Genetic paths to evolutionary rescue

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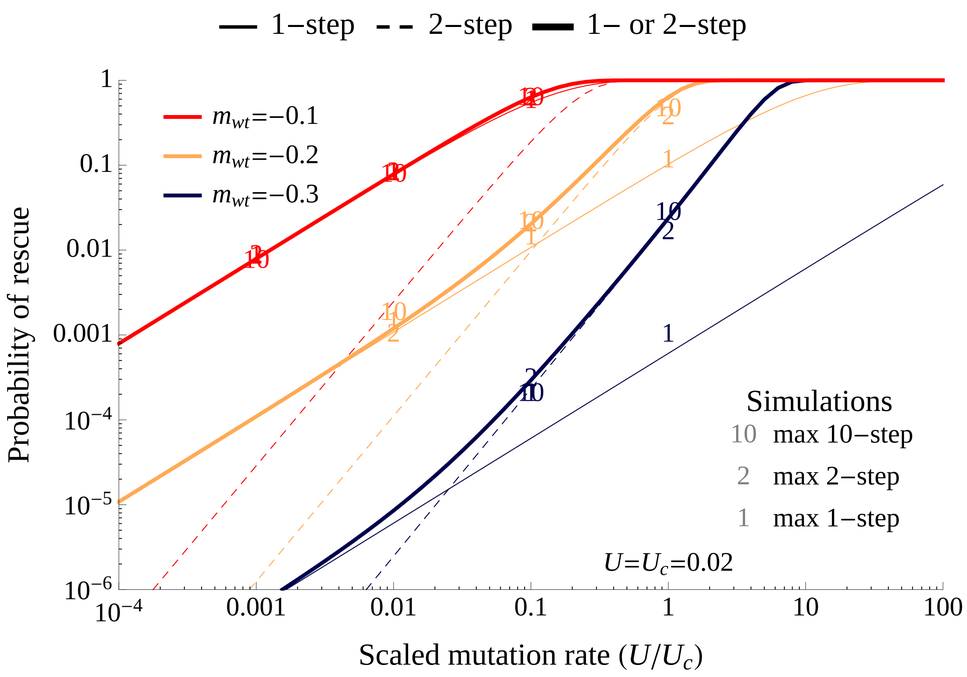
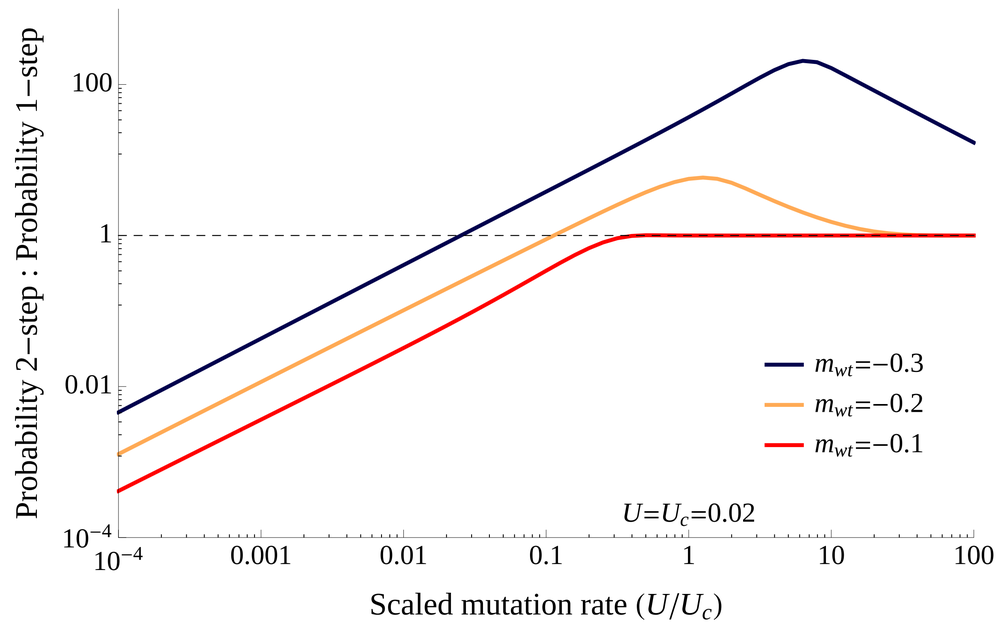
Question 1: *Given a 'wildtype' on its way to extinction, how many mutations will the 1^{st} growing lineages carry?*



Left: Probability of rescue by 1-step, 2-step, or either. **Right:** Probability of 2-step rescue relative to 1-step. Both are shown as functions of scaled mutation rate[1] U/U_c, where $U_c = n^2\lambda/4$. We start with $N_0 = 10^4$ wildtypes with growth rate m_{wt}, mutations have variance $\lambda = 0.005$ in $n = 4$ phenotypic dimensions, and the maximum growth rate is $m_{max} = 0.5$. We assume both mutation and e^m are Gaussian.



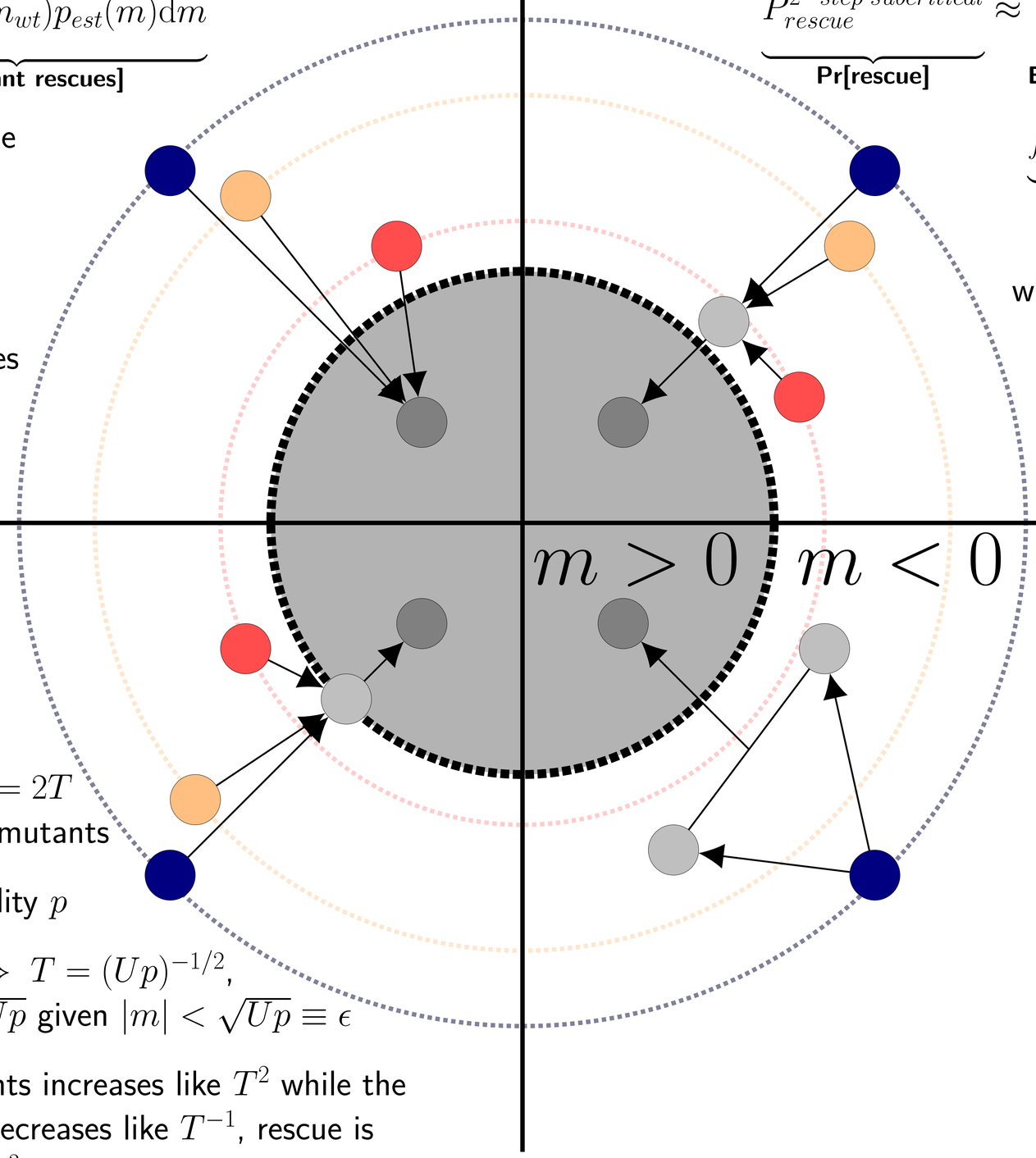
a) 1-step[1]

$$\underbrace{P^{1-step}_{rescue}}_{\textbf{Pr[rescue]}} \approx \underbrace{\frac{N_0}{-m_{wt}}U}_{\textbf{E[\# mutants]}} \underbrace{\int_0^{m_{max}} f(m|m_{wt})p_{est}(m)\mathrm{d}m}_{\textbf{Pr[mutant rescues]}}$$

N_0	initial number of wildtype
U	genomic mutation rate
m_{wt}	growth rate of wildtype
m_{max}	growth rate at optimum
$p_{est}(m)$	probability lineage with growth rate m establishes
$f(m_j\|m_i)$	probability (pdf) of growth rate m_j given mutation from m_i

b) 2-step critical

- While $t < |1/m|$ a lineage with growth rate m behaves "critically"
- Critical lineages persist for time $t = 2T$ with probability $1/T$, make $\sim UT^2$ mutants
- Each mutant rescues with probability p
- Rescue likely when $UT^2p = 1 \implies T = (Up)^{-1/2}$, which happens with probability $2\sqrt{Up}$ given $|m| < \sqrt{Up} \equiv \epsilon$
- Since the number of double mutants increases like T^2 while the probability of persisting for T only decreases like T^{-1}, rescue is dominated by rare long-lived lineages[3]



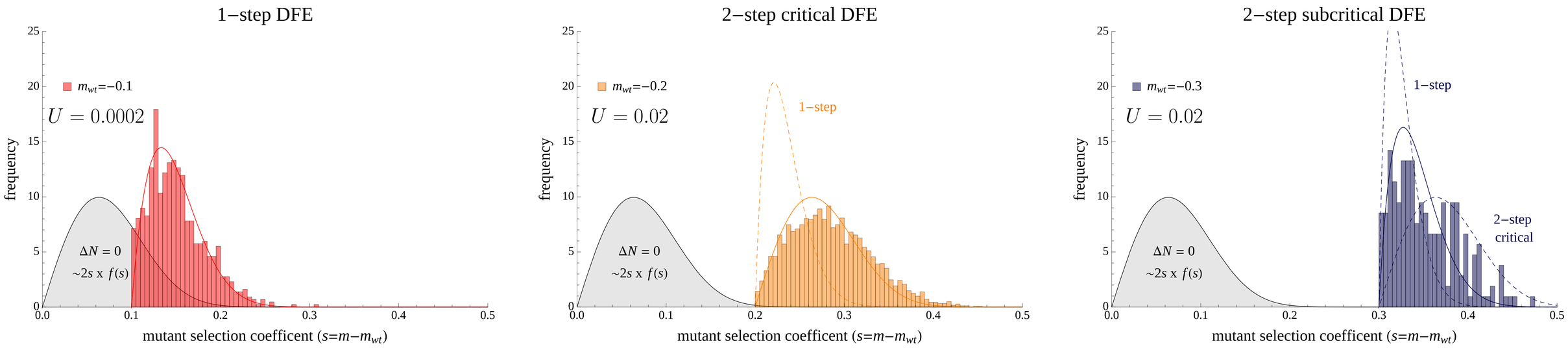
c) 2-step subcritical

$$\underbrace{P^{2-step\ subcritical}_{rescue}}_{\textbf{Pr[rescue]}} \approx \underbrace{\frac{N_0}{-m_{wt}}U}_{\textbf{E[\# mutants]}} \int_{-\infty}^{-\epsilon} \underbrace{f(m_1|m_{wt})\frac{U}{-m_1}}_{\textbf{E[\# dub. muts from } m_1\textbf{]}} \underbrace{\int_0^{m_{max}} f(m_2|m_1)p_{est}(m_2)\ \mathrm{d}m_2}_{\textbf{Pr[double mutant rescues } | \ m_1\textbf{]}} \mathrm{d}m_1$$

where $-\epsilon$ is the minimum growth rate that allows a lineage to behave "critically" long enough to almost surely cause 2-step rescue (for more on this logic, see part b)

d) Recombinant

Question 2: *Given evolutionary rescue, what DFE (distribution of fitness effects) will we see in growing lineages?*



Above: The distribution of selection coefficients of growing genotypes, relative to the wildtype, immediately following rescue. Parameters as in top plots: $N_0 = 10^4$, $\lambda = 0.005$, $n = 4$, $m_{max} = 0.5$.

Refs: 1. Anciaux *et al.* 2018 Genetics, 2. Martin & Lenormand 2015 Evol., 3. Weissman *et al.* 2009 TPB

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