Supplementary text to "**Multi-fidelity analysis for predicting rare events in stochastic computational models**"

Medium-fidelity and low-fidelity analyses enable sensitivity analysis at biologically relevant mutation frequencies

Parallel to results in Figure 7 in the main text, sensitivity analysis can also be performed using LFA. However, resistance period is not available using LFA. Coefficients of variation for both MFA and LFA are shown in Figure S2.

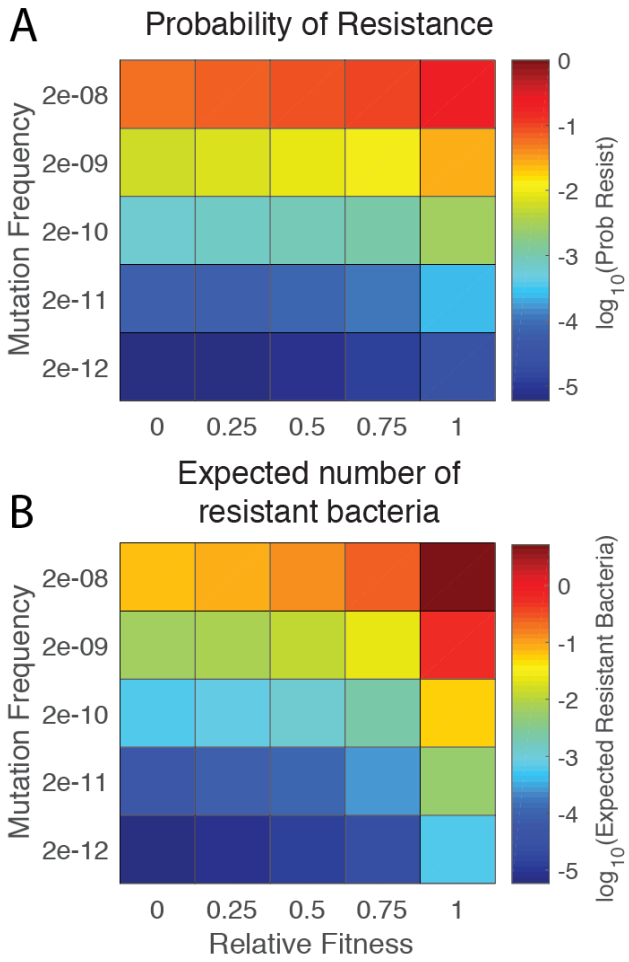

Figure S1: LFA-predicted effect of relative fitness (x-axes) and mutation frequency (y-axes) on the probability of resistance per granuloma after 200 days of infection (A) and expected number of resistant bacteria per granuloma after 200 days of infection (B). Mutation frequency is varied between $2x10^{-12}$ and $2x10^{-8}$ per 10-minute HFM time step, and relative fitness is varied between 0 and 1.

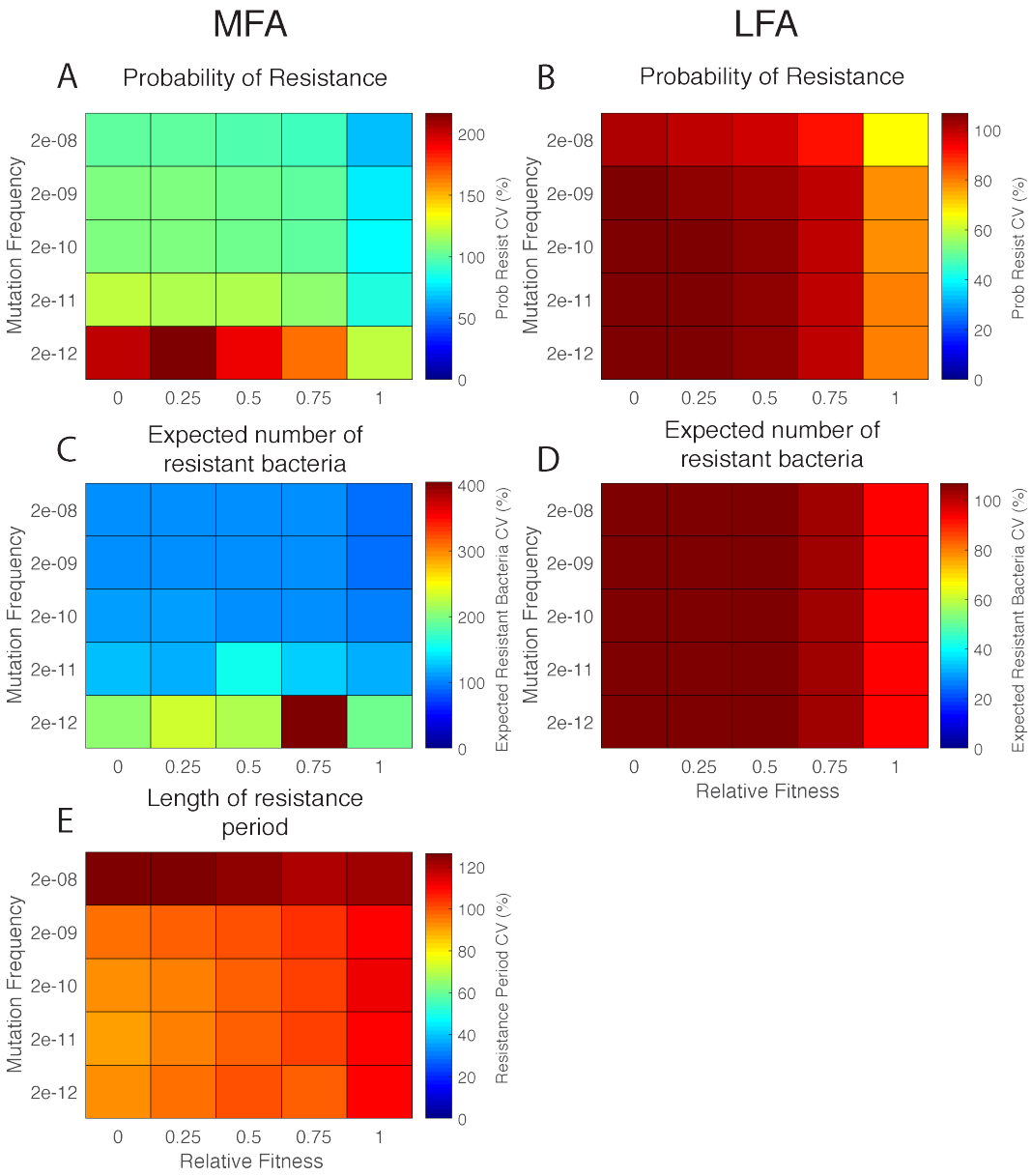

Figure S2: Coefficients of variation corresponding to variables in Figure 6 (A,C,E) and Figure S1 (B,D). Two-way anova indicates that mutation frequency and relative fitness both have an effect on all variables ($p < 0.0001$) and there is statistically significant interaction between mutation frequency and fitness in influencing the probability of resistance and number of resistant bacteria ($p < 0.0001$) but not the length of resistance period ($p = 0.73$).

Medium-fidelity and low-fidelity analyses can discern influence of stochastic events and parameter fluctuations

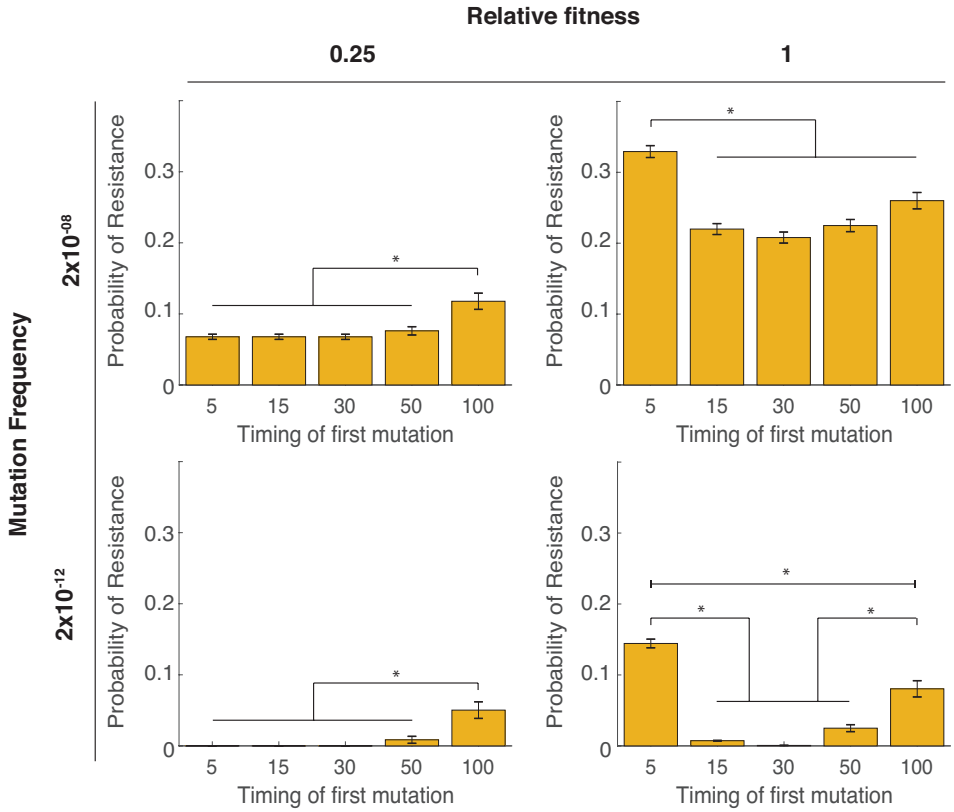

Figure S3: LFA-predicted effect of relative fitness, mutation frequency and timing (in days) of the first mutation on the probability of resistance after 200 days of infection. Mutation frequencies of $2x10^{-8}$ (A,B) and $2x10^{-12}$ (C,D) per 10-minute HFM time step are considered along with relative fitness values of 0.25 (A,C) and 1 (B,D). Bars represent mean probabilities over 348 simulations and error bars represent standard error of the mean. Stars indicate statistically significant differences (p-values < 0.0005) as determined through one-way anova and Scheffe's multiple comparison procedure.

Matlab scripts implementing medium-fidelity and low-fidelity analyses

We include three Matlab scripts that implement MFA and LFA for one HFM simulation. The files included are:

- Run_MFA_LFA.m
    - User specifies: which analysis to do, how many Monte Carlo replications to include (if MFA is done) and what the probability of the rare event is.
    - Loads the population trajectory, division and death series data (popTraj.mat, birthVec.mat, deathVec.mat, respectively) from the HFM simulation
        - Note that two versions of each of each data structure are included: xxx_2881.mat and xxx_28801.mat. These vectors include data for 2881 and 28801 simulation steps of the HFM, respectively.
    - Runs MFA and LFA by calling MFA_LFA_ExampleScript.m
    - Plots comparisons of MFA and LFA results by calling plotMFA_LFA.m
- MFA_LFA_ExampleScript.m
    - Input: user-specified simulation parameters (from Run_MFA_LFA.m)
    - Runs MFA and LFA as described in the main text
    - Saves the results
        - For MFA: probability distribution (probDist_MFA.mat) and individual rare-event trajectories (rareEventTrajectories_MFA.mat)
        - For LFA: probability distribution (probDist_LFA.mat)
- plotMFA_LFA.m
    - Input: time point for which probability distribution should be plotted
    - Loads the MFA and LFA results generated by MFA_LFA_ExampleScript.m
    - Plots for MFA and LFA:
        - Histogram showing the probability distribution of the expected number of mutant bacteria at the user-specified time point
        - Time course of the probability of having at least 1 mutant bacterium

To run the analysis:

- Download the files into one folder
- Open 'Run_MFA_LFA.m' in Matlab (R2017a was used to develop and test the code)
- Specify the appropriate simulation settings and parameter values within 'Run_MFA_LFA.m'
- Click 'Run' in the Editor tab.
- Note that a running a large number of Monte Carlo replications for the longer dataset (28801 time-steps) will take longer to complete.