of growth rates among 1-step rescue mutants (equations 13 and 14)

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

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

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

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

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

$$h0 = \text{Normal}[\text{Series}[h[\psi], \{\psi, 0, 1\}]];$$

$$g_{1m} \text{approx} = \text{Simplify} \left[\frac{\frac{U}{-\text{mwt}} \frac{\sqrt{\rho_{\text{max}}}}{2 \sqrt{\pi}} h0 \text{Exp}[-\rho_{\text{max}} q[\psi]]}{\text{AnciauxEqnA12}} \right]$$

$$\frac{e^{\alpha - \frac{1}{4} \rho_{\text{max}} (\psi - \psi_{\text{wt}})^2} \sqrt{\alpha \rho_{\text{max}}} \psi}{\psi_{\text{wt}} (-1 + e^{\alpha \sqrt{\pi} \sqrt{\alpha} \text{Erfc}[\sqrt{\alpha}]})} /. \text{mwt} \rightarrow \text{mmax} (4 - \psi_{\text{wt}}) \psi_{\text{wt}} / 4, \{\psi_{\text{wt}} < 0, \alpha > 0, \rho_{\text{max}} > 0\}$$

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

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

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

Numerically compare

```

mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
mwt = -0.1;
{
    glm,
    scaleglapprox glmapprox
} /. α → ψwt2 ρmax / 4 /. ρmax → mmax / λ /. θ → n / 2 /. ψwt → 2  $\left(1 - \sqrt{1 - \frac{\text{mwt}}{\text{mmax}}}\right)$  /.

```

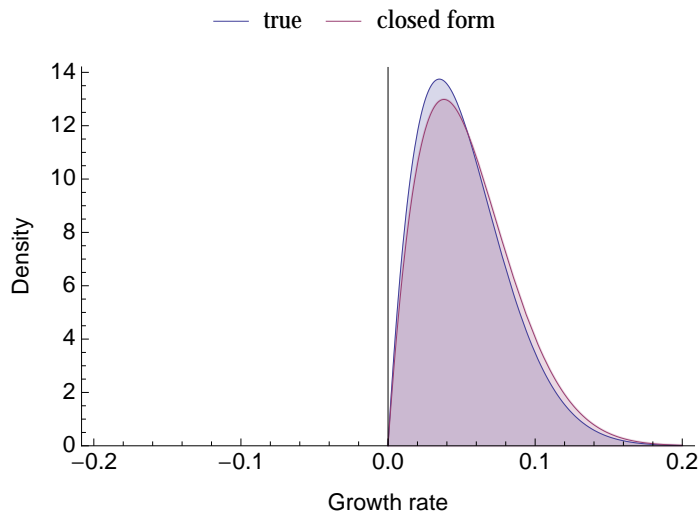
$$\psi \rightarrow 2 \left(1 - \sqrt{1 - \frac{m}{\text{mmax}}}\right);$$

```

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 15)

The rate of 2-step rescue through double mutants with growth rate m_2 is

```

g2numerator[m0_, m2_?NumericQ] := UNIntegrate[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 m_2 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 / 8, 1 / 2}]]];

{
  (*1 step*)
  Table[{m2, glm /. m → m2}, {m2, 0, xmax, 0.005}],
  (*2 step*)
  total = Re[g2denominator[mwt]];
  Table[{m2,  $\frac{1}{\text{total}}$  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 / 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,
  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}}]}
}
]

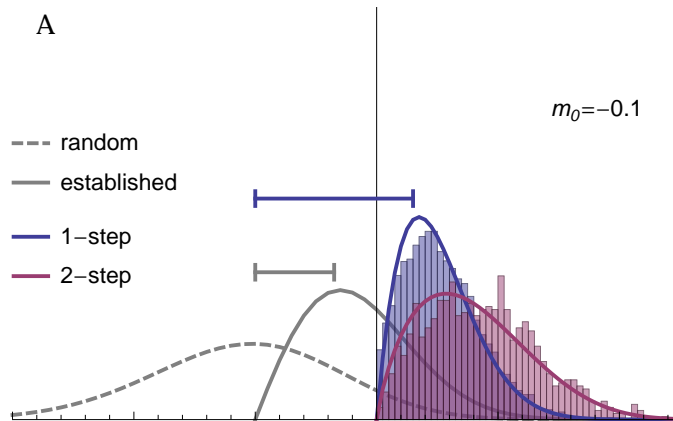
```

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

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,
  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}]}
  }
]

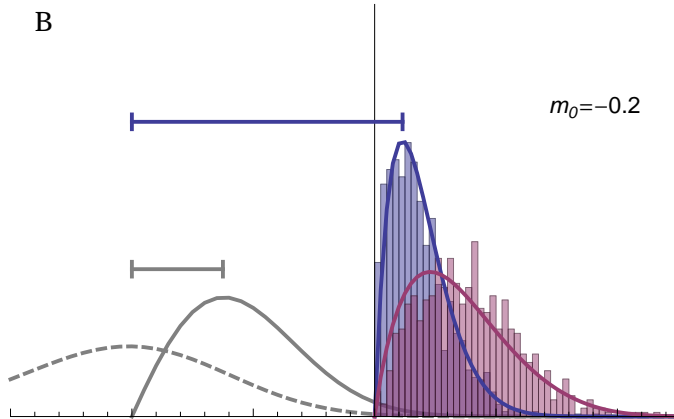
(*Export[imagedir<>"2step_m2_medm0_sims.pdf",%];*)

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, glm /. m → m2}, {m2, 0, xmax, 0.005}],
  (*2 step*)
  total = Re[g2denominator[mwt]];
  Table[{m2,  $\frac{1}{\text{total}}$  g2numerator[mwt, m2]}, {m2, 0, xmax, 0.005}]
};

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

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,
  PlotRange → {{xmin, xmax}, {0, ymax}},

```

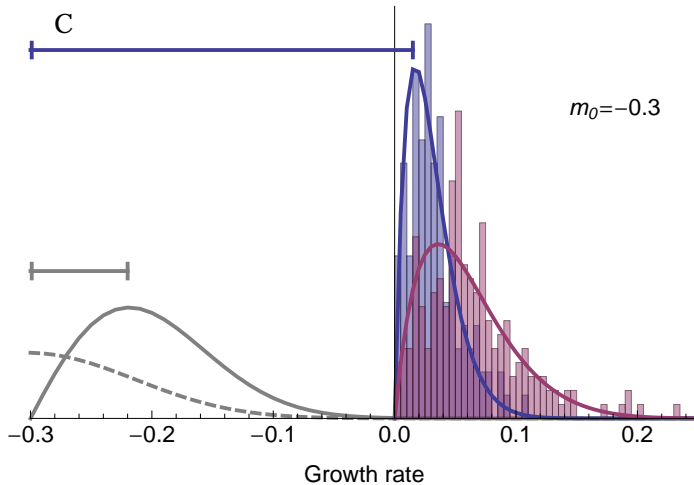
```

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]
```



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

Distribution of first-step growth rates in 2-step rescue genotypes (equation 16)

As, in the 1-step case, we can use the Λ_2 term to write the distribution of growth rates of rescue genotypes

```

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

```

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

For sufficiently subcritical m near $-m^*$ we have

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

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

`smallψapprox`

`%`

$$D\left[2 \left(1 - \sqrt{1 - \frac{m}{m\text{max}}}\right), m\right] \% /. a \rightarrow 2 \left(1 - \sqrt{1 - \frac{m\text{wt}}{m\text{max}}}\right) /. b \rightarrow 2 \left(1 - \sqrt{1 + \frac{m\text{star}}{m\text{max}}}\right) /.$$

$$m\text{star} \rightarrow \sqrt{\Lambda 0\text{approx} / 2} /. \rho\text{max} \rightarrow m\text{max} / \lambda /. \theta \rightarrow n / 2 /.$$

$$\psi\text{wt} \rightarrow 2 \left(1 - \sqrt{1 - \frac{m\text{wt}}{m\text{max}}}\right) /. \psi \rightarrow 2 \left(1 - \sqrt{1 - \frac{m}{m\text{max}}}\right) // \text{Simplify}$$

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

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

Compare distribution of subcriticals

```

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

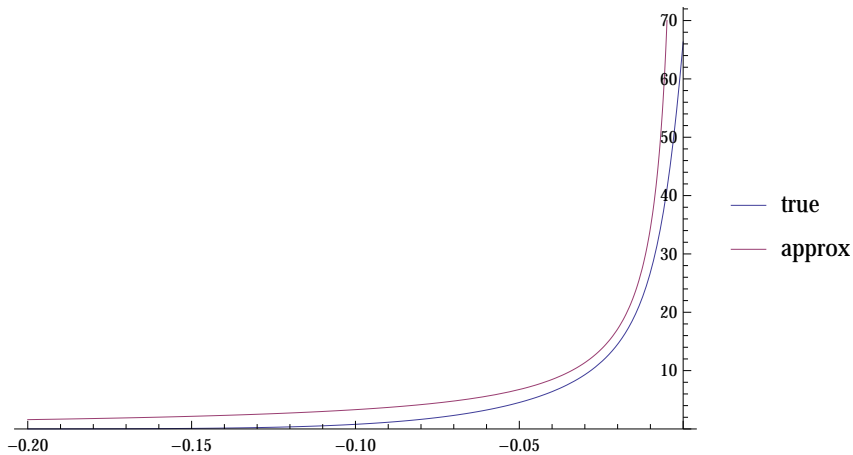
total = UNIntegrate[
  fm[m, mwt, mmax, λ, n] (1 - pest[m]) prescuem[m, λ1[m, mmax, λ, n, U]], {m, -∞, 0}];

Show[
  Plot[ $\frac{1}{\text{total}}$  U fm[m, mwt, mmax, λ, n] (1 - pest[m]) prescuem[m, λ1[m, mmax, λ, n, U]],
    {m, -0.2, 0}, PerformanceGoal → "Speed", PlotRange → {0, All}],

  Plot[ $\left\{, -1 / \left( 2 \left( -1 + \sqrt{1 - \frac{m}{mmax}} \right) \sqrt{1 - \frac{m}{mmax}} mmax \text{Log} \left[ \frac{1 - \sqrt{1 + \frac{\sqrt{U \sqrt{mmax} \lambda}}{mmax \pi^{1/4}}}}{1 - \sqrt{1 - \frac{mwt}{mmax}}} \right] \right) \right\},$ 
    {m, -0.2, 0}, PlotRange → {0, 70}, PlotLegends → {"true", "approx"}]
]

Clear[mmax, λ, Es, n, U, mwt]

```



and for large ρ_{max} we have

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

`Integrate[verylarge\rhoapprox, {\psi, -\infty, 0}, Assumptions -> {\rho\text{max} > 0, \psi\text{wt} < 0}];`
`verylarge\rhoapprox`

`%`

`Simplify[`

$$D\left[2\left(1-\sqrt{1-\frac{m}{m\text{max}}}\right), m\right] \% /. a \rightarrow 2\left(1-\sqrt{1-\frac{m\text{wt}}{m\text{max}}}\right) /. b \rightarrow 2\left(1-\sqrt{1+\frac{m\text{star}}{m\text{max}}}\right) /. m\text{star} \rightarrow$$

$$\sqrt{\Lambda 0\text{approx}/2} /. \rho\text{max} \rightarrow m\text{max}/\lambda /. \theta \rightarrow n/2 /. \psi\text{wt} \rightarrow 2\left(1-\sqrt{1-\frac{m\text{wt}}{m\text{max}}}\right) /.$$

$$\psi \rightarrow 2\left(1-\sqrt{1-\frac{m}{m\text{max}}}\right), \{m < 0, m\text{wt} < 0, m\text{max} > 0, \lambda > 0\}$$

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

$$\text{Erfc}\left[\frac{\sqrt{\rho\text{max}}\psi\text{wt}}{2\sqrt{2}}\right]$$

$$\left(e^{\frac{4m-6m\text{max}+4\sqrt{m\text{max}}(-m+m\text{max})-2\sqrt{m\text{max}}(m\text{max}-m\text{wt})+4\sqrt{(-m+m\text{max})}(m\text{max}-m\text{wt})+m\text{wt}}{2\lambda}}\sqrt{\frac{2}{\pi}}\right)/$$

$$\left(\sqrt{(-m+m\text{max})\lambda}\text{Erfc}\left[\frac{\left(1-\sqrt{1-\frac{m\text{wt}}{m\text{max}}}\right)\sqrt{\frac{m\text{max}}{\lambda}}}{\sqrt{2}}\right]\right)$$

compare distribution of subcriticals

```

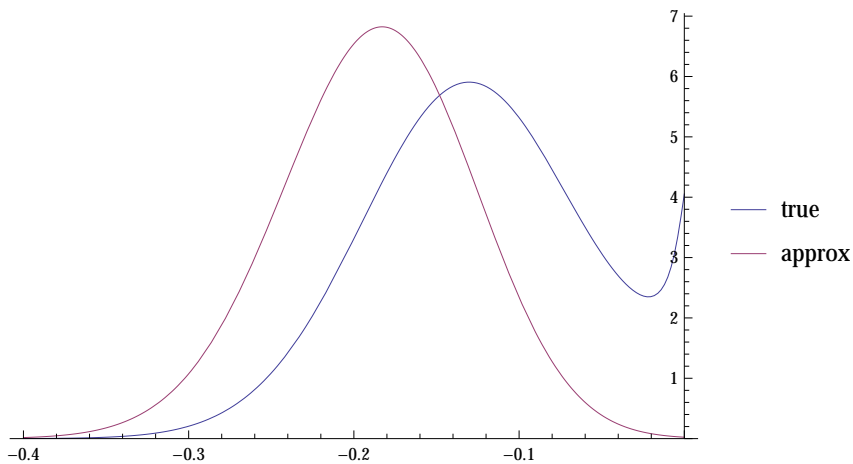
U = 10-3;
mmax = 0.5;
λ = 2 Es / n;
Es = 0.01;
n = 4;
mwt = -0.4;

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

Show[
  Plot[ $\frac{1}{\text{total}}$  U fm[m, mwt, mmax, λ, n] (1 - pest[m]) prescuem[m, Λ1[m, mmax, λ, n, U]],
    {m, -0.4, 0}, PerformanceGoal → "Speed", PlotRange → {0, All}],
  Plot[ $\left\{ \frac{1}{\sqrt{1 - \frac{m}{mmax}} mmax} e^{\frac{4 m + mwt + mmax \left( -6 + 4 \sqrt{1 - \frac{m}{mmax}} - 2 \sqrt{1 - \frac{mwt}{mmax}} + 4 \sqrt{1 - \frac{m}{mmax}} \sqrt{1 - \frac{mwt}{mmax}} \right)}{2 \lambda}} \sqrt{\frac{2}{\pi}} \sqrt{\frac{mmax}{\lambda}} \right\}}{\text{Erfc}\left[\frac{\left(1 - \sqrt{1 - \frac{mwt}{mmax}}\right) \sqrt{\frac{mmax}{\lambda}}}{\sqrt{2}}}\right]}$ , {m, -0.4, 0},
    PlotRange → {0, 70}, PlotLegends → {"true", "approx"}]
]

Clear[mmax, λ, Es, n, U, mwt]

```



Our sufficiently critical approximation is


```

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

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

Simplify[% / %, {mmax > 0, λ > 0}]


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


```

compare distributions of criticals

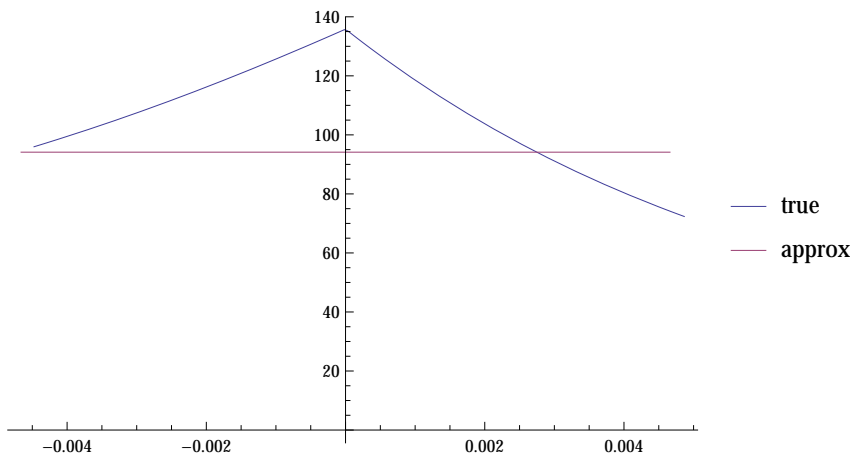
```

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

(*{mneg=FindRoot[2m2-Λ1[m,mmax,λ,n,U],{m,-0.1}],
  mpos=FindRoot[2m2-Λ1[m,mmax,λ,n,U],{m,0.1}]}];
pr0=√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[ $\frac{1}{\text{total}} U \text{fm}[m, \text{mwt}, \text{mmax}, \lambda, n] (1 - \text{pest}[m]) \text{prescuem}[m, \Lambda 1[m, \text{mmax}, \lambda, n, U]]$ ,
    {m, m /. mneg, m /. mpos}, PerformanceGoal → "Speed", PlotRange → {0, All}],
  Plot[ $\left\{, \frac{\pi^{1/4}}{2 \sqrt{U} (\text{mmax} \lambda)^{1/4}}\right\}$ , {m, -pr0, pr0}, PlotRange → {0, All},
    PlotLegends → {"true", "approx"}],
  PlotRange → All
]

Clear[mmax, λ, Es, n, U, mwt]

```



And finally our distribution of supercriticals

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

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

`smallψapprox`

`%`

$$D\left[2\left(1 - \sqrt{1 - \frac{m}{m\text{max}}}\right), m\right] \% /. a \rightarrow 2\left(1 - \sqrt{1 - \frac{m\text{star}}{m\text{max}}}\right) /. b \rightarrow \frac{\sqrt{2}}{\sqrt{\rho\text{max}}} /.$$

$$m\text{star} \rightarrow \sqrt{\Lambda 0\text{approx} / 2} /. \rho\text{max} \rightarrow m\text{max} / \lambda /. \theta \rightarrow n / 2 /.$$

$$\psi\text{wt} \rightarrow 2\left(1 - \sqrt{1 - \frac{m\text{wt}}{m\text{max}}}\right) /. \psi \rightarrow 2\left(1 - \sqrt{1 - \frac{m}{m\text{max}}}\right)$$

Note this is good only to

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

$$\left\{\left\{m \rightarrow \left(-\frac{1}{2} + \sqrt{2} \sqrt{\frac{m\text{max}}{\lambda}}\right) \lambda\right\}\right\}$$

Compare distn of supercriticals

```

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

```

```

total = UNIntegrate[fm[m, mwt, mmax, λ, n]
  (1 - pest[m]) prescuem[m, Δ1[m, mmax, λ, n, U]], {m, 0, mmax}];

```

```
Show[
```

```

Plot[ $\frac{1}{\text{total}}$  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}],

```

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

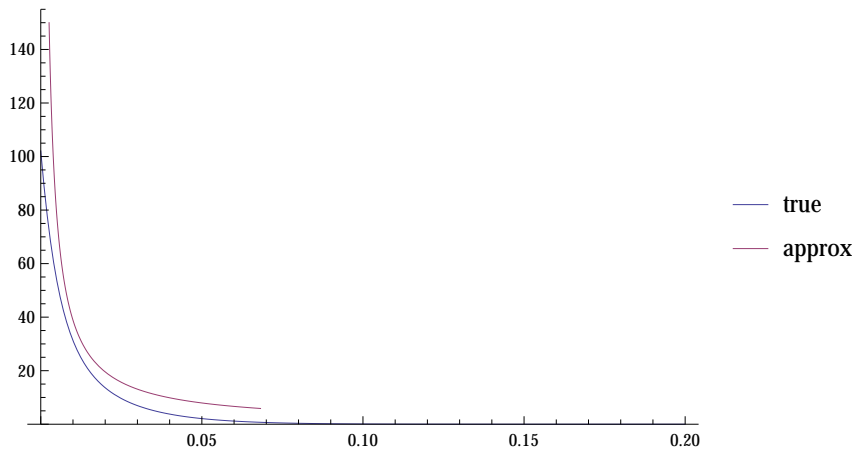
```

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 m12 - Λ1[m1, mmax, λ, n, U], {m1, -0.1}],
 mpos = FindRoot[2 m12 - Λ1[m1, mmax, λ, n, U], {m1, 0.1}]}];
pr0 =  $\sqrt{\Lambda1[m1, mmax, \lambda, n, U] / 2}$ ;

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]  $\sqrt{2 \Lambda1[0, mmax, \lambda, n, U]}$  HeavisideTheta[(m1 + pr0) (pr0 - m1)];

subcritical =
  fm[m1, mwt, mmax, λ, n]  $\frac{\Lambda1[m1, mmax, \lambda, n, U]}{\text{Abs}[m1]}$  HeavisideTheta[(-m1 - pr0)];

supercritical = fm[m1, mwt, mmax, λ, n] (1 - pest[m1])
   $\frac{\Lambda1[m1, mmax, \lambda, n, U]}{\text{Abs}[m1]}$  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}]
];

```

```

{
   $\frac{\text{subcritical}}{\text{allexact}}$ ,  $\frac{\text{critical}}{\text{allexact}}$ ,  $\frac{\text{supercritical}}{\text{allexact}}$ 
};
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}]
];

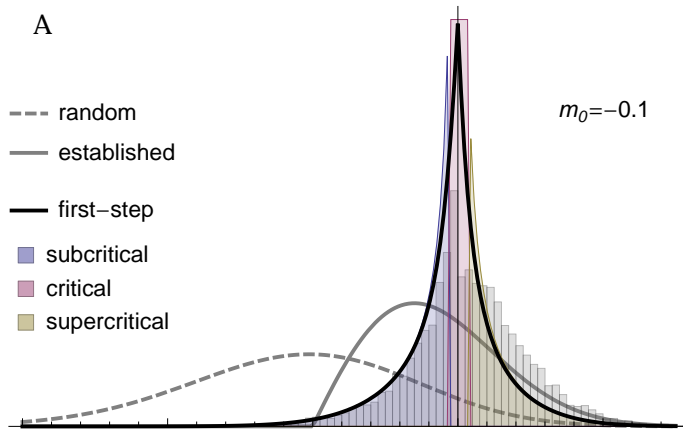
dat = Import[datadir <>
  "int_dfe_poisson_N10000_n4_U0.00200_Es0.01_mmax0.50_mwt-0.10_mutmax10
  _nreps100000.csv"];
Select[dat, #[[2]] == 2 &][[All, 3]];
data = Histogram[%, 50, "PDF",
  AxesOrigin → {0, 0}, ChartStyle → Directive[Gray, Opacity[0.25]]];

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 m12 - Λ1[m1, mmax, λ, n, U], {m1, -0.1}],
 mpos = FindRoot[2 m12 - Λ1[m1, mmax, λ, n, U], {m1, 0.1}]}];
pr0 = √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] √2 Λ1[0, mmax, λ, n, U] HeavisideTheta[(m1 + pr0) (pr0 - m1)];

subcritical =
  fm[m1, mwt, mmax, λ, n]  $\frac{\Lambda1[m1, mmax, \lambda, n, U]}{\text{Abs}[m1]}$  HeavisideTheta[(-m1 - pr0)];
supercritical = fm[m1, mwt, mmax, λ, n] (1 - pest[m1])
   $\frac{\Lambda1[m1, mmax, \lambda, n, U]}{\text{Abs}[m1]}$  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, critical, supercritical
  allexact, allexact, 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
];

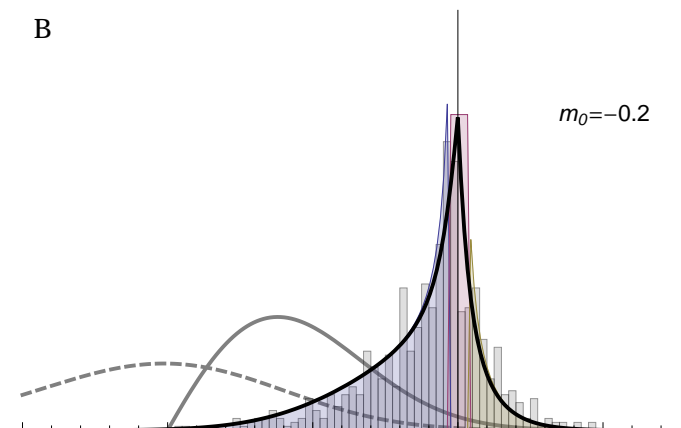
dat = Import[datadir <>
  "int_dfe_poisson_N10000_n4_U0.00200_Es0.01_mmax0.50_mwt-0.20_mutmax10
  _nreps100000.csv"];
Select[dat, #[[2]] == 2 &][[All, 3]];
data = Histogram[%, 50, "PDF",
  AxesOrigin → {0, 0}, ChartStyle → Directive[Gray, Opacity[0.25]]];

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 m12 - Λ1[m1, mmax, λ, n, U], {m1, -0.1}],
 mpos = FindRoot[2 m12 - Λ1[m1, mmax, λ, n, U], {m1, 0.1}]}];
pr0 = √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] √2 Λ1[0, mmax, λ, n, U] HeavisideTheta[(m1 + pr0) (pr0 - m1)];

subcritical =
  fm[m1, mwt, mmax, λ, n]  $\frac{\Lambda1[m1, mmax, \lambda, n, U]}{\text{Abs}[m1]}$  HeavisideTheta[(-m1 - pr0)];
supercritical = fm[m1, mwt, mmax, λ, n] (1 - pest[m1])
   $\frac{\Lambda1[m1, mmax, \lambda, n, U]}{\text{Abs}[m1]}$  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"
];

{
 $\frac{\text{subcritical}}{\text{allexact}}$ ,
 $\frac{\text{critical}}{\text{allexact}}$ ,
 $\frac{\text{supercritical}}{\text{allexact}}$ 
};
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
];

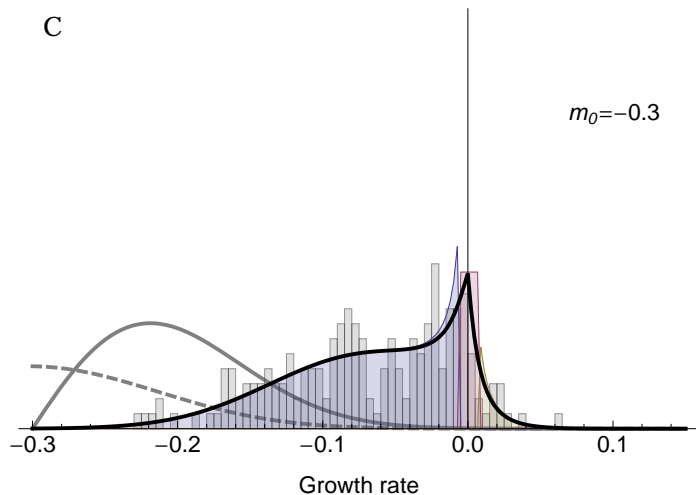
dat = Import[datadir <>
  "int_dfe_poisson_N10000_n4_U0.00200_Es0.01_mmax0.50_mwt-0.30_mutmax10
  _nreps1000000.csv"];
Select[dat, #[[2]] == 2 &][[All, 3]];
data = Histogram[%, 50, "PDF",
  AxesOrigin → {0, 0}, ChartStyle → Directive[Gray, Opacity[0.25]]];

Show[
  oldtheory, data, theory, exactplot,
  Frame → {True, False, False, False},
  FrameLabel → {"Growth rate"},
  PlotRange → {{xmin, xmax}, {0, ymax}},
  LabelStyle → labelstyle,
  Epilog → {Text[Style[" $m_0 = "$  <> 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,  $\lambda$ , 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;
 $\lambda$  = 2 Es / n;
Es = 0.01;
n = 4;

```

```

mwt = -0.2;

{mneg = FindRoot[2 m1^2 -  $\Lambda$ 1[m1, mmax,  $\lambda$ , n, U], {m1, -0.1}],
 mpos = FindRoot[2 m1^2 -  $\Lambda$ 1[m1, mmax,  $\lambda$ , n, U], {m1, 0.1}]}];
pr0 =  $\sqrt{\Lambda$ 1[m1, mmax,  $\lambda$ , n, U] / 2 ;

exact = fm[m1, mwt, mmax,  $\lambda$ , n] (1 - pest[m1]) prescuem[m1,  $\Lambda$ 1[m1, mmax,  $\lambda$ , n, U]];

critical =
  fm[0, mwt, mmax,  $\lambda$ , n]  $\sqrt{2 \Lambda$ 1[0, mmax,  $\lambda$ , n, U] HeavisideTheta[(m1 + pr0) (pr0 - m1)]};

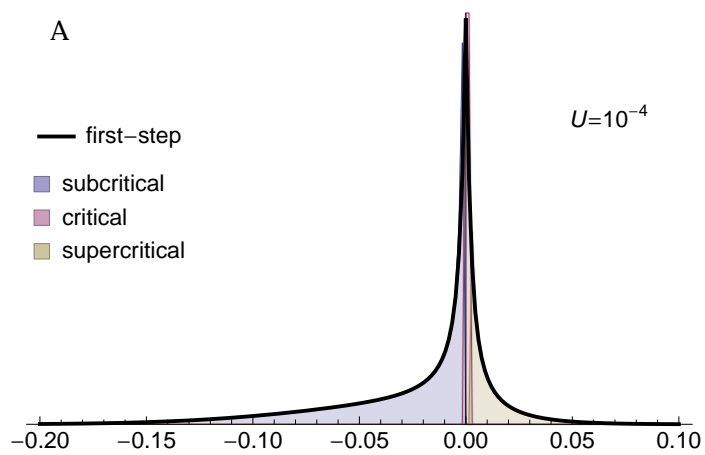
subcritical =
  fm[m1, mwt, mmax,  $\lambda$ , n]  $\frac{\Lambda$ 1[m1, mmax,  $\lambda$ , n, U]}{Abs[m1]} HeavisideTheta[(-m1 - pr0)];
supercritical = fm[m1, mwt, mmax,  $\lambda$ , n] (1 - pest[m1])
   $\frac{\Lambda$ 1[m1, mmax,  $\lambda$ , n, U]}{Abs[m1]} HeavisideTheta[(m1 - pr0)];
total = NIntegrate[exact, {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,  $\lambda$ , Es, n, U, mwt]

```



```

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

{mneg = FindRoot[2 m12 - Λ1[m1, mmax, λ, n, U], {m1, -0.1}],
 mpos = FindRoot[2 m12 - Λ1[m1, mmax, λ, n, U], {m1, 0.1}]}];
pr0 = √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] √2 Λ1[0, mmax, λ, n, U] HeavisideTheta[(m1 + pr0) (pr0 - m1)];

subcritical =
  fm[m1, mwt, mmax, λ, n]  $\frac{\Lambda1[m1, mmax, \lambda, n, U]}{\text{Abs}[m1]}$  HeavisideTheta[(-m1 - pr0)];
supercritical = fm[m1, mwt, mmax, λ, n] (1 - pest[m1])
   $\frac{\Lambda1[m1, mmax, \lambda, n, U]}{\text{Abs}[m1]}$  HeavisideTheta[(m1 - pr0)];

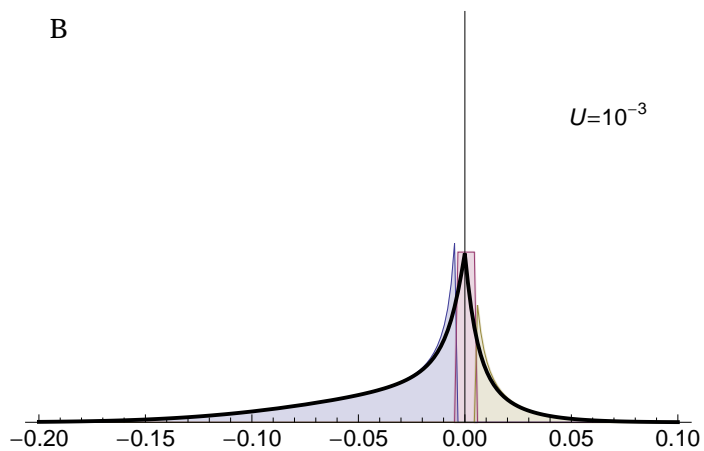
total = NIntegrate[exact, {m1, mwt, 0.1}];

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]

```



```

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

{mneg = FindRoot[2 m12 - Λ1[m1, mmax, λ, n, U], {m1, -0.1}],
 mpos = FindRoot[2 m12 - Λ1[m1, mmax, λ, n, U], {m1, 0.1}]}];
pr0 =  $\sqrt{\Lambda 1[m1, mmax, \lambda, n, U] / 2}$ ;

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]  $\sqrt{2 \Lambda 1[0, mmax, \lambda, n, U]}$  HeavisideTheta[(m1 + pr0) (pr0 - m1)];

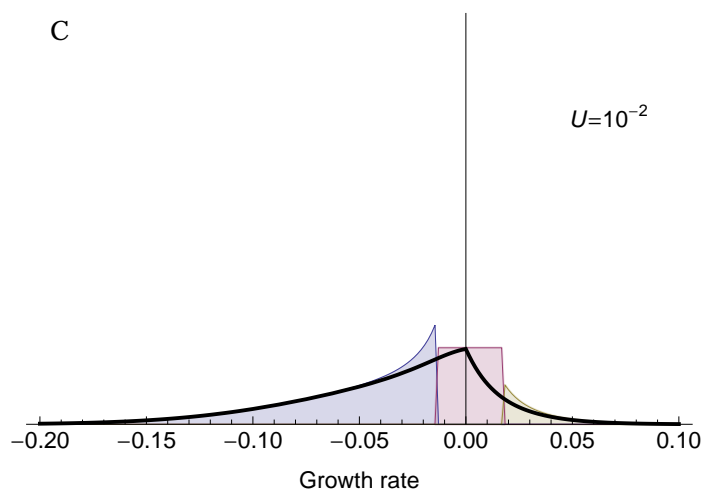
subcritical =
  fm[m1, mwt, mmax, λ, n]  $\frac{\Lambda 1[m1, mmax, \lambda, n, U]}{\text{Abs}[m1]}$  HeavisideTheta[(-m1 - pr0)];
supercritical = fm[m1, mwt, mmax, λ, n] (1 - pest[m1])
   $\frac{\Lambda 1[m1, mmax, \lambda, n, U]}{\text{Abs}[m1]}$  HeavisideTheta[(m1 - pr0)];
total = NIntegrate[exact, {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]
```