MIC-dependent motility

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1 Probability of reaching final well

We discussed that the more appropriate way to model a ciprofloxacin-dependent motility would be to link it to a strains MIC. We implemented this as a step function: below some fraction of its MIC a strain is fully motile, above this cutoff the strain is immotile. This didn't produce huge changes (discussed in previous set of notes) but the way it had been implemented was that immotile cells could still produce mutant offspring. To try and more closely model filamentation, the program now also sets the mutation rate to zero when a cell is immotile. Thus, an immotile cell continues to grow and consume nutrient (or contribute to the carrying capacity of the well) but does not mutate. This change greatly reduces the number of experiments that reach the final well and also the diversity of viable pathways.

The following table shows the number (out of 200) of experiments that reached the final well for various motility cutoffs. Two ciprofloxacin profiles were used, exponential with maxmimums of 300 and 1000 ng/ml. From Bartek's current experimental results, we estimate that we would expect around 17 experiments to reach the final well in the 300 ng/ml case, and for 20 to succeed for 1000 ng/ml. This would suggest a motility cutoff of somewhere between 0.1 and 0.2 of a strains MIC.

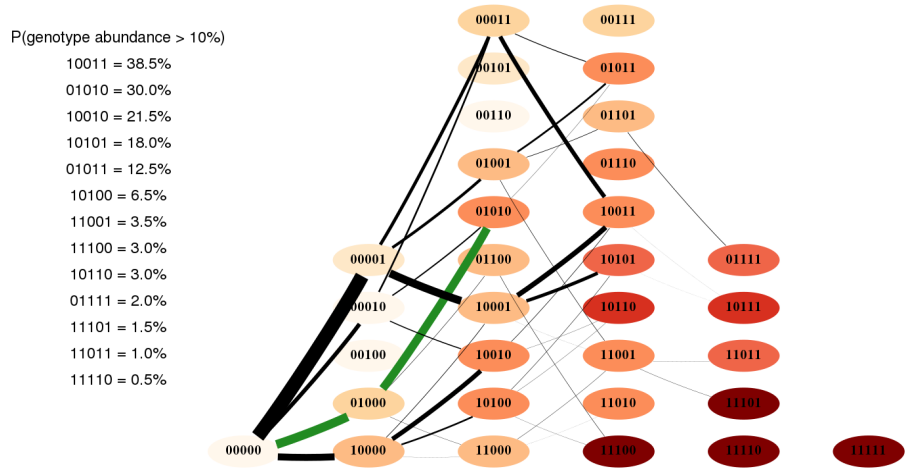
	300 ng/ml	1000 ng/ml
0.5 MIC	200	200
0.2 MIC	82	35
0.15 MIC	53	10
0.1 MIC	11	8
0.05 MIC	3	4

It's also worth noting that from Bartek's experiments, the expected number of successes for 100 ng/ml and 3000 ng/ml are 117 and 4 respectively. Hence increasing the concentration does seem to hinder the emergence of evolution, or at least the timescale for it to occur. (The difference between the 300 and 1000 ng/ml cases is likely not significant but it is worth bearing in mind from previous discussions that since we do not know exactly how ciprofloxacin affects the mutation rate of the wild type, nevermind all of the other strains, it is possible that the relation between maximum concentration and likelihood of evolution is not monotonic: the selective pressure, ciprofloxacin, is actively increasing the rate of evolution through an increased mutation rate and so there could be non-obvious effects here).

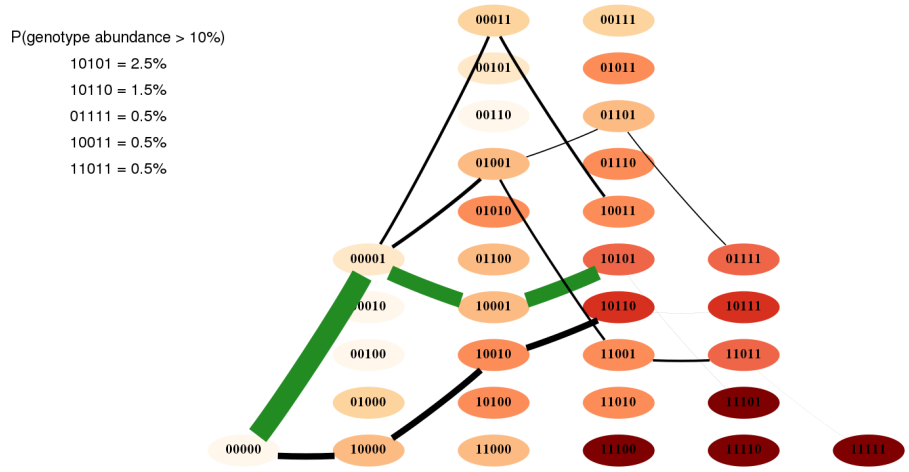
TO FIX: I need to re-implement food explicitly or put a limit on the number of birth events that can occur in a well. When we have this motility cutoff, the well in which a strain becomes immotile acts as a sink: cells cannot leave here so it traps cells migrating from the previous well, keeping it's population below the carrying capacity for longer than normal. Since the current implementation just defines the growth rate with respect to the population density, this increases the number birth events occurring. Not a huge problem, but if we had a high diffusion rate, it would be possible to produce an infinite number of cells in this well preceding the sink well.

2 Effect on diversity of pathways

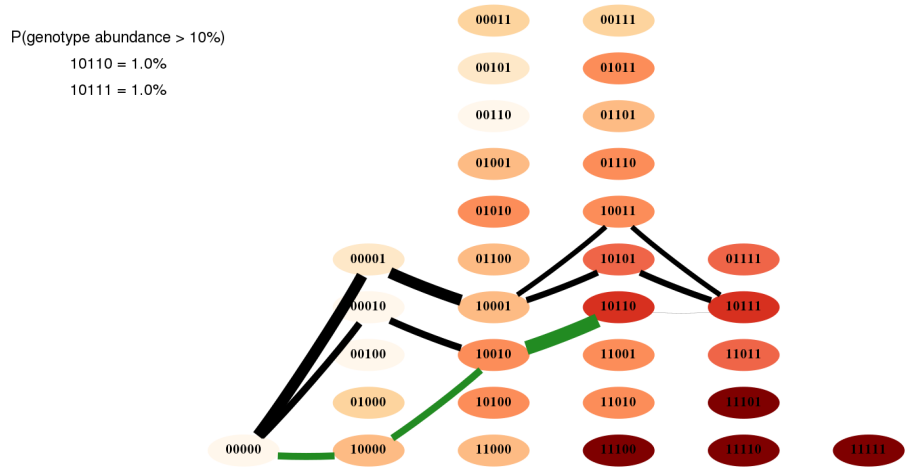
From the above table, implementing lower cutoffs reduces the chances of resistance emerging. It also affects the evolutionary dynamics, reducing the diversity of the pathways observed in the simulations.
Figure **??** illustrates this, showing the weighted mutational graph for various cutoffs.
Figure **??** shows the cumulative probability vs rank of the pathways for the same cutoff values.



(a) Cutoff = 0.5 MIC

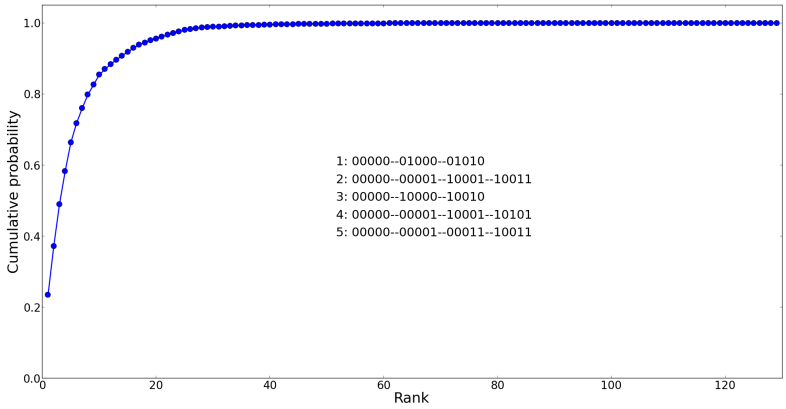


(b) Cutoff = 0.15 MIC

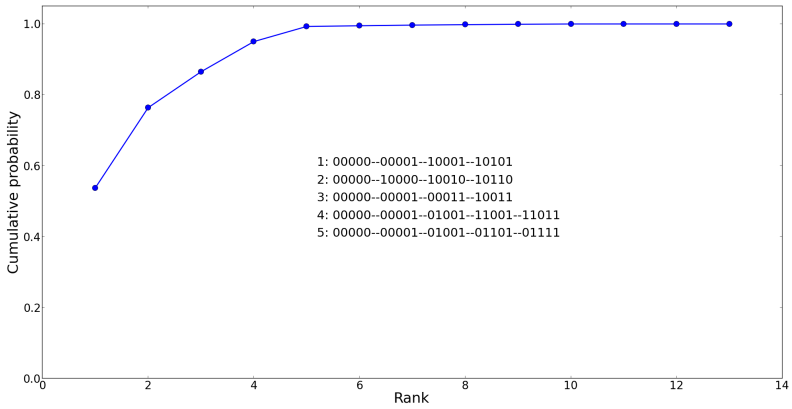


(c) Cutoff = 0.05 MIC

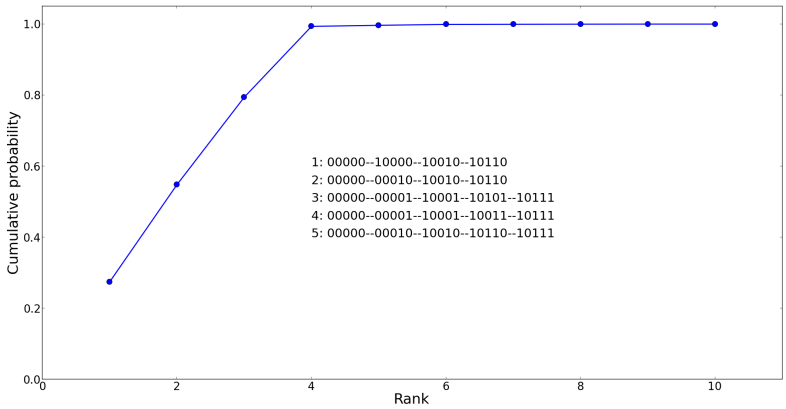
Figure 1: Change in mutational graph for 3 different motility cutoffs. Each is produced from 200 simulations, with a maximum ciprofloxacin of 1000 ng/ml. We can see that decreasing the cutoff both reduces the number of successful experiments, and the diversity of possible trajectories.



(a) Cutoff = 0.5 MIC



(b) Cutoff = 0.15 MIC



(c) Cutoff = 0.05 MIC

Figure 2: For the same data sets of 200 experiments as in previous plot, here is the cumulative probability vs rank of trajectories observed. We see that with a cutoff of 0.5 MIC (a), 8 evolutionary trajectories account for 80% of all trajectories observed but that there are a huge number of possible trajectories. (Note that some of these may be single unviable cells that have managed to migrate into the final well). With a cutoff of 0.15 MIC (b) 5 trajectories basically account for all those observed while in (c) we see that for a cutoff of 0.05 MIC there are 4 trajectories.