Summary on 3 state simulations

"Method"

I originally computed the optimal parameters as in the two state case, that is by analytically computing the average time it would take to consume all the nutrients (T_S). However, to isolate T_S I had to make an assumption that I did not trust on close inspection. Now I have redone the calculations, and computed the optimal parameters without the previous assumption, but instead by numerically determining T_S. For a given set of antibiotic parameters (p, T_0, T_{ab}) I determine T_S for every set of bacterial parameters (λ_d, λ_r, δ). The optimal combination of (λ_d, λ_r, δ) is the one that minimizes T_S.

In addition to the theoretical optimal parameters, I have also computed the competition average parameters. This is done by evolving several species according to the differential equations and using a solver to find T_S for 20 000 consecutive cycles. The different species have parameters $\lambda_{d/r} \in [0.01, T]$ with $d\lambda = 1$ and $\delta \in [0, 0.05]$ with $d\delta = 0.001$.

Coupled nutrients and antibiotics, $T_0 = 0$

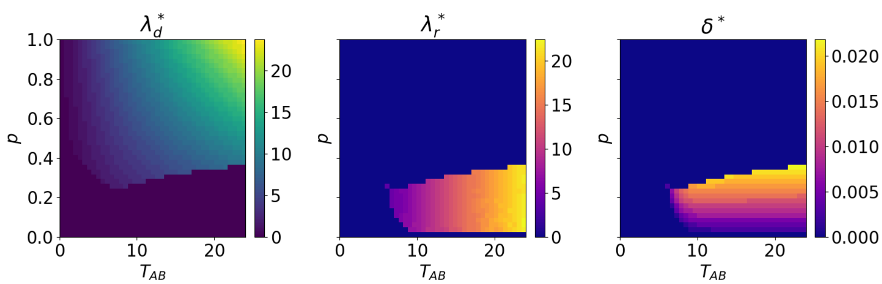

Figure 1: Optimal parameters for $T_0 = 0$

I still get same result as before: optimal strategy is either only triggered persistence, or only spontaneous persistence (see Fig. 1 and Fig. 5). λ_d^* is the same as earlier, i.e. $\lambda_d^* \approx pT$, whereas $\lambda_r^* \approx 0.85T$. The value of δ^* is mainly determined by p. I am a bit surprised that λ_r is not smaller, since bacteria is entering spontaneous persistence both during and after the antibiotics. I assume this is balanced by a low δ^* (though still not as low as experimentaly observed).

The result is confirmed by a competition simulation in Fig. 2, where the dashed lines represent the theoretical optimals from Fig. 1. For $p > 0.1$ the optimal is to have only triggered persistence, whereas for $p = 0.1$ spontaneous persistence is the optimal. $p = 0.3$ is very close to the phase transition, and is therefore fluctuating slightly between the two optimals.

For λ_d the competition average is not perfectly consistent with the theoretical

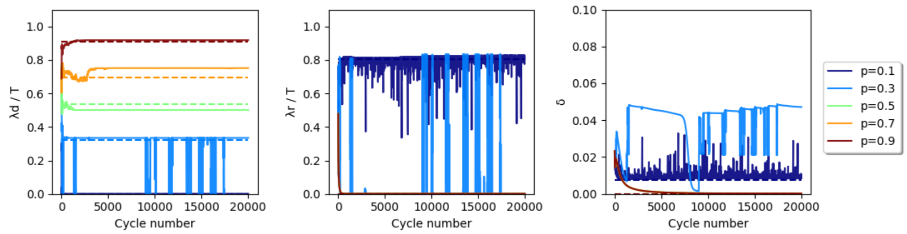

Figure 2: Interspecies competition at $T_0 = 0$, $T_{ab} = 12$

optimal, which I think is because the resolution of the parameters in Fig. 1 is much higher (The competition average is much more computationally heavy to compute).

The behaviour of δ for $p = 0.3$ is a bit weird. What I think happens is that when this weakly bistable system jumps from a low risk state (only spontaneous persistence) to a high risk state (only triggered persistence), it also benefits from the marginal additional protection from having $\delta = \delta_{max} = 0.05$. With time δ decreases toward 0, but since $\lambda_r = 0.01$, the penalty for having non-zero δ is very small, hence the decrease is very slow. The parameter combination of $\lambda_r \approx 0$ and $\delta > 0$ is probably not very realistic.

The last odd feature of the plot is for $p = 0.1$. Whereas λ_r and δ fluctuate a lot, λ_d is not. For $p = 0.1$, antibiotics are so rare that for long periods there are no cycles with antibiotics. During these periods $\lambda_r \to \lambda_{min}$, but as soon as there is a round of antibiotcs λ_r jumps back to the theoretical optimal. It is not really clear to me why δ should be increasing in the absence of antibiotics. I also ran a simulation that starts with $p = 0.1$ for the first 5000 cycles or so, before I set $p = 0$ (see Fig. 7). My intuition is that it is related to the distribution of biomass among the subpopulations, i.e. that the subpopulations with higher δ have grown more than their competitiors during earlier periods with more frequent antibiotics. I think it could also be a numerical effect, but I'm not sure. When I run the competition with $p = 0$ during the entire simulation, I get $(\lambda_d^*, \lambda_r^*, \delta^*) = (0, 0, 0)$ as expected.

Decoupled nutrients and antibiotics, $T_0 > 0$

Also when the antibiotics are decoupled from the addition of nutrients the two strategies are separated (see Fig. 2 and Fig. 6). Again, $\lambda_d^* \approx pT$, $\lambda_r^* \approx 0.85T$, and the value of δ^* is mainly determined by p. I've probably set the upper limit on δ too low.

I have also run a competition simulation in Fig. 4. The figure is a bit messy, but still in agreement with the theoretical optimals. For $p < 0.7$ spontaneous persistence is the optimal strategy, and for $p \geq 0.7$ triggered persistence is the optimal. However, both $p = 0.5$ and $p = 0.7$ are close to the phase boundary,

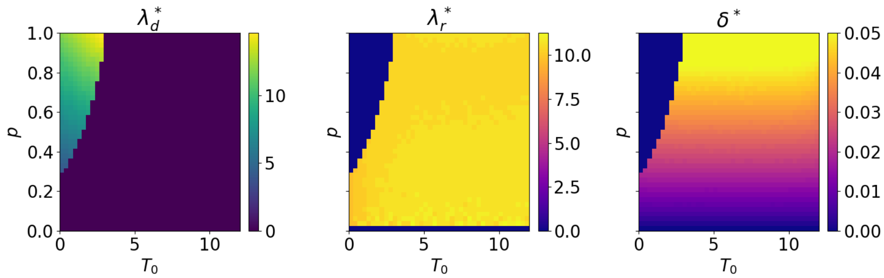

Figure 3: Optimal parameters for $T_{AB} = 12$

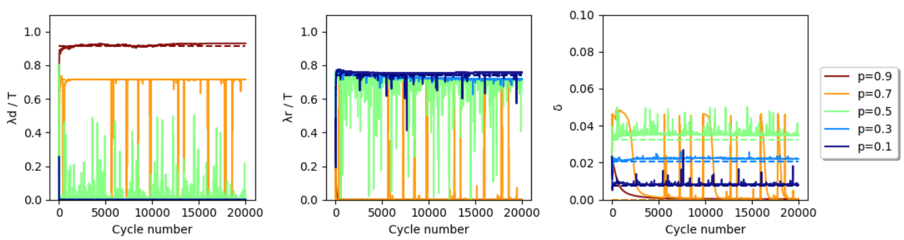

Figure 4: Interspecies competition at $T_0 = 2$, $T_{ab} = 12$

with strong fluctuations. $p = 0.7$ shows similar behavior as $p = 0.3$ in Fig. 2, but with the decay of δ being much faster. I think that is because $\delta^*_{p=0.7,T_0>3} \approx \delta_{max}$ (and that I've probably set the upper limit on δ too low.) The spikes in δ where the decay back to the optimal value happens immediately represent flucuations that are not large enough to the system to switch to spontaneous persistence.

$p = 0.1, 0.3, 0.5$, behave like $p = 0.1$ in Fig. 2, i.e. with fluctuations away from the optimal strategy, but they never switch to triggered persistence. For $p = 0.5$ the optimal strategy of triggered persistence has a finite λ_d, whereas for $p = 0.1$ and $p = 0.3$ it is $\lambda_{min} \approx 0$, which I think is why there are also fluctuations in λ_d at $p = 0.5$, but not for $p < 0.5$. Lastly, I think the fluctuations at $p = 0.3$ are smaller than for both $p = 0.1$ and 0.5 because the penalty for switching phase is the highest at $p = 0.3$.

Mutation

In progess

Rescaled heatmaps

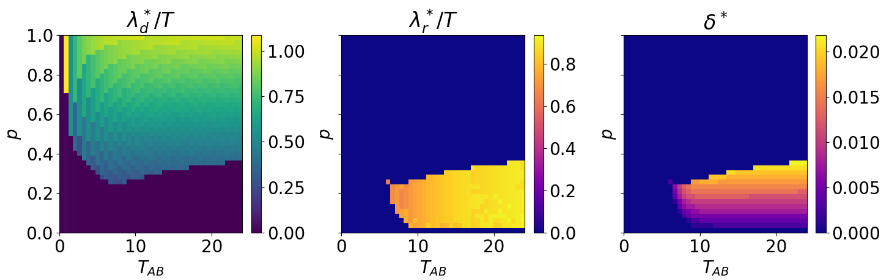

Figure 5: Optimal parameters for $T_0 = 0$

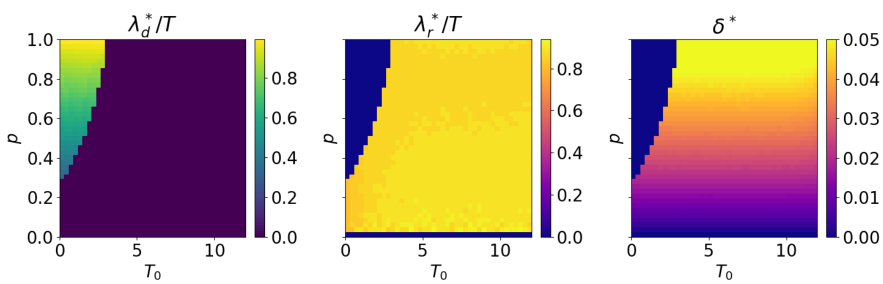

Figure 6: Optimal parameters for $T_{AB} = 12$

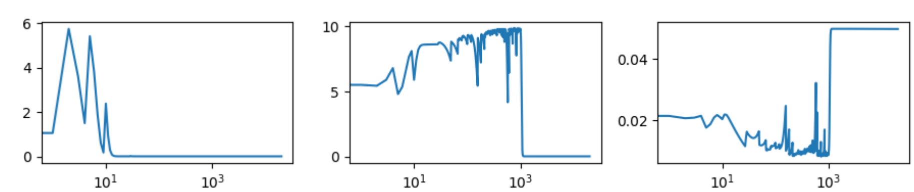

Figure 7: Competition with $p = 0.1$ for the first 1000 cycles, then $p = 0.0$ for the rest.