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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 synergistically to further reduce fitness. Here we studied the effects of two such synergistically 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

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load. 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 honey bee health. Our model provides an assessment of how pesticide stress and infection interact to cause the synergistic breakdown of the within-host dynamics of individual honey bees.

Keywords: stress, immunity, infection, synergistic, within-host dynamics, honey bees

1 **1. Introduction**

2 During their lifetime, organisms are exposed to a wide range of chemical,
3 physical and biological stressors. Exposure to environmental (e.g. anthro-
4 pogenic, climatic) and natural stress (e.g. pathogens, parasites and pre-
5 dation) reduces individual fitness [1]. Recently, there has been increasing
6 interest in multiple stress approaches, examining the potential for stressors
7 to interact synergistically, defined as the combined effects of stress having
8 a greater impact than expected [2]. Understanding the mechanisms behind
9 these synergistic interactions is important for quantifying the true impacts
10 of individual anthropogenic stress on organisms [3].

11 Pesticides are an important class of anthropogenic toxicant stress, with
12 the use of pesticides continuing to increase globally [4, 5, 6]. Pesticides are
13 seen as crucially important to crop productivity, preserving around one-fifth
14 of total crop yield contributing to food security [7]. Concerns about the
15 detrimental impacts of these pesticides [8, 9] have in the past forced policy
16 makers to restrict the application of some insecticides [10]. Non-target insects
17 frequently encounter these insecticides [5], with concentrations able to build
18 up throughout food sources and within various life-stages of the organism
19 [11, 12, 13, 14, 15, 16, 17].

20 Toxicants such as pesticides can cause lethality [18, 19, 20], but more often
21 have other sub-lethal effects such as impairments on foraging [21, 22, 23, 24],
22 feeding [25], learning [26, 27], memory [28, 27] and fecundity [29, 30, 31].
23 Exposure during early life can have both lethal and sub-lethal effects later

24 appearing during adulthood [32, 33]. These environmental contaminants
25 can interact synergistically in combination with other natural stressors. For
26 example, combinations of toxicant exposure with parasite infections can in-
27 crease individual mortality [34, 35], increase the initial pathogen load [36, 37]
28 and increase virulence [38]. Synergistic toxicant-pathogen interactions have
29 been observed in many types of organisms such as insects, snails, water fleas,
30 frogs, salamanders, fish and mussels (see review by Holmstrup et al., 2010).
31 In addition to toxicants causing direct lethality, they can also cause indirect
32 damage to individual immune defence. Individual organisms defend them-
33 selves against various infections via a suite of immune responses, and these
34 can be damaged or inhibited through toxicant exposure [39]. For example,
35 pesticides have been shown to reduce the total hemocyte abundance in in-
36 sects [40, 41], the nodulation initiation [40, 42], the encapsulation response
37 [43, 41] and antiviral defences [44].

38 Of particular recent concern are the widespread losses to global wild and
39 managed honey bee populations [6, 45, 46]. The Western honey bee (*Apis*
40 *mellifera* L.) is widely recognised as the most important commercial insect
41 pollinator [47, 48, 49, 50], contributing to global food security and biodi-
42 versity [51, 52]. While a single cause for these widespread colony losses has
43 yet to be identified, there is agreement that it may have its origins within
44 multiple stressors interacting with each other [53, 54, 55, 56]. Possible candi-
45 dates include neonicotinoid pesticides [12, 13, 57, 27], mites [58, 59], viruses
46 [60, 61, 62] and microsporidia infections [63, 64].

47 In this study, we examine the general mechanism by which immunotox-
48 icants interact with infection to reduce host health. This observed synergy
49 between multiple stressors is currently poorly understood from an immuno-
50 logical perspective [65]. We focus our study on the general ecotoxicological
51 applications of the model, in the case of any immunotoxicant interacting
52 with any parasite infection. We do this by formulating a system of nonlin-
53 ear ordinary differential equations (ODEs) to investigate the consequences of
54 immunosuppression by a toxicant and the effect this has on within-host infec-
55 tion. We first consider a toxicant-free environment to examine the conditions
56 under which the infection can spread. We then consider the interaction be-
57 tween the infection and both lethal and sub-lethal exposure to toxicants and
58 examine the outcome on within-host dynamics. We also consider the case of
59 aggressive direct lethality of toxicants on the production of new tissue cells.

60 **2. The Model**

61 The immune response of any individual relies upon the interdependent
62 defence of physical, humoral and cellular responses, denoted in our model
63 by immune function Z . Nowak and May [66] proposed a general model to
64 describe the interaction between a cellular immune response and a replicat-
65 ing virus, in the setting of self-regulating cytotoxic T lymphocytes (CTLs)
66 targeting infected cells. The model they present is simple but captures the
67 fundamental biological processes governing the immune response to foreign
68 antigens, and following this framework we denote within-host cell density as

69 X . We denote the total parasite/pathogen density as Y . The total number
70 of cells within the model represents a general susceptible subset of animal
71 tissue cells. As a motivating example, our model can be thought of describ-
72 ing the midgut epithelial cells of the honey bee X under a *Nosema ceranae*
73 infection Y [67] with associated immune response Z , although we also pro-
74 pose that our model can be thought of describing any interaction between
75 any immunotoxicant and associated parasite or pathogen in a general host.

76 Toxicants can be lethally toxic to individuals at high enough exposure [18,
77 19, 20]. In addition various functions associated with the immune response
78 are damaged by toxicants [39, 40, 41, 42, 43, 68, 69, 70, 44]. We model
79 both the direct lethality (denoted by parameter r) and indirect sub-lethal
80 immunotoxicity (denoted by parameter h) effects of toxicant exposure Q .
81 For simplicity, we assume fast dynamics of virus replication compared to the
82 replication of other immune or within-host cells resulting in the formulation
83 of the model (Figure 1) as a 3-compartmental set of nonlinear ODEs;

$$84 \quad \frac{dX}{dt} = \lambda - \beta Y X - dX - rQ \quad (1a)$$

$$85 \quad \frac{dY}{dt} = \beta Y X - aY - pYZ \quad (1b)$$

$$86 \quad \frac{dZ}{dt} = c - bZ - hQ \quad (1c)$$

87

88 with $c - hQ > 0$ and $\lambda - rQ > 0$. When $Z = 0$ (the immune response is
89 depleted), we remove equation (1c) from system (1) and the system becomes

90 the two dimensional system of equations (1a) and (1b) without the immune
91 response term $-pYZ$;

$$92 \quad \frac{dX}{dt} = \lambda - \beta YX - dX - rQ \quad (1a)$$

$$93 \quad \frac{dY}{dt} = \beta YX - aY \quad (1b)$$

94

95 We assume that within-host cells are produced at rate λ , and die at per-
96 capita rate d . Parasites are created at rate β via a linear mass action, and
97 are removed at per-capita rate a . The immune response Z is activated upon
98 encountering parasites Y and the removal of parasites occurs at rate p . Al-
99 though in reality, functions involved in immunity are not activated on the
100 instance of meeting the parasite, but there is a complicated intermediary
101 chain between processes which eventually result in the removal of parasites
102 [71]. For simplicity, we assume that this complicated process can be sum-
103 marised by our function pYZ . We assume that the immune dynamics Z are
104 decoupled from those of within-host and parasite density. This represents
105 the simplest possible assumption and various extensions to this assumption
106 are possible. Immunity is therefore produced at rate c , and is removed at
107 per-capita rate b .

108 Within our model we infer the mortality risk of the host through the status
109 of the within-host cells X , so that individual mortality risk is high when the
110 number of cells X is small. This condition enables us to think about the
111 mortality risk of an individual analogous to a highly infected within-host

112 tissue (e.g. parasite infection within the gut of a honey bee).

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

119 **3. Results**

120 In the following section we consider the baseline case of parasite infection
121 in a toxicant-free environment before analysing our within-host system under
122 the addition of a toxicant. We then consider the absence of direct lethal
123 effects of toxicants before presenting the unique case of an aggressive toxicant.

124 *3.1. Toxicant-free model*

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

$$130 \quad (X_A^{DFE}, Y_A^{DFE}, Z_A^{DFE}) = \left(\frac{\lambda}{d}, \quad 0, \quad \frac{c}{b} \right) \quad (2a)$$

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

$$135 \quad (X_A^{EE}, Y_A^{EE}, Z_A^{EE}) = \left(\frac{ab + cp}{\beta b}, \quad -\frac{d}{\beta} + \frac{b\lambda}{ab + cp}, \quad \frac{c}{b} \right) \quad (2b)$$

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

139 3.2. Toxicant-Parasite model

140 Next we consider system (1) under the condition of an infection and
141 toxicant exposure (denoted by subscript B). In this case the model predicts
142 two possible outcomes. First, the parasite infection is removed either by
143 immune suppression or by the direct effects of the toxicant on the production
144 of within-host cells represented by the DFE:

$$145 \quad (X_B^{DFE}, Y_B^{DFE}, Z_B^{DFE}) = \left(\frac{\lambda - rQ}{d}, 0, \frac{c - hQ}{b} \right) \quad (2c)$$

146 so that the addition of any toxicant reduces the total within-host cells by
147 $\frac{rQ}{d}$ and reduces the immune function by $\frac{hQ}{b}$. Secondly the model predicts an

148 infected individual under toxicant exposure represented by the EE:

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

149 (2d)

150 In this case, the parasite density grows rapidly as a result of the toxicant
151 suppressing the immune system. The introduction of the toxicant reduces
152 both within-host cells and immunity in both an infection-free and infected
153 individual, but an initial parasite infection is required for an infection to
154 grow.

155 The effect of toxicant exposure on the net change of within-host cells,
156 parasite density and immunity within the individual is summarised in Table
157 1.

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

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

163
164

165 We summarise the behaviour of the model under this condition (Figure 2)
166 into 3 distinct phases which describe the mechanism underlying the interac-
167 tion between toxicant exposure and infection at the within-host level of the

168 organism, and the parameter dependence of infection and immunity at equi-
169 librium. Note that the total number of cells within an individual organism is
170 not constant. This is because both parasite and within-host cells are removed
171 by either the toxicant exposure or infection and new cells are produced.

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

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

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

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

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

183 In phase three, the immune system has been destroyed and the parasite
184 infection is no longer present leaving only a small fraction of within-host cells.
185 Finally, the lethality of the toxicant causes the mortality of the individual
186 honey bee and production of new cells ceases.

187 Thus we have calculated the conditions under which the within-host dy-
188 namics change according to the level of toxicant exposure. By understanding

189 the relationship between the parameters in the model and toxicant stress, we
190 can make some biological interpretations. We predict that the ratio of the
191 production of immunity to the amount of immunotoxicity ($Q_0^* = \frac{c}{h}$) deter-
192 mines the point at which the infection load is at a maximum. The expression
193 $\frac{c}{h}$ can be thought of as an indicator of immune status, and the point at which
194 the toxicant stress becomes equal ($Q = Q_0^*$) represents the complete inhibi-
195 tion of the immune system. The expression $Q_1^* = \frac{\beta\lambda - ad}{r\beta} = \frac{\lambda}{r} - \frac{ad}{r\beta}$ represents
196 the point at which the ratio of cell production to lethal toxicant mortality
197 (indicator of within-host cell status) compares to the ratio of the loss of cells
198 to the toxicant cell depletion multiplied by the transmission of the infection.
199 Therefore this condition represents the status of within-host dynamics and
200 can be thought of as an indicator of health. When $Q = Q_1^*$, the infection has
201 been removed but the overall health status is very low, from which we infer
202 a higher mortality risk of the host. Therefore we have conditions describing
203 how toxicant exposure relates to that of the immune status Q_0^* and overall
204 health Q_1^* of the organism.

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

210 *3.3. Absence of toxicant lethality*

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

221 *3.4. Aggressive direct mortality*

222 It is worth noting that condition (3) is necessary to explore the interac-
223 tion between toxicant immunosuppression and the immune system. If this
224 were not the case, for example if the parameter r becomes large we would see
225 a situation where the toxicant acts too aggressively upon the host and causes
226 the parasite infection to be killed off (similar to phase II under the original
227 assumption) and following this the within-host cells are destroyed. The im-
228 mune system remains intact as the direct effect of the toxicant on production
229 of within-host cells is greater than the immune effect. We again see three
230 distinct phases as we increase the toxicant from low levels to high (Figure
231 5a). However now the toxicant exposure is more prominent and reduces both

232 parasite and within-host cells, stopping the infection from spreading quickly
233 (Figure 5b). In this situation we also see a somewhat contradictory phase 3
234 in which the host has neither parasite or within-host cells but a small amount
235 of immunity. This result demonstrates the necessity of our original condition.

236 **4. Discussion**

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

247 Through disentangling the individual effects of both lethal and sub-lethal
248 toxicant exposure, we were able to establish the role of each within the break-
249 down of within-host dynamics. Indirect (sub-lethal) suppression of the im-
250 mune system causes rapid proliferation of parasites within the host (Figure
251 3), while direct (lethal) mortality cause both parasites and within-host cells
252 to die. However without the direct effect of the toxicant on the production
253 of new cells, the host remains highly infective (Figure 4). We also predict

254 that an extremely small toxicant exposure can cause the proliferation of a
255 previously manageable infection.

256 The findings we present in this study shed new light on the poorly
257 understood mechanism by which toxicants seem to interact synergistically
258 with infection to increase mortality risk [65]. In the context of the recent
259 losses to honey bees populations [6, 45, 46], the synergistic immunotoxicant-
260 infection interaction studied here is one example of the recent hypothesis that
261 widespread honey bee losses may be multi-factorial [53, 54, 55, 56]. Synergis-
262 tic pesticide-infection interactions have been shown to increase mortality risk
263 within honey bees [34, 35]; for example, *Nosema ceranae* infections and thi-
264 acloprid, a neonicotinoid pesticide act synergistically to increase individual
265 mortality [37]. The findings we present in this paper propose one explanation
266 of how synergy between these toxicants and infection occur at the within-
267 host level. We show that these sub-lethal effects of anthropogenic stress are
268 potentially more damaging to individual health, aggravating parasitic stress.
269 This is in direct agreement to the positive correlation between low level (field
270 condition) neonicotinoid treatment and increases in parasite and viral in-
271 festations in bees [72, 73]. Infections within individual honey bees can be
272 significantly increased by different levels of low or high sub-lethal pesticides
273 [36]. Indeed, honey bees with undetectable levels of neonicotinoid imidaclo-
274 prid which are reared in sub-lethal conditions still have increased infection
275 levels [36]. This suggests that even extremely small sub-lethal exposure to
276 pesticide can result in outbreaks of infection. We show that increasing the

277 pesticide exposure by a small amount ($Q > 0$) can result in a transition from
278 a manageable parasite density level to a highly infected individual.

279 Our results rely upon condition (3) which ensures that the immune re-
280 sponse is destroyed before the within-host cells. This condition is crucial
281 to ensuring reasonable behaviour of the model, and it should be noted that
282 the reverse assumption predicts the presence of immunity even after both
283 infected and within-host cells are dead (Figure 5a). We highlight this limi-
284 tation of our theoretical work but argue that condition (3) is valid since the
285 direct lethality of toxicants only occur at high doses [18] and various immuno-
286 suppressive effects occur from toxicants [39], thus suggesting that toxicants
287 have a greater impact on suppressing the immune system.

288 The framework provided in this study focuses on the failure of the immune
289 system of an individual organism. However individuals interact within popu-
290 lations causing infection to spread to other susceptible individuals, and these
291 populations have associated interdependent immune defences at both the
292 within-host and between-host level. For example, social immunity involves
293 many behavioural and population-level mechanisms such as social fever, a
294 mechanism by which individuals increase the temperature of the surround-
295 ing environment in order to kill parasites [74], guarding, where patrolling
296 guards prevent infected individuals from interacting with healthy individuals
297 [75], hygienic cleaning behavioural traits, by which the population remove
298 diseased or dead individuals [76] and storing antimicrobial food [77]. Hence
299 the main limitation of our framework is that we may have only considered

300 one half of both interdependent within and between-host immunities. Cou-
301 pling population immunity models in the context of an epidemic alongside
302 our individual immunity framework could further explain the synergistic in-
303 teractions between toxicants and infection at both the individual and popula-
304 tion level. Further theoretical work incorporating these multi-level dynamics
305 could address the gap in understanding honey bee sudden collapse as syn-
306 ergistic stressors in similar ways to other models of colony collapse disorder
307 [78, 79, 80].

308 This work highlights the need for further studies which focus on syn-
309 ergistic interactions between various stressors at the within-host level. Our
310 theoretical study presents a starting position to think about these synergistic
311 interactions at the within-host level in the context of the immune system of
312 an individual organism. While our model has an inherently simple structure,
313 the addition of the toxicant function can lead to complicated dynamics that
314 are consistent with empirical observations. This framework can stimulate
315 further empirical and theoretical studies which focus on the interaction be-
316 tween toxicant exposure, infection and the immune system at both the social
317 group and individual level.

318 **5. Acknowledgments**

319 This work was supported by a Japan Society for the Promotion of Science
320 (JSPS) BRIDGE Fellowship and a University of Sheffield PhD scholarship
321 to R.D.B.

322 **6. Competing Interests**

323 We declare we have no competing interests.

324 **7. Authors' Contributions**

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

328 **8. Figures and Tables**

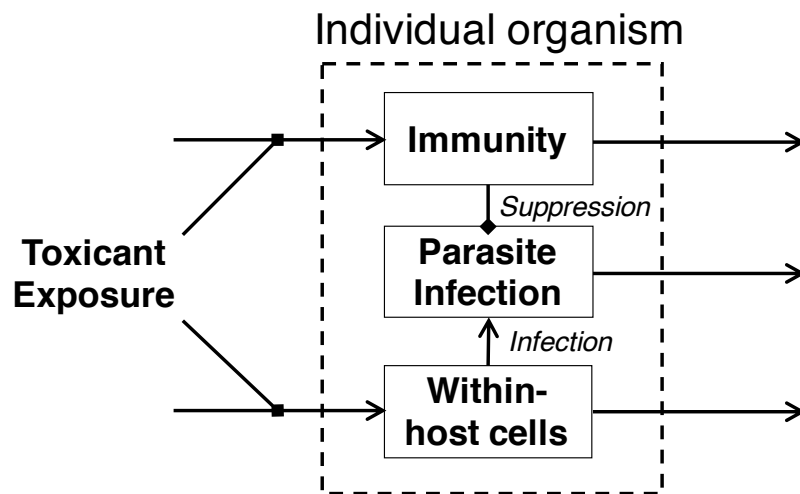


Figure 1: The modelling framework we use to model the interaction between toxicant exposure and parasite infection in an individual. Block arrows represent suppression. We model toxicant exposure as a suppressive effect on immunity and within-host cells.

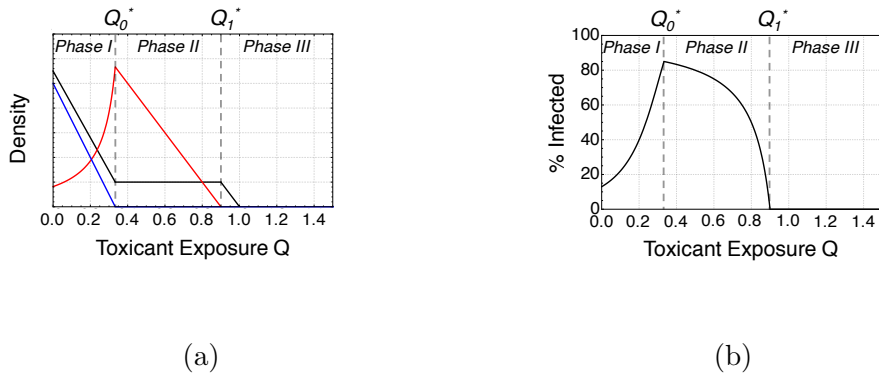


Figure 2: The mechanism of parasite infection under increasing toxicant exposure. This shows the parameter dependence of immunity, parasite density and within-host cells at equilibrium within the dynamics of our model. In (a) the total densities of immune function (blue), parasite load (red) and within-host cells (black) change as an individual is subject to higher toxicant loads. In (b) the total % parasite infection (black) changes as the toxicant load is increased. Parameters as in Table 2.

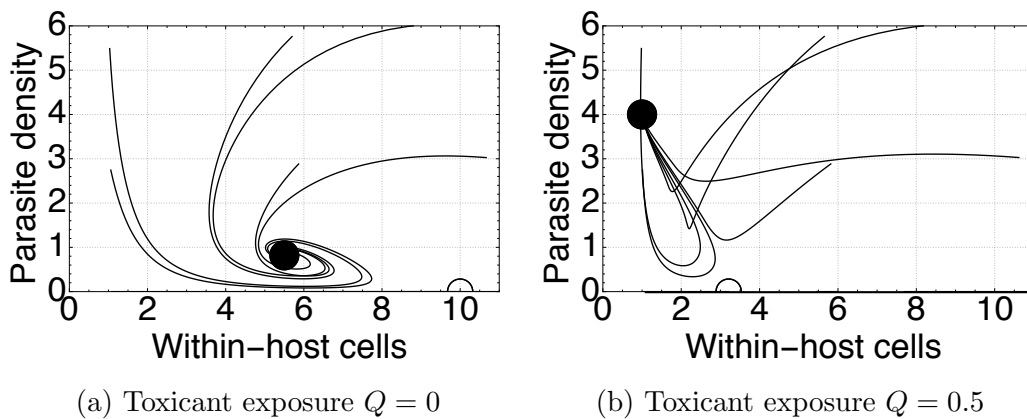
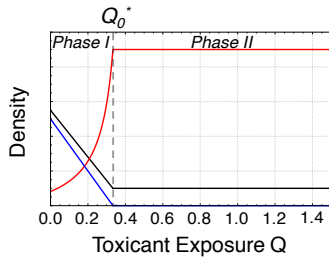
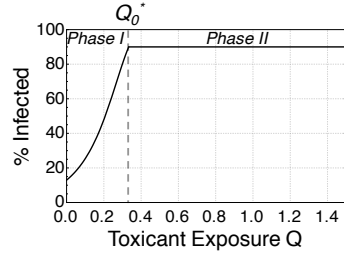


Figure 3: The convergence of the total density of within-host cells and parasites under no toxicant exposure (a) $Q = 0$, and small amounts of toxicant exposure (b) $Q = 0.5$. Black dots show the stable endemic equilibrium, white dots show the unstable disease-free equilibria and lines show the convergence from initial conditions. Parameters as in Table 2 and 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 ($Y \geq 0$).

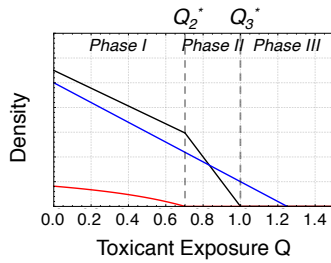


(a)

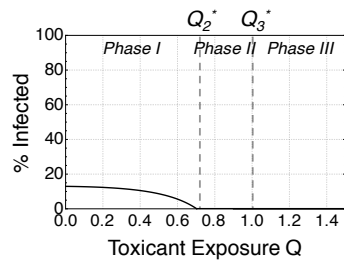


(b)

Figure 4: The mechanism of infection under increasing toxicant exposure, under only the immunosuppression of the toxicant effect. 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. In (b), the total % parasite infection (black) changes as the toxicant load is increased. Parameters as in Table 2.



(a)



(b)

Figure 5: The mechanism of parasite infection under increasing toxicant exposure with aggressive direct mortality. In (a), the total density of immune function (blue), parasite load (red) and within-host cells (black) change as an individual honey bee is subject to higher toxicant loads. In (b), the total % parasite infection (black) changes as the toxicant load is increased. Parameters taken from Table 2, but with a reduced indirect effect $h = 0.08$.

	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 initial and no 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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