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Interactions between immunotoxicants and parasite stress: implications for host health

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Abstract

Many organisms face a wide variety of biotic and abiotic stressors which reduce individual survival, interacting to further reduce fitness. Here we studied the effects of two such interacting stressors: immunotoxicant exposure and parasite infection. We model the dynamics of a within-host infection and the associated immune response of an individual. We consider both the indirect sub-lethal effects on immunosuppression and the direct effects on health and mortality of individuals exposed to toxicants. We demonstrate that sub-lethal exposure to toxicants can promote infection through the suppression of the immune system. This happens through the depletion of the immune response which causes rapid proliferation in parasite load. We pre-

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dict that the within-host parasite density is maximised by an intermediate toxicant exposure, rather than continuing to increase with toxicant exposure. In addition, high toxicant exposure can alter cellular regulation and cause the breakdown of normal healthy tissue, from which we infer higher mortality risk of the host. We classify this breakdown into three phases of increasing toxicant stress, and demonstrate the range of conditions under which toxicant exposure causes failure at the within-host level. These phases are determined by the relationship between the immunity status, overall cellular health and the level of toxicant exposure. We discuss the implications of our model in the context of individual bee health. Our model provides an assessment of how pesticide stress and infection interact to cause the breakdown of the within-host dynamics of individual bees.
Keywords: infection; within-host dynamics; immunity; stress; honey bees

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Highlights

- We present a model to describe the within-host dynamics of an organism under both immunotoxicant and parasite stress.
- We consider both the direct toxicity and indirect sub-lethal immunosuppression of toxicants.
- Sub-lethal exposure to toxicants can rapidly promote an already-present parasite infection, through the suppression of the immune system.
- We find that within-host parasite density is maximised by an interme-

diate toxicant level, depending upon the relative strength of immunosuppression and toxicity.

- We classify the breakdown of the within-host dynamics into three phases of increasing toxicant stress, which are determined by the relationship between the statuses of immunity, cellular health and level of toxicant exposure.

- We discuss the implications of our model in the context of individual bee health under multiple stressors.

1. Introduction

During their lifetime, organisms are exposed to a wide range of chemical, physical and biological stressors, which can be defined as anthropogenic (e.g. toxicant exposure, pollutants) or natural (e.g. pathogens, parasites). Recently, there has been increasing interest in multiple stress approaches, examining the potential for stressors to interact [1]. Understanding the mechanisms behind these interactions is important for quantifying the true impacts of individual anthropogenic stress on organisms [2].

Pesticides are an important class of anthropogenic toxicant stress, with the use of pesticides continuing to increase globally [3, 4, 5]. Pesticides are crucially important to crop productivity, preserving around one-fifth of total crop yield contributing to food security [6] but concerns about detrimental side-effects [7, 8] have forced policy makers to restrict the application of some pesticides [9]. Non-target organisms frequently encounter these pesticides [4], with concentrations able to build up throughout food sources and within various life-stages of the organism [10, 11, 12, 13, 14, 15].

Toxicants such as pesticides can cause lethality [15, 16, 17, 18, 19], but more often have other sub-lethal effects such as impairments on foraging [20, 21, 22, 23], feeding [24], learning [25, 26], memory [27, 26] and fecundity [28, 29, 30]. Exposure during early life can have both lethal and sub-lethal effects later appearing during adulthood [31, 32]. These environmental contaminants can interact in combination with other natural stressors. For example, combinations of toxicant exposure with parasite infections can increase in-

dividual mortality [33, 34], increase the initial pathogen load [35, 36] and increase the impact on reproduction and survival [37]. Toxicant-pathogen interactions have been observed in many types of organisms such as insects, snails, water fleas, frogs, salamanders, fish and mussels (see review by Holmstrup et al., 2010). In addition to toxicants causing direct lethality, they can also cause damage to individual immune defence. Individual organisms defend themselves against various infections via a suite of immune responses, and these can be damaged or inhibited through toxicant exposure [38]. For example, pesticides have been shown to reduce the total hemocyte abundance in insects [39, 40], the nodulation initiation [39, 41], the encapsulation response [42, 40] and antiviral defences [43].

Of particular recent concern are the widespread losses to global wild and managed bee populations [5, 44, 45], because of their importance to global food security and biodiversity [46, 47]. The Western honey bee (*Apis mellifera* L.) is widely recognised as the most important commercial insect pollinator [48, 49, 50], but a single cause for their population decline has yet to be identified. There is agreement that these losses may have their origins within multiple stressors interacting with each other [51, 52, 53, 54]. Possible candidates include neonicotinoid pesticides [11, 55, 26], mites [56, 57], viruses [58, 59, 60] and microsporidia infections [61, 62].

In this study, we examine the mechanism by which immunotoxicants interact with the within-host cellular and immunological dynamics of a host to increase parasite load. We formulate the conditions under which sub-lethal

toxicant exposure intensifies the infection levels within a host. This observed interaction between multiple stressors is currently poorly understood from an immunological perspective [63], while a rich body of theoretical research exists to describe the within-host dynamics of infectious diseases (see review by Mideo et al. [64]). We focus our study on the general ecotoxicological applications of the theoretical model, in the case of any immunotoxicant interacting with any parasite infection. We do this by formulating a system of nonlinear ordinary differential equations (ODEs) to investigate the consequences of immunosuppression by a toxicant and the effect this has on within-host infection. We first consider a toxicant-free environment to examine the conditions under which the infection can spread. We then consider the interaction between the infection and both lethal and sub-lethal exposure to toxicants and examine the outcome on within-host dynamics. We also consider the case of aggressive direct lethality of toxicants on the production of new tissue cells.

2. The Model

The immune response of any individual relies upon the interdependent defence of physical, humoral and cellular responses, denoted in our model by a generalised immune function Z. Nowak and May [65] proposed a general model to describe the interaction between a cellular immune response and a replicating virus, in the setting of self-regulating cytotoxic T lymphocytes (CTLs) targeting infected cells. The model they present is simple but cap-

tures the fundamental biological processes governing the immune response to foreign antigens, and following this framework we denote within-host cell density as X. We denote the total parasite/pathogen density as Y. The total number of cells within the model represents a general susceptible subset of tissue cells. As a motivating example, our model can be thought of describing the midgut epithelial cells of the honey bee X under a *Nosema ceranae* infection Y [66] with associated immune response Z, although we also propose that our model can be thought of describing any interaction between any immunotoxicant and associated parasite or pathogen in a general host.

We assume that toxicant exposure reduces the functionality of the immune system c rather than killing off individual immune cells. We make this assumption in order to simplify the analysis, however this also captures the inhibition and damage that toxicant exposure can have on the various functions associated with the immune response [38, 39, 40, 41, 42, 43, 67, 68, 69]. This means that the linear function $-hQ$ can be thought of as inhibiting the linear immune functionality c. Toxicants are also lethally toxic to individuals at high enough exposure levels [16, 17, 18, 19], and we assume that rather than killing individual cells, the toxicant damages the vital functionality of the host, expressed through the parameter λ. We model both the direct/acute lethality (denoted by parameter r) and indirect sub-lethal immunotoxicity (denoted by parameter h) effects of toxicant exposure Q. For simplicity, we assume fast dynamics of virus replication compared to the replication of other within-host cells or immunity resulting in the formulation

of the model (Figure 1) as a 3-compartmental set of nonlinear ODEs;

$$\frac{dX}{dt} = \lambda - \beta YX - dX - rQ \tag{1a}$$

$$\frac{dY}{dt} = \beta YX - aY - pYZ \tag{1b}$$

$$\frac{dZ}{dt} = c - bZ - hQ \tag{1c}$$

with $c - hQ > 0$ and $\lambda - rQ > 0$. When $Z = 0$ (the immune response is depleted), we remove equation (1c) from system (1) and the system becomes the two dimensional system of equations (1a) and (1b*) without the immune response term $-pYZ$;

$$\frac{dX}{dt} = \lambda - \beta YX - dX - rQ \tag{1a}$$

$$\frac{dY}{dt} = \beta YX - aY \tag{1b*}$$

We assume that within-host cells are produced at rate λ, and die at per-capita rate d. Parasites are created at rate β via a linear mass action, and are removed at per-capita rate a. The immune response Z is activated upon encountering parasites Y and the removal of parasites occurs at rate p. Although in reality, functions involved in immunity are not activated on the instance of meeting the parasite, but there is a complicated intermediary chain between processes which eventually result in the removal of parasites [70]. For simplicity, we assume that this process can be summarised by

our function pYZ. We assume that the immune dynamics Z are decoupled from those of within-host and parasite density. This represents the simplest possible assumption and various extensions to this assumption are possible. Immunity is therefore produced at rate c, and is removed at per-capita rate b.

Within our model we infer the mortality risk of the host through the status of the within-host cells X. Individual mortality risk is high when the number of within-host cells X are small, so that there is a negative correlation between the mortality of the host and the cell density. This condition enables us to think about the mortality risk of an individual analogous to a highly infected within-host tissue (e.g. parasite infection within the gut of a honey bee).

Our system of equations (1) were analysed using standard stability methods from dynamical systems theory and solved numerically with Wolfram Mathematica version number *10.0.2.0*, using parameters taken from Table 2. We performed a full parameter dependence analysis which demonstrated the same universal behaviours of the model which enabled us to choose arbitrary parameter sets.

3. Results

In the following section we consider the baseline case of parasite infection in a toxicant-free environment before analysing our within-host system under the addition of a toxicant. We then consider the absence of direct lethal

effects of toxicants before presenting the unique case of an aggressive toxicant.

3.1. Toxicant-free model

Initially we examine system (1) under the condition of the absence of toxicant exposure (denoted by subscript A). Two possible outcomes are possible. First the infection is removed entirely by the immune system, in which case the total within-host cells and total immunity each reach a constant level at the disease free equilibrium (DFE):

$$(X_A^{DFE}, Y_A^{DFE}, Z_A^{DFE}) = \left(\frac{\lambda}{d}, \quad 0, \quad \frac{c}{b}\right) \tag{2a}$$

where $\frac{\lambda}{d}$ and $\frac{c}{b}$ represent the ratio of total production to total removal of both within-host cells and immunity in the absence of toxicant respectively. Secondly the model predicts that an individual can become infected with parasites ($Y > 0$) under the following endemic equilibrium (EE):

$$(X_A^{EE}, Y_A^{EE}, Z_A^{EE}) = \left(\frac{ab + cp}{\beta b}, \quad -\frac{d}{\beta} + \frac{b\lambda}{ab + cp}, \quad \frac{c}{b}\right) \tag{2b}$$

This shows that it is possible for an individual bee to sustain a partial parasite infection without the addition of any toxicant in our model. The expression $\frac{ab+cp}{\beta b} = \frac{a}{\beta} + \frac{cp}{\beta b}$ represents the reduction in within-host cells.

3.2. Toxicant-Parasite model

Next we consider system (1) under the condition of an infection and toxicant exposure (denoted by subscript B). In this case the model predicts

two possible outcomes. First, the parasite infection is removed either by immune suppression or by the direct effects of the toxicant on the production of within-host cells represented by the DFE:

$$(X_B^{DFE}, Y_B^{DFE}, Z_B^{DFE}) = \Big(\frac{\lambda - rQ}{d}, 0, \frac{c - hQ}{b}\Big) \tag{2c}$$

so that the addition of any toxicant reduces the total within-host cells by $\frac{rQ}{d}$ and reduces the immune function by $\frac{hQ}{b}$. Secondly the model predicts an infected individual under toxicant exposure represented by the EE:

$$(X_B^{EE}, Y_B^{EE}, Z_B^{EE}) = \Big(\frac{ab + cp - hpQ}{\beta b}, \frac{-abd - cdp + dhpQ - bQr\beta + \beta b\lambda}{\beta ab + cp\beta - hpQ\beta}, \frac{c - hQ}{b}\Big) \tag{2d}$$

In this case, the parasite density grows rapidly as a result of the toxicant suppressing the immune system. The introduction of the toxicant reduces both within-host cells and immunity in both an infection-free and infected individual, but an initial parasite infection is required for an infection to grow. The effect of toxicant exposure on the net change of within-host cells, parasite density and immunity within the individual is summarised in Table 1.

Next we assume that the indirect (sub-lethal) effects of toxicant exposure on immunosuppression are more prominent than the direct (lethal) depletion of within-host cells. With an initial infection $Y > 0$ we define this as occurring when the immune status of an individual is destroyed before the

infection is removed or when

$$Z = 0 \quad \text{before} \quad Y = 0 \tag{3}$$

We summarise the behaviour of the model under this condition (Figure 2) into 3 distinct phases which describe the mechanism underlying the interaction between toxicant exposure and infection at the within-host level of the organism, and the parameter dependence of infection and immunity at equilibrium. Note that the total number of cells within an individual organism is not constant. This is because both parasite and within-host cells are removed by either the toxicant exposure or infection and new cells are produced. The following dynamical phases are determined by the stability and feasibility analysis of the model (supplementary information).

Phase I $\quad 0 \leq Q < \frac{c}{h} = Q_0^*$

The model predicts that the initial state of an immune response is able to counter any infection. However, as the toxicant load is increased, the immune system is gradually depleted. Through a weakened immune suppression, this enables the parasite density to increase.

Phase II $\quad Q_0^* = \frac{c}{h} \leq Q < \frac{\beta\lambda - ad}{r\beta} = Q_1^*$

The second phase begins at the point of maximum infection and where the immune system has been completely inhibited. The increase in toxicant stress gradually depletes the parasite density while the within-host cells remain

constant.

Phase III $\quad Q_1^* = \frac{\beta\lambda - ad}{r\beta} \leq Q < \frac{\lambda}{r}$

In phase three, the immune system has been destroyed and the parasite infection is no longer present leaving only a small fraction of within-host cells. Finally, the lethality of the toxicant causes the mortality of the individual bee and production of new cells ceases when $\lambda - rQ$ becomes zero which occurs at $Q = \frac{\lambda}{r}$.

Thus we have calculated the conditions under which the within-host dynamics change according to the level of toxicant exposure. Further additional analysis can be found in the supplementary information. By understanding the relationship between the parameters in the model and toxicant stress, we can make some biological interpretations. We predict that the ratio of the production of immunity to the amount of immunotoxicity ($Q_0^* = \frac{c}{h}$) determines the point at which the infection load is at a maximum. The expression $\frac{c}{h}$ can be thought of as an indicator of immune status, and the point at which the toxicant stress becomes equal ($Q = Q_0^*$) represents the complete inhibition of the immune system. The expression $Q_1^* = \frac{\beta\lambda - ad}{r\beta} = \frac{\lambda}{r} - \frac{ad}{r\beta}$ represents the point at which the ratio of cell production to lethal toxicant mortality (indicator of within-host cell status) compares to the ratio of the loss of cells to the toxicant cell depletion multiplied by the transmission of the infection. Therefore this condition represents the status of within-host dynamics and can be thought of as an indicator of health. When $Q = Q_1^*$, the infection has

been removed but the overall health status is very low, from which we infer a higher mortality risk of the host. Therefore we have conditions describing how toxicant exposure relates to that of the immune status Q_0^* and overall health Q_1^* of the organism.

Our model predicts that a small amount of toxicant can cause the outbreak of an otherwise controlled infection. A healthy immune response can suppress the parasite infection to a very low level (Figure 3a), but a small amount of toxicant can cause the status of both infection-free and infected individuals to decline rapidly (Figure 3b).

3.3. Absence of toxicant lethality ($r = 0$)

In this case, we consider the absence of a direct lethal toxicant effect, therefore assuming that toxicant exposure only impairs the immune system and does not cause direct mortality. This changes the mechanism by which organisms become infected under increasing toxicant exposure. As before the immune system is inhibited leaving the organism vulnerable to attack by parasites. However after reaching a maximum infected threshold, the health status of the individual remains constant regardless of the amount of toxicant exposure (Figure 4a). The individual remains highly infected (Figure 4b) and an increasing exposure to the toxicant no longer causes further damage to organism health status.

3.4. Aggressive toxicant lethality (large r)

It is worth noting that condition (3) is necessary to explore the interaction between toxicant immunosuppression and the immune system. If this were not the case, for example if the parameter r becomes large we would see a situation where the toxicant acts too aggressively upon the host and causes the parasite infection to be killed off (similar to phase II under the original assumption) and following this the within-host cells are destroyed. The immune system remains intact as the direct effect of the toxicant on production of within-host cells is greater than the immune effect. We again see three distinct phases as we increase the toxicant from low levels to high (Figure 5a). However now the toxicant exposure is more prominent and reduces both parasite and within-host cells, stopping the infection from spreading quickly (Figure 5b). In this situation we also see a somewhat contradictory phase 3 in which the host has neither parasite or within-host cells but a small amount of immunity. This result demonstrates the necessity of our original condition.

The three distinct qualitative behaviours (maximised infection at intermediate toxicant, absence of toxicant lethality, and aggressive toxicant lethality) of the model are summarised in Figure 6. This figure shows that the ratio between the parameters r and h determine the relationship between toxicant exposure and infection within a host. If r is too high, then the parasite is inhibited before the immune system. However, if h is sufficiently high then the parasite is maximised at an intermediate toxicant exposure. The small region around $r = 0$ results in the parasite remaining at high density regard-

less of higher toxicant exposure. Additional examples of individual pairwise combinations of both immunosuppressive and lethal effects can be found in the supplementary information for both equilibria phase status (Figure S1a) and total percentage parasite infection (Figure S1b).

4. Discussion

We have shown that interactions between general anthropogenic stress in the form of an immunotoxicant and a parasite can promote within-host infection and reduce health status. This interaction is entirely dependent upon the phase of toxicant exposure. The immune response of the host can be divided into three such phases of increasing toxicant load; phase I, II and III (Figure 2). In the first phase, sub-lethal doses of the toxicant damage the immune system. This results in suppression of the immune system and hence the individual organism becomes highly infected. In the second phase, intermediate exposure to the toxicant reduces the total density of parasites. In the third phase, the extremely high exposure to the toxicant leads to the loss of within-host cells and eventual mortality of the host.

Through disentangling the individual effects of both lethal and sub-lethal toxicant exposure, we were able to establish the role of each within the breakdown of within-host dynamics. Indirect (sub-lethal) suppression of the immune system causes rapid proliferation of parasites within the host (Figure 3), while direct (lethal) mortality cause both parasites and within-host cells to die. However without the direct effect of the toxicant on the production

of new cells, the host remains highly infective (Figure 4). We also predict that an extremely small toxicant exposure can cause the proliferation of a previously manageable infection. These results suggest that the ratio between both lethal and immunosuppressive toxicant effects are important in determining the subsequent interaction with parasite infections. Our model suggests when assessing both sub-lethal and lethal toxicant effects, it is important to consider that higher lethal doses (LD50) could remove the parasite infection from the host and that there exists a range of intermediate sub-lethal exposure under which we predict that the parasite will proliferate.

The findings we present in this study shed new light on the poorly understood mechanism by which toxicants seem to interact with infection to increase mortality risk [63]. In the context of the recent losses to global bee populations [5, 44, 45], the joint immunotoxicant-infection interaction studied here is one example of the recent hypothesis that widespread native and managed bee losses may be multi-factorial [51, 52, 53, 54]. Joint pesticide-infection interactions have been shown to increase mortality risk within bees [33, 34]; for example, *Nosema ceranae* infections and thiacloprid, a neonicotinoid pesticide act jointly to increase individual mortality [36]. The findings we present in this paper propose one explanation of how interactions between these toxicants and infection occur at the within-host level. We show that these sub-lethal effects of anthropogenic stress are potentially more damaging to individual health, aggravating parasitic stress. This is in direct agreement to the positive correlation between low level (field condition) neonicotinoid

treatment and increases in parasite and viral infestations in bees [71, 72]. Infections within individual honey bees can be significantly increased by different levels of low or high sub-lethal pesticides [35]. Indeed, honey bees with undetectable levels of neonicotinoid imidacloprid which are reared in sub-lethal conditions still have increased infection levels [35]. This suggests that even extremely small sub-lethal exposure to pesticide can result in outbreaks of infection. We show that increasing the pesticide exposure by a small amount ($Q > 0$) can result in a transition from a manageable parasite density level to a highly infected individual.

Our results rely upon condition (3) which ensures that the immune response is destroyed before the within-host cells. This condition is crucial to ensuring reasonable behaviour of the model, and it should be noted that the reverse assumption predicts the presence of immunity even after both infected and within-host cells are dead (Figure 5a). We highlight this limitation of our theoretical work but argue that condition (3) is valid since the direct lethality of toxicants only occur at high doses [16] and various immunosuppressive effects occur from toxicants [38], thus suggesting that toxicants have a greater impact on suppressing the immune system. Within our model, we made assumptions about the way in which toxicant exposure acts upon the host. An alternative assumption could frame this exposure as acting through a density dependence upon immunity and within-host cells. We reproduced Figure 2 using the same parameters and this assumption also yields the result that parasite density is maximised at an intermediate

toxicant exposure (sup. info. Figure S2). The qualitative behaviour of the parasite is unchanged by this density dependent assumption.

The framework provided in this study focuses on the failure of the immune system of an individual organism. However individuals interact within populations causing infection to spread to other susceptible individuals, and these populations have associated interdependent immune defences at both the within-host and between-host level. For example, social immunity involves many behavioural and population-level mechanisms such as social fever, a mechanism by which individuals increase the temperature of the surrounding environment in order to kill parasites [73], guarding, where patrolling guards prevent infected individuals from interacting with healthy individuals [74], hygienic cleaning behavioural traits, by which the population remove diseased or dead individuals [75] and storing antimicrobial food [76]. Hence the main limitation of our framework is that we may have only considered one half of both interdependent within and between-host immunities. Coupling population immunity models in the context of an epidemic alongside our individual immunity framework could further explain the interactions between toxicants and infection at both the individual and population level. Further theoretical work incorporating these multi-level dynamics could address the gap in understanding bee decline as interacting stressors in similar ways to other models of colony collapse disorder [77, 78, 79].

This work highlights the need for further studies which focus on interactions between various stressors at the within-host level. Our theoretical

study presents a starting position to think about these interactions at the within-host level in the context of the immune system of an individual organism. While our model has an inherently simple structure, the addition of the toxicant function can lead to complicated dynamics that are consistent with empirical observations. This framework can stimulate further empirical and theoretical studies which focus on the interaction between toxicant exposure, infection and the immune system at both the social group and individual level.

5. Acknowledgments

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6. Competing Interests

We declare we have no competing interests.

7. Authors' Contributions

All authors conceived the idea for the study, constructed the model and analysed and interpreted the material. R.D.B. wrote the manuscript, with contributions from all authors.

8. Figures and Tables

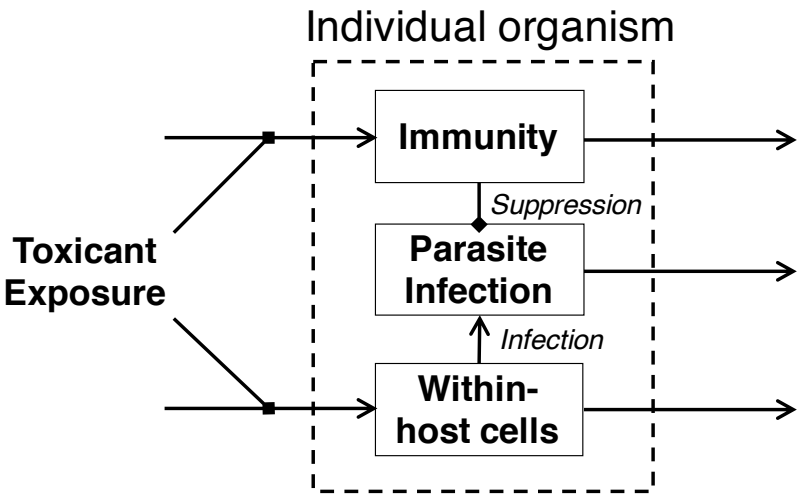
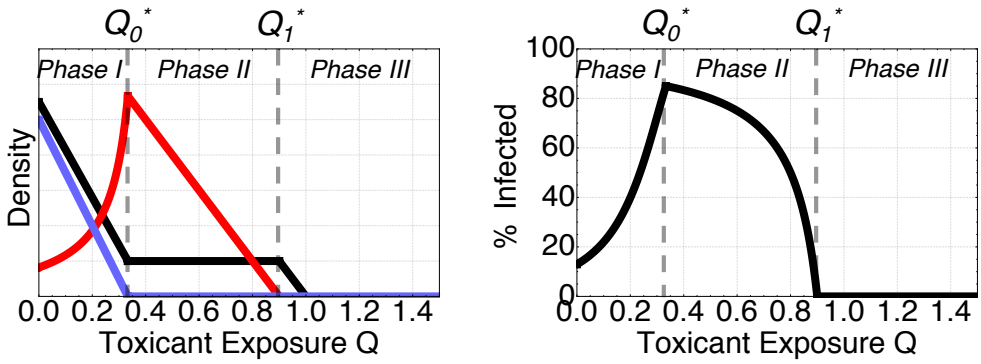
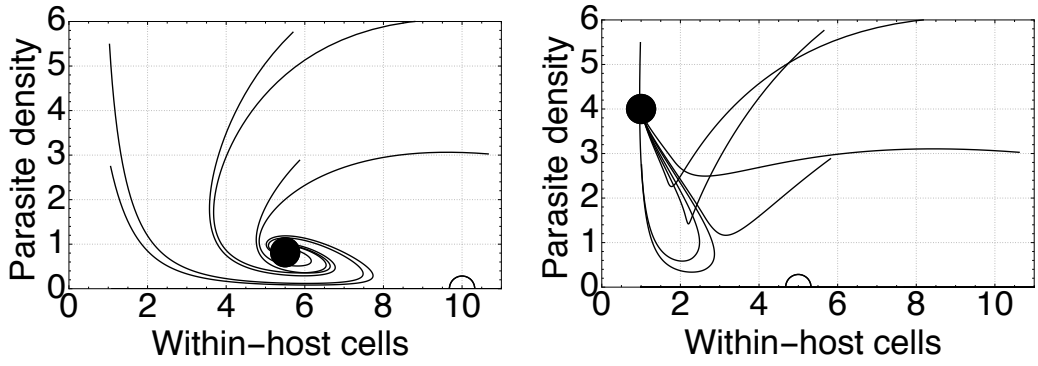


Figure 1: The modelling framework we use to model the interaction between toxicant exposure and parasite infection in an individual. Block arrows represent suppression. We model toxicant exposure as a suppressive effect on immunity and within-host cells.



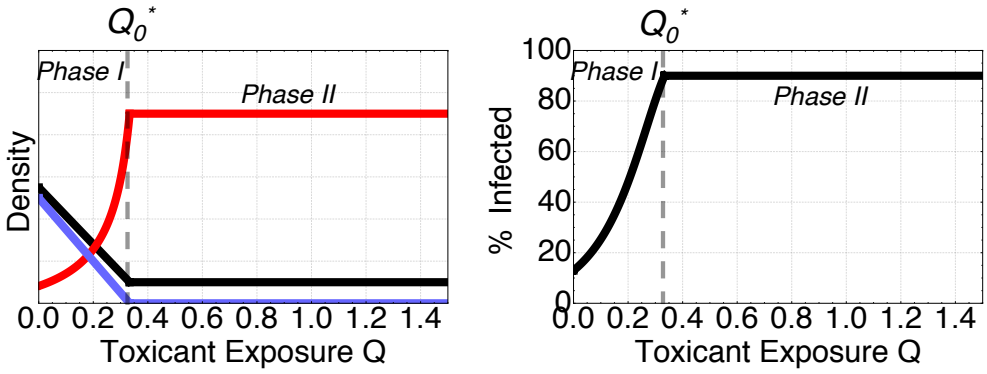
(a) (b)

Figure 2: The mechanism of parasite infection under increasing toxicant exposure, for both immunosuppressive and lethal effects of toxicant with all parameters taken from Table 2. This shows the parameter dependence of immunity, parasite density and within-host cells at equilibrium within the dynamics of our model. In (a) the total densities of immune function (blue), parasite load (red) and within-host cells (black) change as an individual is subject to higher toxicant loads, according to the three phases of the model. In (b) the total % parasite infection (black) increases as the toxicant load is increased, before decreasing to 0 at $Q_1{}^*$.



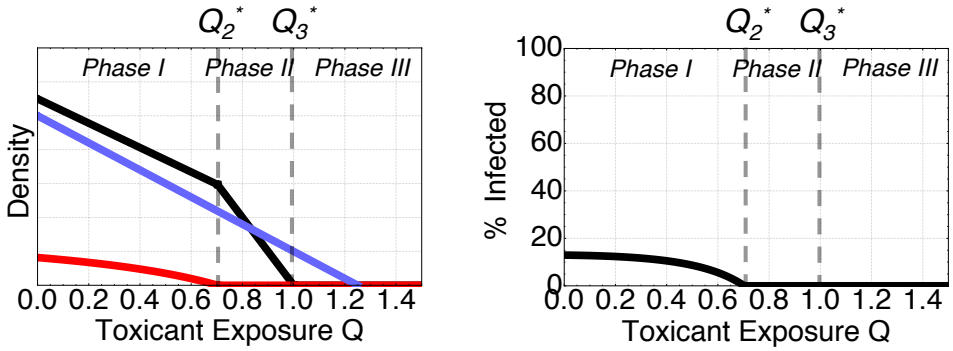
(a) Toxicant exposure $Q = 0$ (b) Toxicant exposure $Q = 0.5$

Figure 3: The convergence of the total density of within-host cells and parasites under no toxicant exposure (a) $Q = 0$, and small amounts of toxicant exposure (b) $Q = 0.5$. All other parameters are taken from Table 2. Black dots show the stable endemic equilibrium, white dots show the unstable disease-free equilibria and lines show the convergence from initial conditions. We assume an initial immune response ($Z = 10$) and an initial amount of within-host cells ($X > 0$), and either zero or positive parasite density ($Y \geq 0$).



(a) (b)

Figure 4: The mechanism of parasite infection under increasing toxicant exposure, for only the immunosuppressive toxicant effect. Parameters taken from Table 2, but with direct toxicant effect $r = 0$. In (a), the total density of immune function (blue), parasite load (red) and within-host cells (black) change as an individual is subject to higher toxicant loads, but now only within 2 phases. In (b), the total % parasite infection (black) increases as the toxicant load is increased, before remaining at equilibrium.



(a) (b)

Figure 5: The mechanism of parasite infection under increasing toxicant exposure with aggressive direct mortality. Parameters taken from Table 2, but with indirect toxicant effect $h = 0.08$. In (a), the total density of immune function (blue), parasite load (red) and within-host cells (black) change as an individual bee is subject to higher toxicant loads, according to 3 phases. In (b), the total % parasite infection (black) decreases as the toxicant load is increased. The phases are determined by new critical levels of toxicant $Q_2{}^*$ and $Q_3{}^*$.

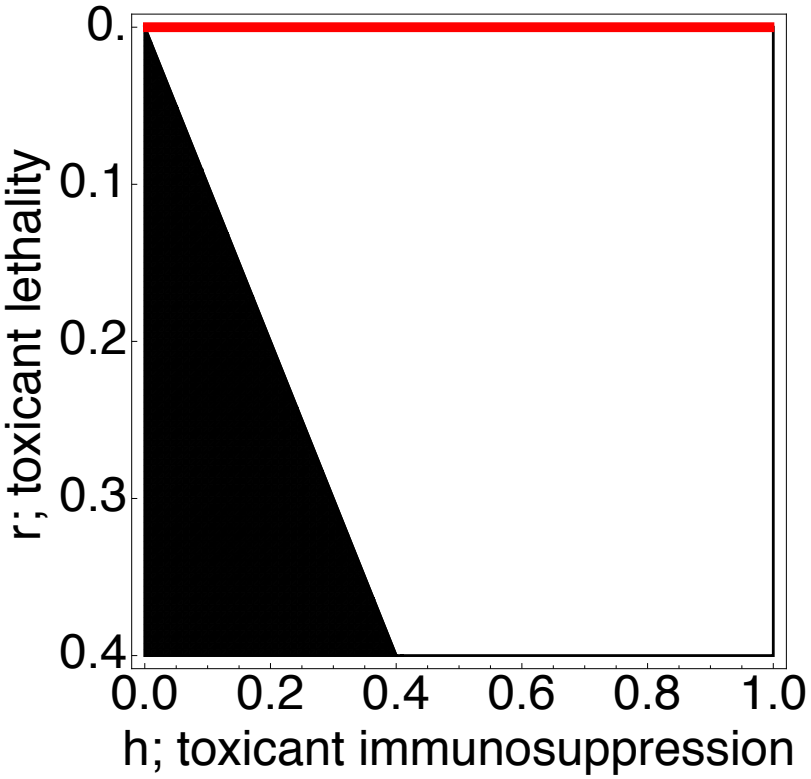


Figure 6: The qualitative behaviour of the model within $r-h$ lethal-immunosuppressive toxicant space. Parameters taken from Table 2, for a range of r and h. The white region represents the case of maximised parasite infection at intermediate toxicant exposure. The red region ($r=0$) represents the toxicant-free parasite equilibrium. The black region represents the aggressive toxicant effect of the model.

	No parasite infection	Initial parasite infection
Within-host cells X	reduced by $\frac{rQ}{d}$	reduced by $\frac{hpQ}{b\beta}$
Parasites Y	no change	increased by $\frac{bQ(hp\lambda-abr-cpr)}{(ab+cp)(ab+p(c-hQ))}$
Immunity Z	reduced by $\frac{rQ}{d}$	reduced by $\frac{hQ}{b}$

Table 1: The net change of immunity, within-host cells and parasites after the introduction of toxicant, compared to the no-toxicant model, for both the absence of parasite infection ($Y=0$) and initial ($Y>0$) parasite infection load.

Parameter	Symbol	Value
production of within-host cells	λ	0.1
rate of parasite infection	β	0.01
death of within-host cells	d	0.01
direct lethal effect of toxicant	r	0.1
toxicant exposure	Q	$[0, 1.5]$
death rate of parasites	a	0.01
immune suppression	p	0.009
production of immunity	c	0.1
removal of immunity	b	0.02
indirect sub-lethal effect of toxicant	h	0.3

Table 2: The parameters used in the analysis of the model.

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