PhD Project Proposal

Modelling Biological Control

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Abstract

Commonly-used techniques for controlling crop diseases, including fungicides and crop rotation, have ecological, economic and environmental disadvantages. Experimentalists have therefore become more interested in biological control, where an antagonist (a natural enemy of the pathogen) is deployed to reduce disease. However, whilst experimentation has elucidated the physiological basis of a number of host-pathogen-antagonist interactions, mathematical models are less well developed and the performance of biological control is beset by variability. This project addresses this, using mathematical models to determine how the efficacy of biological control could be improved, and how biological control should be deployed effectively.

1 Motivation and aims

Global food security concerns are likely to remain prominent for at least the next fifty years, as population growth and climate change increase pressures on food production [29]. With an estimated fourteen percent of world crops lost to disease [1], detailed study of plant epidemiology is vital from both an economic and humanitarian viewpoint. In particular, an ability to predict the spread of crop disease and also the results of deploying different control strategies may help us to increase crop yield and hence influence government policy - mathematical modelling is a tool that could help us to do that.

Increased legislative constraints on using chemicals to control crop disease are being introduced [15] (due to the desire to reduce both the amount of chemical consumed and the chance of pathogens evolving to become resistant). There is also pressure on the use of pathogen-resistant varieties (due to the time and cost of breeding resistance and the ethical objections of some consumers concerning genetic modification) and cultural controls (which are labour intensive and lead to reduced yield). Because of this, experimentalists have become more interested in biological control [7], where an antagonist (a natural enemy of a pathogen) is deployed to reduce disease spread. Soil-borne antagonists (which will be the initial focus of this project) are mostly fungi or bacteria: many people think that, in the long term, they will become a major component of integrated disease management [17].

By building mathematical models of biological control, we hope to answer the following three key questions.

- How are the properties of an effective antagonist conditioned on those of the pathogen and host (or environment)?
- Why has biological control had variable success, and how can it be made more reliable?
- How should biological control be deployed spatially, temporally, and in order to minimise cost yet still be effective?

2 Mathematical modelling of biological control

Mathematical models in epidemiology generally come in two forms: stochastic or deterministic. Simulations of stochastic models often require more computational work, but can reflect the environmental and demographic randomness that is prevalent in epidemiological systems. Deterministic models (such as the SIR model [5, 13] mentioned below), which often involve systems of differential equations (DEs), generally not only require less computational work to obtain a solution (or at least to approximate a solution using numerical methods), but one can also use many tools from DE analysis (such as linear stability analysis [26] and Floquet theory [22]) to explore their behaviour. Both stochastic and deterministic modelling approaches will be utilised in this project.

Most deterministic, mechanistic models in epidemiology are also compartmental models, where the host population is divided into different classes. In the SIR model, the population is divided into three types - those susceptible to the disease (S), those infected (I), and those who have had the disease, can no longer catch it and are so removed from the population (R).

In order to develop a strategy for the optimal deployment of biological control, we will include an antagonist population in our models: this adds complexity not only biologically but also technically (the dynamics become more complicated). We must also consider whether the same models can be applied to multiple types of biological control - for example, models incorporating antibiotic-producing antagonists might be different from models including mycoparasitic antagonists [9, 30].

We must introduce several additional features: spatial heterogeneity [28] (via dispersal kernels of individual-based models, metapopulation theory, or reaction-diffusion equations) and seasonality [24] are two examples. Other possible extensions include the incorporation of time-varying infection rates through the introduction of both latent- and infectious- period infective classes [13], introduction of saprotrophy [3], inclusion of feedback effects on the rate at which new infections arise due to pathogen density [33], addition of multiple pathogen strains (determining whether one generalist antagonist can be deployed to control all pathogen strains, or whether multiple antagonists will be required), and incorporation of pathogen refugia (since often there are pathogen propagules not accessible to the antagonist) [19].

Further to the division of epidemiological models into deterministic and stochastic classes, there are also different scales of model. On a macroscopic scale, members of a population may be entire plants (or even a metapopulation of plant populations [10], such as a collection of fields of crops), whereas on a smaller scale the individual unit of interest may be a leaf or root within a population of leaves or roots [4]. In this project, we will initially examine individual host plants, determining how the efficacy of biological control is affected by the growth habit of the plant. Having examined individual plants, we will go on to consider modelling fields of crops, motivated by our models of individual hosts: by coupling these two types of model, we will better understand the mechanisms behind both disease transmission and its biological control.

Models of biological control have predominantly concerned insect host-parasitoid interactions [16, 25], whereas models of the biological control of soil-borne pathogens (such as those we will consider in this project) are relatively under-developed [12]. Those that do exist generally involve the analysis of particular systems [23], rather than the development of general theory - one exception is the examination of the conditions necessary for diffusion-driven patterning in three-species reaction-diffusion systems [34]. Another example is the analysis of a parasite-hyperparasite system by Gubbins and Gilligan [14] - in this paper, a compartment model is presented with susceptible (S) and infected (I) hosts alongside a hyperparasite population (X). Infection is then assumed to be due to the interaction between susceptible sclerotia of *Sclerotinia minor* and hyperparasites (and therefore of the form $Xf(S, X)$), rather than between susceptible and infected roots (as in the model considered in Section 3). The authors chose the forms of the terms

in their equations representing infection and hyperparasite birth by fitting their model to experimental data, and found that the choice of the hyperparasite birth function is most important in describing the experimental data considered.

A recent development in the theory of biological control modelling of soil-borne pathogens is by Cunniffe and Gilligan [8], who develop earlier biological control models [18, 35]. In the first of the earlier papers, Jeger *et al.* [18] allow tissue that is colonised by the antagonist to enter the removed class, implying that the deployment of an antagonist leads to the removal of host tissue. In the model of Xu *et al.* [35], the colonised tissue instead becomes susceptible again, which seems more biologically plausible. Cunniffe and Gilligan [8] not only incorporate antagonist-pathogen interactions like these in their models, but also allow the antagonist to affect epidemiological mechanisms (such as rates of primary and secondary infection).

Throughout this project, we will have access to data from three different systems involving biological control. Firstly, INRA and ADAS have supplied field data on take-all decline on wheat [6] (*Pseudomonas fluorescens* on *Gaeumannomyces graminis* var. *tritici*). We will also examine lettuce drop (*Sporidesmium sclerotivorum* on *S. minor* [14]) and damping off (*Trichoderma viride* on *Rhizoctonia solani* [2, 11]). Not only will these data be used to set parameter values in our models [12], but it will also aid the formulation and testing of hypotheses [35].

3 An initial modelling framework

This project will begin on a micro-scale, by investigating how the success of biological control depends on interactions between the roots of an individual plant. This model can then be scaled up, in order to inform landscape-scale models, which can be used to decide how to deploy biological control effectively. Initially we consider a model for parasite-antagonist competition - this can be compared with models of multiple pathogen strains [20, 27]. Our model is motivated by the biological control, by *Pseudomonas spp.*, of take-all disease on wheat crops.

Consider a plant, the roots of which can be in one of three states - healthy and susceptible to the pathogen but uncolonised by the antagonist (S), colonised by the antagonist (C), and infected by the pathogen (I). We suppose that new susceptible roots are produced at rate $\rho(S, C, I)$, and that susceptible, colonised and infected roots die at rates δ, δ and $\delta + \mu$ (where μ is positive, indicating that infected roots die at a faster rate than healthy roots), respectively. We assume that susceptible roots become infected at rate β, and colonised at rate α. We also assume that colonised roots become infected at a reduced rate $\epsilon\beta$, where ϵ is less than one, and that colonised roots become susceptible again at rate ν (as the antagonist, but not the root, dies). We also assume that infected roots become colonised at rate ω. These rates are shown in Figure 1a. Then, by the law of mass action [21], we have the system

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= \rho(S,C,I) - \delta S - \alpha SC + \nu C - \beta SI, \\
\frac{\mathrm{d}C}{\mathrm{d}t} &= \alpha SC - (\nu + \delta)C - (\epsilon\beta - \omega)CI, \\
\frac{\mathrm{d}I}{\mathrm{d}t} &= (\epsilon\beta - \omega)CI + \beta SI - (\mu + \delta)I.
\end{aligned} \tag{1}$$

In our initial investigation, in order to characterise the underlying dynamics of the system, we further assume that new susceptible roots replace dying roots, so that

$$\rho(S, C, I) = \delta(S + C + I) + \mu I.$$

Hence, the total number of roots is conserved, and equal to N, say.

We consider two strategies for the introduction of biological control, one preventative and the other eradicative. In the preventative case, we pre-empt the arrival of a pathogen by introducing an antagonist into an entirely susceptible population. A persistence threshold for C, R_0^C, can be calculated, defined to be the mean number of secondary colonised roots when one colonised root is introduced into an entirely susceptible population. If this is greater than unity, then the antagonist will persist in our population (at least initially), whereas if it is less than unity, it will die out. If the antagonist persists in our population,

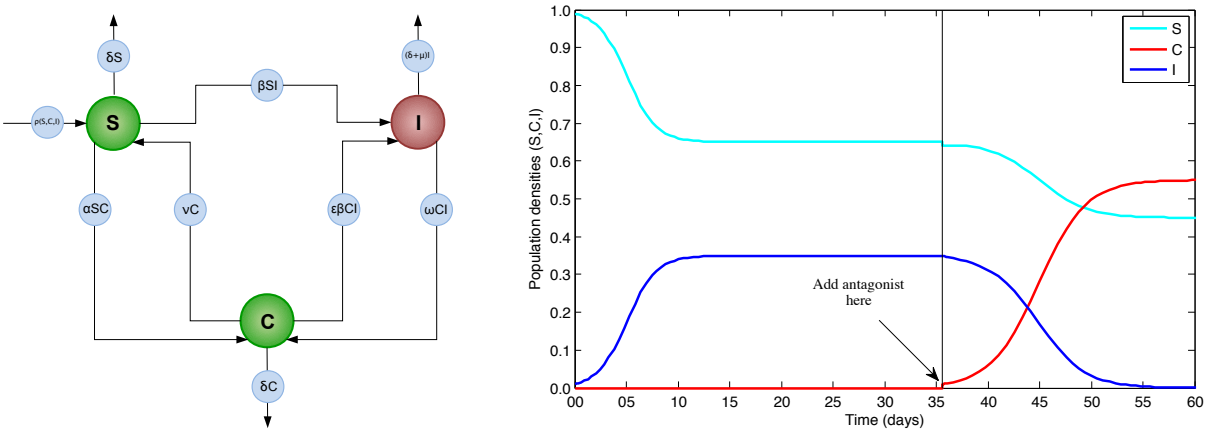

Figure 1: a. Schematic of the interactions in System 1. See text for explanation of parameters.
b. Numerical solution of system (1), with parameters chosen such that $R_0^I > 1$, $R_0^C > g(R_0^I, \omega, \nu, \beta, \delta, \epsilon)$, and initial conditions $(S, C, I) = (1 - 0.01, 0, 0.01)$ at time $t = 0$. The system reaches the stable equilibrium $(S^{**}, 0, I^{**})$, before a small amount of antagonist is applied by setting $(S, C, I) = (S^{**} - 0.01, 0.01, I^{**})$. Here $\alpha = 2$, $\beta = 2$, $\delta = 0.4$, $\epsilon = 0.01$, $\mu = 0.9$, $\nu = 0.5$ and $\omega = 0.1$.

the system reaches the equilibrium state

$$(S, C, I) = (S^*, C^*, 0). \tag{2}$$

Similarly, it is possible to derive a persistence threshold for a pathogen arriving into an entirely susceptible population, R_0^I. If this is greater than unity, the system approaches the equilibrium state

$$(S, C, I) = (S^{**}, 0, I^{**}). \tag{3}$$

It is possible to derive conditions for the pathogen arriving with the system in state (2) to persist, and the antagonist arriving with the system in state (3) to persist, given by

$$R_0^I > f(R_0^C, \omega, \mu, \delta, \epsilon),$$

and

$$R_0^C > g(R_0^I, \omega, \nu, \beta, \delta, \epsilon), \tag{4}$$

respectively. Note that (4) can be expressed as a condition on R_0^I instead (requiring ω to be greater than $\beta\epsilon$ in order to maintain the inequality).

In order to demonstrate our assertions about the interpretation of the persistence thresholds, we can solve the system of equations (1) numerically. For an example, see Figure 1b, where the antagonist introduced overcomes the already present pathogen since R_0^C is greater than $g(R_0^I, \omega, \nu, \beta, \delta, \epsilon)$.

Further, if the parameter values lead to

$$R_0^I > 1, R_0^C > 1, R_0^I < f(R_0^C, \omega, \mu, \delta, \epsilon), R_0^C < g(R_0^I, \omega, \nu, \beta, \delta, \epsilon),$$

then we could infer that it is vital to deploy biological control before the arrival of the pathogen (rather than when the pathogen has taken hold in the system).

Further planned exploration of the model (1) includes examination of its behaviour with different birth functions $\rho(S, C, I)$. In particular, logistic growth of the form

$$\rho(S, C, I) = r\,(S + C)\left(1 - \frac{S + C + I}{K}\right),$$

might be appropriate in a situation where available space inhibits the growth of new roots. Further, initial investigations suggest the possibility of a backwards pitchfork bifurcation [31] for certain growth functions and parameter values.

4 Timeline

In this project, we hope to address three key questions, as stated in Section 1. In order to do this, we present the following timetable.

- Learn C++ as a vehicle to implement new models and review biological and epidemiological literature. Explore individual plant models for biological control, both deterministic (as in Section 3) and stochastic (including models of individual roots, using techniques that have not previously been applied in this context for the implementation of stochastic models on a growing domain [32]) - 6 months.
- Introduce seasonality, and identify the features necessary for the design of an effective antagonist (via parameter variation) - 4 months.
- Explore landscape-scale models of biological control, and introduce seasonality and spatial heterogeneity. In particular, discover whether it is possible to connect the average behaviour of a spatial stochastic system with a deterministic system, as in models of cell migration [32]. Further, consider models with multiple pathogen strains, and whether one generalist antagonist will suffice to control all pathogen strains, or a second antagonist should be introduced - 6 months.
- Couple landscape- and individual plant- scale models (scaling up the predictions of the individual plant-scale models to inform behaviour at the landscape-scale). Develop a strategy for the effective deployment of biological control both spatially and temporally (but also consider the cost of our strategy) - 6 months.

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