Simulation notes 7

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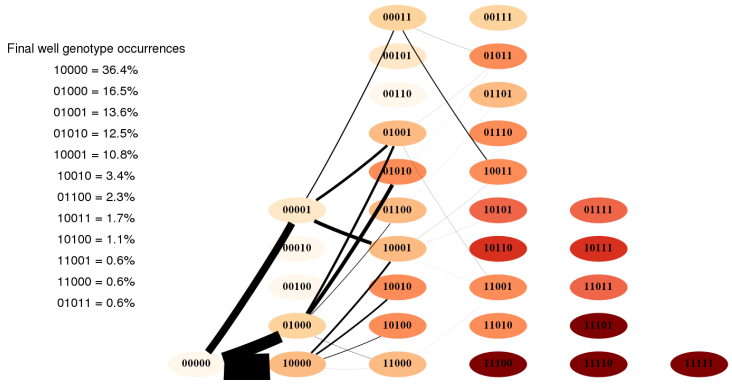
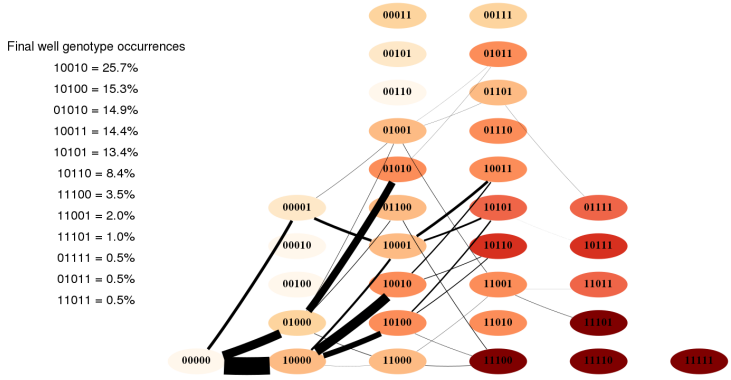
1 The plots

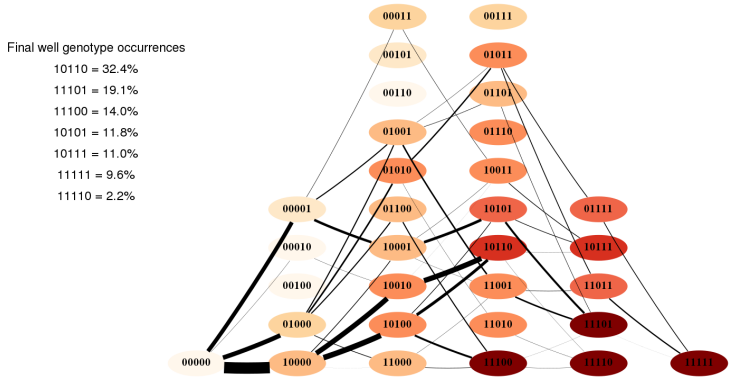


(a)

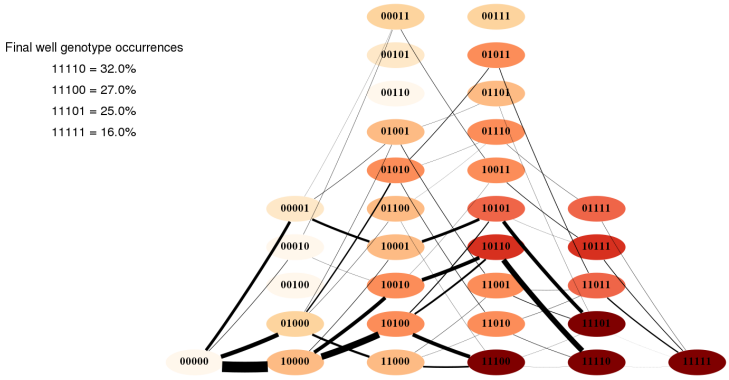


(b)

Figure 1: An idea of the plots I can produce showing evolutionary trajectories. (a) and (b) show results for exponential ciprofloxacin profiles with maximum values of 300 and 1000 ng/ml respectively, with each plot being the product of 100 simulations. From these 100 simulations, the trajectories of the cells found in the final well are determined and the the edges are weighted corresponding to the number of cells in the final well who's evolutionary trajectory contains that mutation. The percentages on the left legend correspond to the probability that these genotypes appear in the final well above some abundance (10%). No they don't, I made an error. Here, it is the probability that I get a given genotype if I choose any one random cell from all the cells in all the 100 final wells. I have corrected this. Is this an interesting measurement in any way? Each node (genotype) has a colour corresponding to its MIC value (white to red corresponding to 16 to 64,000 ng/ml on a logarithmic scale).

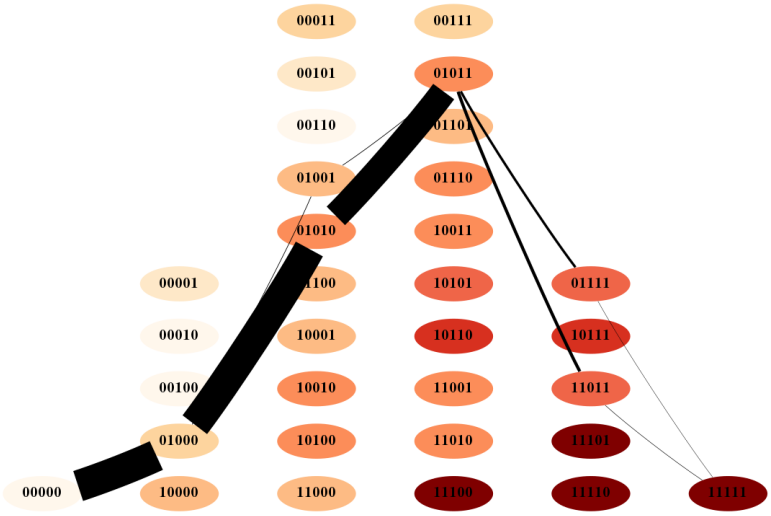


(a)

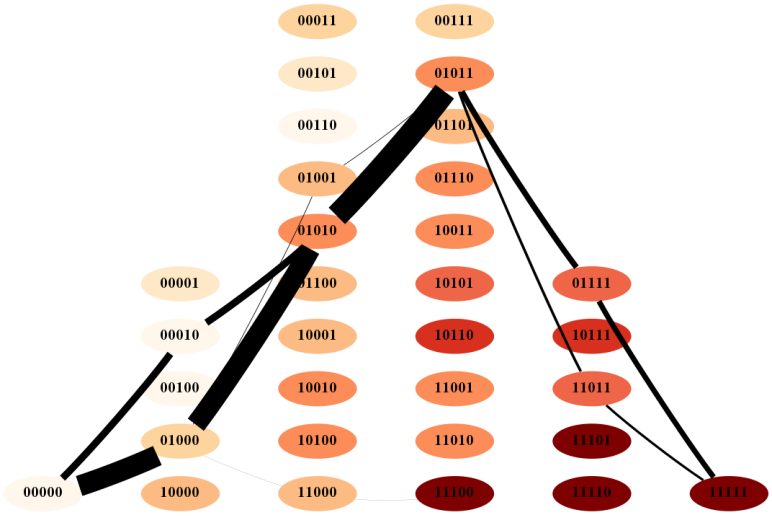


(b)

Figure 2: Same as above but with the maximum concentration being 5000 and 20,000 ng/ml in (a) and (b) respectively. Note that only 4 genotypes are viable in a concentration of 20,000 ng/ml.



(a)



(b)

Figure 3: The previous plots showed only the final well of successful runs. We can also look at the trajectories present in the simulations that did not reach the final well, which happened for max concentration values of 5000 ng/ml (a) and 20000 ng/ml (b). Interestingly, in both cases the genotype 01011 seems to be a dead-end. The problem is that from here, only 2 genotypes containing 3 mutations can be reached, and they are the 2 with the lowest MIC (they also have low fitnesses, containing both the marR and acrR mutations). It could be the case that with the steep concentration profile, these 2 routes are esssentially fitness valleys.

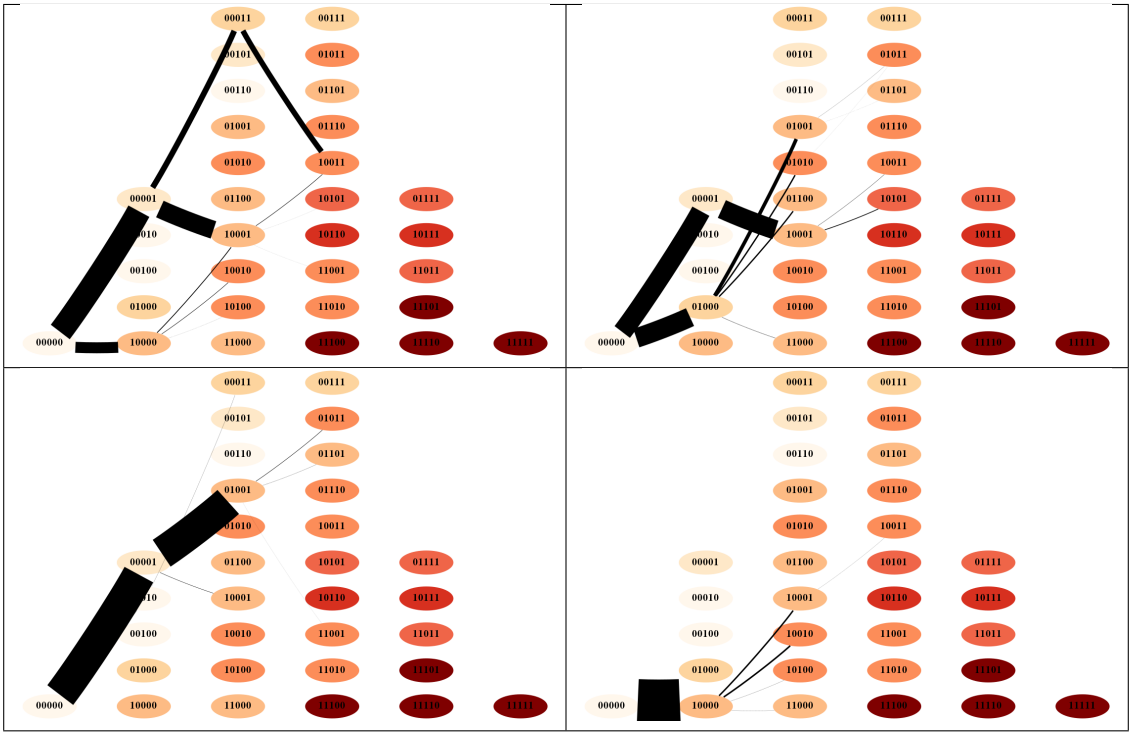


Figure 4: Random selection of single experiments with maximum concentraion 300 ng/ml. In any given experiments, multiple genotypes can be present in the final well, and multiple trajectories could have led to the same genotype. Often this is not the case however and we see a dominant trajectory.

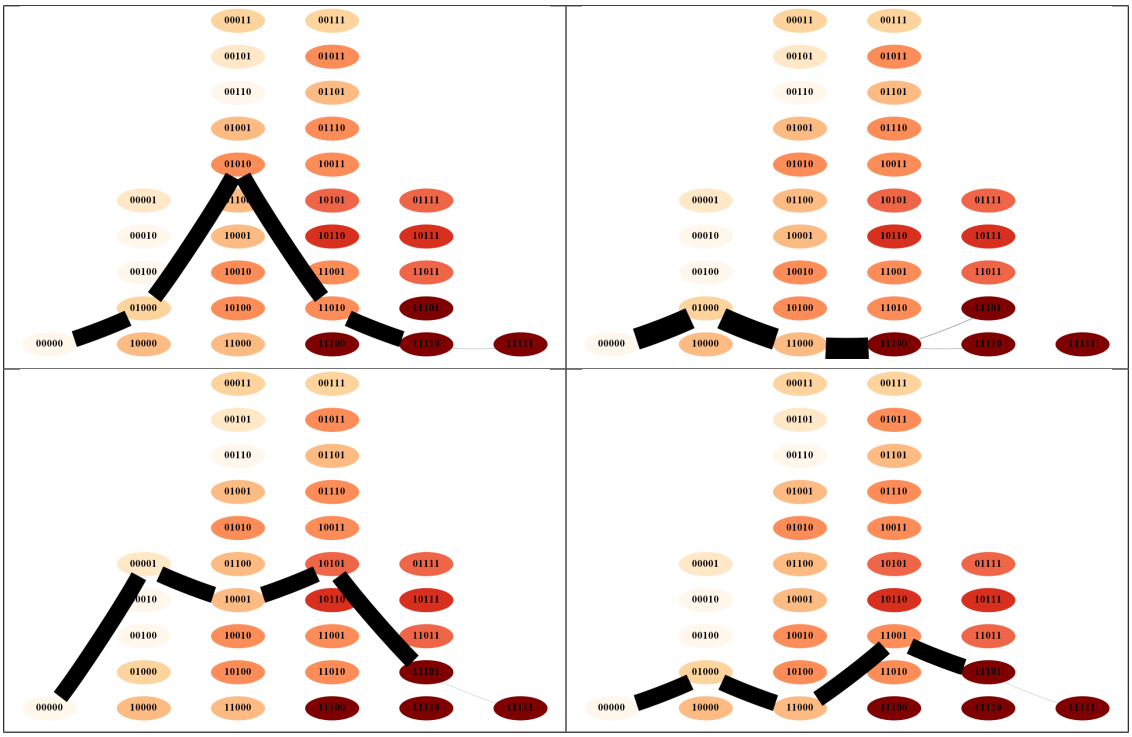


Figure 5: Random selection of single experiments with maximum concentraion 20,000 ng/ml. With a stronger selection gradient, seems to be less variability within each run.

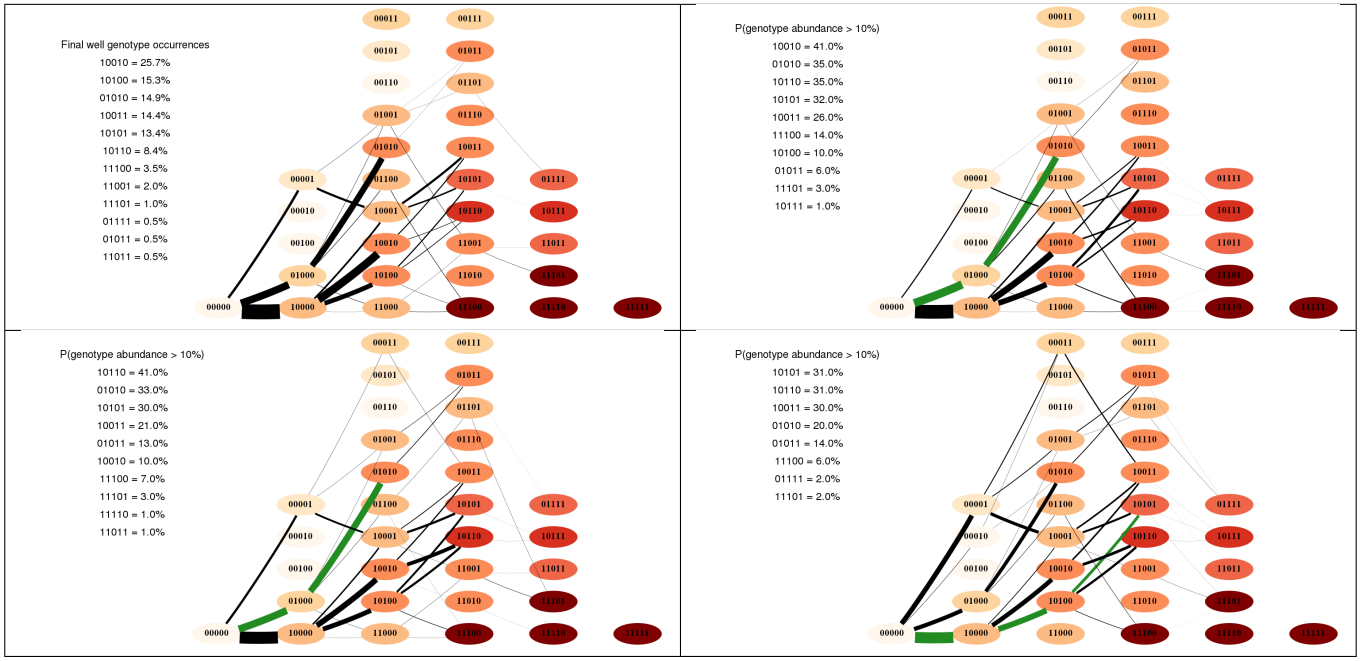
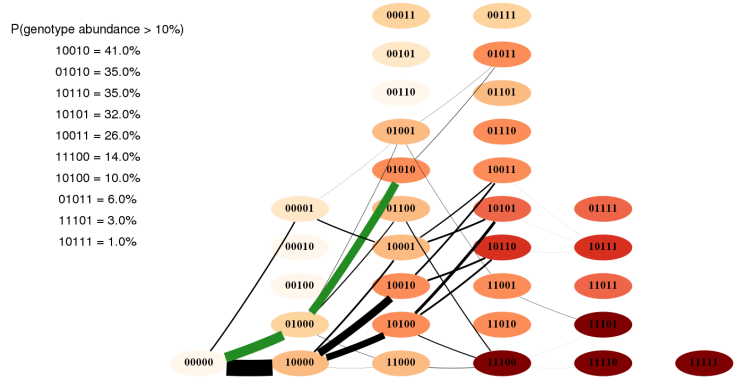
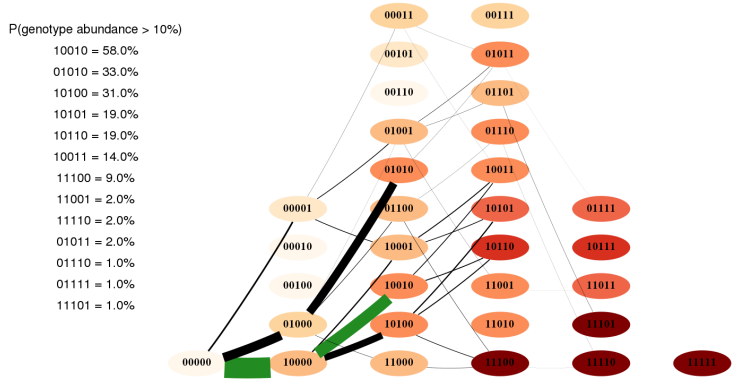


Figure 6: The final well of 4 experiments with ciprofloxacin profiles with a maximum of 1000 ng/ml. The difference is that in (b) there are flat ends, or "plateaus" of 3 wells (i.e. the first 3 wells have 0 ciprofloxacin while the last 3 have 1000 ng/ml) and thus the exponential gradient is steeper in the case of (a) in which there are no plateaus. (c) and (d) contain plateaus of 6 and 9 wells respectively. Hence in (d), the exponential part is restricted to only the 6 middle wells. Although the general mutational graph shows similarities, we can see that this difference in the profiles can affect the outcome of the simulation. Namely, that the plateaus seem to increase evolution, with more advanced genotypes being reached as we increase the length of the plateau. This is probably expected, since more wells at a higher concentration is subjecting the population to a higher selective pressure for a longer time. Investigate what roles the intial and end plateaus play. The initial plateau may allow more mutations to accumulate before the selection pressure is encountered, thus lessening the chance that some dead-end trajectory is followed) while the end plateau will allow further selection and mutation with a higher selection pressure. Note that the trajectories shown in green are the trajectories followed by the largest absolute number of bacterial cells found in the final well (across all experiments).

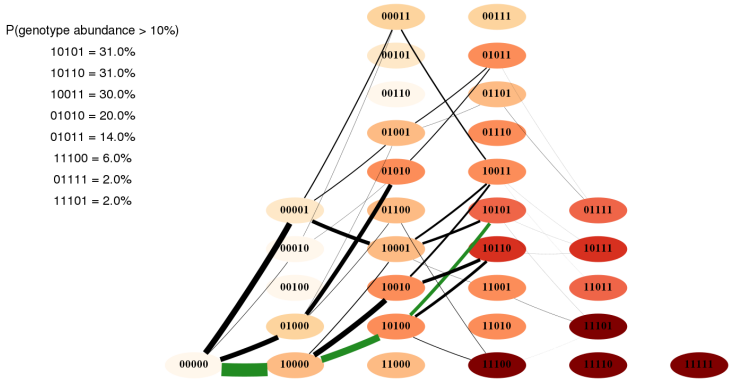


(a)

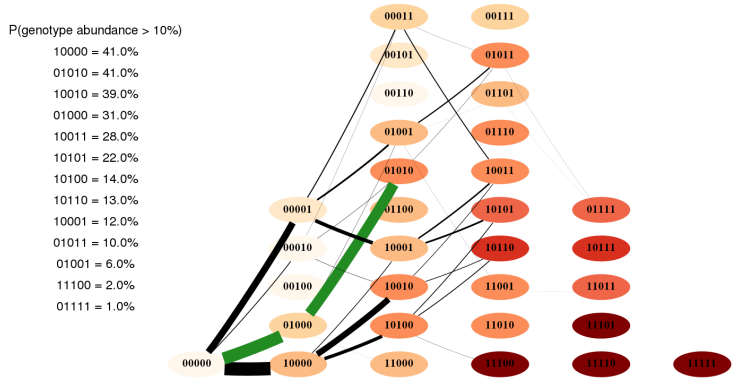


(b)

Figure 7: Simulations with max cipro = 1000 ng/ml where (a) contains plateaus of 3 wells and (b) has these plateaus removed, where we have the same exponential profile but the experiment is only 20 wells long. The lack of plateaus in (b) appears to reduce the prospect of evolving resistance. Notice that the most followed trajectory does not correspond to the most frequently present genotype. This is because even though a certain genotype may be more likely to be present (above 10% cutoff) in final well, it may be the case that this genotype, when present, is usually at a relatively low abundance due to other strains competing (especially it's mutant progeny). Is there a better thing I should be plotting in place of the green "most followed trajectory in terms of absolute cell numbers"?



(a)



(b)

Figure 8: Same as above but (a) has plateaus of length 9 while (b) is the pure exponential profile located in an experiment of just 8 wells. Lack of plateaus hinders evolution. Since experiment is so short, we see genotype 10000 present with abundance above 10% in final well through migration (it is not viable at 1000 ng/ml).