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Models to examine containment and spread of genetically engineered microbes

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Abstract

Genetically engineered microbes (GEMs) have the potential to revolutionize agricultural techniques by facilitating crop protection and increased productivity. However, there has been widespread concern regarding the potential impact these microbes may have on the environment. Here we mathematically model the dynamics of GEMs in an agricultural setting, focusing on parameters that can be used to summarize the potential of modified microbes for persistence and spread. First developing a comprehensive model for the dynamics of GEMs which includes mobile and stationary classes of GEMs as well as competition from indigenous microflora, we then analyse a sequence of simplified mathematical models with a view to answering two fundamental questions: (1) will the GEMs spread (or invade), and if so how quickly? and (2) what are the best strategies for containing the spread of GEMs in a spatially varying environment?

Keywords: agriculture, competition, GEM, invasion, model, spread

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Introduction

Field trials of genetically engineered microbes (GEMs), are likely to be increasingly commonplace in the future because these organisms can provide useful services to farmers (Lindow *et al.* 1989). However, the enthusiasm regarding this new technology has been dampened by the legitimate warnings and admonishments of environmental groups and some professional societies (Tiedje *et al.* 1989). The question of environmental risk concerns both proliferation and spread of released organisms and the potential they have for disrupting the ecosystem and transferring genes to indigenous microbes. In this paper we focus on the microbial population growth and spread, rather than the actual introduced genetic element. Our logic is that if the microbe host does not spread and proliferate, the gene, as present in the GEM host, will be contained in space and time and the risk of gene transfer and ecosystem disruption will be lessened. Conversely, by exploring the prospects for rapid invasion by the microbe host, we can identify scenarios that are most likely to yield substantial gene transfer and ecosystem impact.

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Previous models of microbial population dynamics have tended to fall into two categories: (i) simplified phenomenological models which poorly represent the detail of microbial ecology but yield clearly understood results, and (ii) complex simulations that attend to numerous details, but do not lend themselves to predictions about general rates of invasion in terms of a few essential biological parameters. In this paper we introduce models tailored to reflect key details of microbe ecology and then analyse them with a view to understanding the role of measurable parameters on invasion rates.

The innovations we introduce to the standard theory are: subdividing GEMs into mobile and non-mobile classes and examining the consequences of heterogeneity in the environment. Using these models we determine the rate of spread and strategies that might contain GEMs. Quantitative answers will prove invaluable for assessing risks associated with release. Specifically, we want to determine biological parameters that exert the greatest influence on invasion of GEMS, and whether we can identify strategies for containment that are consistently better (or worse) than alternative strategies.

GEMs are typically different from wild-type microbes with respect to only one or more genes, which means that prior studies of natural microbes are pertinent to model

building for GEMs. Any dispersal/invasion model for a GEM has to include competition as this is an important aspect of microbial ecology. Two key attributes of micro-organisms are (i) sensitivity to the physical environment such that commonplace heterogeneity switches a population from a multiplying and growing phase to an exponential die-off phase, and (ii) compartmentalization of populations depending on whether microbes are suspended in groundwater, on plant surfaces, or in the rhizosphere.

Whereas a traditional ecological approach to modelling an invasion would simply emphasize the details of local competition (Okubo *et al.* 1990), the key to GEM invasions is also the environmental heterogeneity and division of populations into different compartments. If one is interested in either predicting or containing the spread of GEMs, this compartmentalization is especially important because it governs microbe movement. For example, microbes released in an agricultural setting may end up in at least eight distinct compartments, each with different transport or movement attributes (see Fig 1). These compartments are: aerosols, dust, plant surfaces, soil surface, subsurface soil, surface water, groundwater and the rhizosphere.

Microbes on leaf surfaces, soil surface, rhizosphere, or subsurface soil tend to be more sessile, whereas microbes in ground water or aerosol compartments may more easily disperse. Moreover, micro-organisms do not stay in these compartments but transfer between them at varying rates depending on rain (Constantinidou *et al.* 1990), dust

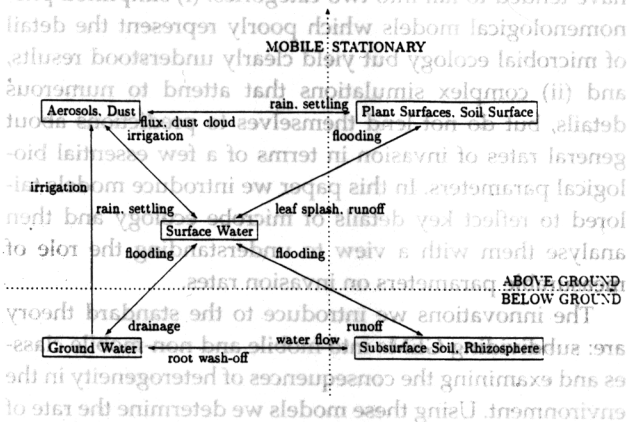

Fig. 1 Detailed model for microbes in an agricultural setting. The five main compartments are shown here in boxes: Aerosols and Dust, Plant Surfaces and Soil Surface, Surface Water, Ground Water, and Subsurface soil and Rhizosphere. Note that the Aerosols and Dust, Surface Water, and Ground Water compartments have movement within the compartment (mobile compartment), while the Plant Surfaces and Soil Surface, and Subsurface Soil and Rhizosphere compartments have no movement within the compartment (stationary compartments). Arrows between the boxes indicate the transfers between the compartments. The labels on the arrows indicate the transfer mechanisms.

clouds arising from wind and agricultural practices (Knudsen 1989), vertical temperature-dependent atmospheric fluxes (Lindemann *et al.* 1982; Lindemann & Upper 1985), removal from roots (Trevors *et al.* 1990; van Elsas *et al.* 1992), surface runoff, leaf splash (Walker & Patel 1964) flooding (van Elsas & Trevors 1991), and irrigation (Fig 1). Secondary transfer mechanisms may include lateral transfer along the leaf surface or soil by chewing insects and movement through the soil by roots (Trevors *et al.* 1990). While chemotactic migration probably occurs in soil, travel distances are likely limited to several centimeters (Bashan 1986). Typically, transport in these aerosol and groundwater mobile classes will have random and directed components, the random component arising from local mixing patterns in the air or water, and the directed component arising from a prevailing flow direction.

Some experimental data on the population biology of GEMs in soil is available (Trevors 1991a,b, 1992; van Elsas *et al.* 1988, 1991, 1992; Kareiva *et al.* 1995). Microcosm and green house studies provide some information on the relative competitive abilities of GEMs versus wild-type microbes, and help guide parameterization of the competition component of a model (England *et al.* 1993). For example, by using a maximum likelihood approach we have found that competition between wild-type *Pseudomonas syringas* and ice-minus *P. syringae* is well described by simple Lotka-Volterra equation (Kareiva *et al.* 1995; cf. Pascual & Kareiva 1995). Field experiments have also been performed using GEMs (Lindow & Panopoulos 1988; Lindow *et al.* 1988; Buttner & Amy 1989), and these experiments may allow statistical parameterization of invasion models just as the greenhouse experiments do for competition models. The ability to translate field and greenhouse experiments using GEMs to risk assessment models hinges on obtaining a simple model (with fewer parameters to estimate) that captures key biological features of the system.

Modelling GEM growth and spread

Our model includes two key processes: local population growth and transport via random motion and bulk convection. For local population growth we adopted simple Lotka-Volterra competition equations. Although these are not as mechanistic as resource uptake equations, they involve fewer parameters to estimate, exhibit similar qualitative behaviour, and can be shown to describe population growth data for the microbes often targeted for genetic engineering (e.g. *Pseudomonas syringae;* Kareiva *et al.* 1995).

Denoting N_w (x, t) to be the density of the wild strain and Ne (x, t) to be the density of the GEM strain, the equations are:

$$\frac{\partial N_w}{\partial t} = r_w N_w \left[1 - \frac{N_w}{K_w} - \frac{C_{ew} N_e}{K_w}\right] + \nabla \cdot (D_w \nabla N_w) - \nabla \cdot (\mathbf{F} N_w) \quad (1)$$

$$\frac{\partial N_e}{\partial t} = r_e N_e \left[1 - \frac{N_e}{K_e} - \frac{C_{we} N_w}{K_e}\right] + \nabla \cdot (D_e \nabla N_e) - \nabla \cdot (\mathbf{F} N_e), \quad (2)$$

Where **x** is the explicit spatial location, t is time, the six growth and competition parameters are given by:

r_w = intrinsic growth rate for wild strain;
r_e = intrinsic growth rate for GEM strain;
K_w = carrying capacity for wild strain;
K_e = carrying capacity for GEM strain;
C_{ew} = competition effect of GEM strain on wild strain;
C_{we} = competition effect of wild strain on GEM strain;

and the movement parameters are given by:

F = a vector describing the magnitude and direction of the bulk flow;
D_w = diffusion coefficient for the mobile wild strain;
D_e = diffusion coefficient for the mobile GEM strain.

With **F** and D constant, the flow and diffusion terms are given in one spatial dimension by:

$$\nabla \cdot (\mathbf{F} N) = \frac{\partial}{\partial x}(FN), \nabla \cdot (D \nabla N) = \frac{\partial}{\partial x}\left(D \frac{\partial N}{\partial x}\right)$$

and in two spatial dimensions by:

$$\nabla \cdot (\mathbf{F} N) = \frac{\partial}{\partial x} F_1 N + \frac{\partial}{\partial y} F_2 N, \; \nabla \cdot (D \nabla N) = \frac{\partial}{\partial x}\left(D \frac{\partial N}{\partial x}\right) + \frac{\partial}{\partial y}\left(D \frac{\partial N}{\partial y}\right).$$

Here the wild strain is the parental strain from which the GEM was engineered. Typically the competition is not limited merely to the two related strains of micro-organisms; in reality the micro-organisms will be competing for space and nutrients with other microflora, including fungi, even if these microflora do not share an identical ecological niche. In the model described in eqns 1–2, the effect of such competition can be incorporated into the intrinsic growth rates r_w and r_e. Similarly, the effect of predation by protozoa is missing from the model. Assuming a fairly constant density of protozoan grazers and a Holling type I functional response of the microbes to predation, we can incorporate the predation term into the intrinsic growth rate. The intrinsic growth rate for a strain is thus defined as the growth rate of that strain in the presence of predation and of competition from other microflora, but in the absence of density-dependent regulation by the strain itself or by the related strain. Our definition of intrinsic growth rate is as measured in the field, rather than the laboratory.

We include a third process in the model: transitions between sedentary and mobile 'pools' of microbes. Here microbes in the mobile pool do not actively disperse, but are spread passively via movement of wind and water. Because we consider transitions between mobile versus sedentary classes of microbes, we note that our state variables are: S_w (**x**, t) for density of sedentary wild-type microbes, M_w (**x**, t) for density of mobile wild-type microbes, S_e (**x**, t) for density of sedentary engineered microbes and M_e (**x**, t) for density of engineered mobile microbes. Thus N_w in 1–2 is replaced by S_w and M_w and N_e is replaced by S_e and M_e.

We assume that microbes in the stationary class do not move, but are subject to growth dynamics. Lastly, there is transfer between mobile and stationery classes. Putting standard Lotka–Volterra equations together with this within-strain transition between dispersal classes, we obtain:

$$\frac{\partial S_w}{\partial t} = r_w S_w \left[1 - \frac{S_w}{K_w} - \frac{C_{ew} S_e}{K_w}\right] + \Lambda_{ms} M_w - \Lambda_{sm} S_w \quad (3)$$

$$\frac{\partial S_e}{\partial t} = r_e S_e \left[1 - \frac{S_e}{K_e} - \frac{C_{we} S_w}{K_e}\right] + \Lambda_{ms} M_e - \Lambda_{sm} S_e \quad (4)$$

$$\frac{\partial M_w}{\partial t} = -\mu_w M_w - \Lambda_{ms} M_w + \Lambda_{sm} S_w + \nabla \cdot (D_w \nabla M_w) - \nabla \cdot (\mathbf{F} M_w) \quad (5)$$

$$\frac{\partial M_e}{\partial t} = -\mu_e M_e - \Lambda_{ms} M_e + \Lambda_{sm} S_e + \nabla \cdot (D_e \nabla M_e) - \nabla \cdot (\mathbf{F} M_e) \quad (6)$$

Where the four positive transfer and mortality parameters are given by:

μ_w = density independent mortality rate for the mobile wild strain;
μ_e = density independent mortality rate for the mobile GEM strain;
Λ_{ms} = transfer rate from mobile to stationary classes;
Λ_{sm} = transfer rate from stationary to mobile classes.

There are many ways of incorporating spatial heterogeneity into the model. One way of representing spatial heterogeneity is to imagine a field or patch inside which population growth rates are high (i.e. 'good' patches), and outside which population growth is reduced. To explore this complexity we consider an extension of eqns 1–2 that specifies variation of population growth and diffusion in space (i.e. as a function of position or **x**), but neglects the detail of separate mobile and sedentary categories of micro-organisms:

$$\frac{\partial N_w}{\partial t} = r_w N_w\left[G_w(\mathbf{x}) - \frac{N_w}{K_w} - \frac{C_{ew}N_e}{K_w}\right] + \nabla\cdot(D_w(\mathbf{x})\nabla N_w) - \nabla\cdot(\mathbf{F}N_w) \quad (7)$$

$$\frac{\partial N_e}{\partial t} = r_e N_e\left[G_e(\mathbf{x}) - \frac{N_e}{K_e} - \frac{C_{we}N_w}{K_e}\right] + \nabla\cdot(D_e(\mathbf{x})\nabla N_e) - \nabla\cdot(\mathbf{F}N_e) \quad (8)$$

where

$$G_w(\mathbf{x}) = \begin{cases} 1 & \text{in a good patch} \\ g_w \le 1 & \text{in a bad patch} \end{cases} \quad (9)$$

$$G_e(\mathbf{x}) = \begin{cases} 1 & \text{in a good patch} \\ g_e \le 1 & \text{in a bad patch} \end{cases} \quad (10)$$

$$D_w(\mathbf{x}) = \begin{cases} D_w^+ & \text{in a good patch} \\ D_w^- & \text{in a bad patch} \end{cases}$$

$$D_e(\mathbf{x}) = \begin{cases} D_e^+ & \text{in a good patch} \\ D_e^- & \text{in a bad patch} \end{cases}$$

We therefore have three models: eqns 1–2, 3–6 and 7–8, the first describing the simultaneous growth and dispersal of the microbe strains, the second including separate stationary and mobile classes, and the third describing growth and movement with spatially varying coefficients.

Mathematical results and biological implications

The models described in the previous section assume that the wild and engineered strains grow and compete continuously. The models do not include temporal variations in weather and field conditions, demographic or environmental stochasticity and age or stage-structuring of the microbe population. Thus they do not have the level of detail to accurately predict microbe densities long into the future. Rather, the purpose is to use the models to investigate how the chance of spread or the rate of spread can be understood in terms of environmental spatial variations and mobile-stationary transfer rates as well in terms of as more traditionally studied parameters such as growth rates, competitive differences between strains, and dispersal rates.

We ask the following specific questions:

1 Under what conditions can the GEM strain invade the environment, and under what conditions will there be a spatial wave of GEM spread that sweeps through a habitat driving the wild-type competitor to extinction?

2 How does the presence of separate stationary and mobile classes of each microbe strain change the spatial dynamics?

3 What effect does a spatially varying environment have on the spatial dynamics?

Mathematicians have investigated invasions using models such as eqns 1–2 by seeking what they call travelling wave solutions, and then quantifying the velocity of these waves. The idea is that the density of the invading strain will eventually achieve a characteristic wave-like profile that moves with some corresponding constant velocity. It is these spatial profiles and corresponding velocities that are mathematically referred to as travelling wave solutions and travelling wave velocities, respectively. By definition, the travelling wave solution moves with both a constant velocity and a constant profile as it sweeps across a given region. One nice feature of these travelling wave solutions is that their velocity provides a convenient summary of an organism's invasiveness – the higher its velocity the more invasive the organism.

Simple competition with advection and diffusion

Well established results already exist from analysis of invasion rates via travelling wave solutions to partial differential equation models. For example, in the absence of a competing strain ($N_w = 0$) and bulk flow ($\mathbf{F} = 0$), travelling wave solutions to eqn 2 exists with a characteristic invasion velocity of $2\sqrt{r_e D_e}$ (see, for example, Murray 1989).

When both competing strains are present, we consider first the simplest model describing the interactions between the strains eqns 1–2. As expected, in one dimension the bulk flow (convection) term $F\partial n/\partial x$ to the right-hand sides of eqns 1–2 merely shifts the entire solution at a velocity F. Employing the change of variables: $t^* = t$ and $x^* = x - Ft$, and dropping asterisks for notational simplicity, we regain eqns 1–2 without the convection term.

The question arises whether GEMs introduced to a field can invade spatially into a population of wild microbes that are initially at their carrying capacity. It turns out that the answer to this question is intimately tied to the relative strengths of the interstrain vs. intrastrain competitive effects on the GEM strain,

$$\gamma_e = C_{we}K_w/K_e, \quad (11)$$

and the ratio of interstrain vs. intrastrain competitive effects on the wild strain

$$\gamma_w = C_{ew}K_e/K_w. \quad (12)$$

Consequently three possible outcomes pertain:

1 Competitive coexistence ($\gamma_e < 1$, $\gamma_w < 1$). In this case an invasion by the GEM will always occur. It can be shown the speed that this invasion eventually achieves (denoted by c) lies in the following interval:

$$2\sqrt{r_e D_e(1-\gamma_e)} \le c \le 2\sqrt{r_e D_e} \quad (13)$$

(Bramson 1988). The upper bound is the speed the invasion would achieve if the wild strain N_w were completely absent and thus no interstrain competition, and the lower bound is the speed the invasion would achieve if the

density of the competing wild strain were held fixed at its carrying capacity $N_w = K_w$ and not allowed to vary.

2 Competitive exclusion, dependent upon initial conditions ($\gamma_e > 1$, $\gamma_w > 1$). See, for example, Murray (1989) for analysis of this situation in the absence of any spatial transport terms. It has been proven that travelling wave solutions, describing the invasion of one strain and corresponding extinction of the other, do exist (Conley & Gardner 1989). Two questions remain unanswered, however: (i) which of the two strains (GEM or wild) will invade? (ii) if the GEM has the potential to invade, precisely how large an area need be inoculated and at what GEM density in order to initiate the invasion? All other things being equal, the competitor with the highest growth rate (r_e or r_w) and/or strongest competition coefficient (C_{ew} or C_{we}) will likely be the successful invader. In this case, a necessary condition for invasion by the GEM would be that it is introduced at a high enough cell density to be in the region of stability where the GEM strain dominates and the wild strain becomes extinct or approaches extinction.

3 In competitive exclusion, a given strain always wins, regardless of initial densities ($\gamma_e > 1$ and $\gamma_w < 1$) or ($\gamma_e < 1$ and $\gamma_w > 1$). Numerical simulations indicate travelling waves correspond to an invasion by the superior competitor (Okubo *et al.* 1990). In a special case, where the competing strains are closely related, the invasion speed can be calculated (Okubo *et al.* 1990). This case is

$$r_e = r_w = r,\ D_e = D_w = D,\ \gamma_w + \gamma_e = 2. \tag{14}$$

The last constraint ($\gamma_w + \gamma_e = 2$) is satisfied approximately when one strain is a slightly better competitor. We consider the case where it is the GEM that is slightly competitively superior (see Appendix for further discussion of this). Then if eqn 14 is satisfied the spread rate for GEMs is

$$2\sqrt{(1-\gamma_e)rD}. \tag{15}$$

The case where the parent strain is the superior competitor is analogous except that the parent strain now invades, driving the GEM strain extinct. Note that as the two strains become identical competitors the invasion stalls.

Simple competition with mobile and sedentary classes

The results we have discussed so far are in keeping with our biological intuition and do not shed new light on the invasion process. However, the addition of mobile and sedentary classes leads to less transparent results. The general formula for calculating invasion rates for eqns 3–6 is quite complex (see Appendix). When the GEM is the superior competitor but the strains are otherwise identical the invasion rate is given in nondimensional terms in the Appendix by eqn 40. Even so, if we focus on the case with the mortality rate in the dispersing class equal to zero, and transfer rates Λ_{ms} and Λ_{sm} equal, the speed of invasion is much simplified eqn 41 and is given in dimensional terms as precisely half that of eqn 15.

However the calculation in expression 15 assumed that reproduction and dispersal occur in the same class. The result of dividing the population into equally balanced mobile and sedentary classes is the effective halving the growth rate r and diffusion coefficient D; any individual microbe will spend about half of its time in each of the mobile and sedentary classes. Thus having r and D in 15 we effectively halve the resulting speed.

Using methods similar to those previously used by Lewis & Schmitz (unpublished data) it can be proved that when Λ_{ms} and Λ_{sm} are not balanced the invasion rate slows significantly. In other words, whenever the transfer rates differ markedly, one or the other categories can become a bottleneck to invasion. For example, if $\Lambda_{sm} \gg \Lambda_{ms}$ in eqns 3–6, then micro-organisms will accumulate in the mobile class which may disperse readily, but does not multiply. Conversely, when $\Lambda_{ms} \gg \Lambda_{sm}$ micro-organisms will accumulate in the sedentary class which will multiply but not disperse readily. For an invasion to succeed both growth and dispersal are necessary. This trade-off between dispersal and mortality is shown in Fig. 2, which also indicates the interesting feature that even the tiniest transfer between sedentary to mobile classes accelerates invasion velocity.

Surprisingly, whereas decoupling of mobile and stationary classes will prevent an invasion, an infinitesimal coupling (Λ_{sm} and Λ_{ms} very small) results in invasion at a significant rate.

Since the case with strong balanced links between mobile and sedentary classes represents the situation with the greatest invasion velocities, we can develop a 'worst-case scenario' model. Specifically, if we assume $\Lambda_{sm} \to \infty$, $\Lambda_{ms} \to \infty$ and $\rho = \Lambda_{sm}/\Lambda_{ms}$ and that the strains are identical except for their abilities to compete, we obtain the following model:

$$(1+\rho)\frac{\partial S_w}{\partial t} = rS_w\left[1 - \frac{\rho\mu}{r}\frac{S_w}{K} - \frac{C_{ew}S_e}{K}\right] + \rho D\frac{\partial^2 S_w}{\partial x^2} \tag{16}$$

$$(1+\rho)\frac{\partial S_e}{\partial t} = rS_e\left[1 - \frac{\rho\mu}{r}\frac{S_e}{K} - \frac{C_{we}S_w}{K}\right] + \rho D\frac{\partial^2 S_e}{\partial x^2} \tag{17}$$

Using eqn 15 we see that analysis of the case where the GEM is the slightly better competitor gives the spread rate for the GEMs as

$$\frac{2\left[D(1-C_{we})(r-\mu\rho)\rho\right]^{1/2}}{1+\rho} \tag{18}$$

While analysis of the case where the wild population is the slightly better competitor gives an identical formula for

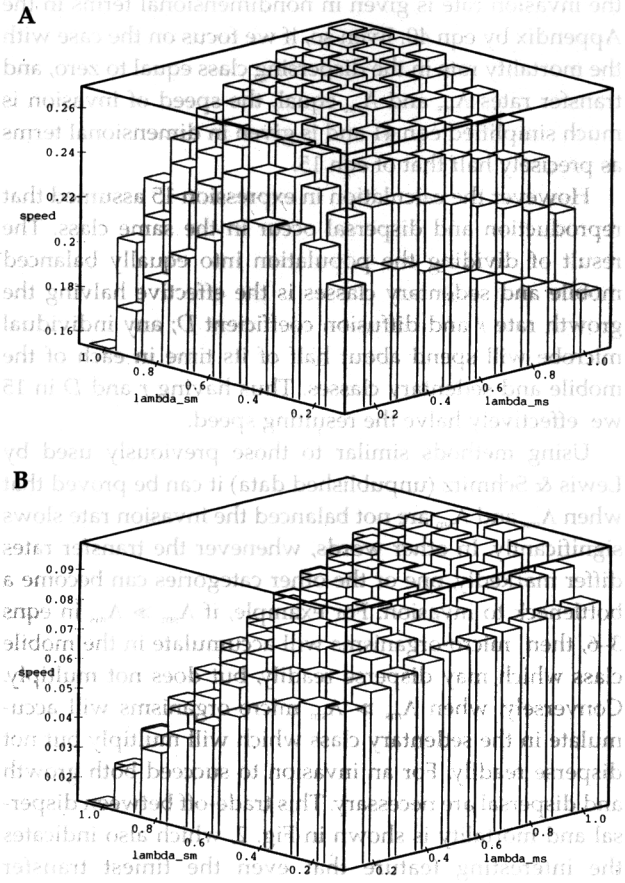

Fig. 2 Speed of invasion for eqns. 3–6 as a function of transfer rates. the wave speed shown here is valid for the following class of problems: $r_e = r_w = r$, $D_e = D_w = D$, $\gamma_e = 0.9$, γ_w 1.1, $\mathbf{F} = \mathbf{0}$, $\lambda_{sm} = \Lambda_{sm}/r$ and $\lambda_{ms} = \Lambda_{ms}/r$. The mortality rates are given by (a) $\mu_w/r = \mu_e/r = \mu = 3.0$ and (b) $\mu_w/r = \mu_e/r = \mu = 3.0$. The nondimensionalization process given in the Appendix shows that, because the diffusion coefficient D and the intrinsic growth rate r are not specified, the wave speed is scaled by $1/\sqrt{Dr}$ and is thus a dimensionless function of D and r. The values given for γ_e and γ_w indicate that the engineered microbe is a slightly better competitor than the wild-type. The microbes are otherwise indistinguishable. The values given for μ indicate that in (a) microbes in the mobile class die at 30% of the rate that they grow in the stationary class and in (b) microbes in the mobile class die at three times the rate that they grow in the stationary class. For these mortality and competition rates, and for any r and D, we can then choose scaled transfer rates λ_{sm} and λ_{ms} and read off the dimensionless speed as the height of the surface. We then multiply this speed by $\sqrt{Dr}$ to get the invasion speed in dimensional units. The method of calculating surface depicting wave speed is given in detail in the Appendix.

the spread rate of the wild population, but with C_{we} replaced by C_{ew}. This formula also indicates that, for a strongly linked system, a necessary condition for spread is $r > \mu\rho$; in other words the growth rate in the stationary class must dominate the mortality rate in the mobile class.

The worst or speediest invasion occurs when ρ is given by the Λ_{sm} and Λ_{ms} that satisfy

$$\Lambda_{sm} = \frac{\Lambda_{ms}}{1+2\mu/r}. \tag{19}$$

In this case the invasion speed eqn 18 is

$$\left[\frac{rD(1-C_{we})}{1+\frac{\mu}{r}}\right]^{1/2} \tag{20}$$

Note that as the mortality in the mobile class μ also approaches zero, the above speed eqn 20 approaches exactly half the speed given in eqn 15 with $K_e = K_w = K$.

Simple competition and a heterogeneous environment

Finally our spatially heterogenous model comprising alternating 'good' and 'bad' patches is used to examine containment strategies. This model was analysed in detail by Cruywagen *et al.* (1995). Here we simply apply the results of the analysis. For example, we can ask whether surrounding an agricultural field that has been inoculated by GEMs with a hostile environment is likely to contain the spread of the released GEMs. In this case it can be shown that the final result depends does not depend on the diffusion coefficients D_e and D_w, but depends critically upon the following dimensionless parameters: the ratio of interstrain vs. intrastrain competitive effects on the GEM strain γ_e (eqn 11), the ratio of interstrain vs. intrastrain competitive effects on the wild strain, γ_w (eqn 12), the proportional change in the growth rate of the GEM strain in the bad patch g_e (eqn 10), the proportional change in growth rate on the wild strain in the bad patch g_w (eqn 9), and the ratio of lengths of good and bad patches l_1/l_2.

In each of the patches considered separately we have the cases of (i) coexistence, (ii) GEM strain wins, (iii) wild strain wins, and (iv) winner determined by the initial conditions. As described in the previous section, these outcomes depend on the sizes of γ_e and γ_w compared to unity (good patch) or compared to g_w g_e or its inverse (bad patch).

However, when patches are juxtapositioned, with the possibility of fluxes of microbes between the patches, the case is complicated considerably because it is possible that microbes in one patch can invade adjacent patches and consequently the relative sizes of the good and bad patches are now involved. In this case the absolute values of g_w and g_e are important. In cases (i) to (iii) above the approximate for the wild type to invade from one patch to the ajacent patch where GEMs would otherwise dominate is

$$(1-\gamma_w)l_1 + (g_w - g_e\gamma_w)l_2 > 0, \tag{21}$$

and the approximate condition for the GEM to invade

from one patch to the adjacent patch where the wild type would otherwise dominate is

$$(1-\gamma_e)l_1 + (g_e - g_w\gamma_e)l_2 > 0, \quad (22)$$

where the good patch has length l_1 and the bad patch has length l_2 (Cruywagen *et al.* 1995) In the case where is competitive exclusion depending upon initial conditions in either or both patches, spread depends sensitively on the initial levels of microbes in each patch there is apparently no simple formula for predicting the outcome.

Even in the face of such complex results as given above, we can still propose strategies for the complete containment of GEMs so that they are eventually driven extinct everywhere: (i) be certain that the wild strain is the superior competitor in both patch types $C_{we} K_w/K_e < \min\{1, g_e/g_w\}$ and $C_{we} K_e/K_w < \min\{1, g_w/g_e\}$, and (ii) if the GEM is the superior competitor in the good patch, then make sure that these good patches are sufficiently small and that the GEM is at a competitive disadvantage in adjacent bad patches of sufficient size, thereby satisfying eqn 21. Lastly, if a field is surrounded by bad habitat designed to contain the spread of the GEM, it is crucial to evaluate the affect of this habitat on the wild strains; a drastic reduction in the growth rates of these competing strains may render such a containment strategy ineffective.

The extinction of GEMs everywhere may not be an optimal strategy if the GEM is to be used effectively in the good patch. The more interesting case where the GEM persists in a good patch, but is driven extinct in surrounding bad patches is addressed in the Discussion.

Discussion

Our approach has been to modify explicit spatial spread models to reflect microbe biology. An alternative approach would be to drop the explicit space dependence and use metapopulation models (see, for example, Hanski & Gyllenburg 1993; Nee & May 1992). Such models are admirably suited to evaluate persistence questions. By way of contrast, we have opted for explicitly spatial models so as to be able to evaluate the critical parameters controlling the spatial spread of GEMs.

One result has arisen that we would have never predicted without the model: so long as there is any transfer at all between mobile and stationary classes of microbes the velocity of invasive speed can be substantial. Since the majority of some microbial populations are closely associated with plant roots or possibly sedentary, one might guess that extremely infrequent dispersal would have negligible effect. Our analyses show just the opposite.

We have also provided formulas for (i) estimating the rate of spread of a competitively superior GEM, based on its competitive edge over wild strains, transfer rates, growth rates and its diffusion coefficient (eqns 15, 18 and 40); and (ii) determining whether a 'bad' patch is sufficiently large to stem the spread of GEMs from adjacent 'good' patches (inequalities 21 and 22). The simplicity of our models precludes putting exact confidence intervals about these formulas. With the best possible data, we expect the formulas will do no more than predict orders of magnitude for spread rates or required patch sizes. The models nonetheless give a clear indication of how each of the following parameters effect spread of GEMs: mobile stationary and stationary–mobile transfer rates, the scales of 'good' and 'bad' patches, mean squared displacements of individuals per unit time (diffusion coefficient), intrinsic growth rates and inter and intraspecific competition. More complex future models may make improvements.

One way of evaluating the potential use of GEMs in an agricultural setting is based on the ability to maintain them at high densities in some regions while preventing their spread into surrounding areas. In view of this, the optimal arrangement is for the wild strain to win in the bad patch and for the GEM to win or coexist with the wild strain in the good patch. This would require that

$$1 > \gamma_e > g_e/g_w, \quad \gamma_n < g_w/g_e \quad (23)$$

(wild type wins in isolated bad patch, and GEM wins or coexists in isolated good patch) and that inequality 22 is violated so that

$$\frac{l_2}{l_1} > \frac{1-\gamma_e}{g_w\gamma_e - g_e} \quad (24)$$

Both the numerator and denominator of the right hand side are positive, so this would simply require that the size of the bad patch l_2 is sufficiently large. Inequality 23 would be satisfied if the strains typically coexisted, but the growth rate of the GEM g_e was reduced in the bad patch.

The presence of a chemically controlled suicide gene in the GEM (see, for example, Molin *et al.* 1993) could precisely facilitate the reduction in growth rate. The good patch would then be the agricultural field with the suicide gene inhibited, and the bad patch would be the a surrounding area with the suicide gene turned on. Then if the suicide gene caused a p per cent reduction in the growth rate of the GEM in the bad patch, formula 24 with $g_e = 1 - p$ and $g_w = 1$ would give a simple estimate for the width of the hostile zone l_2 needed to stem the GEM.

If GEMs do eventually spread out of the target area, the key question then is the rate at which spread occurs. For example, GEMs that take longer than a single season to substantially spread from an agricultural field will then be subjected to crop changes and yearly weather changes. Our mathematical formula for spread rates indicates that when the wild and GEM strains are almost equal competitors, spread rates can be arbitrarily slow. In this case we

should look to other variables to determine whether the GEMs will spread substantially. In this manner the speed calculated from eqn 40 can be used to predict whether within-season spread is significant.

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Appendix

Wave speed calculation for competition with mobile and sedentary classes

Equations 3–6, in the absence of convective transport take the form

$$\left.\begin{aligned}\frac{\partial S_w}{\partial t} &= r_w S_w\left[1-\frac{S_w}{K_w}-\frac{C_{ew}S_e}{K_w}\right]+\Lambda_{ms}M_w-\Lambda_{sm}S_w\\ \frac{\partial S_e}{\partial t} &= r_e S_e\left[1-\frac{S_e}{K_e}-\frac{C_{we}S_w}{K_e}\right]+\Lambda_{ms}M_e-\Lambda_{sm}S_e\\ \frac{\partial M_w}{\partial t} &= -\mu_w M_w-\Lambda_{ms}M_w+\Lambda_{sm}S_w+D_w\nabla^2 M_w\\ \frac{\partial M_e}{\partial t} &= -\mu_e M_e-\Lambda_{ms}M_e+\Lambda_{sm}S_e+D_e\nabla^2 M_e\end{aligned}\right\} \quad (25)$$

This system models microbe growth, death, competition and movement.

We consider here the one-dimensional case. To simplify analysis and facilitate the assessment of relative importance of model parameters, we nondimensionalize eqn 25 making the following substitutions:

$$x^* = x\left(\frac{r_w}{D_w}\right)^{\frac{1}{2}}, t^* = r_w t, s_w = S_w/K_w, S_e = S_e/K_e$$

$$m_w = M_w/K_w, m_e = M_e/K_e, \lambda_{ms} = \frac{\Lambda_{ms}}{r_w}, \lambda_{sm} = \frac{\Lambda_{sm}}{r_w}, r = \frac{r_e}{r_w}, \delta = \frac{D_e}{D_w},$$

$$\gamma_w = \frac{C_{ew}K_e}{K_w}, \gamma_e = \frac{C_{we}K_w}{K_e}, \mu^*_w = \frac{\mu_w}{r_w}, \mu^*_e = \frac{\mu_e}{r_w}.$$

Dropping the asterisks for notational simplicity, the following system of nondimensional equations is obtained:

$$\left.\begin{aligned}\frac{\partial s_w}{\partial t} &= s_w\left(1-s_w-\gamma_w s_e\right)+\lambda_{ms}m_w-\lambda_{sm}s_w\\ \frac{\partial s_e}{\partial t} &= rs_e\left(1-s_e-\gamma_e s_w\right)+\lambda_{ms}m_e-\lambda_{sm}s_e\\ \frac{\partial m_w}{\partial t} &= -\mu_w m_w-\lambda_{ms}m_w+\lambda_{sm}s_w+\frac{\partial^2 m_w}{\partial x^2}\\ \frac{\partial m_e}{\partial t} &= -\mu_e m_e-\lambda_{ms}m_e+\lambda_{sm}s_e+\partial\frac{\partial^2 m_e}{\partial x^2}\end{aligned}\right\} \quad (26)$$

We now investigate the rate at which a genetically engineered strain with superior ability to withstand competition invades spatially into an environment that contains the wild strain. Mathematically, an invasion will be seen as a travelling wave solution to the system of partial differential eqns 26. The competitive edge of the genetically engineered microbes over the wild strain is expressed mathematically by assuming that $\gamma_w > 1$ and $\gamma_e < 1$. In this manner, the effective growth rate of s_e is reduced less by s_w than is the effective growth rate of s_w by s_e. To analyse competition alone, it is assumed that the wild and genetically engineered strains are identical in all other respects. For example, in the ice nucleation activity deficient mutants, it has been shown experimentally that this assumption is valid (Lindemann & Suslow 1987). Thus, to illustrate this effect we assume $r = 1$, $\delta = 1$, and $\mu_w = \mu_e = \mu$.

Experiments have shown that the competition coefficients are also expected to be very similar (Lindemann & Suslow 1987). A very slight competitive advantage for the genetically engineered microbes means, in terms of the original dimensional equations, that the growth rate for S_w is reduced less by competition than the growth rate for S_e. This can arise in two possible ways: (1) the carrying capacity for GEMs is slightly higher than the carrying capacity for wild microbes ($K_e/K_w = 1+\varepsilon$, $0 < \varepsilon \ll 1$) or (2) the interspecific competition coefficient C_{we} is slightly larger than the interspecific competition coefficient C_{ew} e.g. $C_{we} = 1-\varepsilon$, $0 < \varepsilon \ll 1$ and $C_{ew} = 1+\varepsilon$). In either case we have that $\gamma_w > 1$, $\gamma_e < 1$, but $\gamma_w + \gamma_e = 2$ to $\mathcal{O}(\varepsilon^2)$.

Thus equation 26 is given to $\mathcal{O}(\varepsilon^2)$ as

$$\left.\begin{aligned}\frac{\partial s_w}{\partial t} &= s_w\left[1-s_w-(2-\gamma_e)s_e\right]+\lambda_{ms}m_w-\lambda_{sm}s_w\\ \frac{\partial s_e}{\partial t} &= s_e\left(1-s_e-\gamma_e s_w\right)+\lambda_{ms}m_e-\lambda_{sm}s_e\\ \frac{\partial m_w}{\partial t} &= -\mu m_w-\lambda_{ms}m_w+\lambda_{sm}s_w+\frac{\partial^2 m_w}{\partial x^2}\\ \frac{\partial m_e}{\partial t} &= -\mu m_e-\lambda_{ms}m_e+\lambda_{sm}s_e+\frac{\partial^2 m_e}{\partial x^2}\end{aligned}\right\} \quad (27)$$

The spatially independent version of eqn 27 has the following equilibrium points:

Equilibrium Point:

$$\begin{aligned}\text{A} &= (0,0,0,0)\\ \text{B} &= (0,\bar{w},0,\bar{z})\\ \text{C} &= (\bar{w},0,\bar{z},0)\\ \text{D} &= \left[\frac{\bar{w}(1-\gamma_w)}{1-\gamma_w\gamma_e},\frac{\bar{w}(1-\gamma_e)}{1-\gamma_w\gamma_e},\frac{\bar{z}(1-\gamma_w)}{1-\gamma_w\gamma_e},\frac{\bar{z}(1-\gamma_e)}{1-\gamma_w\gamma_e}\right]\end{aligned}$$

where

$$\bar{w} = \frac{\mu(1-\lambda_{sm})+\lambda_{ms}}{\mu+\lambda_{ms}} \quad (28)$$

and

$$\bar{z} = \frac{\lambda_{sm}}{\mu+\lambda_{ms}}\bar{w}. \quad (29)$$

Point A represents a solution in which all the species are extinct. At Point C, the genetically engineered microbes are extinct and the wild microbes are endemic. At Point B, the genetically engineered are endemic and the wild type is extinct, and at Point D, the genetically engi-

neered and wild type coexist.

We make the biologically plausible assumption that the transfer rate, Λ_{sm}, between the stationary and mobile pools, is less than the intrinsic growth rate, r_w. Then, because $\lambda_{sm} = \Lambda_{sm}/r_w$, we have $\lambda_{sm} < 1$ and thus $\bar{w}$ and $\bar{z}$ are positive equilibrium points. Point D cannot be positive because $1 - \gamma_w$ and $1 - \gamma_e$ have opposite signs and the denominator is the same for each co-ordinate. We conclude that the biologically realistic equilibrium points are Point A, Point B and Point C, Point A representing the extinction of both strains.

We now consider a travelling wave solution joining equilibrium Point C, $(\bar{w}, 0, \bar{z}, 0)$, to equilibrium Point B, $(0, \bar{w}, 0, \bar{z})$. These points are chosen because they indicate populations before and after an invasion of genetically engineered microbes. Before genetically engineered microbes are introduced, the native species will have a stable population $\bar{w}$ and $\bar{z}$ for the stationary and mobile classes respectively (Point C). If an invasion occurs, and the genetically engineered microbes drive the native species to extinction, the genetically engineered microbes will have a stable population $\bar{w}$ and $\bar{z}$, which corresponds to equilibrium Point B. Thus, the biology behind the model indicates we should look for travelling wave solutions whose trajectory connects equilibrium Point C and equilibrium Point B. Furthermore, these two points lie on the manifold

$$s_w + s_e = \bar{w}, \quad m_w + m_e = \bar{z}. \tag{30}$$

We now show that a travelling wave solution to eqn 27 must satisfy eqn 30. To investigate the stability of the manifold eqn 30 we define

$$w(x,t) = s_w(x,t) + s_e(x,t) \tag{31}$$

and

$$z(x,t) = m_w(x,t) + m_e(x,t). \tag{32}$$

We add the first and second equation of eqn 27, and the third and fourth equations to get the reduced system

$$\left.\begin{aligned} \frac{\partial w}{\partial t} &= w(1-w) + \lambda_{ms} z - \lambda_{sm} w \\ \frac{\partial z}{\partial t} &= -\mu z - \lambda_{ms} z + \lambda_{sm} w + \frac{\partial^2 z}{\partial x^2} \end{aligned}\right\} \tag{33}$$

The variables w and z now represent the total number of microbes, both genetically engineered and wild, in the stationary pool and the mobile pool, respectively. This system has spatially homogeneous steady-state solutions (0,0) and $(\bar{w}, \bar{z})$. Using contracting rectangle arguments (Smoller 1982) it can be shown that $(\bar{w}, \bar{z})$ is a globally stable equilibrium point for eqn 33 (Schmitz 1993). Thus, a travelling wave solution connecting Point C and Point B that is valid for all $t > 0$ must satisfy eqn 30. In other words, solutions that are not identically zero approach eqn 30 uniformly in x for large t. This allows us to reduce the system eqn 27 to a system of two differential equations in S_w and m_w only and to look for travelling wave solutions, which correspond to invasions of the genetically engineered microbes.

We thus choose t sufficiently large so that we can make the simplification

$$s_w = \bar{w} - s_e \tag{34}$$

and

$$m_w = \bar{z} - m_e \tag{35}$$

Substituting into eqn 27 we obtain a system of equations with only population densities of the genetically engineered microbes as dependent variable:

$$\left.\begin{aligned} \frac{\partial s_e}{\partial t} &= s_e\left[1 - s_e - \gamma_e(\bar{w} - s_e)\right] + \lambda_{ms} m_e - \lambda_{sm} s_e \\ \frac{\partial m_e}{\partial t} &= -\mu m_e - \lambda_{ms} m_e - \lambda_{sm} s_e + \frac{\partial^2 m_e}{\partial x^2}. \end{aligned}\right\} \tag{36}$$

The fact that $\bar{w} < 1$ (eqn 28) and $\gamma_e < 1$ means that eqn 36 describes logistic growth in the stationary state and switching between stationary state and a mobile state. See Lewis & Schmitz (1995) for analysis of a similar system.

We now look for a solution representing a wave of genetically engineered microbes invading space previously occupied by wild microbes. This is given by a travelling wave solution moving at a constand speed, c, and with a constant profile:

$$(s_e, m_e)(x,t) = (S,M)(x - ct) = (S,M)(z). \tag{37}$$

Thus the solution is assumed to move with velocity c in the positive x direction. In the new co-ordinate, the system of partial differential equations 36 becomes a system of autonomous ordinary differential equations.

$$\left.\begin{aligned} -cS' &= -S^2(1-\gamma_e) + S(1 - \gamma_e\bar{w} - \lambda_{sm}) + \lambda_{sm} M \\ -cM' &= -\mu M - \lambda_{ms} M + \lambda_{sm} S + M'' \end{aligned}\right\} \tag{38}$$

where prime denotes differentiation with respect to z.

Because s_e and m_e represent population densities, we seek nonnegative travelling wave solutions S and M joining (0,0) ahead of the wave to $(\bar{w}, \bar{z})$ behind the wave. The appropriate boundary conditions are

$$\left.\begin{aligned} S(-\infty)&=\overline{w}, \quad M(-\infty)=\overline{z},\\ S(\infty) &= 0, \quad M(\infty)=0. \end{aligned}\right\} \tag{39}$$

Here $S(-\infty)$ means $\lim_{a\to\infty} S(a)$, etc.

Calculation of the travelling wave speed for a very closely related model is given in Lewis & Schmitz (1995). Reapplying their approach of linearizing about the leading edge of the travelling wave and constraining the solution to be nonnegative it can be shown that the expected travelling wave speed is given by the larger of the two real positive solutions to

$$R(c)=D_3c^6+D_2c^4+D_1c^2+D_0=0 \tag{40}$$

where

$$\begin{aligned} D_3 &= -4(\lambda_{sm}\lambda_{ms}+k_1k_2)-(k_2-k_1)^2\\ D_2 &= 6(\lambda_{sm}\lambda_{ms}+k_1k_2)(k_2-3k_1)\\ &\quad +2(k_2-k_1)^2(k_2-2k_1)\\ D_1 &= 6k_2(\lambda_{sm}\lambda_{ms}+k_1k_2)(k_2-3k_1)\\ &\quad -k_2^2(k_2-k_1)^2+27(\lambda_{sm}\lambda_{ms}+k_1k_2)^2\\ D_0 &= -4(\lambda_{sm}\lambda_{ms}+k_1k_2)k_2^3. \end{aligned}$$

and

$$k_1=(\mu+\lambda_{ms})$$
$$k_2=1-\gamma_e\overline{w}-\lambda_{sm}.$$

(see also Schmitz 1993). This is the method we use for calculating the wave speed in Fig 2. When the mortality rate $\mu = 0$ and the transfer rates λ_{sm} and λ_{ms} are identical the algebra is much simpler and the valid solution to eqn. 40 is given by

$$c=\sqrt{1-\gamma_e}. \tag{41}$$

This work is the result of interdisciplinary collaboration between two mathematicians (Mark Lewis and Greg Schmitz), a theoretical ecologist (Peter Kareiva) and a microbial ecologist (Jack Trevors), aiming to understand the fundamental processes that control the spread of GEMs in a field setting. The study was initiated when Mark Lewis was a postdoctoral research fellow working with Peter Kareiva at the University of Washington. A key interest of Mark Lewis is the realistic modelling of movement and spatial spread of organisms. Under his supervision graduate student Greg Schmitz developed and analysed a model for GEM growth, competition and movement. Peter Kareiva's research involves a mix of theory and field experiment in the modelling spatial processes in ecology. Jack Trevors research includes environmental risk assessment for GEMs and the survival, respiration and movement of GEMs in soil.
