

Supplementary material for “Coexistence of Virulent Phage and Bacteria on the Boundary of Self-organized Refuges”

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1 Details of the Model Implementation

1.1 Basic Model

Time is discrete and incremented in steps of constant size $\Delta t = 1$. At each time step, for each site in the $L \times L$ grid (the order of choosing sites is random) the following steps are taken in the following order:

1. If the site contains an infected bacterium and the current time matches the time of lysis stored in the lytic counter then for the next time step that site is labeled as empty and the number of phage is increased by β , the burst size.
2. If the site contains a healthy bacterium and the current time matches the replication time stored in the replication counter then for the next time step this bacterium divides with a probability $E/4$, where E is the number of empty neighbors the bacterium has in its Von Neumann neighborhood. If the bacterium divides then one daughter cell occupies the same site and the second occupies one of the empty neighboring sites, randomly chosen. The replication counters of both daughter cells are set to the current time plus T , which is the bacterial generation time.
3. If the site contains a healthy bacterium and a non-zero number of phage N_0 , then in the next time step it becomes infected with a probability

$$p_\alpha = 1 - \exp\left(-N_0\alpha\left(\frac{1 - \exp(-\delta\Delta t)}{\delta}\right)\right). \quad (1)$$

The number of phage is decreased by one and the lytic counter of the infected bacterium is set to the current time plus τ , the latent time of the phage.

4. Each phage in the site decays with a probability $p_\delta = 1 - e^{-\delta\Delta t}$.
5. Each phage in the site jumps to a neighboring site (randomly chosen from the Von Neumann neighborhood) with a probability $p_\lambda = 1 - e^{-\lambda\Delta t}$.

See ref. [2, 1] for a more detailed explanation for the assumptions and choices underlying these rules.

1.2 Fixed Refuge Model

The implementation is identical to the basic model, except that one or more of the parameters $\alpha, \delta, \beta, \lambda, \tau$ may take different (but fixed and pre-specified) values in the two half-planes that the $L \times L$ grid is divided into.

1.3 Self-organized Refuge Model

The implementation of this is quite similar to the basic model with the addition of a density counter at each site and a pre-specified functional dependence of the parameters $\alpha, \delta, \beta, \lambda, \tau$ on the density counter value at that site. Thus, $\alpha, \delta, \beta, \lambda, \tau$ may take different values at different sites, and this depends only on the density counter value at that site. Wherever these parameters are mentioned below, they refer to the value of that parameter at the site under consideration.

Time is discrete and incremented in steps of constant size $\Delta t = 1$. At each time step, for each site in the $L \times L$ grid (the order of choosing sites is random) the following steps are taken in the following order:

1. If the site contains an infected bacterium and the current time matches the time of lysis stored in the lytic counter then for the next time step that site is labeled as empty and the number of phage is increased by β , the burst size.
2. If the site contains a healthy bacterium and the current time matches the replication time stored in the replication counter then for the next time step this bacterium divides with a probability $E/4$, where E is the number of empty neighbors the bacterium has in its Von Neumann neighborhood. If the bacterium divides then one daughter cell occupies the same site and the second occupies one of the empty neighboring sites, randomly chosen. The replication counters of both daughter cells are set to the current time plus T , which is the bacterial generation time.
3. If the site contains a healthy bacterium and a non-zero number of phage N_0 , then in the next time step it becomes infected with a probability

$$p_\alpha = 1 - \exp\left(-N_0\alpha\left(\frac{1 - \exp(-\delta\Delta t)}{\delta}\right)\right). \quad (2)$$

The number of phage is decreased by one and the lytic counter of the infected bacterium is set to the current time plus τ , the latent time of the phage.

4. Each phage in the site decays with a probability $p_\delta = 1 - e^{-\delta\Delta t}$.
5. Each phage in the site jumps to a neighboring site (randomly chosen from the Von Neumann neighborhood) with a probability $p_\lambda = 1 - e^{-\lambda\Delta t}$.
6. If the site contains a bacterium (healthy or infected) then the density counter value for that site is incremented by two if there are 4 neighboring bacteria (healthy or infected), incremented by one if there are 3 neighboring bacteria, decremented by one if there are 2 neighboring bacteria, and decremented by two if there are 1 or 0 neighboring bacteria. The density counter value is bounded below by zero, and above by 100.
7. If the site is empty the density counter value is set to zero.

Typically, we let the degradation rate and the infection rate depend as step functions on the density counter value: $\delta(v) = \delta_{out}$ when the density counter value $v \leq v_\delta^*$ and $\delta(v) = \delta_{in}$ when $v > v_\delta^*$; $\alpha(v) = \alpha_{out}$ when $v \leq v_\alpha^*$ and $\alpha(v) = \alpha_{in}$ when $v > v_\alpha^*$. To generate figure S 1 we used: $\delta_{out} = 0.05 \cdot 10^{-1} \text{min}^{-1}$, $\delta_{in} = 5 \cdot 10^{-1} \text{min}^{-1}$, $\alpha_{out} = 1.0 \cdot 10^{-1} \text{min}^{-1}$, $\alpha_{in} = 0.01 \cdot 10^{-1} \text{min}^{-1}$, $v_\delta^* = v_\alpha^* = 100/2$. We have also tried smoother, sigmoidal, functions of the form: $\delta(v) = (\delta_{in} - \delta_{out}) \cdot \left(\frac{v^h}{v^h + v_\delta^{*h}}\right) + \delta_{out}$

A high density counter will be correlated with a bacteria having been in a high cell density environment for a while. As seen in figure S 1AB these rules result in a "steady state" with a highly bimodal density counter distribution regardless of whether the parameters depend on the density counter as a step function or as a sigmoid function. Cells end up mostly having either have a very low density counter or having the maximal density counter value either way. This explains why the details of how exactly the parameters depend on the density counter value does not matter (both step functions and more gradual sigmoidal functions give the same overall behavior) and also why the exact threshold density counter value where the step function or sigmoidal function changes does not matter. We also tried letting the density counter decrease and increase at a slower rate than indicated in the rules above, but also here saw quantitatively the same behavior. These observations lets us conclude that the details of how the parameters (like for example the degradation rate) is varied as a function of the density counter does not matter for the overall result. As long as the extreme end values, (in the case of δ this is δ_{in} and δ_{out}) are on opposite sides of the coexistence region, (for δ this means above and below respectively of δ_{max} and δ_{min}), we get see coexistence of phage and bacteria for time spans much longer than the bacterial generation time.

We use the time length of the transient where there is coexistence as a measure for coexistence. Whenever the duration of coexistence (presence of both phage and bacteria) exceeds 1000 bacterial generations the simulation is stopped (see fig. S 3 and S 4). It is clearly seen in the two figures S 3 and S 4 that the timescales of extinction for different parameter values (but the same initial condition) vary enormously; whenever $\delta_{in} > \delta_{max}$ and $\delta_{out} < \delta_{min}$ or $\alpha_{in} < \alpha_{min}$ and $\alpha_{out} > \alpha_{max}$ the length of time when there is coexistence in the system seems to diverge and in most cases to exceed the simulation cut of 1000 bacterial generations. The long lifetime of coexistence inside these regions is due to the formation of phage hostile bacteria refuge islands with phage proliferating on the edges on susceptible bacteria produced by the protected bacteria further in.

1.4 Self-organized Refuge Model with Evolution

This model is very similar to the self-organized refuge model except that $\delta_{in}, \delta_{out}$ and $\alpha_{in}, \alpha_{out}$ are no longer constants. Instead, each individual phage has its own $(\delta_{out}, \alpha_{out})$ and each individual bacterium has its own value of $(\delta_{in}, \alpha_{in})$. When the δ -values are allowed to evolve for example, whenever a bacterium divides, the offspring get a new value of δ_{in} drawn from a normal distribution centered around the parent value and with the variance $\mu_{bacteria}$, and whenever a phage has a batch of offspring, each new phage get a new value of δ_{out} drawn from a normal distribution with a mean equal to the parent value and the variance μ_{phage} . We tried implementing evolution in two ways. Firstly by letting the mutant δ and α values take normally distributed steps from the parent value and secondly by letting the mutant exponent x (where e.g. $\delta = 10^x$) take normally distributed steps away from the parent exponent value, (see fig. S 16 and S 17).

We have examined a range of different values and different initial conditions (see fig. S 16 and S 17), and the results are qualitatively similar: δ_{in} values tend to increase and δ_{out} values tend to decrease, pushing the system deeper into the coexistence region. Similar simulations were done keeping δ_{in} and δ_{out} a constant, but allowing each bacterium to have its own α_{in} and each phage to have its own α_{out} value, (see fig. S 18). Here α_{in} values tend to decrease and α_{out} values tend to increase, pushing the system deeper into the coexistence region (the blue region). Lastly we tried letting all four parameters evolve at the same time and observed the same pattern. Note however that when both δ and α values are evolving the coexistence "safe zone" is no longer just given by the blue regions in fig S 16, S 17 and S 18, since these are only defined for fixed $\delta_{in} = \delta_{out} = 0.1$ and $\alpha_{in} = \alpha_{out} = 1.0$ respectively.

Since we use quite small system sizes we were forced to use relatively large μ_{phage} and $\mu_{bacteria}$ in order to see results within a reasonable time frame (in the range 0.01-0.1). We observed that evolution of δ_{in} and δ_{out} from the initial condition of $\delta_{in} = \delta_{out} = 1.0 \cdot 10^{-1} min^{-1}$ was able to bring the system into the blue region where $\delta_{in} > \delta_{max}$ and $\delta_{out} < \delta_{min}$ even when $\mu_{phage}/\mu_{bacteria} = 0.1$ and $\mu_{phage}/\mu_{bacteria} = 5$ in a system with a grid size of 80x80. Thus we can conclude that provided that μ_{phage} and $\mu_{bacteria}$ are not too small or too different and that the initial conditions are not too extreme or the grid size too small then the system usually successfully manage to move within the blue region before extinction of either phage or bacteria even when initial conditions lie a bit outside the region. The requirement for this is simply that the timescales for getting mutants of both phage and bacteria with parameter values within the blue region is faster than the extinction time scale at the parameter start values. These timescale depends on μ_{phage} , $\mu_{bacteria}$ and on the ratio $\mu_{bacteria}/\mu_{phage}$ as well as the system size and on the initial numbers of phage and bacteria and the initial values of the parameters which are allowed to evolve and it is thus hard to characterize exactly what conditions will ensure coexistence. We can however say that the tendency in all simulations clearly indicates that phage evolution tend to push δ_{out} to lower values while α_{out} to higher values while conversely bacteria evolution pushes δ_{in} to higher values while α_{in} to lower values, (see e.g. fig. S 15 A). As seen in figure S 15 B, the dynamics of a simulation with evolution usually starts out being quite dramatic with big changes in both phage and bacteria densities over short time scales. Later when the system have reached well within the coexistence safe zone, it stays more or less completely static with well defined bacteria refuges and phage proliferating on the edges even though parameters are still evolving. This tells us that a system with parameters within the coexistence safe zone if moved suddenly to another parameter point far away (but also within the safe zone) would not experience drastic population fluctuation on a short time scale even though the evolutionary move for example doubled the phage half-life or halved the infection rate, something which would in most cases end coexistence and in all cases result in great and rapid fluctuations in phage/bacteria numbers in the basic model (see fig. 1 in the paper).

2 Self-organizing "life on the edge" is robust

The phenomenon seen in the self-organized refuge model, of long-lasting coexistence on the edge of self-organized density-dependent refuges occurs for a huge range of parameter values and is stable against many changes in the model rules. Figure 5 shows the duration of coexistence as a function of δ_{out} and δ_{in} , for simulations where the only parameter that depends on the density counter is δ , (δ_{out} and δ_{in} are the values of δ for sites with minimal and maximal density counter values respectively, see Fig. 3). In the region where $\delta_{in} > \delta_{max}$ and $\delta_{out} < \delta_{min}$, we find that coexistence times rise steeply compared to the values outside this region. Thus, whenever δ_{in} is chosen from the dark red "phage too inefficient" region ($\delta_{in} > \delta_{max}$) of figure 1 and δ_{out} from the dark blue "phage too efficient" region ($\delta_{out} < \delta_{min}$), phage coexist with bacteria on the edges of the bacteria colonies for several hundreds or thousands of generations.

In simulations done to produce the data shown in figure 5, the δ dependence on the density counter was a step function, but we find that long-lasting coexistence does not depend on the precise shape of the function. If the increase in δ is a smoother, e.g. sigmoidal, function of the counter value we get a similar result. Other details which did not matter was the precise threshold counter value at which δ increases from δ_{out} to δ_{in} , and the rate of change of the counters as a function of time or the number of neighbors.

Further, if different, but fixed, values of other parameters such as α are chosen then, as expected, the

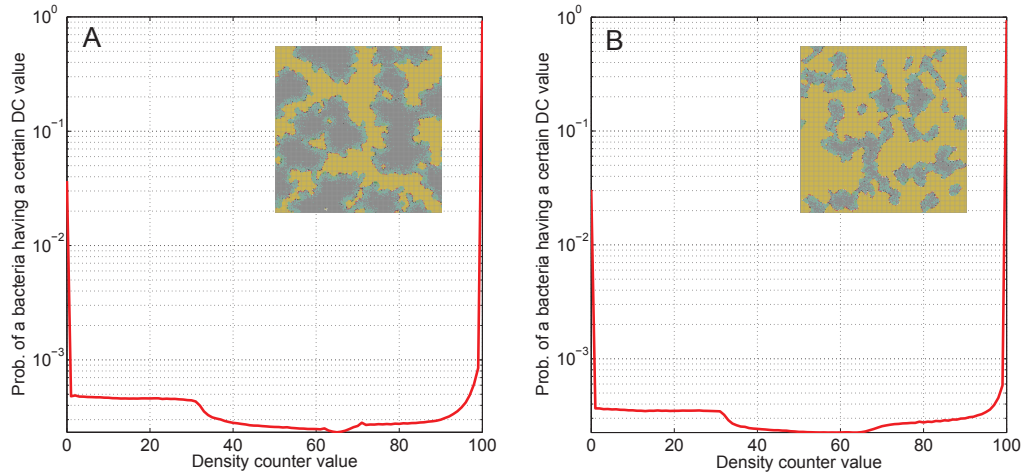


Figure 1: **Bimodal density counter value distribution** The average distribution of density counter values found in a simulation of the selforganized bacteria refuge model with parameters: $\delta_{out} = 0.05 \cdot 10^{-1} min^{-1}$, $\delta_{in} = 5.0 \cdot 10^{-1} min^{-1}$, $\alpha_{out} = 1.0 \cdot 10^{-1} min^{-1}$, $\alpha_{in} = 0.01 \cdot 10^{-1} min^{-1}$ (same as the parameters in fig. 4.), after it has reached a static pattern (see inserts). Note that the probability of finding bacteria with either very low or very high density counter is much higher than finding a bacteria with an intermediate density counter value. **A:** The dependence of δ and α on the density counter is a step function. **B:** The dependence of δ and α on the density counter is a sigmoid function with hill-factor 4. Grid size: 200x200. Initial conditions was randomly scattered bacteria and bacteria infected with phage.

values of δ_{min} and δ_{max} change but the above condition ($\delta_{in} > \delta_{max}$ and $\delta_{out} < \delta_{min}$) for long-lasting coexistence still holds. The same is true if instead of varying δ , α is made a decreasing function of the density counter while δ kept fixed. In this case, as shown in supplementary material, the requirement for selforganized refuge formation is that $\alpha_{in} < \alpha_{min}$ and $\alpha_{out} > \alpha_{max}$ (where α_{max} and α_{min} are the upper and lower boundaries of the coexistence region in figure 1 for a fixed value of δ). These results are also robust to changes in other parameters of the model. For example, the above simulations used a bacterial generation time of 300 minutes, assuming that in natural phage-bacteria ecosystems the bacteria would typically grow much slower than in laboratory conditions. However, even using a generation time of 30 min, as in rich laboratory conditions, the values of $\delta_{max,min}$ and $\alpha_{max,min}$ change but coexistence still occurs when the above conditions are met (see supplementary material). What is required for coexistence on the edge of bacterial refuges is merely that the bacteria in the center of the colony are so resilient that phage cannot sustain themselves in there, while newborn bacteria on the edge of the colonies are (possibly very) susceptible to phage infection.

Fig. 4 shows an example of how the dynamics of the model looks when the phage degradation rate δ is made an increasing function of the density counter, and the phage infection rate α is made a decreasing function of the density counter while all other parameters are kept fixed everywhere in the system (using a combination of α and δ allows us to get coexistence with smaller differences between the values of these parameters at low and high density counter values). The system develops a static pattern of islands of self-constructed bacterial refuges, with phage proliferating on new bacteria produced on the edges of the islands. The spreading infection fronts become almost stationary after around 10 bacterial generations (see supplementary material for plots of front speed as a function of parameter values). On a longer timescale they tend to straighten from an initial crumbling pattern into more smooth boundaries. The boundaries thus seem to act like there is an effective surface tension; the perimeters of the bacterial colonies decrease over time because sections with high curvature see a higher local density of phage. There also appears to be an effective nucleation threshold: very small colonies tend to die out in the beginning of the simulation while larger colonies stabilize and persist (see supplementary figures 9, 10, 13 and 14).

References

- [1] Heilmann S, Sneppen K, Krishna S (2010) Sustainability of virulence in a phage-bacterial ecosystem. *J Virol* 84:3016–3022.
- [2] Heilmann S (2009) Survival of the mediocre killers - space and mutability in phage-bacteria ecosystems. <http://www.nbi.dk/heilmann/silja/thesisdownload.php>.

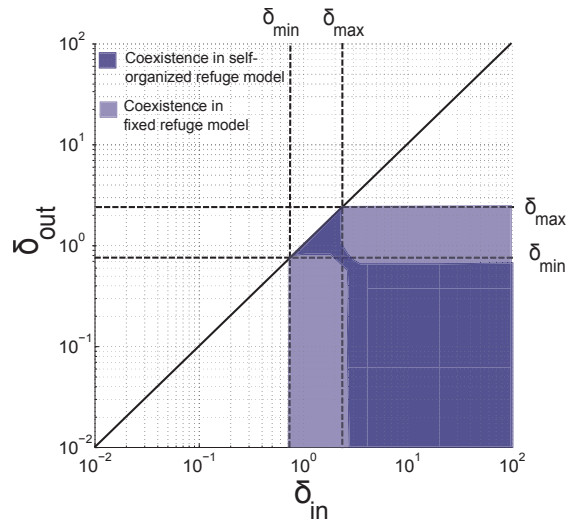


Figure 2: **Comparison between coexistence in fixed refuge model and selforganized refuge model.** Schematic figure showing the rough outline of the coexistence regions for the fixed refuge model (light blue) and for the selforganized refuge model (dark blue) in the parameter space of δ_{in} and δ_{out} . (For the fixed refuge model δ_{in} would be the phage degradation rate used in the upper part of the plane and δ_{out} the degradation rate used in the lower half). Coexistence is here defined as having both phage and bacteria present in the system for longer than 1000 bacterial generations.

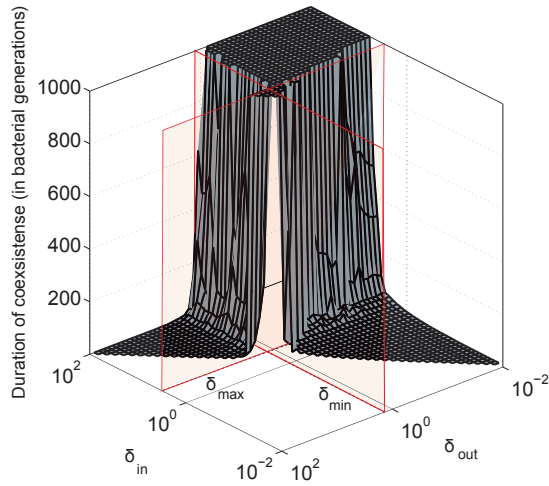


Figure 3: **Long lived coexistence for a broad range of δ_{in} and δ_{out} .** Surface shows length of coexistence for different sets of δ_{in} and δ_{out} , if coexistence lasted longer than an upper cut off value of a 1000 bacteria generations the simulation was stopped. Grid size: 100x100 Initial conditions for simulations where phage infected bacteria placed on a straight colony edge of healthy bacteria, were bacteria had max density counter value from $t=0$.

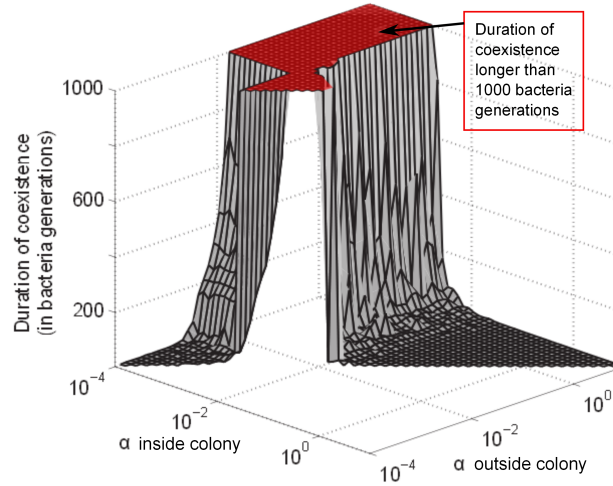


Figure 4: **Long lived coexistence for a broad range of α_{in} and α_{out} .** Surface shows length of coexistence for different sets of α_{in} and α_{out} , if coexistence lasted longer than an upper cut off value of a 1000 bacteria generations the simulation was stopped. Note that the α axis runs in opposite direction of the δ -axis in fig. Grid size: 100x100 Initial conditions for simulations where phage infected bacteria placed on a straight colony edge of healthy bacteria, were bacteria had max density counter value from $t=0$.

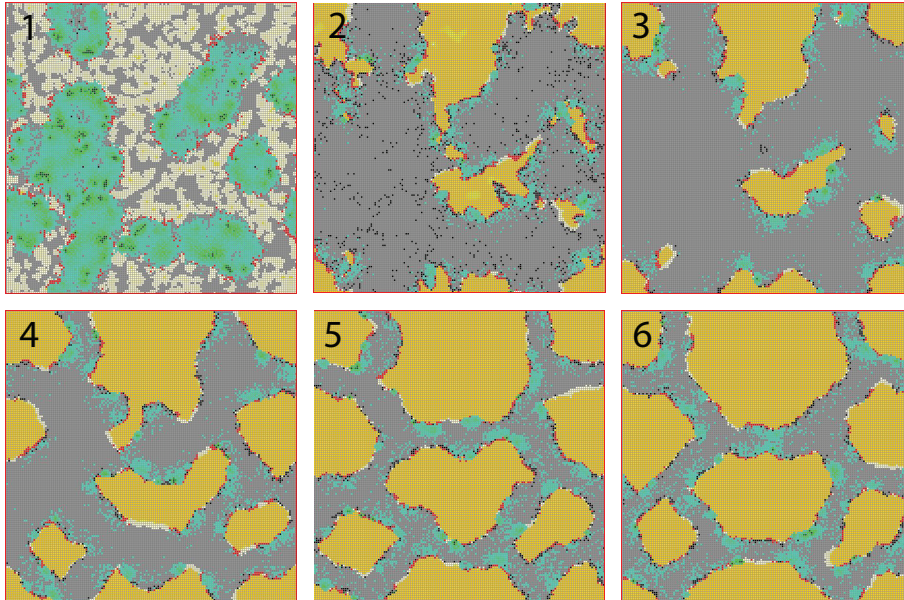


Figure 5: **(1)** snapshot taken 4 generations after $t=0$. **(2)** 12 generations after. **(3)** 100 generations after. **(4)** 500 generations after. **(5)** 1666 generations after. **(6)** 3333 generations after. Here $\alpha_{out} = \alpha_{in} = 1$ and $\delta_{in} = 10 \cdot 10^{-1} min^{-1}$ and $\delta_{out} = 0.05 \cdot 10^{-1} min^{-1}$. For these parameters the refuge fronts are not entirely stationary but phage and bacteria still manage to coexist for a time span much longer than 3000 bacteria generations - Note how little change there is between (5) and (6) between which 1666 bacteria generations go by. Grid size: 200x200. Initial conditions was randomly scattered bacteria and bacteria infected with phage.

Table 1: Parameters

Symbol	Explanation	Value or range explored in real units (assuming a bacteria generation time of 5hr and bacteria length scale of $1\mu m$).
T	Bacteria generation time.	5hr
λ	Rate of phage jumping from one site to a neighboring site.	$10^{-1}min^{-1}$ (corresponding to a diffusion constant of $D = 2.5 \cdot 10^{-2}\mu m^2/min$).
β	Burst size: number of phage released at burst.	80
τ	Latent time: time between infection and burst.	5hr
δ	Degradation rate of phage.	$10^{-4} - 10^0min^{-1}$
α	Infection rate per phage per bacterium.	$10^{-4} - 10^0min^{-1}$
δ_{max}	For a fixed value of α , δ_{max} is the value above which phage become too ineffective to coexist with the bacteria in the Basic model.	e.g. for $\alpha = 10^{-1}min^{-1}$, $\delta_{max} \sim 3 \cdot 10^{-1}min^{-1}$
δ_{min}	For a fixed value of α , δ_{min} is the value below which phage become too effective to coexist with the bacteria in the Basic model.	e.g. for $\alpha = 10^{-1}min^{-1}$, $\delta_{min} \sim 1 \cdot 10^{-1}min^{-1}$
α_{max}	For a fixed value of δ , α_{max} is the value above which phage become too effective to coexist with the bacteria in the Basic model.	e.g. for $\delta = 10^{-2}min^{-1}$, $\alpha_{max} \sim 2 \cdot 10^{-3}min^{-1}$
α_{min}	For a fixed value of δ , α_{min} is the value below which phage become too ineffective to coexist with the bacteria in the Basic model.	e.g. for $\delta = 10^{-2}min^{-1}$, $\alpha_{min} \sim 2 \cdot 10^{-4}min^{-1}$
δ_{in}	The degradation rate at a site occupied by a bacterium with a density counter that has reached maximal value in the Self-organized bacteria refuge model.	$10^{-4} - 10^0min^{-1}$
δ_{out}	The degradation rate at a site occupied by a bacterium with a density counter equal to zero in the Self-organized bacteria refuge model.	$10^{-4} - 10^0min^{-1}$
α_{in}	The infection rate at a site occupied by a bacterium with a density counter that has reached maximal value in the Self-organized bacteria refuge model.	$10^{-4} - 10^0min^{-1}$
α_{out}	The infection rate at a site occupied by a bacterium with a density counter equal to zero in the Self-organized bacteria refuge model.	$10^{-4} - 10^0min^{-1}$

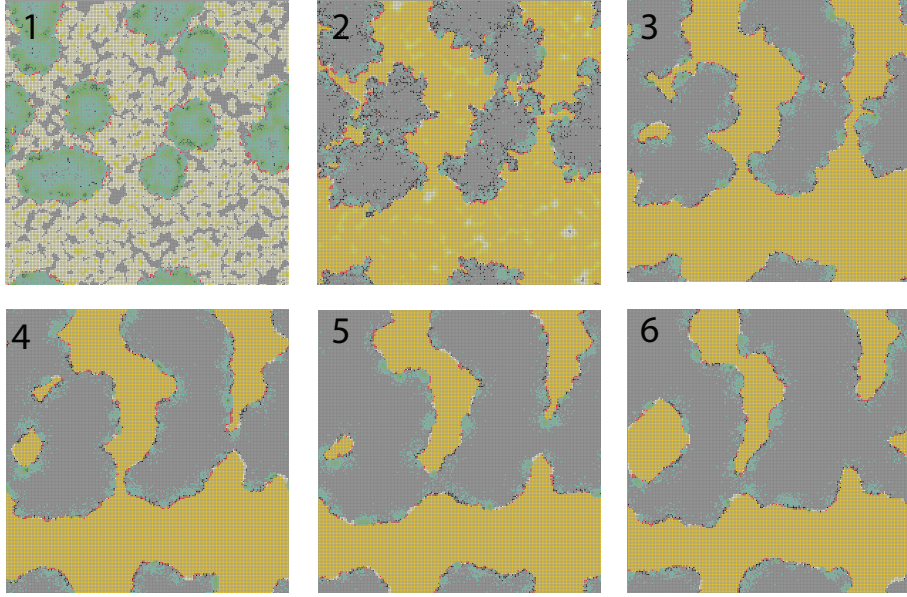


Figure 6: **(1)** snapshot taken 4 generations after $t=0$. **(2)** 8 generations after. **(3)** 100 generations after. **(4)** 400 generations after. **(5)** 800 generations after. **(6)** 1200 generations after. Here $\alpha_{out} = \alpha_{out} = 1 \cdot 10^{-1} min^{-1}$ and $\delta_{in} = 100 \cdot 10^{-1} min^{-1}$ and $\delta_{out} = 0.04 \cdot 10^{-1} min^{-1}$. Grid size: 200x200. Initial conditions was randomly scattered bacteria and bacteria infected with phage.

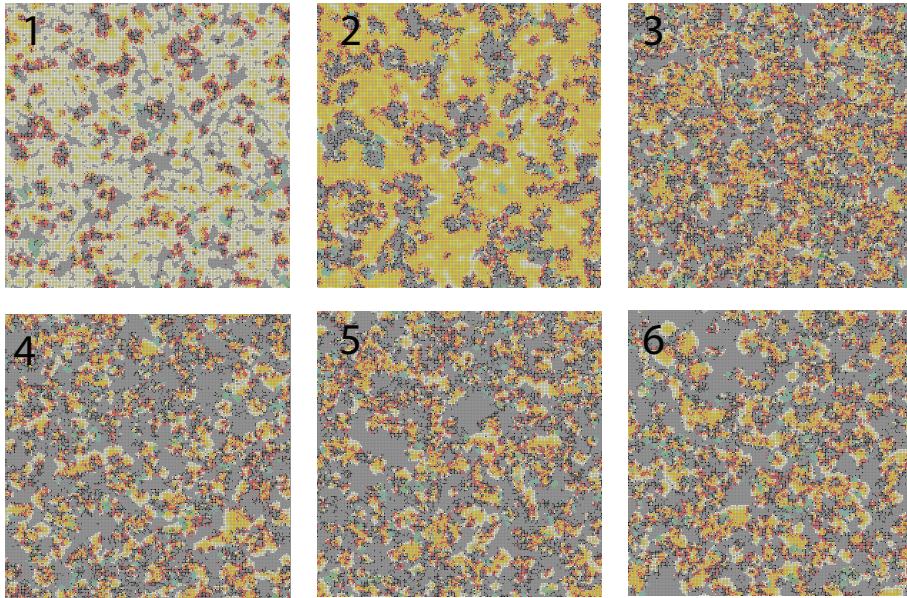


Figure 7: **(1)** snapshot taken 4 generations after $t=0$. **(2)** 8 generations after. **(3)** 33 generations after. **(4)** 66 generations after. **(5)** 533 generations after. **(6)** 1666 generations after. Here $\alpha_{out} = \alpha_{out} = 1 \cdot 10^{-1} min^{-1}$ and $\delta_{in} = 3.3 \cdot 10^{-1} min^{-1}$ and $\delta_{out} = 0.8 \cdot 10^{-1} min^{-1}$. Notice that the relative difference between the inside and out side degradation rates is just a factor 4; the δ_{in} and δ_{out} values lie very close to but just above and below δ_{max} and δ_{min} respectively. For these parameters the refuge fronts are not stationary but phage and bacteria manage to coexist for a time span much longer than 3000 bacteria generations. Grid size: 200x200. Initial conditions was randomly scattered bacteria and bacteria infected with phage.

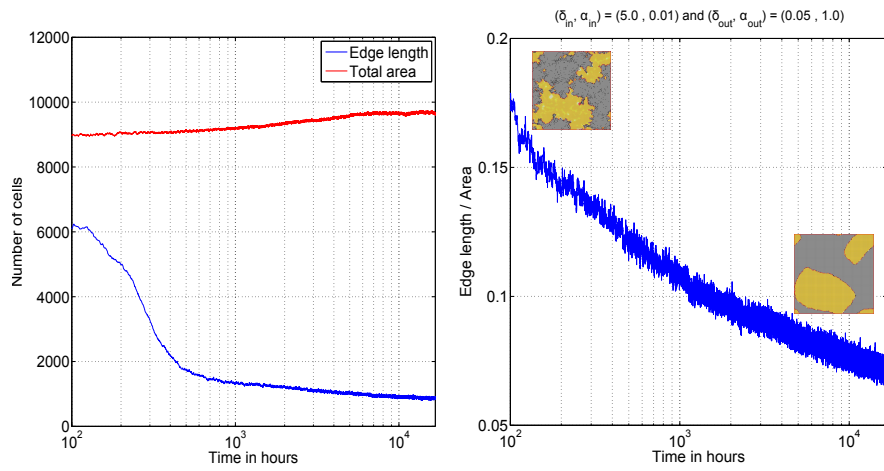


Figure 8: **Refuge edges become smoother over time.** Left: Length of refuge edges and total area (both measured in nr. of cells) as a function of time (measured in hours), for a simulation with the parameters $(\delta_{in}, \alpha_{in}) = (5.0 \cdot 10^{-1} \text{min}^{-1}, 0.01 \cdot 10^{-1} \text{min}^{-1})$ and $(\delta_{out}, \alpha_{out}) = (0.05 \cdot 10^{-1} \text{min}^{-1}, 1.0 \cdot 10^{-1} \text{min}^{-1})$. Right: (refuge edge length)/(refuge area) as a function of time (measured in hours), this ratio can be conceived as a measure of the degree of smoothness of the refuge boundaries. Inserts: snapshots of simulation after $t = 6$ bacteria generations (one bacteria generation is here assumed to be $5hr$) and after $t = 3333$ bacteria generations. Grid size: 150×150 . Initial conditions was randomly scattered bacteria and bacteria infected with phage.

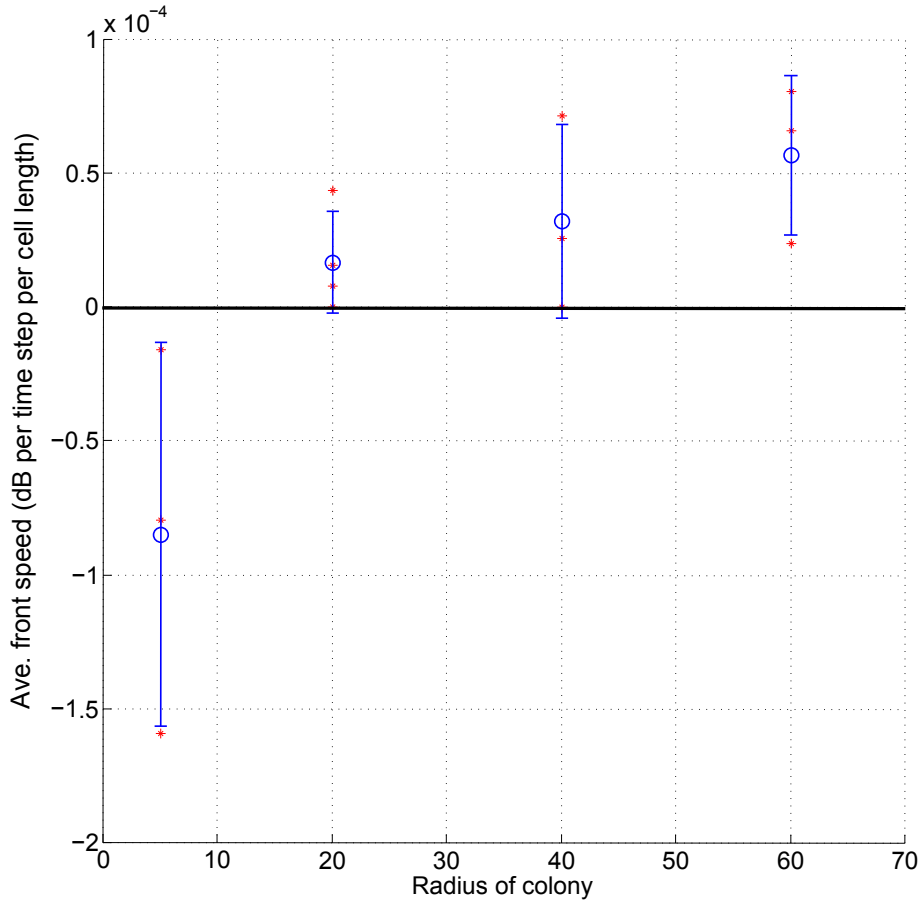


Figure 9: **Refuge front speed depends on local curvature. Higher curvature (smaller radius) means colony shrinks slowly since phage density at edge on average is higher. Lower curvature (larger radius) means colony is slowly growing.** Average front speed measured in change in bacteria numbers per time step per edge length as a function of radius of colony at simulation start $t = 0$, for simulations with the parameters $(\delta_{in}, \alpha_{in}) = (10.0 \cdot 10^{-1} min^{-1}, 1.0 \cdot 10^{-1} min^{-1})$ and $(\delta_{out}, \alpha_{out}) = (0.01 \cdot 10^{-1} min^{-1}, 0.01 \cdot 10^{-1} min^{-1})$. In each simulation the front speed of one round colony with a specific initial radius was monitored. Red points: average front speeds for three different simulations done for $r = 5 \mu m$, $r = 20 \mu m$, $r = 40 \mu m$ and $r = 60 \mu m$ respectively. Blue: mean of the three simulation with error bars (standard deviation).

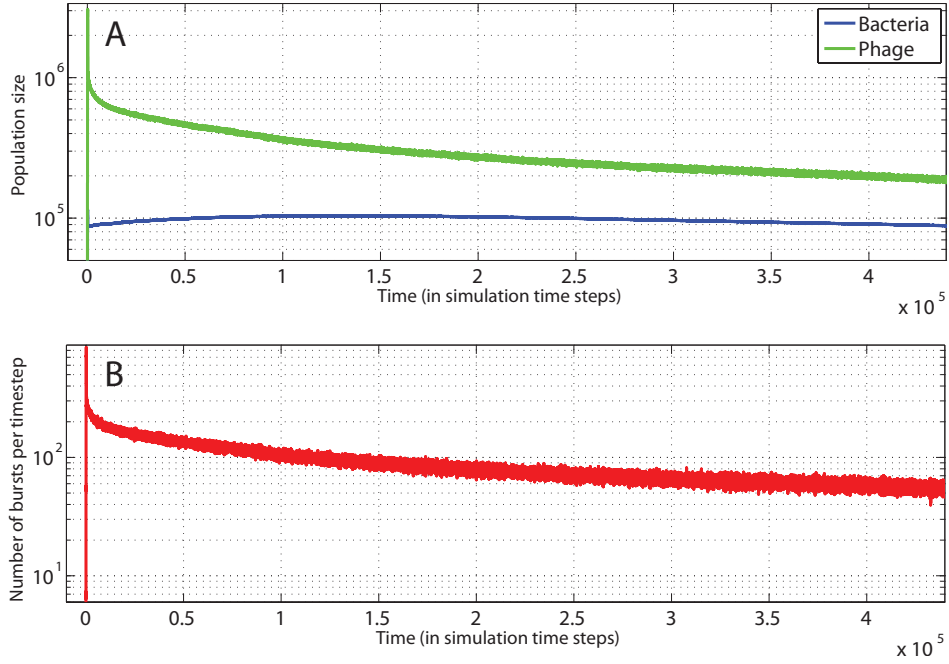


Figure 10: **Stable populations and large turn over rates for a long time span.** A) Bacteria numbers, phage numbers and B) number of phage bursts per time step as a function of time, (one time step is $1/30$ of a bacteria generation), (simulation cut off was after approx 15000 bacteria generations), the parameters used were the same ones as the ones used in fig 4. $(\delta_{in}, \alpha_{in}) = (5.0 \cdot 10^{-1} \text{min}^{-1}, 0.01 \cdot 10^{-1} \text{min}^{-1})$ and $(\delta_{out}, \alpha_{out}) = (0.05 \cdot 10^{-1} \text{min}^{-1}, 1.0 \cdot 10^{-1} \text{min}^{-1})$. Used grid size 500×500 . For these parameters and random initial conditions, both phage and bacteria numbers eventually slowly decrease over time (note that at the first 300 generations the bacteria population is slowly growing), if we assume that the bacteria numbers are decreasing linearly we can predict extinction of bacteria for this simulation to happen after roughly a time span of 8000 bacterial generations. Note that since the front speed depend on the curvature of the front (see fig. S 9) it is possible to have a system with the same parameters as the one shown here where bacteria numbers would steadily increase over time. Initial conditions was randomly scattered bacteria and bacteria infected with phage.

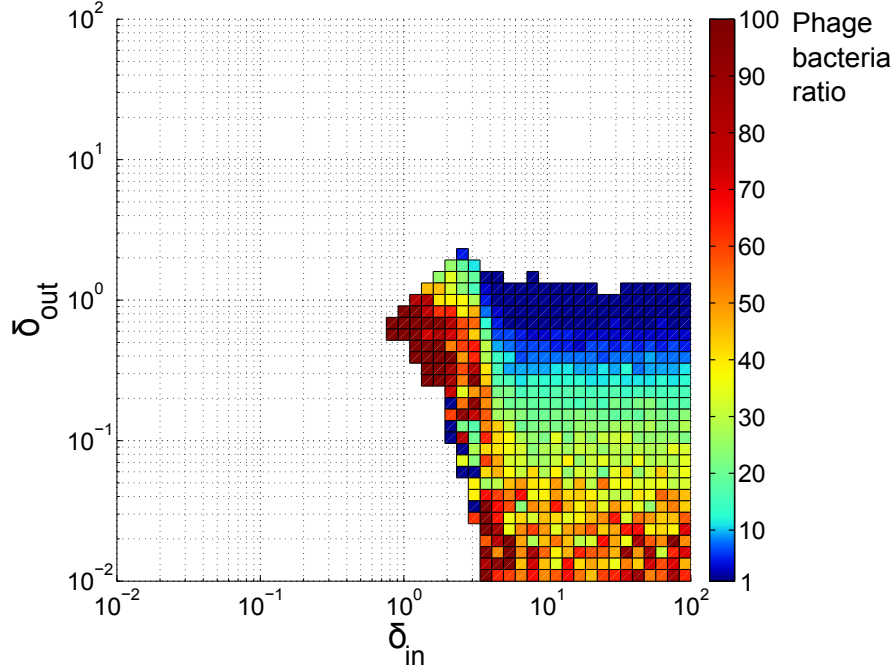


Figure 11: **Ratio of phage and bacteria.** The color map shows the average ratio of phage to bacteria after 20 bacterial generations as a function of δ_{in} and δ_{out} in simulations with random initial conditions, (initial density of healthy bacteria was 0.08 and initial density of infected bacteria was 0.004. Grid size was 200x200). In the points with no color (white) either phage or bacteria had died out before 20 bacterial generations had passed. Initial conditions was randomly scattered bacteria and bacteria infected with phage.

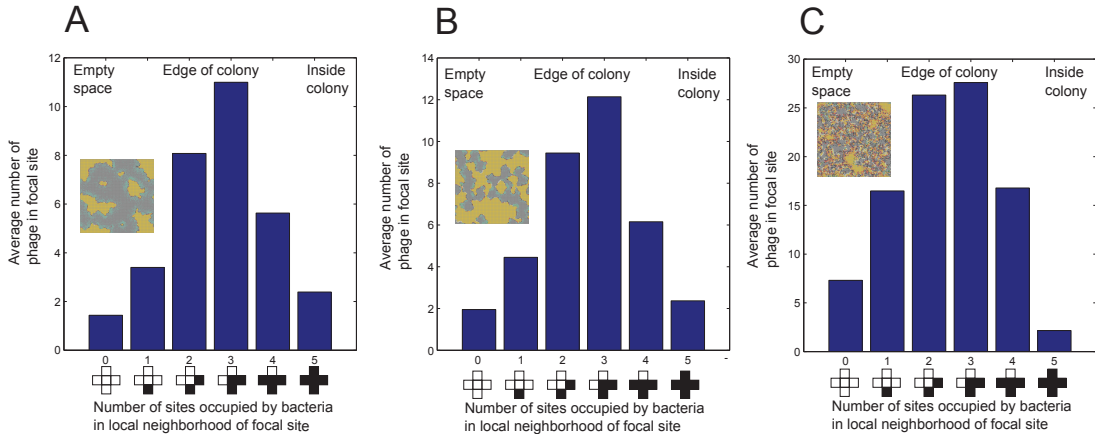


Figure 12: **Phage are co-localized with colony edges.** Average number of phage per site as a function of the fraction of sites occupied by bacteria in the local neighborhood of the site. The probability of finding phage at sites with both empty and occupied sites in the vicinity is higher than the probability of finding phage in sites where all sites in the vicinity are either completely occupied or completely empty. This signifies that phage are most abundant at the colony edges. grid size: 200x200. Initial conditions was randomly scattered bacteria and bacteria infected with phage. **A:** $\alpha_{out} = \alpha_{in} = 1 \cdot 10^{-1}min^{-1}$ and $\delta_{in} = 100 \cdot 10^{-1}min^{-1}$ and $\delta_{out} = 0.04 \cdot 10^{-1}min^{-1}$. **B:** $\alpha_{out} = \alpha_{in} = 1 \cdot 10^{-1}min^{-1}$ and $\delta_{in} = 10 \cdot 10^{-1}min^{-1}$ and $\delta_{out} = 0.05 \cdot 10^{-1}min^{-1}$. **C:** $\alpha_{out} = \alpha_{in} = 1 \cdot 10^{-1}min^{-1}$ and $\delta_{in} = 3.3 \cdot 10^{-1}min^{-1}$ and $\delta_{out} = 0.8 \cdot 10^{-1}min^{-1}$

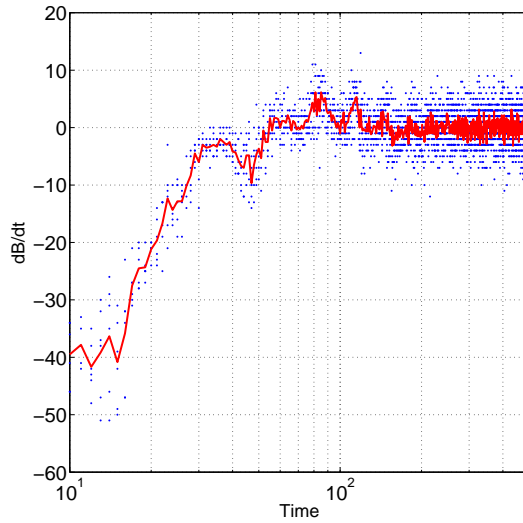


Figure 13: **Infection front speed slow down over time.** Blue dots show dB/dt as a function of time (in units of simulation time steps) for six different simulations with same parameters as in fig. 4 ($(\delta_{out}, \alpha_{out}) = (0.05 \cdot 10^{-1} min^{-1}, 1.0 \cdot 10^{-1} min^{-1})$ and $(\delta_{in}, \alpha_{in}) = (5.0 \cdot 10^{-1} min^{-1}, 0.01 \cdot 10^{-1} min^{-1})$), red line show average value. Grid size: 200×200 . Initial condition was phage placed on the edge of a straight colony edge. The bacteria in the colony had all density counters set to zero at $t=0$. In the beginning before bacteria reach a high density counter values phage infection front eat rapidly through the colony. After roughly 2 bacteria generations the bacteria have reached higher density counter numbers and the advancing infection fronts slow down and become almost stationary.

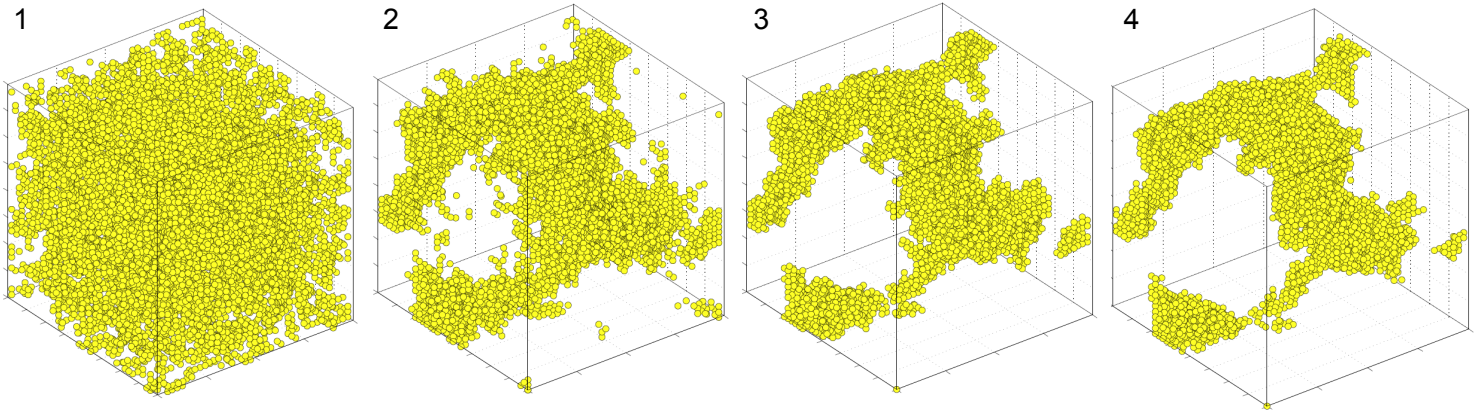


Figure 14: **3D model has similar dynamics as 2D model.** $40 \times 40 \times 40$ grid with periodic boundary conditions. Initial conditions was randomly scattered bacteria and bacteria infected with phage. Yellow dots show sites occupied by healthy bacteria, sites with infected bacteria and diffusing phage are not shown (for clarity). Parameters were $(\delta_{out}, \alpha_{out}) = (0.05 \cdot 10^{-1} min^{-1}, 1.0 \cdot 10^{-1} min^{-1})$ and $(\delta_{in}, \alpha_{in}) = (5.0 \cdot 10^{-1} min^{-1}, 0.01 \cdot 10^{-1} min^{-1})$ (same as parameters of fig. 4). **(1)** snapshot taken 4 bacterial generations after $t=0$. **(2)** after 6 bacterial generations. **(3)** after 70 bacterial generations. **(4)** after 140 bacterial generations.

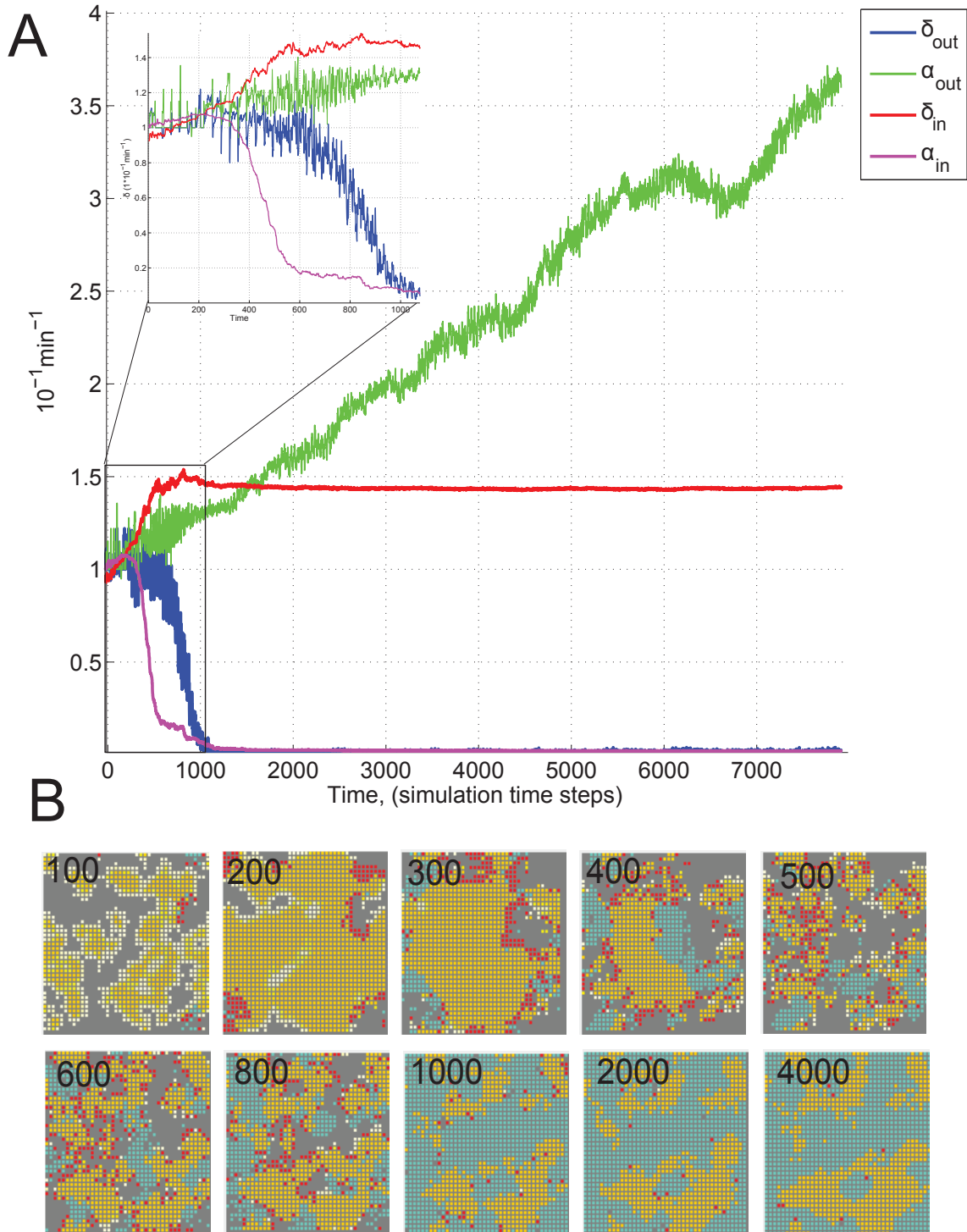


Figure 15: **Evolution pushes selforganizing bacteria refuge system into parameter region with stable coexistence** 40x40 grid with periodic boundary conditions. Initial conditions was randomly scattered bacteria and bacteria infected with phage. Both δ_{in} , δ_{out} , α_{in} and δ_{out} was allowed to evolve. Offspring values for these parameters was allowed to take normal distributed steps away from the parent value with mean $\mu_{phage} = 0.05$ for δ_{out} and α_{out} and $\mu_{bacteria} = 0.5$ for δ_{in} and α_{in} respectively, (but not to go below zero). (Since grid size was small we used unrealistically large evolutionary steps in order to ensure a reasonable short simulation time). **B**) Yellow show sites occupied by healthy bacteria, red sites with infected bacteria and green sites with diffusing phage.

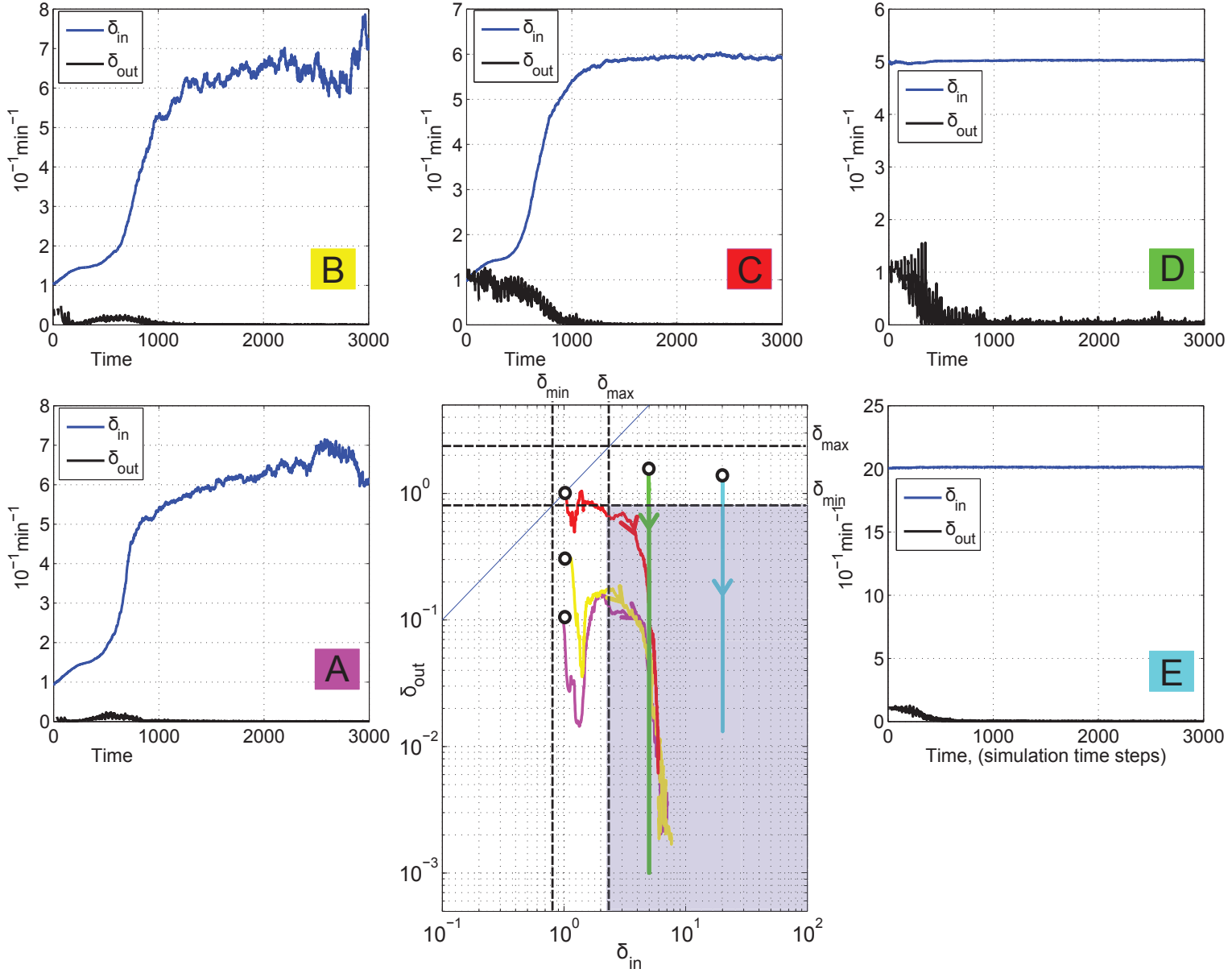


Figure 16: **Degradation rate evolution with normal steps 80x80 grid.** $\alpha_{in} = \alpha_{out} = 1.0 \cdot 10^{-1} \text{min}^{-1}$ at all times. Offspring values for these parameters was allowed to take normal distributed steps away from the parent value with mean $\mu_{phage} = 0.05$ for δ_{out} and α_{out} and $\mu_{bacteria} = 0.5$ for δ_{in} and α_{in} respectively, (but not to go below zero). A: Initial condition $(\delta_{in}, \delta_{out}) = (1.0 \cdot 10^{-1} \text{min}^{-1}, 0.1 \cdot 10^{-1} \text{min}^{-1})$. B: Initial condition $(\delta_{in}, \delta_{out}) = (1.0 \cdot 10^{-1} \text{min}^{-1}, 0.3 \cdot 10^{-1} \text{min}^{-1})$. C: Initial condition $(\delta_{in}, \delta_{out}) = (1.0 \cdot 10^{-1} \text{min}^{-1}, 1.0 \cdot 10^{-1} \text{min}^{-1})$. D: Initial condition $(\delta_{in}, \delta_{out}) = (5.0 \cdot 10^{-1} \text{min}^{-1}, 3.0 \cdot 10^{-1} \text{min}^{-1})$. E: Initial condition $(\delta_{in}, \delta_{out}) = (20.0 \cdot 10^{-1} \text{min}^{-1}, 2.0 \cdot 10^{-1} \text{min}^{-1})$. Trajectories show how the system averages of δ_{in} and δ_{out} change during a simulation which lasts 3000 time steps.

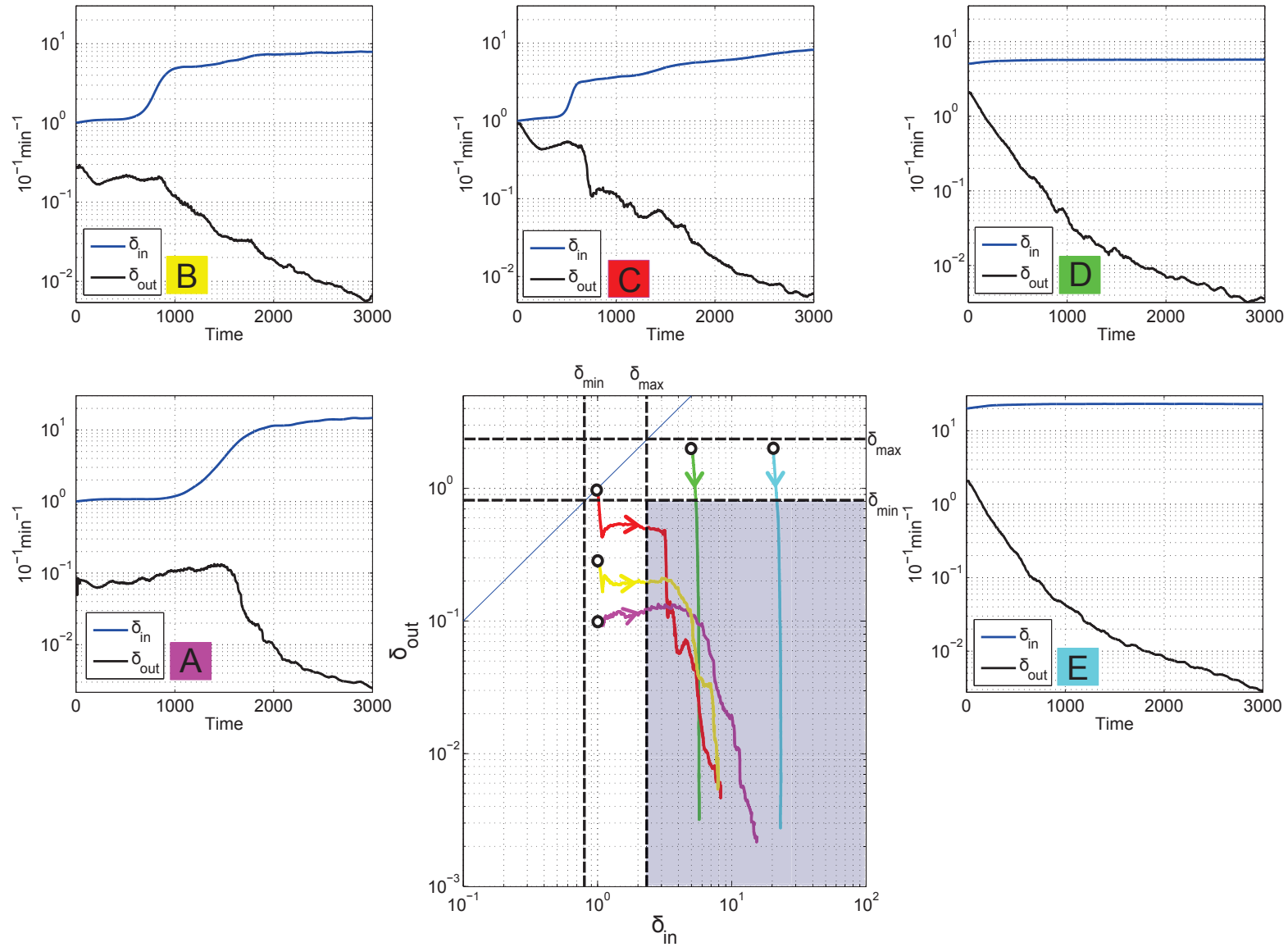


Figure 17: **Degradation rate evolution with logarithmic steps** 150×150 grid. $\alpha_{in} = \alpha_{out} = 1.0 \cdot 10^{-1} \text{min}^{-1}$ at all times. $\mu_{phage} = 0.07 \mu_{bacteria} = 0.1$, here it is the exponent x of $\delta = 10^x$ which is drawn from a normal distribution centered about the parent exponent value - note that when evolution takes logarithmic steps like this the mean of any value tends to increase if there is no selection, this explains why the red yellow and purple curves in some parts (where bacteria is plentiful and there is not much selection) have a slight tendency to drift towards higher δ_{out} values). A: Initial condition $(\delta_{in}, \delta_{out}) = (1.0 \cdot 10^{-1} \text{min}^{-1}, 0.1 \cdot 10^{-1} \text{min}^{-1})$. B: Initial condition $(\delta_{in}, \delta_{out}) = (1.0 \cdot 10^{-1} \text{min}^{-1}, 0.3 \cdot 10^{-1} \text{min}^{-1})$. C: Initial condition $(\delta_{in}, \delta_{out}) = (1.0 \cdot 10^{-1} \text{min}^{-1}, 1.0 \cdot 10^{-1} \text{min}^{-1})$. D: Initial condition $(\delta_{in}, \delta_{out}) = (5.0 \cdot 10^{-1} \text{min}^{-1}, 2.0 \cdot 10^{-1} \text{min}^{-1})$. E: Initial condition $(\delta_{in}, \delta_{out}) = (20.0 \cdot 10^{-1} \text{min}^{-1}, 2.0 \cdot 10^{-1} \text{min}^{-1})$. Trajectories show how the system averages of δ_{in} and δ_{out} change during a simulation which lasts 3000 time steps.

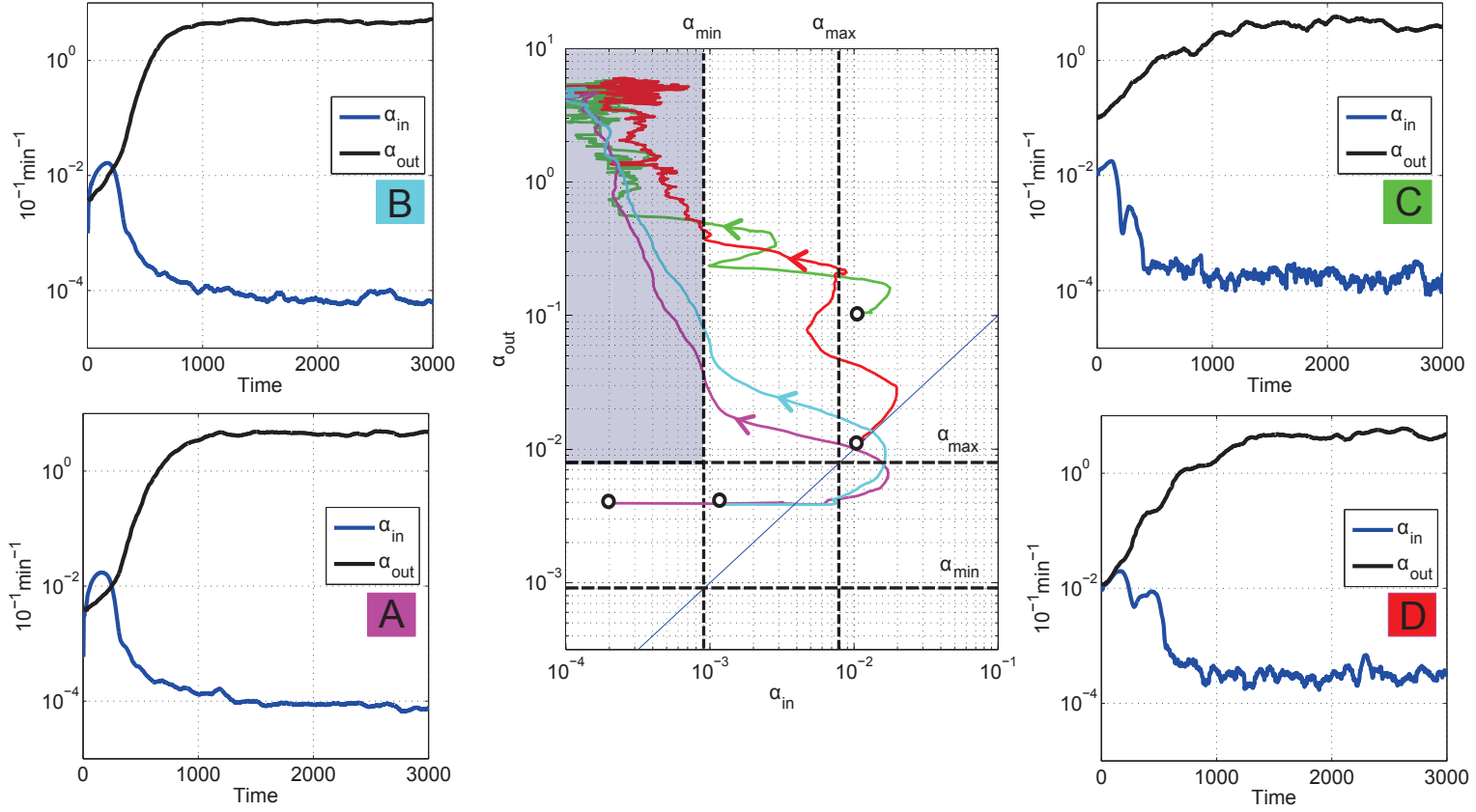


Figure 18: **Infection rate evolution with normal steps** 40x40 grid. Random Initial conditions. $\delta_{in} = \delta_{out} = 0.1 \cdot 10^{-1} min^{-1}$ at all times. Offspring values for these parameters was allowed to take normal distributed steps away from the parent value with mean $\mu_{phage} = 0.025$ for δ_{out} and α_{out} and $\mu_{bacteria} = 0.025$ for δ_{in} and α_{in} respectively, but not to go below zero. A (purple): initial values $\alpha_{in} = 0.0002 \cdot 10^{-1} min^{-1}, \alpha_{out} = 0.004 \cdot 10^{-1} min^{-1}$. B (light blue): initial values $\alpha_{in} = 0.001 \cdot 10^{-1} min^{-1}, \alpha_{out} = 0.004 \cdot 10^{-1} min^{-1}$. C (green): initial values $\alpha_{in} = 0.01 \cdot 10^{-1} min^{-1}, \alpha_{out} = 0.1 \cdot 10^{-1} min^{-1}$. D (red): initial values $\alpha_{in} = 0.01 \cdot 10^{-1} min^{-1}, \alpha_{out} = 0.01 \cdot 10^{-1} min^{-1}$. Trajectories show how the system averages of α_{in} and α_{out} change during a simulation which lasts 3000 time steps. Note that in the beginning of each simulation selection pressure on α_{in} is low since there are few phage and bacteria and they are relatively far apart in the random initial condition. Since we do not allow α_{in} to take on negative values the average tend to drift up when there is no strong selection, which is the reason why all trajectories initially go to higher α_{in} values, before moving in to the blue region.

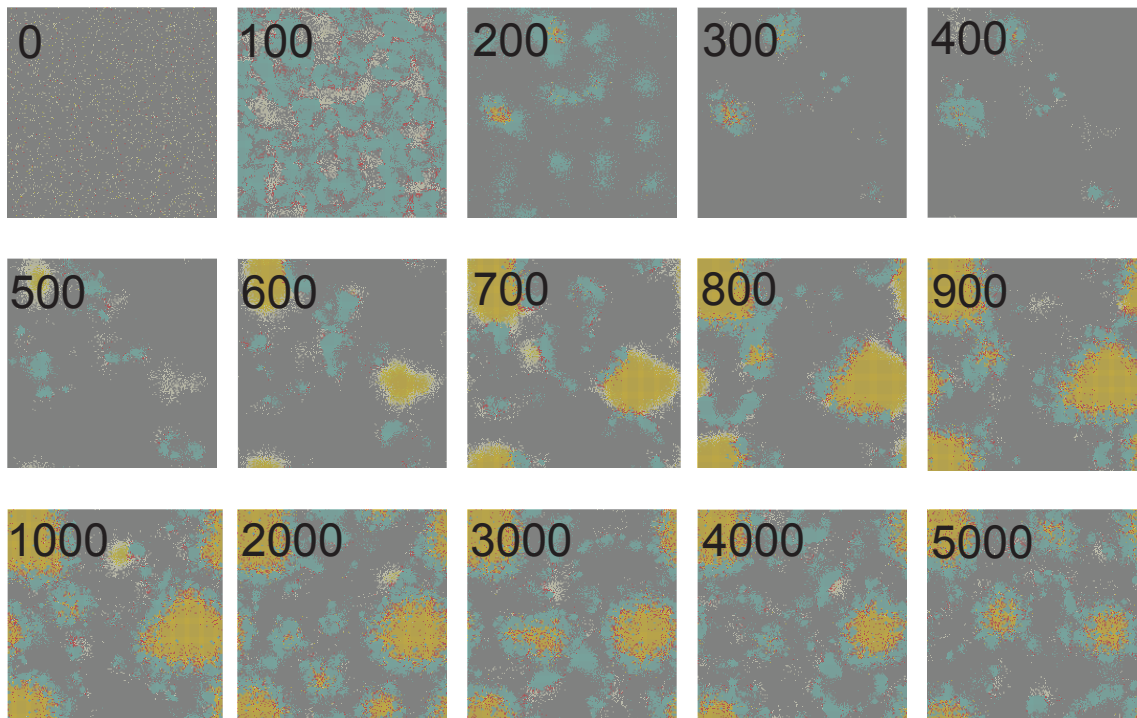


Figure 19: **Even very high cell diffusion/motility does not stop refuges from forming 200x200 grid.** Random Initial conditions. $\delta_{in} = 5 \cdot 10^{-1} min^{-1}$, $\delta_{out} = 0.1 \cdot 10^{-1} min^{-1}$, $\alpha_{in} = 0.001 \cdot 10^{-1} min^{-1}$ and $\alpha_{out} = 1 \cdot 10^{-1} min^{-1}$. At every time step we went through each cell in a random order and with a probability of 0.5 they shifted place with a neighbor, (occupied or empty). This corresponds to a bacteria diffusion constant of half that of the phage, and no crowding effects reducing movement inside the dense colonies.

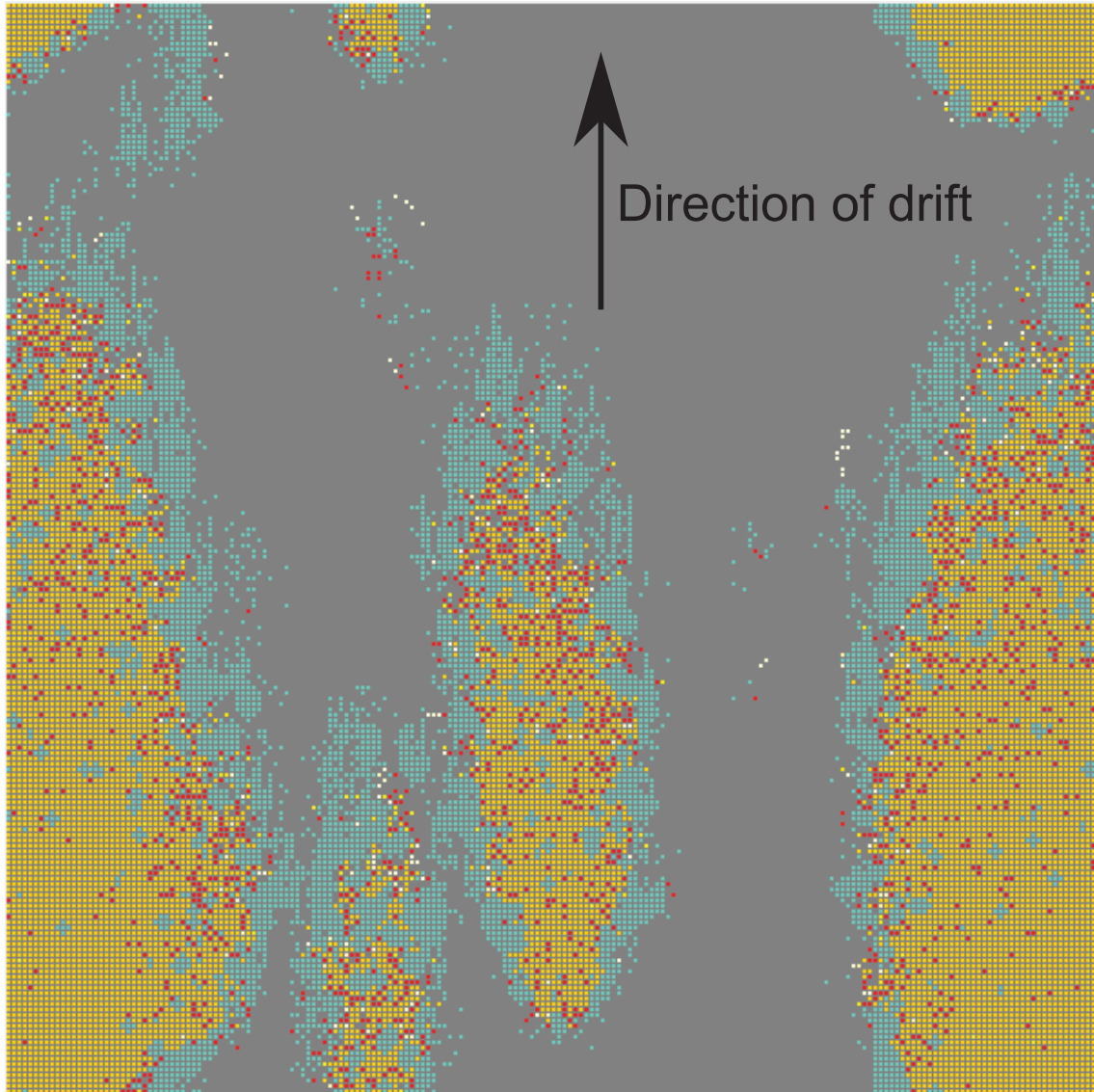


Figure 20: **Diffusion with drift does not stop refuge formation** 200x200 grid. Random Initial conditions. $\delta_{in} = 5 \cdot 10^{-1} \text{min}^{-1}$, $\delta_{out} = 0.1 \cdot 10^{-1} \text{min}^{-1}$, $\alpha_{in} = 0.001 \cdot 10^{-1} \text{min}^{-1}$ and $\alpha_{out} = 1 \cdot 10^{-1} \text{min}^{-1}$. Bacteria diffusion constant was set to 1/10 of the phage diffusion constant and on top of diffusion both phage and bacteria were exposed to a drift upwards (when diffusing bacteria and phage were 50% more likely to move upwards than in the other three directions).