The Case for Multiple First-Line Therapies

David L. Smith

Associate Professor, Department of Zoology

Associate Director for Disease Ecology, Emerging Pathogens Institute

University of Florida

CDDEP THE CENTER FOR Disease Dynamics, Economics & Policy

WASHINGTON DC • NEW DELHI

…all models are wrong, but some are useful.

George E. P. Box

Robustness in the strategy of scientific model building
in Robustness in Statistics
R.L. Launer and G.N. Wilkinson, Editors
1979, Academic Press: New York

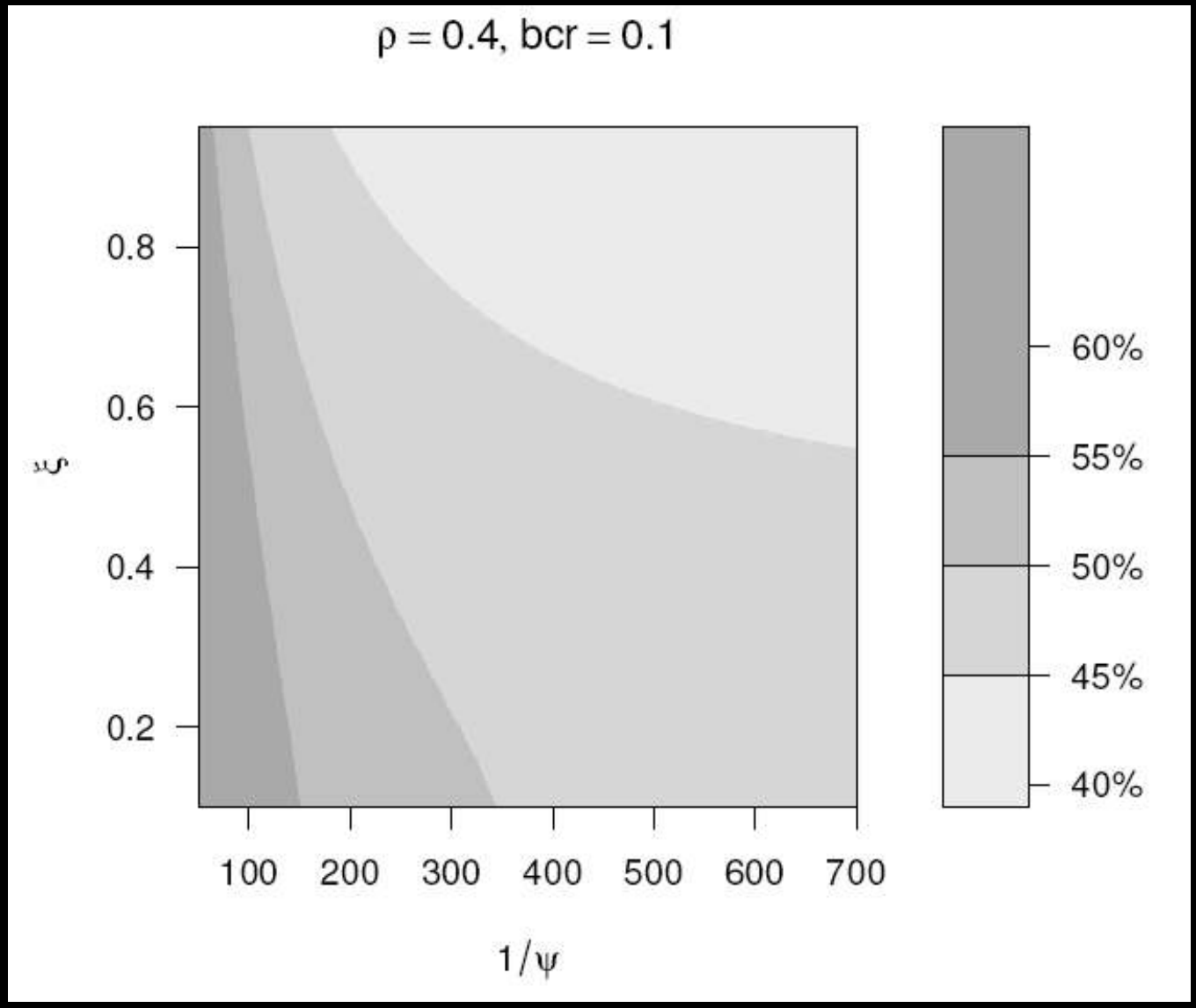
Drug Pressure & Parasite Fitness

- Clinical Malaria:
  # clinical malaria episodes, per person per day
- Drug pressure:
  % clinical episodes treated and/or cured
- Parasite competition
  - In the human host
  - In the mosquito host
- Fitness / Reproductive Number:
  # infected humans per infected human

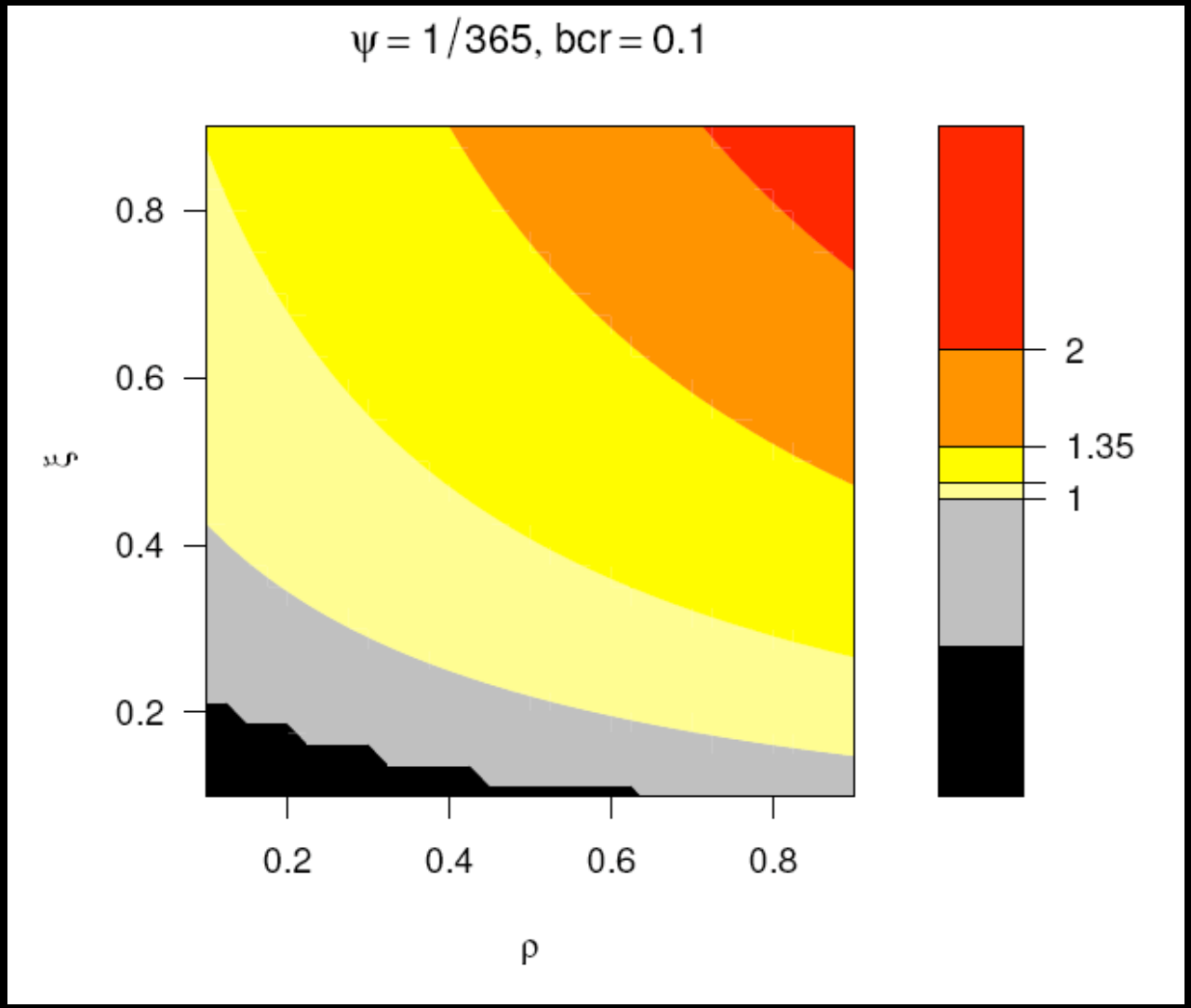
Drug Pressure & Parasite Fitness

- Disadvantage to sensitive phenotypes:
  Shorter infectious period
- Advantages to resistant phenotypes:
  i.e. *Gametocyte flush*
- Disadvantage to resistant phenotypes:
  "intrinsic" competitive disadvantage in the absence of drug pressure (Biological cost of resistance)

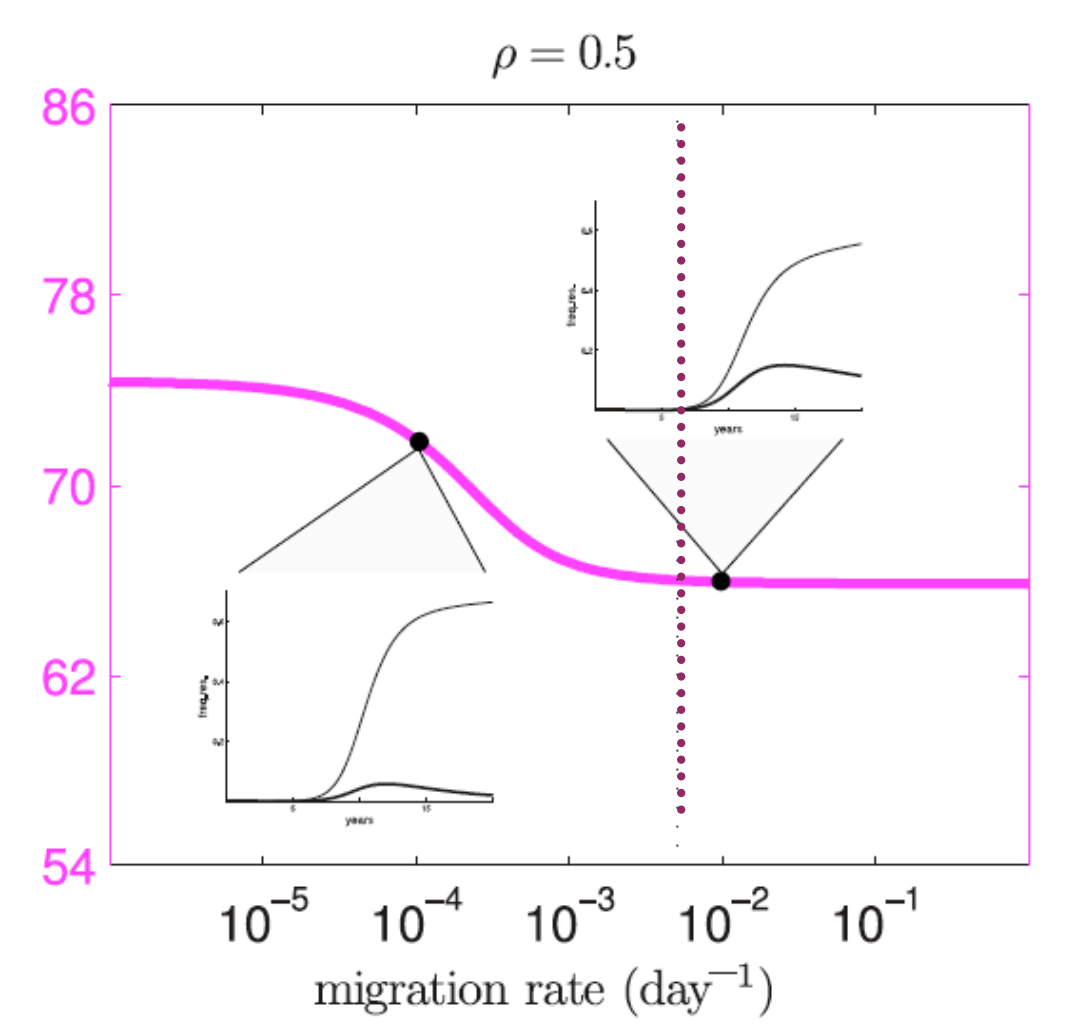
Two 1st-line therapies *vs.* "Rationing"



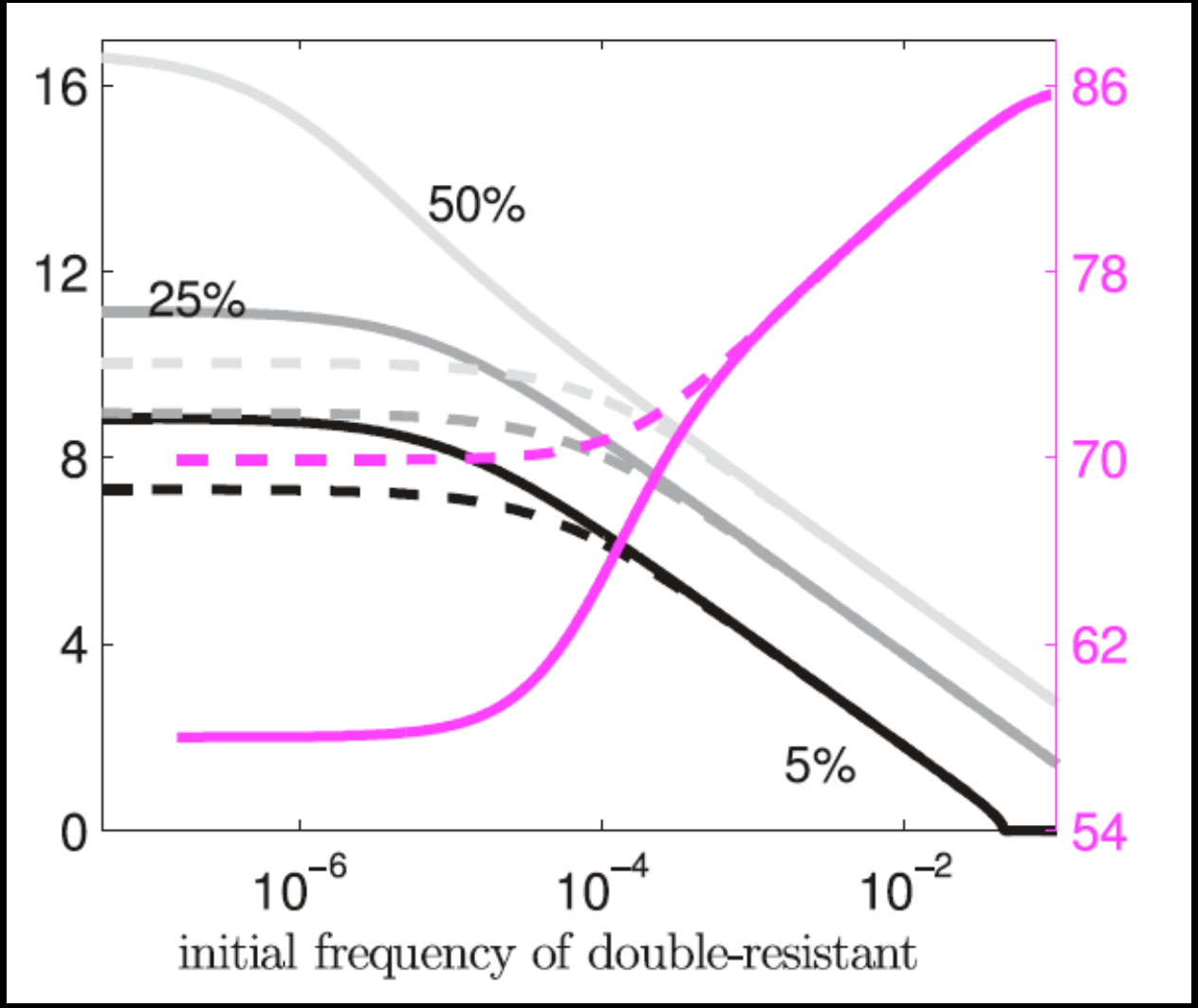
MFT: Resistant Parasite Fitness
(when the wild-type is at the steady state)



Spatial Scale of MFT



Multi-Drug Resistance

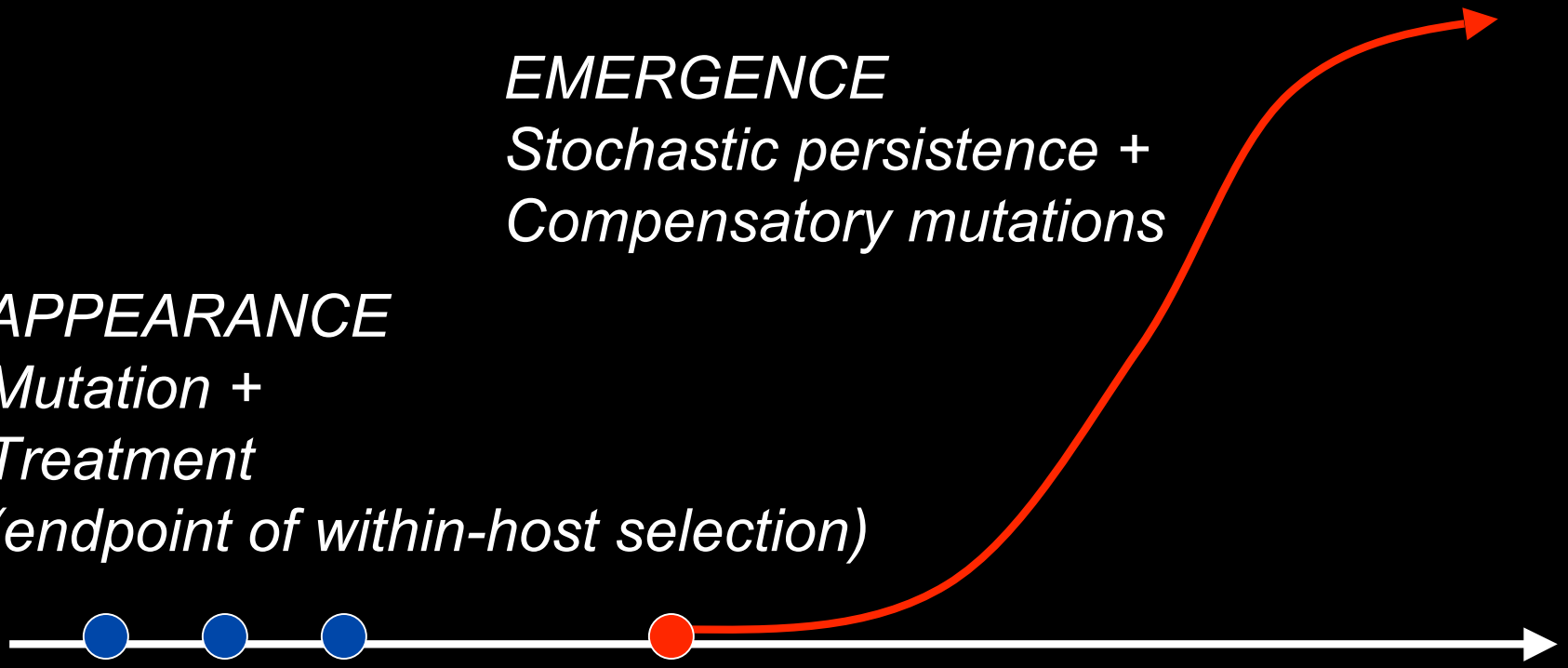


EVOLUTION of RESISTANCE

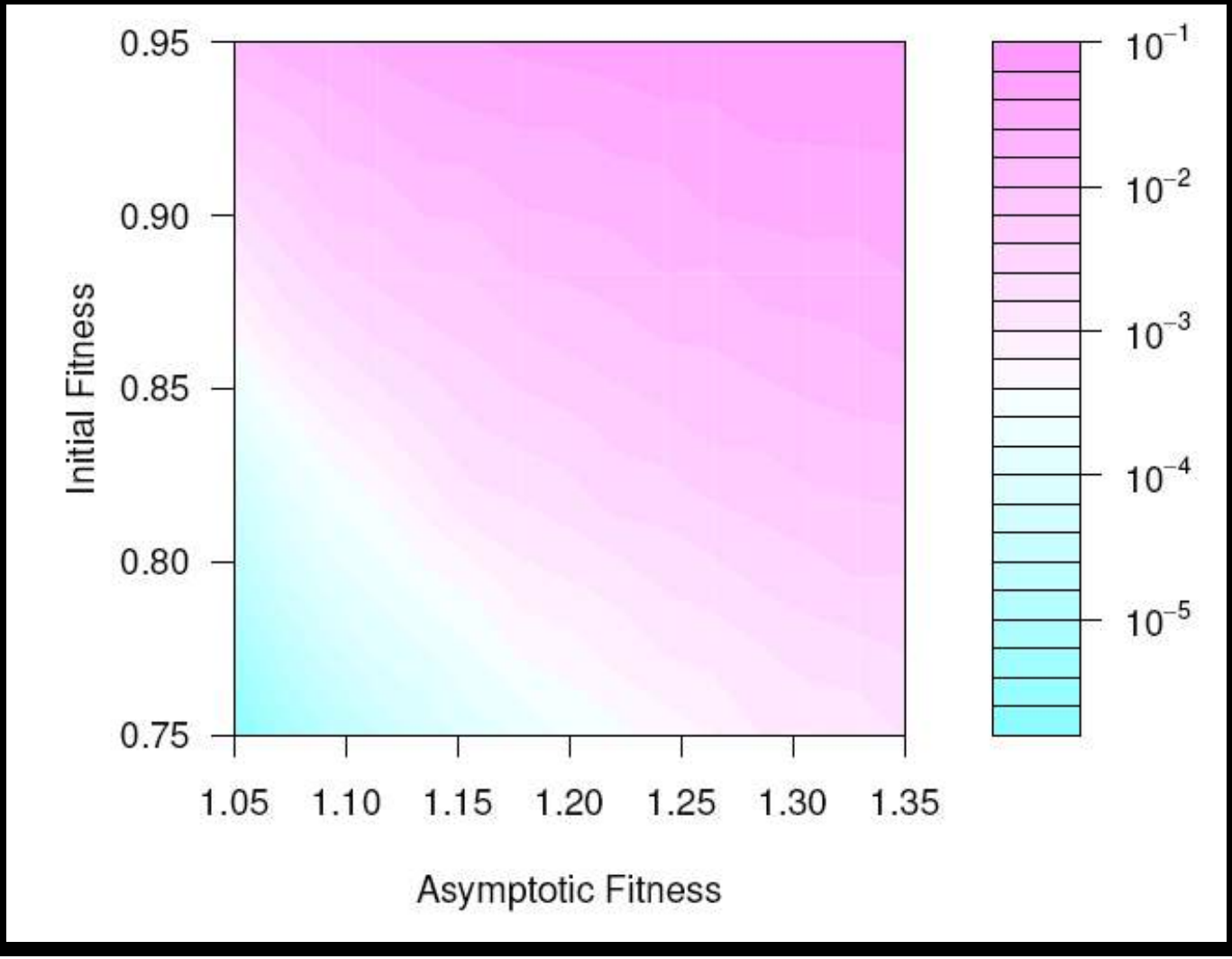
SPREAD
Transmission +
Selection

EMERGENCE
Stochastic persistence +
Compensatory mutations

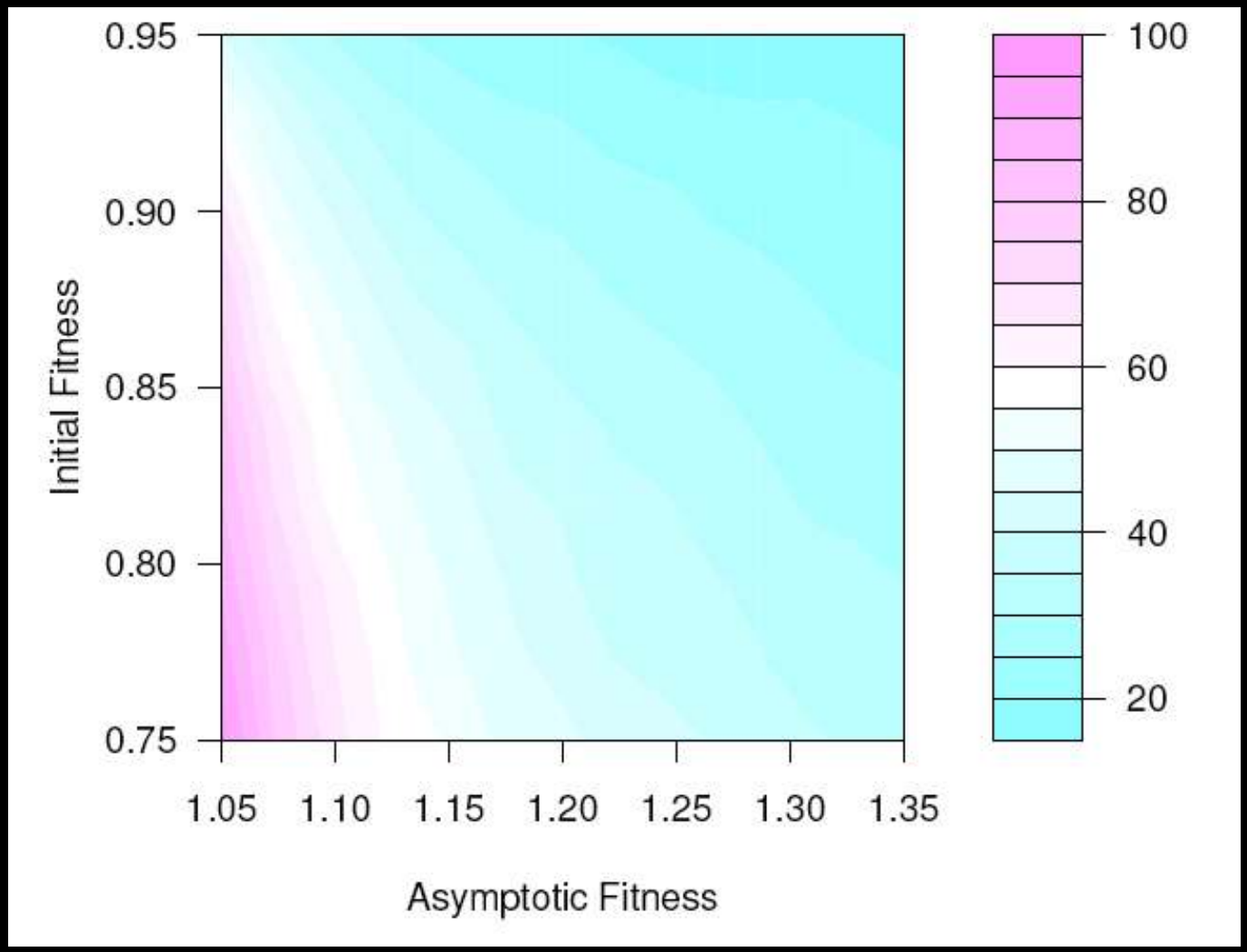
APPEARANCE
Mutation +
Treatment
(endpoint of within-host selection)



Probability of Emergence

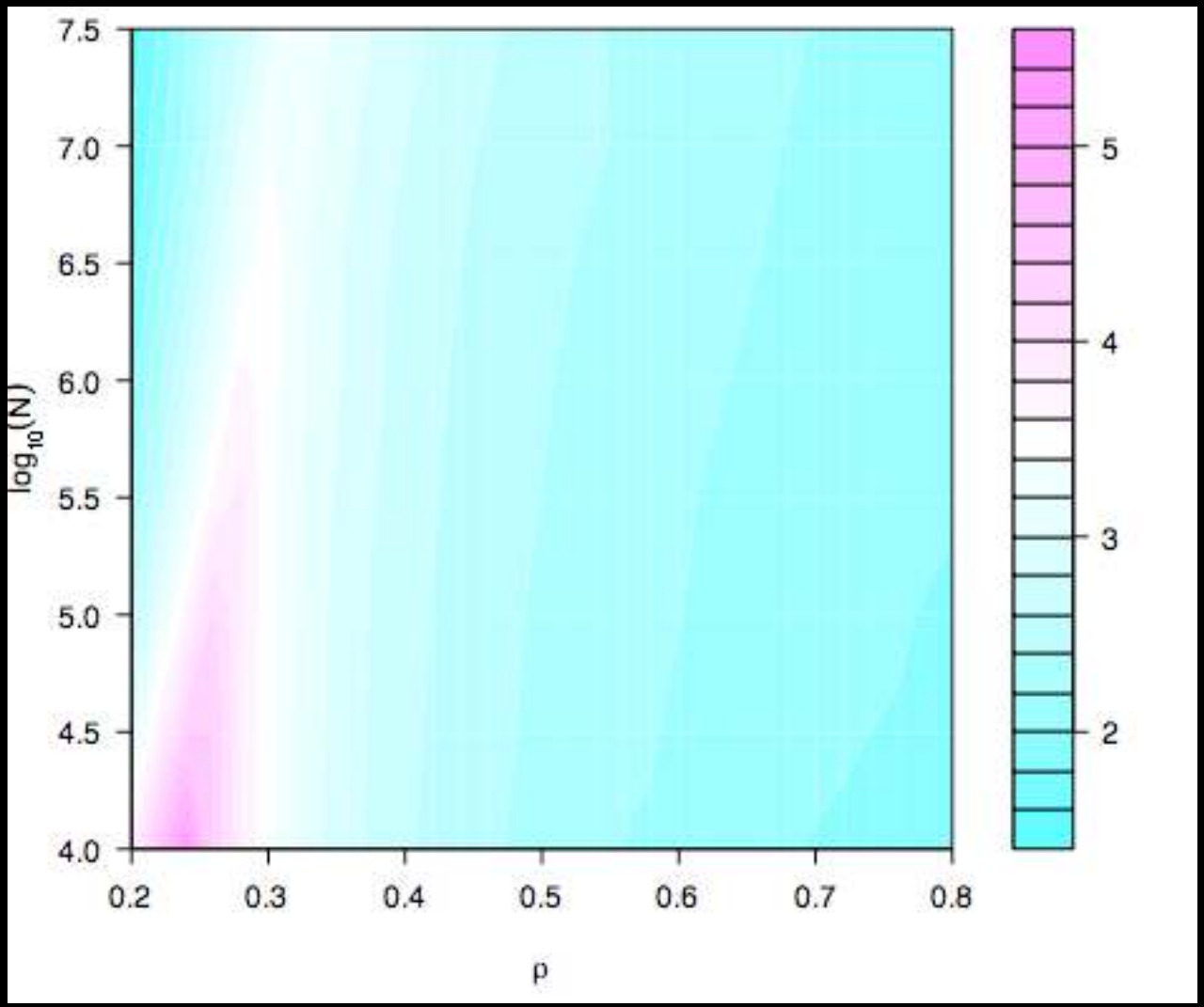


Generations to Emergence



Delayed Time to 10%

(Ratio: Two 1st-line / One 1st-line)



Appearance / Emergence / Spread

- Time to failure depends on…
  - Drug pressure (and its relation to fitness)
  - Cost of resistance
  - Mutation rates
  - Clinical incidence

$$\mathcal{T}_F = \frac{T_a(\rho, \Lambda N, \mu, P)}{Q(\rho, \xi, \psi, C_0, C_\infty)} + gT_g(\rho, \xi, \psi, C_0, C_\infty) + T_f(\rho, \xi, \psi, C_\infty, V, N)$$

Parameters are poorly characterized for CQ & SP resistance and poorly understood for ACTs

Comparisons

- Time to Failure (TTF):
  - Monotherapy to Combination
  - Single vs. Two First-Line Combinations
- TTF Ratios depend on Population Size!
  - $N = 10^5$: 8.1 vs. 5.8
  - $N = 10^6$: 1.6 vs. 4.3
  - $N = 10^7$: 1.1 vs. 2.6
  - $N = 10^8$: 1.0 vs. 2.5

Conclusions

- Multiple first-line therapies
  - delay emergence, delay spread, and complement combinations
  - work poorly after multi-drug resistance emerges
  - are deployed to best advantage before resistance emerges
  - when we know very few specific details about resistance
- We must justify the policy on the basis of theory

The theoretical justification for multiple first-line therapies is as strong as the case for combinations…

and at a global scale, our analysis suggests that they would delay emergence just as well (or better).

Appearance
endpoint of within-host selection

- Rate of Appearance $\rho\Lambda N 10^{P-\mu}$
- $\rho\Lambda N$: # clinical episodes treated, per year, in a population of size N
- $10^{P-\mu}$: # resistant parasites, per infection
  - Parasites, per infection (10^{P})
  - Mutation rate, per cell division ($10^{-\mu}$)

Emergence

compensatory mutations / stochastic persistence

- Evolving Branching Process
  - One new mutant
  - "Initial" Fitness = Fit_0
  - # Offspring ~Poisson(Fit_g)
  - Mutate: $Fit_g = Fit_{g-1} + B'(\alpha,\beta)$
  - Repeat until:
    - Failure: No offspring remain
    - Success: 10 Parasites with Fitness > 1
- How many "failures" per success?
- How many generations elapsed?