

## Bacterial predator–prey dynamics in microscale patchy landscapes

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1 **Title:** Bacterial predator-prey dynamics in micro-scale patchy landscapes

2

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5

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15 **Abstract**

16 **Soil is a microenvironment with a fragmented (patchy) spatial structure in which many**  
17 **bacterial species interact. Here we explore the interaction between the predatory**  
18 **bacterium *Bdellovibrio bacteriovorus* and its prey *Escherichia coli* in microfabricated**  
19 **landscapes. We ask how fragmentation influences the prey dynamics at the microscale,**  
20 **and compare two landscape geometries: a patchy landscape and a continuous landscape.**  
21 **By following the dynamics of prey populations with high spatial and temporal resolution**  
22 **for many generations, we find that the variation in predation rates is twice as large in**  
23 **the patchy landscape and the dynamics is correlated over shorter length scales. We also**  
24 **find that while the prey population in the continuous landscape is almost entirely driven**  
25 **to extinction, a significant part of the prey population in the fragmented landscape**  
26 **persists over time. We observe significant surface-associated growth, especially in the**  
27 **fragmented landscape and we surmise that this sub-population is more resistant to**  
28 **predation. Our results thus show that microscale fragmentation can significantly**  
29 **influence bacterial interactions.**

30

31 **Keywords:** bdellovibrio bacteriovorus/metapopulation/nanofabricated landscapes/predator-  
32 prey

### 33 **Introduction**

34 Bacterial habitats, such as soil, our gastrointestinal tract, and even the ocean are spatially  
35 structured at the micro-scale [1,2]. Soil typically contains particles with sizes that vary  
36 between 2  $\mu\text{m}$  or less for clay and 1 mm for sand [3,4] (Fig 1a). It is within the confines of the  
37 interconnected cavities in between soil particles that microorganisms, such as bacteria,  
38 interact. Most of our knowledge of population dynamics in such highly structured landscapes  
39 comes from a large body of theoretical [5–7] and experimental studies [8–11] concerning  
40 macroscopic organisms in macroscopic landscapes. Due to technical challenges, however,  
41 experimental study and even a clear theoretical framework of the population dynamics of  
42 microorganisms in spatially structured microhabitats such as soil is lacking, especially for  
43 interacting bacterial populations such as predator-prey communities.

44 One may hypothesize that for bacteria, a landscape with constrictions with a size of only  
45 a few microns can be considered fragmented. This hypothesis predicts that the population  
46 dynamics differ significantly between individual patches and that the dynamics of interacting  
47 bacteria at the local (patch) level become decorrelated quickly with increasing distance [12].  
48 Habitat fragmentation may also influence the lifetime of the population as a whole [5,8,12,13].  
49 However, bacteria differ in important ways from “large” animals: bacteria grow to higher  
50 densities, possibly reducing stochastic fluctuations that may lead to local extinction. Bacteria  
51 are also highly mobile, in terms of their swimming speed [14] as well as in terms of their  
52 ability to pass through small constrictions [15]. Furthermore, while diffusion of signaling  
53 molecules, food, and waste is very efficient at microscopic scales, diffusion at larger scales is  
54 negligible. Finally, bacteria can adopt very different lifestyles, living clustered together in  
55 biofilms with greatly reduced mobility, or as motile planktonic individuals [16]. For these  
56 reasons, it is unclear whether bacterial habitats that are spatially structured at the micro-scale  
57 can be considered “fragmented” or not. Because macroscopic fragmentation has been shown  
58 to affect key parameters such as the global lifetime of a population [8–11] we believe there is  
59 reason to assume that microscopic fragmentation could be of importance for understanding  
60 bacterial life in natural structured habitats such as soil. However, the question of how  
61 fragmentation affects predator-prey dynamics at the micro-scale has remained unanswered.

62 Over the past few years, microfabrication techniques have allowed for the creation of  
63 micro-scale synthetic ecosystems that are structured at the spatial scales relevant to bacterial  
64 populations [17–21]. It thus has become technically feasible to quantify bacterial predator-  
65 prey interactions in each of the individual micron-scale patches of a landscape under  
66 controlled conditions over many generations. Taking advantage of these recent advances, we  
67 fabricated a micro-scale fragmented habitat and a non-fragmented habitat, and contrasted  
68 bacterial predator-prey dynamics in these two habitat types. We studied the bacterial predator

69 *Bdellovibrio bacteriovorus* preying upon *Escherichia coli*. *B. bacteriovorus* is a small  
70 (0.4x1µm) and highly motile (it can swim over 160 µm/s, or 160 body lengths per second  
71 [22]) predator of Gram-negative bacteria, that occurs *e.g.* in soil, in the human gut, and in  
72 water [23]. To complete its life cycle, *B. bacteriovorus* inserts itself into the periplasmic space  
73 of its prey, and converts it into a round-shaped “bdelloplast” [24]. *B. bacteriovorus*  
74 subsequently extracts and ingests solutes from its prey and increases in length, after which it  
75 divides and 4-6 progeny are produced per *E. coli* prey. Approximately 3-4 hours after  
76 invasion, *B. bacteriovorus* lyses its host and swims away to hunt for the next prey [23]. While  
77 *B. bacteriovorus* are ferocious predators, a small fraction of prey may survive predation due  
78 to plastic phenotypic resistance, preventing the total eradication of the prey population [25].

79 Studying the *B. bacteriovorus* – *E. coli* interaction in both fragmented and continuous  
80 landscapes allows us to test the hypothesis that a bacterial habitat featuring micro-scale  
81 constrictions is fragmented and as such influences the predator-prey interaction. Specifically,  
82 we address the question to what extent a spatially structured microhabitat gives rise to  
83 variations in predation rates, and at what scale predator-prey dynamics are spatially correlated  
84 in a micro-structured landscape such as soil. Can *B. bacteriovorus* predate effectively in  
85 spatially structured landscapes? Does fragmentation increase the persistence of the prey  
86 population? Furthermore, given that *B. bacteriovorus* has shown potential to protect crops,  
87 reduce biofouling, and to serve as a “living antibiotic” [26–29], it would be useful to know  
88 how its effectiveness in structured habitats, such as human tissue, relates to its effectiveness  
89 as measured in well-mixed (unstructured) culture flasks [30–32]. In this regard, *B.*  
90 *bacteriovorus* has also attracted significant interest because of its potential to eradicate  
91 bacterial biofilms which are spatially structured at the micro-scale [33,34].

92

## 93 **Materials and methods**

94

### 95 **Strains and growth conditions**

#### 96 *Growth of E. coli*

97 We used strain JEK 1036 previously described in [18], which is wild-type *E. coli* W3110  
98 labeled with a green fluorescent protein (*lacZY::GFPmut2*). JEK 1036 was grown O/N from  
99 glycerol in LB broth at 30° C shaken at 200 rpm, diluted 1000-fold the next morning in  
100 Diluted Nutrient Broth (DNB, 0.8 g/L NB, 2mM CaCl<sub>2</sub>·2H<sub>2</sub>O, 3mM MgCl<sub>6</sub>·2H<sub>2</sub>O, pH 7.6)  
101 and grown to OD<sub>600</sub> ~1. Fluorescence expression was induced by adding 100 µM of Isopropyl  
102 β -D-1-thiogalactopyranoside (IPTG, Promega) to the medium.

103

104 *Growth of Bdellovibrio bacteriovorus and microhabitat inoculation*

105 *E. coli* JEK 1036 [18] was cultivated to maximum turbidity ( $OD_{600} \sim 4$ ) in LB broth, then  
106 concentrated to  $OD_{600} = 10$  by centrifugation and subsequently resuspended in HEPES buffer  
107 (25 mM HEPES, 2 mM  $CaCl_2 \cdot 2H_2O$ , 3 mM  $MgCl_6 \cdot 2H_2O$ , pH 7.8). *B. bacteriovorus* HD100,  
108 with a chromosomal fusion of the HuaA histone like protein gene [24] to monomeric Teal  
109 protein (mTeal), was added to this medium from glycerol stock, and was incubated O/N in a  
110 volume of 2 ml while shaking at 280 rpm at 28° C, until a transparent liquid was obtained.  
111 The culture's transparency indicates that all *E. coli*, except for a minute fraction that is  
112 phenotypically resistant, have been lysed. The culture was then spun down at 3000 rpm for 10  
113 min and resuspended in 2 ml fresh DNB, at 28°C. The microhabitat was simultaneously  
114 inoculated with approximately 3  $\mu$ l of resuspended *B. bacteriovorus* culture and  
115 approximately 3  $\mu$ l of pure *E. coli* culture in DNB medium in a 1:1 ratio (measured by optical  
116 density) from opposite sides.

117

## 118 **Experimental set-up**

119

### 120 *Microfabrication of microhabitats*

121 To emulate the patchy geometry of natural bacterial habitats with relevant spatial dimensions  
122 (Fig. 1a), and to allow for the quantitative study of predator-prey interactions as a function of  
123 space and time, we created a well-defined linear array of habitat patches on a silicon chip, that  
124 are connected to each other by narrow corridors (Fig. 1b and d, top) [18,35]. As a control for  
125 the patchiness of the patchy geometry, we also designed a continuous landscape of identical  
126 volume that consists of one large habitat without internal constrictions (Fig. 1e).  
127 Microhabitats were fabricated in silicon using a two-step procedure of photolithography and  
128 reactive ion etching following a previously published protocol [18,35]. The patchy  
129 microhabitats consist of 85 patches (each 100  $\mu$ m in length, 100  $\mu$ m in width and 15  $\mu$ m in  
130 depth) connected by corridors (50x5x15  $\mu$ m), the continuous microhabitats consist of a single  
131 patch (8500x100x15  $\mu$ m) with a total volume identical to the volume of the patchy habitat.  
132 The 180 nm deep slits are too shallow for the passage of bacteria and thus preclude them from  
133 leaving the microhabitats and entering the reservoirs. On the other hand, the slits do allow for  
134 the diffusion of *e.g.* nutrients and waste [18,35]. At the start of an experiment the reservoirs  
135 (having a volume  $\sim 15$  times the habitat) are filled with fresh DNB medium (supplemented  
136 with 100  $\mu$ M IPTG) to ensure that plenty of nutrients are available to the *E. coli* for the entire  
137 duration of the experiment. Two ports to inoculate bacteria were drilled through the silicon,  
138 one at each end of the habitat, furthermore, ports were drilled to allow for the filling of the  
139 reservoirs. After short exposure to  $O_2$ -plasma to facilitate proper bonding, a silicon  
140 microhabitat was bonded to a polydimethylsiloxane (PDMS) coated cover slip. The

141 microhabitats and reservoirs were then filled with fresh DNB medium (supplemented with  
142 100  $\mu$ M IPTG). Subsequently, cultures of *B. bacteriovorus* and *E. coli* were inoculated from  
143 opposite ends as described above. Medium in the device was not replenished during the  
144 experiment. After the habitat and reservoirs had been filled and the habitat had been  
145 inoculated with bacteria, the inlet holes were sealed with quick drying PDMS. Data was  
146 acquired for periods up to 3 days, the exact duration of each experiment is shown on the time  
147 axis of the relevant figures. All experiments were performed in triplicate.

148

#### 149 *Microhabitat imaging*

150 To capture the dynamics of the prey population in the presence (and absence) of the predator,  
151 microhabitats were imaged every 20 minutes using an Olympus IX81 inverted microscope  
152 controlled with MicroManager 1.4.14 software [36], equipped with a 20x 0.75NA objective,  
153 an Andor Neo sCMOS camera, and a motorized stage (Marzhauser). The sample was  
154 illuminated using an X-cite 120 Q (Lumen dynamics) light source. We use the total  
155 fluorescence intensity in the GFP channel as a proxy for prey density which was previously  
156 shown to be a valid approach [35,37]. Due to the limited brightness of *B. bacteriovorus*,  
157 predator cells were not continuously monitored. The fluorescent mTeal fusion, however,  
158 allowed us to periodically verify the presence of *B. bacteriovorus* using a 100x objective. The  
159 set-up was enclosed in an incubator set to 28°C.

160

#### 161 *Image processing and data analysis*

162 Images were processed in Matlab using a custom script. Briefly, each patch was subdivided in  
163 98x98 regions (we left out a margin from the edges of the patches to remain unbiased by the  
164 limited precision of the microscope stage movement) from which fluorescence time traces  
165 were obtained by binning into bins of 3x3 pixels. By dividing the patches into subregions, we  
166 are able to quantify variation of predation rates *within* individual patches (see Results and  
167 below), while the binning reduces noise in the fluorescence signal. To render the analysis of  
168 the continuous landscape as comparable as possible to the patchy landscape, artificial “virtual  
169 patches” of identical size and inter-patch spacing were computationally generated in the  
170 continuous landscape during analysis (Fig 1b). In designing the habitat geometries, we chose  
171 to keep the total habitat volume of the patchy and continuous landscapes identical, and  
172 therefore, given the different geometries of the two landscapes, the continuous landscape  
173 consists of 55 “virtual patches” vs. 85 patches for the patchy landscape. Next, we performed a  
174 background correction for each time trace and smoothed time traces using a 5-point window.  
175 Subsequently, the maximal predation rates were calculated for each time trace by calculating  
176 the maximal negative slope (maximal predation rate) beyond the maximum value of a time  
177 trace (Figure 2a and Figure 3a). Using this algorithm, each of the patches yields  $10^4$  values for

178 the maximal predation rates. We exclude time traces originating from empty regions within  
179 the patch (typically a few percent of the traces, defined by a maximum that is 10% or less  
180 than the most frequent maximal value of all time traces in the patch). The values for the  
181 maximal predation rates were then plotted in histograms such as the blue histograms in Figure  
182 2b and 3b. To usefully compare the variance of this distribution between patches, also in  
183 cases where the mean values differ, we divide the maximal predation rate by its mean. We  
184 thus describe the variation as the coefficient of variation (CV), defined as the standard  
185 deviation of the distribution divided by the mean of the distribution. The within-patch CV  
186 thus obtained for each patch was averaged over all patches yielding two values: one for all of  
187 the patches in the patchy geometry ( $CV_{l,p}$ ), and one for all of the “virtual patches” in the  
188 continuous geometry ( $CV_{l,c}$ ). To compare the local CV of the patches with the CV of the  
189 landscape as a whole, we generate two more numbers: one that describes the global CV for  
190 the entire landscape for a patchy geometry ( $CV_{g,p}$ ) and one that describes the global CV of the  
191 entire landscape for the continuous geometry ( $CV_{g,c}$ ). The degree to which the global CV for  
192 the entire landscape and that of the individual patches (local CV) differ is expressed in terms  
193 of their ratio R according to  $R = \text{Global CV} / \text{Local CV}$  for each repeat experiment where a  
194 ratio equal to one means that the variation at the local scale is equal to the variation at the  
195 global scale. This analysis yields 6 ratios: three repeat measurements for the patchy landscape  
196  $R_p$  and three repeat measurements for the continuous landscape  $R_c$ . To test whether  $R_p$  and  $R_c$   
197 differ significantly, we use a Wilcoxon rank-sum test.

198

### 199 *Spatial Correlation*

200 To calculate the spatial correlation between patches, time traces were used as shown in Figure  
201 1, where a single fluorescence time trace represents the dynamics in a single patch. Spatial  
202 correlations were calculated as a function of increasing inter-patch distance using the *corrcoef*  
203 function in Matlab.

204

### 205 *Survival Analysis*

206 For the survival analysis, we used the fluorescence signal originating from all 98x98  
207 subregions in the patches. As is described in the “Results” section, the typical fluorescence  
208 signal rises first (due to bacterial growth) and subsequently reaches a maximum, after which it  
209 declines (due to predation). First, the time-point associated with the maximum value in the  
210 fluorescence is determined. Second, the time-point at which the fluorescence crosses the  
211 cutoff fluorescence value associated with a region that does not contain any bacteria is  
212 determined. This time-point is recorded and designated as the “time-of-death” for that  
213 particular region in space. This procedure is repeated for all time traces, and Kaplan-Meier  
214 survival curves are generated using the log-rank function of Matlab. As the patchy- and



215 continuous-habitat experiments were performed in triplicate, we obtain three sets of survival  
216 curves (supplementary figure), each quantifying the surviving population fractions in the  
217 patchy and continuous landscapes over time. The log-rank algorithm determines this fraction,  
218 as well as whether the two survival curves for the patchy and continuous landscapes are  
219 statistically different, including the associated  $p$ -value. Additionally, the algorithm determines  
220 the residual values, i.e. the population fraction that persists.

221 The survival analysis as described above was also performed separately for the  
222 periphery (the outer rim of the habitat patch, measuring 15  $\mu\text{m}$  or less to the closest sidewall)  
223 and center (the remaining  $70 \times 70 \times 10 \mu\text{m}^3$  central volume element) of habitat patches. The  
224 center of the habitat patches has a low surface to volume ratio ( $0.20 \mu\text{m}^{-1}$ ) as only a top and  
225 bottom surface are present, whereas the periphery is enclosed by the sidewalls increasing the  
226 surface to volume ratio ( $0.28 \mu\text{m}^{-1}$  and  $0.27 \mu\text{m}^{-1}$  for the patchy and continuous habitats  
227 respectively).

228

### 229 *Real-time movies*

230 Real-time and time-lapse movies provide additional insights beyond those extracted from  
231 total fluorescence intensity time traces. For example, movies help to identify different modes  
232 of prey growth such as surface-associated growth, which manifests itself as an increase in  
233 fluorescence at the edges of an observed microcolony in combination with limited (or even  
234 the absence of) motility. Furthermore, the process and timing of predation can be followed.  
235 While we are unable to observe the exact time of entry of the predator, we do clearly observe  
236 the formation of bdelloplasts when rod-shaped prey is converted into round-shaped  
237 bdelloplasts, followed by their sudden disappearance due to lysis (Movies S1, S4 and S5).

238





## 239 **Results**

240 Prior to studying the dynamics between predator and prey, we perform a control  
241 experiment in which the landscape is only inoculated with prey (Fig. 1b and c). This  
242 experiment shows that *E. coli* quickly populates the entire landscape, though some spatial  
243 variation is present (Figure 1b). The mean fluorescence intensity of all patches over time  
244 (Figure 1c) shows that the prey initially grows exponentially, until it reaches stationary phase  
245  $\sim 10$  h after inoculation. In the following 30 hours the population does not collapse, as  
246 evidenced by an approximately constant mean fluorescent intensity. We conclude that in the  
247 absence of predator, and in good agreement with previous studies of *E. coli* in  
248 microfabricated landscapes [18,38], the bacterial prey population inoculated in the  
249 microfabricated landscape exhibits all familiar phases of growth and does not show  
250 population collapse even after two days.

251 A different picture emerges when predator and prey are both inoculated from  
252 opposite sides. Figure 1 shows prey dynamics as a function of space and time in the presence  
253 of the predator, for the patchy landscape (Fig. 1d) and for the continuous landscape (Fig. 1e).  
254 An experiment is typically characterized by four phases in the predator-prey dynamics  
255 (labeled (i) through (iv) in Fig. 1d). Initially, (phase (i)), growth of the prey population is  
256 dominant over predation and consequently the population density increases. During phase (i),  
257 the majority of *E. coli* bacteria are planktonic, motile, and migrate between patches rapidly,  
258 whereas in phase (ii), the majority of *E. coli* become sessile and show an increase in surface  
259 associated growth [16]. Without predator (Figure 1b and c), one observes phases (i) and (ii)  
260 only (see [38] for a detailed analysis of the colonization process). When prey and predator are  
261 both (simultaneously) inoculated, predation starts to dominate in phases (ii) and (iii) and the  
262 population density of *E. coli* starts to decline approximately 10-20 hours after inoculation. In  
263 the final phase (iv), the prey density reaches a steady-state, where most of the prey population  
264 is eradicated, except for a small number of prey that is presumably characterized by plastic  
265 phenotypic resistance to predation [25]. We note that while the specific spatial pattern, e.g.  
266 the presence of two separated predation foci in the patchy landscape in Fig. 1d, varies from  
267 experiment to experiment (see Supplemental Figure), all six independent experiments showed  
268 the four phases described above. Supplemental Movie S1 shows the predation process in  
269 more detail, including the formation of round bdelloplasts and their sudden disappearance as  
270 they get lysed by *B. bacteriovorus*. We conclude that *B. bacteriovorus* do indeed predate *E.*  
271 *coli* populations in the structured landscapes and that the prey population is driven towards  
272 extinction.

273 We then ask how habitat topology influences the variation of prey dynamics at local  
274 vs. global spatial scales. To address this, we first quantify how much the maximal predation  
275 rate of the prey population varies *within* patches in the patchy landscape (local scale), where  
276 the conditions are presumably uniform, and compare this quantity to the spread of the  
277 maximal decay rate *across* patches (global scale). To compare spreads with slightly different  
278 means, we use the coefficient of variation (CV) as a measure of the spread (see the “Image  
279 processing and data analysis” section of the Materials and Methods for details). We calculate  
280 four values of the CV: 1)  $CV_{l,p}$  (local, patchy; variation within patches in the patchy  
281 landscape), 2)  $CV_{g,p}$  (global, patchy; variation in the entire patchy landscape), 3)  $CV_{l,c}$  (local,  
282 continuous; variation within the virtual “patches” in the continuous landscape) and 4)  $CV_{g,c}$   
283 (global, continuous; variation in the entire continuous landscape). The values obtained, as  
284 well as a schematic representation of the regions for which the CVs are calculated, are  
285 summarized in Table 1.

286

	Mean $\pm$ SEM	Scale	Graphical representation
$CV_{l,p}$	$0.51\pm 0.06$	local	 $\langle CV \rangle$ of all patches in patchy landscape
$CV_{g,p}$	$1.53 \pm 0.66$	global	 CV of entire patchy landscape
$CV_{l,c}$	$0.55\pm 0.06$	local	 $\langle CV \rangle$ of all “patches” in continuous landscape
$CV_{g,c}$	$0.74\pm 0.08$	global	 CV of entire continuous landscape

288

289 Table 1. Local and global coefficients of variation in the patchy and continuous landscape.  
290 Values are the mean  $\pm$  the standard error of the mean (SEM) of three independent  
291 experiments.

292

293 First, we observe that in the patchy landscape the variation within a patch (local  
294 scale) is smaller than the variation between patches ( $CV_{l,p} < CV_{g,p}$ ). A statistical comparison of  
295  $CV_{l,p}$  and  $CV_{g,p}$  is provided below. This observation is consistent with the notion that  
296 conditions that affect predator-prey dynamics, *e.g.* fluctuations in predator and prey densities,  
297 vary across patches in a patchy landscape. The source of the increased variation across the  
298 landscape is not obvious as both the limited migration due to the patchiness of the landscape  
299 and the increasing physical distance between ever more distant regions could contribute to  
300 this result. To uncouple the influences of the patchy structure and physical distance, we  
301 compare the patchy landscape to the continuous landscape that does not contain structural  
302 patchiness. We find that the local CV of the decay rates within the “virtual patches” in the  
303 continuous landscape,  $CV_{l,c}$ , is  $0.55 \pm 0.06$ , very similar to the local CV in the patchy  
304 landscape ( $CV_{l,p} \approx CV_{l,c}$ ). This similarity is expected since both distributions represent local  
305 dynamics within an identical area (and volume) in the landscapes. The maximal decay rates of  
306 all time traces across the entire continuous landscape (red traces in Fig. 3c), have a relatively  
307 narrow distribution (Figure 3d) and has a global  $CV_{g,c}$  of  $0.74 \pm 0.08$ . This number is larger  
308 than the average local  $CV_{l,c}$  of the “virtual patches” in the continuous landscape, indicating  
309 that conditions in the entire continuous landscape are somewhat more diverse than in a small  
310 fraction of the entire landscape. However, it is important to note that the global  $CV_{g,c}$  of the

311 continuous landscape is considerably smaller than the global  $CV_{g,p}$  of the patchy landscape  
312 ( $CV_{g,p} = 1.53 \pm 0.66$ ).

313 To properly address the question whether the patchiness of the patchy landscape  
314 increases variation, we calculate the ratios  $R_p = CV_{g,p}/CV_{l,p}$  for the patchy landscape and  $R_c =$   
315  $CV_{g,c}/CV_{l,c}$  for the continuous landscape. This assessment shows that  $R_p$  is indeed larger than  
316  $R_c$  ( $R_p = 2.8 \pm 0.9$ ,  $R_c = 1.3 \pm 0.02$  mean  $\pm$  SEM of  $n = 3$  experiments,  $R_p > R_c$   $p = 0.05$ , using a  
317 single-sided Wilcoxon rank-sum test). We may thus conclude that our findings support the  
318 hypothesis that patchiness increases the variation in population decay rates of the prey by  
319 approximately a factor of two.

320 While the measurements described above show that patchiness influences the  
321 predator-prey interaction at the global level, these measurements do not provide insight into  
322 the extent to which the prey dynamics is correlated in space. Spatial correlation gives insights  
323 into the connectivity between patches and the ease at which bacteria can move between  
324 patches. To quantify this we analyze the correlation between the time-traces of patches as a  
325 function of patch distance. Figure 4a shows the dependence on distance of the Pearson's  
326 correlation coefficient, for the patchy (red) and continuous (black) landscapes (see the  
327 'Spatial Correlation' section of the Materials and Methods). As expected, both landscapes  
328 show a decrease in correlation with increasing distance. However, while the two landscapes  
329 lose correlation similarly for distances up to approximately 15 patches, this analysis also  
330 shows that the patchy landscape loses correlation faster than the continuous landscape beyond  
331 15 patches. Spatial dynamics in the patchy landscape thus extend beyond a single patch, yet  
332 are correlated over shorter distances than in the continuous landscape, a high migration rate of  
333 bacteria between adjacent patches in the initial phases of the experiment may explain  
334 correlations beyond the patch size. A high migration rate between patches would be expected  
335 to contribute to a high coupling between patches and synchronization in the dynamics  
336 between patches. Indeed, real-time movies of the initial phases of the experiment (Movie S2  
337 and S3) show that up to hundreds of bacteria can migrate between patches per minute,  
338 depending on bacterial density. This finding suggests that the migration rate in the patchy  
339 landscape is apparently sufficiently high to generate correlation in the dynamics between a  
340 few adjacent patches, but over long ( $>15$  patches) distances, the effects of the patchy  
341 landscape on the dynamics become apparent. As such, the present spatial configuration  
342 represents an unexplored intermediate regime between a coherent well-mixed state and an  
343 entirely fragmented state [12].

344 Given our finding that patchiness affects variation and spatial correlation of the prey  
345 dynamics, we now ask what the ramifications of these findings are for the survival of prey.  
346 Does patchiness, like in various macroscopic systems [5,8,12,13] give rise to an increased  
347 persistence of the prey population, or do specific bacterial properties (such as high mobility,

348 high density, and surface growth) render the analogy to macroscopic organisms invalid? To  
349 answer this question, we perform a survival analysis for prey in both the patchy and  
350 continuous landscapes. Using fluorescence as a proxy for prey persistence we generated  
351 survival curves representing the spatial fraction of the prey population that survives (see Fig.  
352 4b and the ‘Survival Analysis’ section of the Materials and Methods for details). After the  
353 onset of predation (in this experiment app. after 10 h), survival curves in both the patchy and  
354 continuous landscape start to decline. Interestingly, the survival functions of the patchy and  
355 continuous populations are not equal, ( $p < 0.00001$  using a log-rank test). Survival curves for  
356 all the experiments are displayed in the Supplementary Figure g-i. These results show that  
357 while almost the entire population dies in the continuous landscape (residual  
358 value =  $0.04 \pm 0.04$ ,  $n=3$ ), a significant fraction of the population in the patchy landscape  
359 survives ( $0.36 \pm 0.10$ ,  $n=3$ ) demonstrating that prey survival in the patchy landscape is  
360 increased compared to the continuous landscape ( $p=0.05$ , using a single-sided Wilcoxon rank-  
361 sum test). The increased survival in the patchy landscape is not caused by a lower per capita  
362 predation rate as the absolute values for the per capita predation rates are  $0.06 \pm 0.01$  and  
363  $0.05 \pm 0.01$  per hour for the patchy geometry and continuous landscapes respectively, in good  
364 agreement with previously measured batch values [30–32]. This control shows that a) the  
365 geometry of the landscape does not influence the kinetics of the predator-prey interaction and  
366 that b) the rates measured in the microchip are comparable to those previously measured.

367

## 368 **Discussion**

369 This work was inspired by studies macro-scale patchy landscapes showing that  
370 patchiness can greatly impact the spatiotemporal dynamics of predator-prey systems, such as  
371 an extended lifetime of a macroscopic population (Holyoak and Lawler, 1996; Dey and Joshi,  
372 2006; Sutcliffe *et al.*, 1997; Ellner *et al.*, 2001)). We investigated to what extent bacterial  
373 predator-prey systems in micro-fragmented landscapes exhibit similar behaviors. The present  
374 patchy landscape can be considered “mildly” fragmented as on the one hand fragmentation  
375 increases the variation in predation rates, but on the other hand spatial correlations extend  
376 over multiple patches. The presence of this intermediate regime should perhaps be considered  
377 in the context of the fundamental differences between macroscopic animals inhabiting  
378 macroscopic landscapes and microscopic organisms inhabiting microscopic landscapes. First,  
379 compared to macroscopic animals, bacteria (and especially *B. bacteriovorus*) move through  
380 space fast and grow to high densities. If one were to simply scale up the microfragmented  
381 landscape and its microbial inhabitants to macroscopic proportions, one would obtain the  
382 following (rather absurd) large-scale animal equivalent: hundreds of cheetahs racing at  
383 approximately 500 km/h in random directions while hunting on a few hundred antelopes that  
384 run around at 100 km/h in a square field of only 100m x 100m. Such exceedingly high density

385 and mobility would likely give rise to relatively homogeneous spatial dynamics within the  
386 field and result in spatial correlations that extend beyond it. Moreover, bacteria can adopt  
387 distinct lifestyles, existing as individual planktonic cells that swim freely, or growing as  
388 multi-cellular surface-associated colonies. Bacteria exhibiting one of these two lifestyles  
389 differ in myriad ways including cellular mobility, capacity to forage, resistance to  
390 environmental insults, and physiology. By impacting core processes like colonization,  
391 survival, and extinction; lifestyles switching plays a central role in bacterial ecology. Another  
392 distinction between the microscopic and macroscopic worlds is that signaling molecules,  
393 nutrients, and waste diffuse across space highly efficiently. For example, a small molecule  
394 such as glucose traverses the length of a patch (100  $\mu\text{m}$ ) in approximately 10 s and a distance  
395 of 15 patches in approximately an hour (which is on the order of one bacterial division time).  
396 Such environmental homogenization may be less apparent for macroscopic animals. A future  
397 theory of microbial ecology that draws from macroscopic theory would have to take into  
398 account these fundamental differences.

399         Perhaps the most salient effect described in this manuscript is the observation that a  
400 significant fraction of prey in the fragmented landscape persists, in contrast to the prey  
401 population in the continuous landscape that is nearly eradicated. As this effect cannot be  
402 attributed to a difference in predation rates (the maximal predation rates in the two landscapes  
403 are equal), the increased persistence may be attributed to the geometry of the patchy  
404 landscape. Classical metapopulation dynamics, in which a given patch becomes extinct after  
405 which it is “rescued” by migration of prey from an adjacent patch, could be responsible for  
406 the increased survival in the patchy landscape. However, while this scenario cannot be ruled  
407 out completely, the limited extend to which lateral movement (migration) is visible in the  
408 kymographs leads us to favor a different explanation.

409         Previous work has shown that while *B. bacteriovorus* can predate an *E. coli* biofilm a  
410 significant fraction of the biofilm often remains [39], in contrast to predation on planktonic *E.*  
411 *coli* cultures where only a minute fraction of the population survives due to phenotypic  
412 resistance. In the microhabitats under investigation here, part of the prey population grows as  
413 a surface-associated biofilm (see Movies S1, S4 and S5). Surface-associated growth  
414 concentrates in the periphery of habitat patches where, due to the presence of sidewalls, the  
415 surface to volume ratio is higher when compared to the center of habitat patches. An increase  
416 in the population fraction adopting a surface-associated lifestyle may render it more resistant  
417 to predation and could result in an increased survival in the periphery of patches. To test this  
418 hypothesis, we performed a survival analysis for the periphery and center of habitat patches  
419 separately. This analysis revealed that prey persistence in the patchy habitat is indeed  
420 significantly higher in the periphery compared to the center of patches (peripheral residual  
421 fraction of  $0.49 \pm 0.14$ , versus  $0.30 \pm 0.10$ ,  $p < 0.02$  using a one-tailed paired t-test). In contrast,

422 we did not observe a significant difference when comparing survival in the periphery and  
423 center of (virtual) patches in the continuous habitat ( $0.05 \pm 0.05$  and  $0.04 \pm 0.05$ , respectively).  
424 Two effects may explain the difference observed between the patchy and continuous habitats:  
425 (i) patches in a patchy habitat have 4 sidewalls, whereas (virtual) patches in the continuous  
426 habitat only have 2, lowering the surface to volume ratio; (ii) patches in a patchy habitat have  
427 corners facilitating bacterial adhesion [40], while corners are absent in the continuous habitat.  
428 Both the increase in surface to volume ratio and the presence of corners, facilitate surface-  
429 associated growth. As a result, geometry-induced enhancement of surface-associated growth  
430 may be responsible for the increased persistence of prey we observe in the patchy habitat.  
431 While in our experiments the persisting bacteria did not divide, the exact physiological state  
432 of these remaining bacteria remains unknown. Assessing the capacity of these persisting prey  
433 to grow and divide will be of importance when utilizing *B. bacteriovorus* for water cleaning,  
434 crop protection, and as additional means to fight bacterial infections.

435  
436

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441

#### 442 **Competing interests**

443 We have no competing interests.

444

#### 445 **Authors' contributions**

446 FJHH, DAK, EJ, and CD conceived and designed the experiments. FJHH and DAK  
447 performed experiments and analyzed the data. OR designed and contributed protocols. FJHH  
448 and DAK wrote the manuscript. All authors read and approved the final manuscript.

449

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455

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- 563
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- 565

566 **Figure captions**

567

568 Figure 1.

569 On-chip predator-prey system. (a). Soil consists of a three-dimensional network of micron-  
570 sized patches. (b). A control experiment, in which only prey is introduced to a patchy  
571 landscape, consisting of coupled patches (top). A heatmap of a kymograph (depicting space  
572 horizontally and time vertically) showing the population dynamics of fluorescently labeled *E.*  
573 *coli* in log-scale. (c) The mean prey growth dynamics over all patches shows the familiar  
574 phases of bacterial growth: exponential phase and entry into stationary phase (at  $t=10h$ ). (d, e)  
575 Predator-prey dynamics in the presence of predator in a patchy landscape (d) and a  
576 “continuous” landscape (e). Software-generated “virtual” patches that are used in data  
577 analysis of the continuous habitat are indicated by red dashed lines. In both habitats there  
578 initially is a steep rise in fluorescence which corresponds to growth of *E. coli*, followed by a  
579 death phase in which *E. coli* lyse after predation. Each pixel represents a single habitat patch.  
580 Microscopy images show representative snapshots of the population dynamics in phases i - iv,  
581 arrows indicate the approximate space and time of image acquisition.

582

583 Figure 2.

584 Predation rates in a patchy landscape. (a) Yellow dots indicate 98x98 points (for clarity, only  
585 16x16 are shown) that were used to generate time traces (thin blue lines show single time  
586 traces for one patch, the fat black line represents the mean) from patches of the fragmented  
587 landscape. The maximum predation rate is extracted from individual traces. (b) Distribution  
588 of the maximal rate of decay of four patches. (c) All time traces of all patches within a patchy  
589 habitat (thin red lines show single time traces for one patch, the fat black line represents the  
590 mean). (d) The distributions of the maximum decay rates calculated for all points in all  
591 patches within the patchy landscape.

592

593 Figure 3.

594 Predation rates in the continuous landscape. (a) Yellow dots indicate 98x98 points (for clarity,  
595 only 16x16 are shown) that were used to generate time traces (thin blue lines show single  
596 time traces for one virtual patch, the fat black line represents the mean) from patches of the  
597 continuous landscape. The maximum predation rate is extracted from individual traces. (b)  
598 Distribution of the maximal rate of decay of four virtual patches. (c) All time traces of all  
599 virtual patches within a continuous habitat (thin red lines show single time traces for one  
600 patch, the fat black line represents the mean). (d) The distributions of the maximum decay  
601 rates calculated for all points in all virtual “patches” within the continuous landscape.

602

603 Figure 4  
604 Correlation in patchy and continuous habitats. (a) The temporal correlation of the population  
605 dynamics decreases with increasing patch distance. Beyond approximately 15 patches,  
606 correlation in the patchy landscape (red) is lost more rapidly than in the continuous landscape  
607 (black). (b) Kaplan-Meier survival functions for a patchy landscape (red) and a continuous  
608 landscape (black). The two functions differ ( $p < 0.00001$ ) and the fraction of prey population  
609 that remains in the patchy landscape is higher than in the continuous landscape ( $p = 0.05$ ), see  
610 Results).