Invasion speeds in microbial systems with toxin production and quorum sensing

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The theory of invasions and invasion speeds has traditionally been studied in macroscopic systems. Surprisingly, microbial invasions have received less attention. Although microbes share many of the features associated with competition between larger-bodied organisms, they also exhibit distinctive behaviors that require new mathematical treatments to fully understand invasions in microbial systems. Most notable is the possibility for long-distance interactions, including competition between taxa mediated by diffusible toxins and cooperation among individuals of a single taxon using quorum sensing. In this paper, we model bacterial invasion using a system of coupled partial differential equations based on Fisher's equation. Our model considers a competitive system with diffusible toxins that, in some cases, are expressed in response to quorum sensing. First, we derive analytical approximations for invasion speeds in the limits of fast and slow toxin diffusion. We then test the validity of our analytical approximations and explore intermediate rates of toxin diffusion using numerical simulations. Interestingly, we find that toxins should diffuse quickly when used offensively, but that there are two optimal strategies when toxin is used as a defense mechanism. Specifically, toxins should diffuse quickly when their killing efficacy is high, but should diffuse slowly when their killing efficacy

is low. Our approach permits an explicit investigation of the properties and characteristics of diffusible compounds used in non-local competition, and is relevant for microbial systems and select macroscopic taxa, such as plants and corals, that can interact through biochemicals.

INTRODUCTION

Understanding the factors governing the spread of a newly introduced species has long been an active area of research in the field of invasion biology¹⁻⁴. Both empirical and theoretical studies have sought to clarify the organismal, community and environmental traits that can influence the invasion process⁵⁻⁷. Early theoretical work, for example, highlighted the role of species fecundity and dispersal as major determinants of invasion success⁸. Later models were extended to include species properties such as stage structure⁹, Allee effects¹⁰, population-level heterogeneity¹¹ and evolution¹². Other studies examined the role of the environment¹³ and interspecific interactions¹⁴. Notably, negative interspecific interactions like competition were found to be particularly effective at slowing, stopping or even reversing the spread of an invading species¹⁵.

The concept of an established species or community acting as a barrier to invasion is not unique to macroscopic systems. Indeed, a similar idea recurs in the medical literature as ‘colonization resistance,’ where the invading taxon is a pathogen and the established community is the commensal microflora of a person’s body^{16,17}. In such cases, pathogen invasion speeds have a strong bearing on the outcome of a disease, and, with some fast-spreading infections, delayed intervention can have dire consequences¹⁸. It is well known that microscopic and macroscopic invasions have a number of features in common. For example, bacteria display many of the same competitive interactions as their macroscopic counterparts, including overuse of nutritional resources^{19,20} and exclusion from

favorable locations in space²¹. However, despite the similarity between microscopic pathogens and macroscopic invasive species, few of the theoretical models from classical invasion biology have been translated and applied to study infections in humans or other organisms. Consequently, little is known about how the traits of different bacteria and bacterial communities affect the invasion speeds of pathogens.

The lack of theoretical work on bacterial invasion speeds is striking because, although similar in many ways to macroscopic systems, bacteria also demonstrate behaviors that are uncommon among macroscopic organisms and may affect the invasion process in distinctive ways. Most notable is bacterial production of small, diffusible compounds. Importantly, these compounds usually diffuse faster than the bacterial cells producing them, meaning that bacteria can strongly affect other bacteria—both competitors and collaborators—over relatively large distances. Therefore, unlike macroscopic competition, bacterial competition not only takes place through direct (cell-to-cell) contact, but also through indirect interactions mediated by toxins²⁰ and frequently regulated through quorum sensing (QS)^{22–26}. Modeling these and other non-local effects is critical for understanding invasion in the microbial world. (It is worth noting that some plants and corals can produce diffusible biochemicals that influence the growth and survival of competitors^{27–30}, a phenomenon known as allelopathy. As with bacterial invasions, the role of diffusible compounds on invasion speeds in these systems has also received little theoretical attention.)

Depending on the bacterial taxa involved, diffusible toxins can take a variety of different forms. In the simplest case, the toxin is a metabolic by-product. For example, the dominant member of the human skin microbiome, *Propionibacterium acnes*, produces propionic acid³¹ while the most common vaginal commensals, *Lactobacillus* spp., produce lactic acid³², both as by-products of fermen-

tation. These two toxins acidify the environment, which, in turn, has been shown to inhibit a range of pathogens, including *Staphylococcus aureus* on the skin³¹ and *Candida albicans*, *Gardnerella vaginalis* and *Mobiluncus* spp. in the vagina³³. Interestingly, fermentation by-products are not the only diffusible toxin produced by lactobacilli: members of this genus, along with some streptococci, also produce hydrogen peroxide (H₂O₂), which is another small molecule that is effective against a range of catalase-negative human pathogens, including *Staphylococcus aureus*³⁴ and the respiratory pathogen *Haemophilus influenzae*³⁵.

In addition to acids and oxidizing agents, which typically act on a broad range of microbes, many bacteria also produce a range of more specialized antimicrobials. Of these, some of the best characterized are bacteriocins³⁶, which are proteinaceous toxins that typically inhibit the growth of closely related bacterial strains (although occasionally bacteriocins have been observed suppressing more distantly related taxa³⁷). Bacteriocins exhibit a high degree of variation among types. Class I bacteriocins (known as lantibiotics), for example, are small, thermostable peptides comprising only around 19–38 amino acid residues. By contrast, Class III bacteriocins are large, thermolabile proteins (>30 kDa) with complex structures and functions³⁸. The potencies of different bacteriocins are also highly heterogeneous, as are their modes of action³⁹. The lantibiotic nisin, for example, binds to cell wall precursors, inhibiting cell wall formation in competitor taxa⁴⁰. Similarly, lactic acid bacteria produce a range of bacteriocins that are capable of forming destructive pores in a competitor's cell membrane⁴¹. However, other bacteriocins, including colicins (particularly those produced by *Escherichia coli*), work by targeting protein synthesis in competitor taxa, negatively affecting both deoxyribonuclease⁴² and ribonuclease⁴³ activity.

Understanding the role of toxins in microbial colonization is directly relevant to human health

and well-being because we use natural antimicrobials in food^{37,44} and textile⁴⁵ production, and, increasingly, as a source of novel pharmaceuticals⁴⁶. Moreover, toxins produced by bacteria are a central component of our healthy microbiome, helping to protect us from pathogens that might otherwise colonize the surfaces of our bodies. One recent study, for example, identified approximately 4800 supposed bacteriocins from the Human Microbiome Project⁴⁷. Despite the prevalence and importance of microbial toxins, few studies have specifically considered their effect on bacterial invasion and colonization. At a fundamental level, knowledge of how different types of antimicrobials affect colonization rate and success may offer insights into the evolutionary forces driving toxin acquisition and use. In terms of application, improved understanding of invasion speeds will allow us to identify unusually problematic pathogens, as well as ways of promoting bacteria that offer beneficial services, such as probiotics⁴⁸.

Of the previous studies that have investigated the role of bacteriocins on invasion outcomes^{49–51}, only a handful have examined trajectories of invasions^{52,53} and none have explicitly considered the role of toxin characteristics, for example size and mode/efficacy of killing. Strictly in terms of theoretical work, the majority of existing literature has focused on a few select topics: the role of bacteriocins in maintaining bacterial population coexistence^{49–51} and establishing microbial diversity^{54,55}, cost-benefit analyses of bacteriocin production by bacteria⁵⁶, and the environmental conditions favoring bacteriocin evolution^{57,58}. The few studies that have examined invasion rates have done so either in the context of serial dilutions⁵² or with moving population boundaries⁵³. However, neither of these approaches permits an examination of the properties of the toxins themselves, such as how physical characteristics like compound size or chemical structure—common determinants of toxin diffusion rate—might affect pathogen invasion speeds.

In this study, we use a system of coupled partial differential equations (PDEs) based on Fisher's equation to describe the invasion of a pathogen into a one-dimensional domain populated by an established competitor. We derive analytical approximations for the shape of the wavefront of a diffusible toxin under several limiting conditions. We then use these results to approximate pathogen invasion speeds under similar limiting conditions. We supplement our analytical treatment with numerical simulations, which allow us to explore additional scenarios that are not analytically tractable, including systems with intermediate rates of toxin diffusion and systems where toxin production is regulated by QS. In total, we consider four cases: i) the invading taxon constitutively produces a toxin; ii) the established taxon constitutively produces a toxin; iii) the invading taxon produces a toxin that is regulated by QS; and iv) the established taxon produces a toxin that is regulated by QS.

METHODS

For each system that we consider, we assume two bacterial taxa — the invader population, $A = A(x, t)$, and the established population, $B = B(x, t)$. When the invader population produces a toxin, we denote the corresponding toxin profile $S = S(x, t)$. When the established population produces a toxin, we denote the toxin profile $T = T(x, t)$.

Constitutive toxin production

Eqn 1 describes a system in which two bacterial taxa both produce toxins:

$$\frac{\partial A}{\partial t} = D_A \frac{\partial^2 A}{\partial x^2} + r_A A(1 - A - \alpha_{AB}B) - k_{AT}AT \quad (1a)$$

$$\frac{\partial S}{\partial t} = D_S \frac{\partial^2 S}{\partial x^2} + r_S A - m_S S \quad (1b)$$

$$\frac{\partial B}{\partial t} = D_B \frac{\partial^2 B}{\partial x^2} + r_B B(1 - B - \alpha_{BA}A) - k_{BS}BS \quad (1c)$$

$$\frac{\partial T}{\partial t} = D_T \frac{\partial^2 T}{\partial x^2} + r_T B - m_T T \quad (1d)$$

where D_A and D_B are diffusion coefficients for invader and established bacterial taxa respectively and D_S and D_T are diffusion coefficients for their toxins. Bacterial growth rates are given by r_A and r_B , toxin production rates by r_S and r_T and toxin decay rates by m_S and m_T . We assume that local competition between the invader and the established taxon follows Lotka-Volterra dynamics⁵⁰ with interaction terms α_{AB} and α_{BA} , representing, for example, competition for space or nutrients in the immediate vicinity of competing cells. The toxin produced by each bacterial taxon acts at a distance and kills competitor cells at rates k_{BS} and k_{AT} . Linear determinacy conditions for this PDE system—which will be important for interpreting our numerical results—are included in *Appendix I*.

For simplicity, we restrict our analysis to systems with $D_A = D_B$ and $r_A = r_B$ and focus on two cases: only the invading taxon produces a toxin and only the established taxon produces a toxin. When only the invading taxon produces a toxin, Eqn 1 reduces to

$$\frac{\partial A}{\partial t} = D_A \frac{\partial^2 A}{\partial x^2} + r_A A(1 - A - \alpha_{AB}B) \quad (2a)$$

$$\frac{\partial S}{\partial t} = D_S \frac{\partial^2 S}{\partial x^2} + r_S A - m_S S \quad (2b)$$

$$\frac{\partial B}{\partial t} = D_B \frac{\partial^2 B}{\partial x^2} + r_B B(1 - B - \alpha_{BA}A) - k_{BS}BS \quad (2c)$$

139 and when only the established taxon produces a toxin, Eqn 1 reduces to

$$\frac{\partial A}{\partial t} = D_A \frac{\partial^2 A}{\partial x^2} + r_A A(1 - A - \alpha_{AB} B) - k_{AT} AT \quad (3a)$$

$$\frac{\partial B}{\partial t} = D_B \frac{\partial^2 B}{\partial x^2} + r_B B(1 - B - \alpha_{BA} A) \quad (3b)$$

$$\frac{\partial T}{\partial t} = D_T \frac{\partial^2 T}{\partial x^2} + r_T B - m_T T \quad (3c)$$

140 As most toxins are small molecules and therefore usually diffuse faster than the cells producing

141 them, we also assume $D_S, D_T \geq D_A, D_B$.

142 **QS-regulated toxin production**

143 When toxin production is regulated by additional diffusible compounds, Eqn 1 can be modified to

$$\frac{\partial A}{\partial t} = D_A \frac{\partial^2 A}{\partial x^2} + r_A A(1 - A - \alpha_{AB} B) - k_{AT} AT \quad (4a)$$

$$\frac{\partial Q}{\partial t} = D_Q \frac{\partial^2 Q}{\partial x^2} + v_0 A + v_{max} A \frac{Q^{n_Q}}{Q^{n_Q} + K_Q^{n_Q}} - m_Q Q \quad (4b)$$

$$\frac{\partial S}{\partial t} = D_S \frac{\partial^2 S}{\partial x^2} + \psi \left(v_0 A + v_{max} A \frac{Q^{n_Q}}{Q^{n_Q} + K_Q^{n_Q}} \right) - m_S S \quad (4c)$$

$$\frac{\partial B}{\partial t} = D_B \frac{\partial^2 B}{\partial x^2} + r_B B(1 - B - \alpha_{BA} A) - k_{BS} BS \quad (4d)$$

$$\frac{\partial R}{\partial t} = D_R \frac{\partial^2 R}{\partial x^2} + w_0 B + w_{max} B \frac{R^{n_R}}{R^{n_R} + K_R^{n_R}} - m_R R \quad (4e)$$

$$\frac{\partial T}{\partial t} = D_T \frac{\partial^2 T}{\partial x^2} + \eta \left(w_0 B + w_{max} B \frac{R^{n_R}}{R^{n_R} + K_R^{n_R}} \right) - m_T T \quad (4f)$$

144 where $Q = Q(x, t)$ and $R = R(x, t)$ are densities of QS signaling chemical produced by the in-

145 vading pathogen and established taxon, respectively, D_Q and D_R are chemical diffusion coefficients

for the two QS signals and m_Q and m_R are QS-signal decay rates. We assume that singaling chemicals and toxins are both produced at a ‘leakage’ rate of v_0 and a maximum ‘on’ rate of v_{max} by the invading taxon and, correspondingly, at rates w_0 and w_{max} by the established taxon. We also assume density-dependent production of the QS signals, which we describe by a Hill function where K_Q and K_R are the threshold densities for half-maximal signal production and n_Q and n_R determine the change in signal production around the threshold densities. By using the same threshold densities, ‘leakage’ and ‘on’ rates for the singaling molecules and the toxins that they regulate, we are essentially assuming that both diffusible compounds are regulated by the same promoter. This is the simplest scenario, although systems with differential regulation are also possible. To capture differences in expression levels between singaling chemicals and toxins, we scale toxin production by factors ψ and η for invading and established taxa, respectively.

As with our analysis of constitutive toxin production, we focus on two cases: only the invading taxon produces a toxin and only the established taxon produces a toxin. When only the invading taxon produces a toxin, Eqn 4 reduces to

$$\frac{\partial A}{\partial t} = D_A \frac{\partial^2 A}{\partial x^2} + r_A A(1 - A - \alpha_{AB} B) \quad (5a)$$

$$\frac{\partial Q}{\partial t} = D_Q \frac{\partial^2 Q}{\partial x^2} + v_0 A + v_{max} A \frac{Q^{n_Q}}{Q^{n_Q} + K_Q^{n_Q}} - m_Q Q \quad (5b)$$

$$\frac{\partial S}{\partial t} = D_S \frac{\partial^2 S}{\partial x^2} + \psi \left(v_0 A + v_{max} A \frac{Q^{n_Q}}{Q^{n_Q} + K_Q^{n_Q}} \right) - m_S S \quad (5c)$$

$$\frac{\partial B}{\partial t} = D_B \frac{\partial^2 B}{\partial x^2} + r_B B(1 - B - \alpha_{BA} A) - k_{BS} B S \quad (5d)$$

and when only the established taxon produces a toxin, Eqn 4 reduces to

$$\frac{\partial A}{\partial t} = D_A \frac{\partial^2 A}{\partial x^2} + r_A A(1 - A - \alpha_{AB} B) - k_{AT} AT \quad (6a)$$

$$\frac{\partial B}{\partial t} = D_B \frac{\partial^2 B}{\partial x^2} + r_B B(1 - B - \alpha_{BA} A) \quad (6b)$$

$$\frac{\partial R}{\partial t} = D_R \frac{\partial^2 R}{\partial x^2} + w_0 B + w_{max} B \frac{R^{n_R}}{R^{n_R} + K_R^{n_R}} - m_R R \quad (6c)$$

$$\frac{\partial T}{\partial t} = D_T \frac{\partial^2 T}{\partial x^2} + \eta \left(w_0 B + w_{max} B \frac{R^{n_R}}{R^{n_R} + K_R^{n_R}} \right) - m_T T \quad (6d)$$

161 As with toxins, most signaling chemicals are small molecules and therefore usually diffuse faster
 162 than the cells producing them, so we assume $D_Q, D_R \geq D_A, D_B$.

163 **Numerical solutions**

164 Although invasion speeds are defined, mathematically, on an infinite domain, we confirm analytical
 165 results and obtain additional results using numerical solutions of Eqns 2, 3, 5 and 6 on large but
 166 finite domains. Simulations begin with the established taxon at a constant population density (equal
 167 to its single-taxon equilibrium) across the entire, finite domain. We then introduce a small pulse of
 168 the invading taxon at the center of the domain. After allowing for a period of transient dynamics, we
 169 record the position of the invader wavefront at fixed time intervals to determine the invasion speed,
 170 which is constant. For all simulations where the invader produces a toxin, we set the domain to
 171 be large enough so that invader and toxin densities remain below a small threshold level (1×10^{-4}
 172 molecules per unit length) at domain boundaries. Software was written in *Python 2.7.10* and uses a
 173 finite-difference method for solving PDEs.

174 RESULTS

175 *Constitutive toxin production*

176 *Analytical approximations for toxin wavefronts*

177 We derive expressions for toxin wavefronts with the following assumptions: toxins are not inhibitory
 178 ($k_{BS} = 0$ and $k_{AT} = 0$), the invading taxon is not affected by local competition ($\alpha_{AB} = 0$), the
 179 established taxon is strongly inhibited by local competition ($\alpha_{BA} = 2$) and the growth and diffusion
 180 rates of the two bacterial taxa are identical ($r_A = r_B = r_C$ and $D_A = D_B = D_C$).

181 With these assumptions, the wavefront of the invading taxon can be approximated as the solu-
 182 tion to Fisher's equation and the wavefront of the established taxon as one minus the expression for
 183 the invader wavefront:

$$A(x, t) \approx \frac{1}{1 + e^{\frac{x}{2D_C} - r_C t}} \quad (7a)$$

$$B(x, t) \approx 1 - \frac{1}{1 + e^{\frac{x}{2D_C} - r_C t}} \quad (7b)$$

184 From Eqn 7, we can derive approximations for toxin wavefronts (see *Appendix II*). When the invader
 185 produces the toxin, the toxin wavefront is given by

$$S(x, t) \approx -\frac{r_S}{2m_S} \left(e^{\sqrt{\frac{m_S}{D_S}}(x - 2D_C r_C t)} - 2 \right) \quad \text{for } x < 2D_C r_C t \quad (8a)$$

$$S(x, t) \approx \frac{r_S}{2m_S} e^{-\sqrt{\frac{m_S}{D_S}}(x - 2D_C r_C t)} \quad \text{for } x > 2D_C r_C t \quad (8b)$$

186 When the established taxon produces the toxin, the toxin wavefront is given by

$$T(x, t) \approx \frac{r_T}{2m_T} e^{-\sqrt{\frac{m_T}{D_T}}(x-2D_C r_C t)} \quad \text{for } x < 2D_C r_C t \quad (9a)$$

$$T(x, t) \approx -\frac{r_T}{2m_T} \left(e^{\sqrt{\frac{m_T}{D_T}}(x-2D_C r_C t)} - 2 \right) \quad \text{for } x > 2D_C r_C t \quad (9b)$$

187 which, unsurprisingly, is the mirror opposite of Eqn 8.

188 *Analytical approximations for invasion speeds*

189 We consider two limiting cases for invasion speeds (see *Appendix III*). One limit is $D_S \rightarrow 0$, yielding
 190 c_0^* , which is appropriate for systems with slow toxin diffusion. (Strictly, when $D_S = 0$ the toxin does
 191 not diffuse and is left behind by the moving bacterial cells.) The other limit is $D_S \rightarrow \infty$, yielding
 192 c_∞^* , which is appropriate for systems with fast toxin diffusion.

193 When the invader produces the toxin, the two limiting invasion speeds are

$$c_0^* = 2\sqrt{D_A r_A (1 - \alpha_{AB})} \quad (10a)$$

$$c_\infty^* = 2\sqrt{D_A r_A (1 - \alpha_{AB} (1 - \frac{k_{BS} r_S}{2m_S r_B}))} \quad \text{for } k_{BS} r_S < 2m_S r_B \quad (10b)$$

$$c_\infty^* = 2\sqrt{D_A r_A} \quad \text{for } k_{BS} r_S > 2m_S r_B \quad (10c)$$

194 When the established taxon produces the toxin, the two limiting invasion speeds are

$$c_0^* = 2\sqrt{D_A r_A (1 - \alpha_{AB} - \frac{k_{AT} r_T}{r_A m_T})} \quad (11a)$$

$$c_\infty^* = 2\sqrt{D_A r_A (1 - \alpha_{AB} - \frac{k_{AT} r_T}{2r_A m_T})} \quad (11b)$$

Notice that in both Eqns 10 and 11 invasion speeds are faster when the toxin diffuses quickly compared to when it diffuses slowly. This is an intuitive result. However, as we shall see below, this outcome is reversed in some scenarios where linear determinacy no longer holds.

We use numerical simulations to test the validity of our analytical approximations in Eqns 10 and 11, and to explore intermediate toxin diffusion rates. Because we are interested in how toxin killing efficacy (k_{BS} , k_{AT}) and diffusion rate (D_S , D_T) interact to affect invasion speeds, we set the remaining parameters in Eqns 2 and 3 to $D_A = D_B = 1$, $r_A = r_B = r_S = r_T = 1$, $m_S = m_T = 1$, $\alpha_{AB} = 0.5$ and $\alpha_{BA} = 5$.

Numerical solutions when the invading taxon produces a toxin

As expected, a non-diffusing (purely local) toxin produced by the invader does not affect its invasion speeds. In this case, the invader wavefront moves at speeds (Eqn 10a) consistent with classic results¹⁴ from invasion ecology (Fig. 1). However, invasion speeds increase and approach the analytical approximation for infinitely-fast toxin diffusion (Eqns 10b and 10c) as diffusion rates increase from $D_S = 1$ to $D_S = 100,000$. Notice that in the limit $D_S \rightarrow \infty$ for $k_{BS} r_S \geq 2m_S r_B$ toxin killing is so rapid that the established taxon is completely eliminated and the invader moves unimpeded at its maximum (Fisher's) invasion speed. Therefore, depending on the particular combination of toxin killing efficacy and diffusion rate, the invasion speed of a pathogen that produces a toxin can range

Figure 1: Invasion speeds when the invading taxon produces a toxin. Markers represent individual simulation runs and no markers indicate theoretical results (in this and subsequent figures). Invasion speeds increase from the classic theoretical result with no toxin (grey curve labeled as $D_S = 0$, Eqn 10a) and gradually approach the theoretical approximation for the limit of fast toxin diffusion (grey curve labeled as $D_S = \text{infinity}$, Eqn 10b) as diffusion rates increase from $D_S = 1$ to $D_S = 100,000$. In the limit of fast toxin diffusion for $k_{BS} \geq 2$ the established taxon has been completely eliminated and the invader moves unimpeded at its maximum speed (labeled as $D_S = \text{infinity}$, Eqn 10c), which for the set of parameters used is at $c_\infty^* = 2$.

from a lower bound given by classic results on invasion in a competitive system¹⁴ to an upper bound given by Fisher's spreading speed⁵⁹.

Numerical solutions when the established taxon produces a toxin

Invasion speeds are expected to decrease when toxin is used as a defense mechanism by the established taxon. In keeping with this expectation, we find that invasion speeds decrease with increasing toxin killing efficacy until the invader is not able to colonize at all when k_{AT} is high (Fig. 2). Interestingly, however, invasion speeds do not appear to agree well with our approximation for the limit of slow toxin diffusion (Eqn 11a). This is because the linear determinacy conditions required for this approximation only hold at very small k_{AT} when α_{AB} is large (see the final condition, Eqn 16d, in Appendix I). We see much better agreement with the slow-diffusion approximation for simulations with the same parameter values except with $\alpha_{AB} = 0.05$ instead of $\alpha_{AB} = 0.5$ (Fig. S1). Linear determinacy is satisfied much more easily when D_T is large (see Eqns 15c and 16d), and invasion speeds gradually approach our approximation for fast toxin diffusion (Eqn 11b) as diffusion rates increase from $D_T = 1$ to $D_T = 100,000$.

One interesting consequence of the failure of linear determinacy at low toxin diffusion rates involves the relationship between killing efficacy and D_T . We find that invasion speeds decrease with increasing killing efficacy at a *decreasing* rate for small D_T (concave up), but at an *increasing* rate for large D_T (concave down, notice the increase in downward curvature with increasing D_T in the left-hand panel of Fig. 2). As a result, when toxin killing efficacy is low, a slowly diffusing toxin results in the largest reduction in invasion speed; however, when toxin killing efficacy is high, a quickly diffusing toxin results in the largest reduction in invasion speed. This suggests two strategies

Figure 2: Invasion speeds when the established taxon produces a toxin. Left: Invasion speeds do not agree well with the theoretical approximation for the limit of slow toxin diffusion (grey curve labeled as $D_T = 0$, Eqn 11a) because the linear determinacy conditions required for this approximation only hold at very small k_{AT} (see main text). However, invasion speeds gradually approach the theoretical approximation for the limit of fast toxin diffusion (grey curve labeled as $D_T = \text{infinity}$, Eqn 11b) as diffusion rates increase from $D_T = 1$ to $D_T = 100,000$. Interestingly, invasion speeds decrease at a decreasing rate at small D_T but decrease at an increasing rate at large D_T (notice the increase in downward curvature with increasing D_T). The value of k_{AT} at which the invader cannot colonize decreases with increasing D_T ; failure to colonize is associated with negative invasion speeds, which are omitted for clarity. Right: The change in profile of invasion-speeds curves as D_T increases suggests two optimal strategies for toxin production: i) the toxin should not diffuse too quickly when k_{AT} is small, e.g., when $k_{AT} = 0.5$, invasion speeds are slower at low D_T ; and ii) the toxin should diffuse more quickly when k_{AT} is large, e.g., when $k_{AT} = 1.5$, invasion speeds are slower at high D_T .

for toxin production by an established taxon: i) the toxin should not diffuse too quickly (small D_T) when k_{AT} is small; and ii) the toxin should diffuse more quickly (large D_T) when k_{AT} is large. These two strategies can be clearly identified in the right-hand panel of Fig. 2.

QS-regulated toxin production

Compared to constitutive toxin production, QS will generally reduce the amount of toxin in the system. Consequently, invasion speeds are expected to decrease when QS regulates toxin production by the invader, but increase when QS regulates toxin production by the established taxon. However, as QS signals are often metabolically less costly than toxins, QS may serve to prevent unnecessary toxin production when bacterial cell density is insufficient for toxin to have a significant effect on the invasion process. Indeed, empirical studies have shown that toxin production often takes place under QS regulation^{22,23}.

Unfortunately, the complexity of the equations involving QS-regulated toxin production means that, unlike with constitutive toxin production, we are not able to derive analytical expressions for invasion speeds. As such, we focus on numerical solutions to Eqns 5 and 6. Similar to the previous section, we are interested in how toxin killing efficacy (k_{BS} , k_{AT}), toxin diffusion rate (D_S , D_T) and, now, signaling chemical diffusion rate (D_Q , D_R) interact to affect invasion speeds. For most parameters, we assume the same values as were used previously. However, when the invader produces toxin, we set the local competitive effects of the invader to $\alpha_{BA} = 0.5$. This balances competition due to local and non-local effects, allowing us to focus closer examination on the impact of QS regulation. In addition, we set $m_Q = m_R = 1$, $\psi = 1$, $\eta = 0.5$, $v_0 = w_0 = v_{max} = w_{max} = 0.5$, $K_Q = K_R = 0.5$ and $n_Q = n_R = 100$ in Eqns 5 and 6. Notice that, with these parameter choices, $\eta = 0.5$ implies

254 that total toxin production by the established population is half as high in the scenario with QS reg-
255 ulated toxin production as compared to the scenario with constitutive toxin production. We make
256 this assumption because it allows us to investigate the effect of QS regulated toxin production over
257 a larger range of killing efficacies

258 *Numerical solutions when the invading taxon produces a toxin regulated by QS*

259 To aid interpretation of results for systems with toxin production by the invader, we consider invasion
260 speeds scaled between two extreme scenarios: no toxin production (slowest invasion speeds, which
261 we set to $c' = 0$) and toxin production without QS (fastest invasion speeds, which we set to $c' = 1$).
262 From Eqn 5, it is clear that there are two intermediate states between these two extremes: i) a low-
263 speed state where there is only leakage of the toxin, i.e., the system is below the QS-threshold;
264 and ii) a high-speed state where additional toxin production has been turned ‘on’, i.e., the system
265 is above the QS-threshold. Depending on system parameters and initial conditions, some systems
266 will naturally transition into and remain in a low-speed state, whereas others will transition into and
267 remain in a high-speed state. For example, when toxin killing efficacy, k_{BS} , is small, the density
268 of the established taxon remains large enough to suppress the density of the invader through direct
269 competition to such an extent that the invader cannot produce enough signaling chemical at the
270 wavefront to exceed the QS-threshold. As a result the system is more likely to transition into a
271 low-speed rather than high-speed state.

272 At killing efficacies of $k_{BS} = 1$ and $k_{BS} = 2$, systems naturally transition into high-speed
273 states, even from initial conditions with no toxin or QS signal present (i.e., when only a small
274 population of invader cells are introduced). For these systems, QS initially suppresses invasion

Figure 3: Scaled invasion speeds when the invading taxon produces a toxin regulated by quorum sensing, without (left) and with (right) the application of a spike in signaling chemical at the invader wavefront. Invasion speeds are scaled between no toxin (slowest invasion speeds, $c' = 0$) and toxin production without quorum sensing (fastest invasion speeds, $c' = 1$). Results are shown for $D_S = 100$ and invasion speeds do not change significantly for $D_Q > D_S$. Left: Systems with $k_{BS} = 0.25$ and $k_{BS} = 0.5$ naturally transition into low-speed states, which are independent of D_Q . By contrast, systems with $k_{BS} = 1$ and $k_{BS} = 2$ naturally transition into high-speed states and quorum sensing suppresses invasion speeds when D_Q is relatively small. However, as $t \rightarrow \infty$ the toxin will eventually diffuse from behind the invader wavefront and result in a constant invasion speed that is independent of D_Q . Smaller values of D_Q require longer times to reach constant invasion speeds, which, given that simulations run for a finite amount of time, explains the monotonically increasing curves for $k_{BS} = 1$ and $k_{BS} = 2$. Right: The effect of applying a fixed-amount spike in signaling chemical with height $h = 1000$. Spiking has no effect on systems that naturally transition into high-speed states. However, with $k_{BS} = 0.5$, the spike drives the system into a high-speed state at small D_Q , but dissipates at large D_Q before sufficient signaling chemical has accumulated to shift states and the system remains in a low-speed state. Applying smaller amounts of signaling chemical ($h = 10$ and $h = 100$) reduces the value of D_Q at which the system can be forced into a high-speed state. For the system with $k_{BS} = 0.25$, even a spike with $h = 1000$ is insufficient to force the system into a high-speed state.

275 speeds, particularly when D_Q is small (Fig. 3, left-hand panel). This is because QS restricts toxin
 276 production, with smaller D_Q resulting in lower concentrations of toxin at the invader wavefront and
 277 therefore slower invasion speeds. However, as $t \rightarrow \infty$ toxin eventually diffuses from behind the
 278 invader wavefront. Because this accumulation of toxin is large compared to any differences in toxin
 279 loss due to different D_Q , invasion speeds essentially become independent of D_Q over long time
 280 periods. Not unexpectedly, smaller values of D_Q require longer times to reach limiting invasion
 281 speeds. This explains why curves for $k_{BS} = 1$ and $k_{BS} = 2$ increase monotonically in Fig. 3, which
 282 were all run for the same number of simulated time steps.

283 In contrast to the systems with $k_{BS} = 1$ and $k_{BS} = 2$, a comparable system with $k_{BS} = 0.5$
 284 is bistable: for the same initial conditions, the system with $k_{BS} = 0.5$ naturally transitions into a
 285 low-speed state, but can be forced into a high-speed state by applying a fixed spike of QS signal
 286 at the invader wavefront. Successful transition into the high speed state depends on the amount of
 287 QS signal applied and its diffusion rate (Fig. 3, right-hand panel). For a small QS-spike with small
 288 D_Q , the spike drives the system into a high-speed state, where it remains indefinitely. However,
 289 for a small QS-spike with large D_Q , the spike dissipates before sufficient signaling chemical has
 290 accumulated, causing the system to transition back to a low-speed state, where it remains indefinitely.
 291 Thus, all else being equal, larger QS spikes are required to force systems with larger D_Q into a high-
 292 speed state. For the comparable system with $k_{BS} = 0.25$, no amount of QS-spike we tried was
 293 enough to force the system into a high-speed state.

294 The observed relationships between scaled invasion speeds and D_Q/D_S (shown for $D_A =$
 295 $D_B = 1$) are similar for $D_A = D_B = 10$ and $D_S = 1000$, and $D_A = D_B = 100$ and $D_S = 10,000$,
 296 i.e., when $D_S/D_A = 100$. The relationships are present but less pronounced when $D_S/D_A = 10$

297 and $D_S/D_A = 1000$. Patterns are qualitatively similar when ‘leakage’ and ‘on’ rates are set to more
 298 biologically-realistic values of $v_0 = 0.05$ and $v_{\max} = 0.95$ instead of $v_0 = v_{\max} = 0.5$, although the
 299 reduction in basal amounts of toxin due to the lower ‘leakage’ rate means that systems are less likely
 300 to naturally transition into high-speed states (Fig. S2).

301 *Numerical solutions when the established taxon produces a toxin regulated by QS*

302 As suggested above, QS regulation over toxin production by the established taxon is expected to
 303 increase invasion speeds. However, because the initial density of the established taxon across the
 304 finite domain is so much larger than that of the invader, signaling chemical and toxin are quickly
 305 produced at their maximum rates, meaning that QS regulation (and therefore D_R) has a minimal
 306 effect on invasion speeds. Consequently, when the total toxin production is the same under QS
 307 regulated and constitutive toxin production, i.e., $\eta = 1$, there is essentially no difference in the
 308 relationship between invasion speed, D_T , and k_{AT} , regardless of whether or not QS occurs (not
 309 shown). When we consider QS regulation using a lower toxin expression level ($\eta = 0.5$), curves for
 310 invasion speed versus toxin killing efficacy are, unsurprisingly, less pronounced. That is, curves are
 311 flatter and closer to their maximum value, which corresponds to no defensive toxin production. As
 312 a result, changes in curvatures for the different toxin diffusion rates are less dramatic. Nevertheless,
 313 the general profiles of the curves are similar with and without QS (Fig. 4). This means that the
 314 same *qualitative* patterns seen with constitutive toxin production (Fig. 2) are also present when
 315 toxin production is regulated by QS — at low k_{AT} invasion speeds are slowest when D_T is low (e.g.,
 316 $D_T = 10$) but at high k_{AT} invasion speeds are slowest when D_T is high (e.g., $D_T = 1000$). Invasion
 317 speeds are very similar when ‘leakage’ and ‘on’ rates are set to more biologically-realistic values of
 318 $w_0 = 0.05$ and $w_{\max} = 0.95$ instead of $w_0 = w_{\max} = 0.5$ (Fig. S3).

Figure 4: Invasion speeds when the established taxon produces a toxin regulated by quorum sensing. With quorum sensing (black), the level of toxin expression is, by design, half that specified in the case with constitutive toxin production (grey, curves are the same as in Fig. 2). Notice that this means changes in invasion speeds with k_{AT} are less marked for QS regulated scenarios (black). Consequently, in the QS example, invasion speeds are closer to their maximum value, which corresponds to no defensive toxin production. Nevertheless, for both sets of curves we see the same qualitative trends — at low k_{AT} invasion speeds are slower when D_T is low (e.g., $D_T = 10$) but at high k_{AT} invasion speeds are slower when D_T is high (e.g., $D_T = 1000$). Results are shown for $D_R/D_T = 1$ and invasion speeds do not change significantly for $D_R < D_T$ or $D_R > D_T$.

DISCUSSION

Many studies have examined the environmental factors that promote toxin production, but less is known about which types of toxins should evolve under different conditions. This is surprising given the large range of physical and chemical properties exhibited by the toxins secreted by microorganisms^{32,38–41,43,47}. Our work paves the way for understanding how and why different toxin characteristics may be favored, depending on the various selection pressures faced by bacteria. For example, we find that fast toxin diffusion can be advantageous for an invader moving into a region that is already occupied by a competitor. However, when an established taxon is defending against an invader, slower toxin diffusion can be more effective, at least when the killing efficacy of the toxin is low (i.e., the strategy is to keep the weaker toxin at the invader wavefront where it is more effective at halting the invader, as opposed to the toxin diffusing to regions where it is less likely to have lasting impacts). This finding needs reconciling with real-world properties of toxins because large and more potent molecules generally diffuse slower than small and less potent molecules. This may represent a physical constraint; however, it is worth investigating whether and how different bacteria may have partially or fully overcome this constraint. Indeed, combining our approach with an explicit assessment of the costs involved in toxin production—related to toxin size, complexity and metabolic burden, among other considerations—would help explain the use of different toxins by microbes across different microbial niches.

Here we focused on modeling toxins that are not used up during the killing process. This is the simplest case and is appropriate for mechanisms where killing results from a change in ambient conditions, such as acidification of the environment by bacteria. This assumption also covers mechanisms where killing involves the action of a compound that can quickly revert back to its

original state, such as enzymes based on redox chemistry. With other mechanisms, however, the toxin is destroyed or made otherwise unavailable during killing. This could occur, for example, if the toxin binds to cell walls or membranes in its target. Besides allowing for toxin consumption during use, another extension would be to consider the simultaneous production of different types of toxin. Many lactobacilli, for example, are capable of secreting a range of different compounds with different physical characteristics and modes of action⁶⁰. It would be interesting to explore how interactions among different toxins might alter predictions of the current model. This also motivates the study of larger communities. Existing theoretical models of toxin production in three-member systems have shown that bacteriocins can promote diversity through non-transitive interactions^{54,55}. It remains to be seen how similar patterns of toxin immunity and sensitivity might play out within the context of multiple concurrent invasions into established communities of diverse taxa. Non-transitive competition has also been observed among corals²⁸, suggesting that an extended version of our approach would also be relevant to macroscopic systems involving allelopathy and allelochemical interactions. A final extension could involve invasion scenarios on planar surfaces (e.g., human mouths or gut walls), which could be tackled using a combination of the current approach and integro-difference methods⁷.

CONCLUSION

In this paper, we have taken a first step toward understanding how the non-local aspects of microbial competition alter classic predictions of invasion speeds. We found that toxin production can have a large effect on colonization success, with invasion speeds dependent on properties of the toxin, how toxin production is regulated and whether the toxin is used for offense or defense. Our work provides a basis for exploring further aspects of toxin use in the microbial world, including broader

community analyses and investigation of evolutionary processes.

In conventional invasion models with competition¹⁻⁴, a common analytical technique involves separating species into two teams such that each species cooperates with the other species in its team and competes with those in the other team. For our system (Eqn 1), one team is the invader and its toxin (A and S) while the other team is the established taxon and its toxin (B and T). This allows invasion speeds to be determined under the condition of linear determinacy³ by using a change of variables to convert the competition model into a cooperative system. However, linear determinacy conditions (e.g., Eqn 16) may not be satisfied if toxin diffusion is fast (i.e., $D_S, D_T \gg D_A, D_B$). Indeed, our analytical approximations for invasion speeds, which are supported by numerical simulations, show that invasion speeds are above those predicted by linear determinacy when D_S and D_T are large and D_A and D_B are nonzero. Therefore, our phenomenological approach to invasion speeds motivates the search for rigorous proofs for invasion speeds in systems with diffusible toxins. This will be a challenging but important line of inquiry because new analytical techniques are required to explore how nonlinear growth and interspecific interactions affect spatial spreading.

For many years, macroscopic ecological systems have inspired a wealth of mathematical systems with interesting biological and dynamical features. With advances in technology, we are now in a position to explore many of the same questions of microorganisms that have been posed for decades with larger organisms. And while many fundamental behaviors are retained across scales, microbes bring with them distinct traits and characteristics that are not found, or even possible, in macro-scale communities. Indeed, as demonstrated by our example of toxins and long-range competition, the microbial world poses new and interesting questions. Questions that give us the opportunity to learn more about the tools we know well and the systems we are only beginning to discover.

386 **Linear determinacy conditions for the PDE system where two bacterial taxa produce toxins**

387 Using the change of variables $\tilde{B} = 1 - B$ and $\tilde{T} = \frac{r_T}{m_T} - T$, we convert Eqn 1 into the system

$$\frac{\partial A}{\partial t} = D_A \frac{\partial^2 A}{\partial x^2} + r_A A(1 - \alpha_{AB} - A + \alpha_{AB} \tilde{B}) - k_{AT} A \left(\frac{r_T}{m_T} - \tilde{T} \right) \quad (12a)$$

$$\frac{\partial S}{\partial t} = D_S \frac{\partial^2 S}{\partial x^2} + r_S A - m_S S \quad (12b)$$

$$\frac{\partial \tilde{B}}{\partial t} = D_B \frac{\partial^2 \tilde{B}}{\partial x^2} + r_B(1 - \tilde{B})(\alpha_{BA} A - \tilde{B}) + k_{BS}(1 - \tilde{B})S \quad (12c)$$

$$\frac{\partial \tilde{T}}{\partial t} = D_T \frac{\partial^2 \tilde{T}}{\partial x^2} + r_T \tilde{B} - m_T \tilde{T} \quad (12d)$$

388 which is cooperative in the biologically-realistic range $0 \leq A \leq 1$; $0 \leq \tilde{B} \leq 1$; $0 \leq S \leq \frac{r_S}{m_S}$ and

389 $0 \leq \tilde{T} \leq \frac{r_T}{m_T}$. The moment generating matrix associated with the linearized version of Eqn 12 is

$$\begin{bmatrix} D_A \mu^2 + r_A(1 - \alpha_{AB}) - \frac{k_{AT} r_T}{m_T} & 0 & 0 & 0 \\ r_S & D_S \mu^2 - m_S & 0 & 0 \\ r_B \alpha_{BA} & k_{BS} & D_B \mu^2 - r_B & 0 \\ 0 & 0 & r_T & D_T \mu^2 - m_T \end{bmatrix} \quad (13)$$

390 where μ is a variable. The first eigenvalue of the moment generating matrix is $\lambda_1(\mu) = D_A \mu^2 +$

391 $r_A(1 - \alpha_{AB}) - \frac{k_{AT} r_T}{m_T}$, which is associated with an invasion speed $c^* = \inf_{\mu > 0} \frac{\lambda_1(\mu)}{\mu} = \frac{\lambda_1(\mu_1)}{\mu_1} =$

392 $2\sqrt{D_A r_A(1 - \alpha_{AB} - \frac{k_{AT} r_T}{r_A m_T})}$ with $\mu_1 = \sqrt{\frac{r_A(1 - \alpha_{AB} - \frac{k_{AT} r_T}{r_A m_T})}{D_A}}$. The first eigenvalue at $\mu = \mu_1$ has

393 a corresponding eigenvector:

$$\begin{bmatrix} \zeta_1 \\ \zeta_2 \\ \zeta_3 \\ \zeta_4 \end{bmatrix} \quad (14)$$

394 where

$$\zeta_1 = \frac{(\lambda_1(\mu_1) - D_S\mu_1^2 + m_S)(\lambda_1(\mu_1) - D_B\mu_1^2 + r_B)(\lambda_1(\mu_1) - D_T\mu_1^2 + m_T)}{r_S k_{BS} + r_B \alpha_{BA}(\lambda_1(\mu_1) - D_S\mu_1^2 + m_S)} \quad (15a)$$

$$\zeta_2 = \frac{r_S(\lambda_1(\mu_1) - D_B\mu_1^2 + r_B)(\lambda_1(\mu_1) - D_T\mu_1^2 + m_T)}{r_S k_{BS} + r_B \alpha_{BA}(\lambda_1(\mu_1) - D_S\mu_1^2 + m_S)} \quad (15b)$$

$$\zeta_3 = \lambda_1(\mu_1) - D_T\mu_1^2 + m_T \quad (15c)$$

$$\zeta_4 = r_T \quad (15d)$$

395 Linear determinacy equates the invasion speed for the nonlinear system in Eqn 12 with the invasion
 396 speed in the linearized system, as long as Eqn 12 is dominated by the linearized system in the
 397 direction determined by the above eigenvector³. Conditions for linear determinacy are then

$$\lambda_1(\mu_1) - D_S\mu_1^2 + m_S > 0 \quad (16a)$$

$$\lambda_1(\mu_1) - D_B\mu_1^2 + r_B > 0 \quad (16b)$$

$$\lambda_1(\mu_1) - D_T\mu_1^2 + m_T > 0 \quad (16c)$$

$$\zeta_3 \leq \min \left\{ \frac{r_A \zeta_1 - k_{AT} \zeta_4}{r_A \alpha_{AB}}, \frac{r_B \alpha_{BA} \zeta_1 + k_{BS} \zeta_2}{r_B} \right\} \quad (16d)$$

which are relevant for Eqns 1, 2 and 3. The conditions given in Eqn 16 ensure that the invasion speed of the nonlinear model (Eqn 12) is the above c^* .

APPENDIX II

Analytical approximation for the toxin wavefront of the invading taxon

Consider an invading taxon that is not strongly affected by the established taxon (or any toxin produced by the established taxon). This is equivalent to invasion in the absence of a competitor and Eqn 1 reduces to

$$\frac{\partial A}{\partial t} = D_A \frac{\partial^2 A}{\partial x^2} + r_A A(1 - A) \quad (17a)$$

$$\frac{\partial S}{\partial t} = D_S \frac{\partial^2 S}{\partial x^2} + r_S A - m_S S \quad (17b)$$

We nondimensionalize Eqn 17 by making the following substitutions:

$$\tau = r_A t \quad (18a) \quad \chi = x \sqrt{\frac{r_A}{D_A}} \quad (18d)$$

$$\rho = \frac{D_S}{D_A} \quad (18b) \quad \omega = \frac{m_S}{r_A} \quad (18e)$$

$$s = \frac{r_A}{r_S} S \quad (18c) \quad a = A \quad (18f)$$

which gives

$$\frac{\partial a}{\partial \tau} = \frac{\partial^2 a}{\partial \chi^2} + a(1 - a) \quad (19a)$$

$$\frac{\partial s}{\partial \tau} = \rho \frac{\partial^2 s}{\partial \chi^2} + A - \omega s \quad (19b)$$

408 Notice that Eqn 19a is Fisher's equation (also known as the Fisher-KPP equation), which has a
 409 constant invasion speed as a solution⁵⁹. By substituting $z = \chi - c\tau$ we shift to a moving reference
 410 frame, where c is the invasion speed. We assume that c also holds for the diffusing toxin and so

$$-c \frac{\partial a}{\partial z} = \frac{\partial^2 a}{\partial z^2} + a(1 - a) \quad (20a)$$

$$-c \frac{\partial s}{\partial z} = \rho \frac{\partial^2 s}{\partial z^2} + A - \omega s \quad (20b)$$

411 As Eqn 20a does not depend on Eqn 20b, an approximate solution follows directly by using a stan-
 412 dard approach for solving Fisher's equation. Substituting $Z = z/c$ in Eqn 20a gives

$$-\frac{\partial a}{\partial Z} = \varepsilon \frac{\partial^2 a}{\partial Z^2} + a(1 - a) \quad (21)$$

413 where $\varepsilon = 1/c^2$. Expanding a in powers of ε gives

$$a(Z, \varepsilon) = a_0(Z) + \varepsilon a_1(Z) + \varepsilon^2 a_2(Z) \dots \quad (22)$$

414 Substituting Eqn 22 into Eqn 21 and matching powers gives the zeroth order approximation as

$$-\frac{\partial a_0}{\partial Z} = a_0(1 - a_0) \quad (23)$$

415 and therefore

$$A \approx a_0 = \frac{1}{1 + e^Z} = \frac{1}{1 + e^{z/c}} \quad (24)$$

416 Substituting Eqn 24 in Eqn 20b gives

$$-c \frac{\partial s}{\partial z} = \rho \frac{\partial^2 s}{\partial z^2} + \frac{1}{1 + e^{z/c}} - \omega s \quad (25)$$

417 As we are interested in the case where the toxin diffuses ahead of the invader wavefront, we assume

418 $\rho \gg 1$. Substituting $\rho = 1/\varrho^2$ in Eqn 25 we obtain

$$-c \frac{\partial s}{\partial z} = \frac{1}{\varrho^2} \frac{\partial^2 s}{\partial z^2} + \frac{1}{1 + e^{z/c}} - \omega s \quad (26)$$

419 where $\varrho \ll 1$. Following Olsen *et al.*⁶¹, we can rescale z such that the domain of influence of the

420 toxin is invariant in a new ξ -domain, where $\xi = \varrho z$. Eqn 26 then becomes

$$-c\varrho \frac{\partial s}{\partial \xi} = \frac{\partial^2 s}{\partial \xi^2} + \frac{1}{1 + e^{\xi/\varrho c}} - \omega s \quad (27)$$

421 As $\varrho \ll 1$, Eqn 27 can be approximated as

$$\begin{aligned} 0 &\approx \frac{\partial^2 s}{\partial \xi^2} + 1 - \omega s & \text{for } \xi < 0 \\ 0 &\approx \frac{\partial^2 s}{\partial \xi^2} - \omega s & \text{for } \xi > 0 \end{aligned} \quad (28)$$

422 Solving Eqn 28 when assuming that $\lim_{\xi \rightarrow \infty} s(\xi) = 0$, $\lim_{\xi \rightarrow -\infty} s(\xi) = 1/\omega$ and $s(0) = 1/2\omega$ gives

$$\begin{aligned} s(\xi) &\approx -\frac{1}{2\omega} \left(e^{\sqrt{\omega}\xi} - 2 \right) & \text{for } \xi < 0 \\ s(\xi) &\approx \frac{1}{2\omega} e^{-\sqrt{\omega}\xi} & \text{for } \xi > 0 \end{aligned} \quad (29)$$

423 And rewriting Eqn 29 in terms of original parameters:

$$\begin{aligned}
S(z) &\approx -\frac{r_S}{2m_S} \left(e^{\sqrt{\frac{D_A m_S}{D_S r_A}} z} - 2 \right) & \text{for } z < 0 \\
S(z) &\approx \frac{r_S}{2m_S} e^{-\sqrt{\frac{D_A m_S}{D_S r_A}} z} & \text{for } z > 0
\end{aligned} \tag{30}$$

424 which is the shape of the toxin wavefront produced by the invading taxon in a moving reference
425 frame, assuming that the invader is not strongly inhibited by the established taxon.

426 ***Analytical approximation for the toxin wavefront of the established taxon***

427 Consider a retreating population of established taxon due to invasion by a competitor taxon. For the
428 special case that $\alpha_{BA} = 2$, $r_A = r_B$ and $D_A = D_B$, and assuming that the invader does not produce
429 a toxin and is not inhibited by the established population or its toxin, Eqn 1 reduces to

$$\frac{\partial A}{\partial t} = D_A \frac{\partial^2 A}{\partial x^2} + r_A A(1 - A) \tag{31a}$$

$$\frac{\partial B}{\partial t} = D_A \frac{\partial^2 B}{\partial x^2} + r_A B(1 - B - 2A) \tag{31b}$$

$$\frac{\partial T}{\partial t} = D_T \frac{\partial^2 T}{\partial x^2} + r_T B - m_T T \tag{31c}$$

430 We nondimensionalize Eqn 31 by making the following substitutions:

$$\tau = r_A t \quad (32a) \quad \chi = x \sqrt{\frac{r_A}{D_A}} \quad (32d)$$

$$\rho = \frac{D_T}{D_A} \quad (32b) \quad \omega = \frac{m_T}{r_A} \quad (32e)$$

$$y = \frac{r_A}{r_T} T \quad (32c) \quad a = A \quad (32f)$$

$$b = B \quad (32g)$$

which gives

$$\frac{\partial a}{\partial \tau} = \frac{\partial^2 a}{\partial \chi^2} + a(1 - a) \quad (33a)$$

$$\frac{\partial b}{\partial \tau} = \frac{\partial^2 b}{\partial \chi^2} + b(1 - b - 2a) \quad (33b)$$

$$\frac{\partial y}{\partial \tau} = \rho \frac{\partial^2 y}{\partial \chi^2} + B - \omega y \quad (33c)$$

As above, we substitute $z = \chi - c\tau$ to shift to a moving reference frame, where now c simultaneously represents the invasion speed, the retreating speed of the established population and the retreating speed of the toxin. This gives

$$-c \frac{\partial a}{\partial z} = \frac{\partial^2 a}{\partial z^2} + a(1 - a) \quad (34a)$$

$$-c \frac{\partial b}{\partial z} = \frac{\partial^2 b}{\partial z^2} + b(1 - b - 2a) \quad (34b)$$

$$-c \frac{\partial y}{\partial z} = \rho \frac{\partial^2 y}{\partial z^2} + B - \omega y \quad (34c)$$

Because we set $\alpha_{BA} = 2$, notice that a solution to Eqns 34a and 34b is $b = 1 - a$. This allows us to approximate the wavefront of the retreating, established population as

$$B \approx b_0 = 1 - \frac{1}{1 + e^{z/c}} \quad (35)$$

438 Substituting Eqn 35 in Eqn 34c gives

$$-c \frac{\partial y}{\partial z} = \frac{1}{\varrho^2} \frac{\partial^2 y}{\partial z^2} + 1 - \frac{1}{1 + e^{z/c}} - \omega y \quad (36)$$

439 As above, we rescale z such that the domain of influence of the toxin is invariant in the ξ -domain

440 and Eqn 36 becomes

$$-c\varrho \frac{\partial y}{\partial \xi} = \frac{\partial^2 y}{\partial \xi^2} + 1 - \frac{1}{1 + e^{\xi/\varrho c}} - \omega y \quad (37)$$

441 Again, we assume that the toxin diffuses much faster than either bacterial population (i.e., $\rho \gg 1$

442 and $\varrho \ll 1$) and so Eqn 37 can be approximated as

$$\begin{aligned} 0 &\approx \frac{\partial^2 y}{\partial \xi^2} - \omega y & \text{for } \xi < 0 \\ 0 &\approx \frac{\partial^2 y}{\partial \xi^2} + 1 - \omega y & \text{for } \xi > 0 \end{aligned} \quad (38)$$

443 Solving Eqn 38 and rewriting in terms of original parameters:

$$\begin{aligned} T(z) &\approx \frac{r_T}{2m_T} e^{-\sqrt{\frac{D_A m_T}{D_T r_A}} z} & \text{for } z < 0 \\ T(z) &\approx -\frac{r_T}{2m_T} \left(e^{\sqrt{\frac{D_A m_T}{D_T r_A}} z} - 2 \right) & \text{for } z > 0 \end{aligned} \quad (39)$$

444 which is the shape of the toxin wavefront produced by the established taxon in a moving refer-
 445 ence frame, assuming that the invader does not produce a toxin and is not strongly inhibited by the
 446 established taxon or its toxin. Unsurprisingly, Eqn 39 is the mirror opposite of Eqn 30.

447 **APPENDIX III**

448 **Analytical approximations for invasion speeds when the invading taxon produces a toxin**

449 The conventional approach to calculating invasion speeds (without toxin) is to convert a competitive
 450 system like Eqn 2 to a linear cooperative system. This is done using the substitution $B = B^\dagger -$
 451 δ , where $B^\dagger$ is the population density of the established taxon before the arrival of the invading
 452 population and δ is a small perturbation. This approach, however, is not as straightforward when the
 453 invading taxon produces a toxin with non-local effects.

454 Consider Eqn 2a. Substituting $B = B^\dagger - \delta$ and retaining only first order terms gives

$$\frac{\partial A}{\partial t} \approx D_A \frac{\partial^2 A}{\partial x^2} + r_A A (1 - \alpha_{AB} B^\dagger) \quad (40)$$

455 In a moving reference frame with invasion speed c , i.e., $z = x - ct$, Eqn 40 becomes

$$-c \frac{\partial A}{\partial z} \approx D_A \frac{\partial^2 A}{\partial z^2} + r_A A (1 - \alpha_{AB} B^\dagger) \quad (41)$$

456 Eqn 41 has exponential solutions $A = f(z) = e^{-\mu z}$ where $c\mu = D_A \mu^2 + r_A (1 - \alpha_{AB} B^\dagger)$. Solving
 457 for μ :

$$\mu = \frac{c \pm (c^2 - 4D_A r_A (1 - \alpha_{AB} B^\dagger))^{\frac{1}{2}}}{2D_A} \quad (42)$$

which is real if $c > c^* = 2\sqrt{D_A r_A (1 - \alpha_{AB} B^\dagger)}$. However, if $B^\dagger = 1$ then it is clear that we have linearized away the effect of the toxin. We therefore require a modified value for $B^\dagger$ which takes into account the negative effect of the toxin on the established taxon.

If we assume that the toxin is fast diffusing then $r_B \alpha_{BA} A \ll k_{BS} S$. With this assumption, Eqn 2c can be approximated as

$$\frac{\partial B}{\partial t} \approx D_B \frac{\partial^2 B}{\partial x^2} + r_B B(1 - B) - k_{BS} B S \quad (43)$$

If we assume that the killing rate of the toxin is large then $k_{BS} \gg 1$ and $D_B/k_{BS} \ll 1$; if we also assume that the growth rate of the established taxon is sufficiently fast to keep pace with killing due to the toxin then $r_B/k_{BS} \sim 1$. With these assumptions, Eqn 43 simplifies to

$$B = 1 - \frac{\kappa}{\sigma} S = 1 - \frac{k_{BS}}{r_B} S \quad (44)$$

which is an expression for the density of the established taxon for a given density of toxin. Let us assume that toxin density can be described by Eqn 30, even though this expression is only strictly correct in the case that the established taxon does not inhibit the invader. Clearly, $S = 0$ when $D_S = 0$, which suggests that in the limit $D_S \rightarrow 0$ the system exhibits only local competition. For this case, it is well known that the competitive strength of the invader has no influence on invasion

471 speed¹⁴, which is then given by the classic result:

$$c_0^* = 2\sqrt{D_A r_A (1 - \alpha_{AB})} \quad (45)$$

472 If, however, the toxin diffuses ahead of the invader wavefront, then we can assume that the population
 473 density of the established taxon is reduced by an amount commensurate with toxin density, which,
 474 in the limit of infinitely-fast toxin diffusion, is given by Eqn 30 with $D_S = \infty$, i.e.,

$$B_\infty^\dagger = 1 - \frac{k_{BS} r_S}{2m_S r_B} \quad (46)$$

475 For real solutions to μ in Eqn 42 with $B_\infty^\dagger$:

$$c_\infty^* = 2\sqrt{D_A r_A (1 - \alpha_{AB} (1 - \frac{k_{BS} r_S}{2m_S r_B}))} \quad \text{for } k_{BS} r_S < 2m_S r_B \quad (47a)$$

$$c_\infty^* = 2\sqrt{D_A r_A} \quad \text{for } k_{BS} r_S > 2m_S r_B \quad (47b)$$

476 where we have set $B^\dagger = 0$ for situations where the toxin kills sufficiently quickly that the established
 477 taxon is eradicated across the entire domain.

478 ***Analytical approximations for invasion speeds when the established taxon produces a toxin***

479 Consider Eqn 3. As in the previous section, we expand around $B = B^\dagger - \delta$, where $B^\dagger$ is the
 480 population density of the established taxon in the absence of the invader and δ is a small perturbation.

481 Retaining only first order terms in Eqn 3a gives

$$\frac{\partial A}{\partial t} \approx D_A \frac{\partial^2 A}{\partial x^2} + r_A A (1 - \alpha_{AB} B^\dagger) - k_{AT} A T \quad (48)$$

482 In the limit of slow toxin diffusion $D_T \rightarrow 0$, we similarly assume that $T = T^\dagger - \delta$ and Eqn 48
 483 becomes

$$\frac{\partial A}{\partial t} \approx D_A \frac{\partial^2 A}{\partial x^2} + r_A A(1 - \alpha_{AB} B^\dagger) - k_{AT} A T^\dagger \quad (49)$$

484 Eqn 49 has exponential solutions $A = f(z) = e^{-\mu z}$, which can be solved, as above, to give the
 485 invasion speed in the limit of no diffusion of toxin:

$$c_0^* = 2\sqrt{D_A r_A (1 - \alpha_{AB} - \frac{k_{AT} r_T}{r_A m_T})} \quad (50)$$

486 where we have set $B^\dagger = 1$ and $T^\dagger = \frac{r_T}{m_T}$ to reflect densities in the uninvaded system. In the limit of
 487 fast toxin diffusion $D_T \rightarrow \infty$, we assume $D_T = \infty$ in Eqn 39 and therefore substitute $T = \frac{r_T}{2m_T}$ into
 488 Eqn 48 to give

$$\frac{\partial A}{\partial t} \approx D_A \frac{\partial^2 A}{\partial x^2} + r_A A(1 - \alpha_{AB} B^\dagger) - k_{AT} A \frac{r_T}{2m_T} \quad (51)$$

489 The invasion speed in the limit of infinitely-fast toxin diffusion is then

$$c_\infty^* = 2\sqrt{D_A r_A (1 - \alpha_{AB} - \frac{k_{AT} r_T}{2r_A m_T})} \quad (52)$$

490 where we have set $B^\dagger = 1$.

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