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A theoretical exploration of dietary collective medication in social insects

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ABSTRACT

Animals often alter their food choices following a pathogen infection in order to increase immune function and combat the infection. Whether social animals that collect food for their brood or nestmates adjust their nutrient intake to the infection states of their social partners is virtually unexplored. Here we develop an individual-based model of nutritional geometry to examine the impact of collective nutrient balancing on pathogen spread in a social insect colony. The model simulates a hypothetical social insect colony infected by a horizontally transmitted parasite. Simulation experiments suggest that collective nutrition, by which foragers adjust their nutrient intake to simultaneously address their own nutritional needs as well as those of their infected nestmates, is an efficient social immunity mechanism to limit contamination when immune responses are short. Impaired foraging in infected workers can favour colony resilience when pathogen transmission rate is low (by reducing contacts with the few infected foragers) or trigger colony collapse when transmission rate is fast (by depleting the entire pool of foragers). Our theoretical examination of dietary collective medication in social insects suggests a new possible mechanism by which colonies can defend themselves against pathogens and provides a conceptual framework for experimental investigations of the nutritional immunology of social animals.

1. Introduction

Animals select foods in order to reach physiological states maximising growth, reproduction, metabolic health and survival, depending on their sex, age, and reproductive status (Lee et al., 2008; Solon-Biet et al., 2015). Nutrient regulatory behaviours have been most effectively studied using nutritional geometry, a conceptual framework for modelling the nutritional interactions between animals and their environments (Simpson and Raubenheimer, 1993, 2012). In this approach, the challenge for the animals is to regulate their intake of multiple nutrients simultaneously (typically but not necessarily, the macronutrients protein, carbohydrates and fat) at amounts and balances enabling them to maintain nutritional states maximising fitness traits. This optimal intake is known as the nutrient ‘intake target’ (Simpson et al., 2015a). The multi-dimensional aspect of nutritional geometry is critical for capturing the complexity of animal nutritional decisions, by breaking down food intake into specific amounts and ratios of nutrients that can have independent and/or interacting effects on the physiology and behaviour of animals (Simpson et al., 2015b).

Several recent studies based on this framework show how animals can dynamically adjust their nutrient intake following an infection in

order to boost their immune system and combat parasites or pathogens (Ponton et al., 2011, 2015). For instance, many insects increase their intake of dietary protein required for the synthesis of peptides in immune pathways (Lee et al., 2006; Povey et al., 2009; Povey et al., 2014; Mason et al., 2014). This behavioural response is analogous to self-medication, when sick animals ingest specific substances that are not usually part of their diets (Clayton and Wolfe, 1993; de Roode et al., 2013). In these individuals, the selective ingestion of curative substances in food produces measurable benefits to host fitness and negative effects on the pathogen.

While most research on dietary self-medication has been conducted on solitary animals (Abbot, 2014) or isolated individuals in the lab (Lee et al. 2006; Peck et al., 1992), nutrient balancing may also constitute a highly efficient, yet unexplored, mechanism to limit pathogen spread in animal groups, where the increased rate of contact between individuals induces a higher susceptibility to pathogens (Schmid-Hempel, 2017). In social animals the nutritional decisions of an individual not only depends on its own nutritional needs but also critically on the needs of other group members, as individuals will either cooperate or compete to access food (Lihoreau et al., 2015). Recent applications of nutritional geometry to social species indicate that animals can efficiently track

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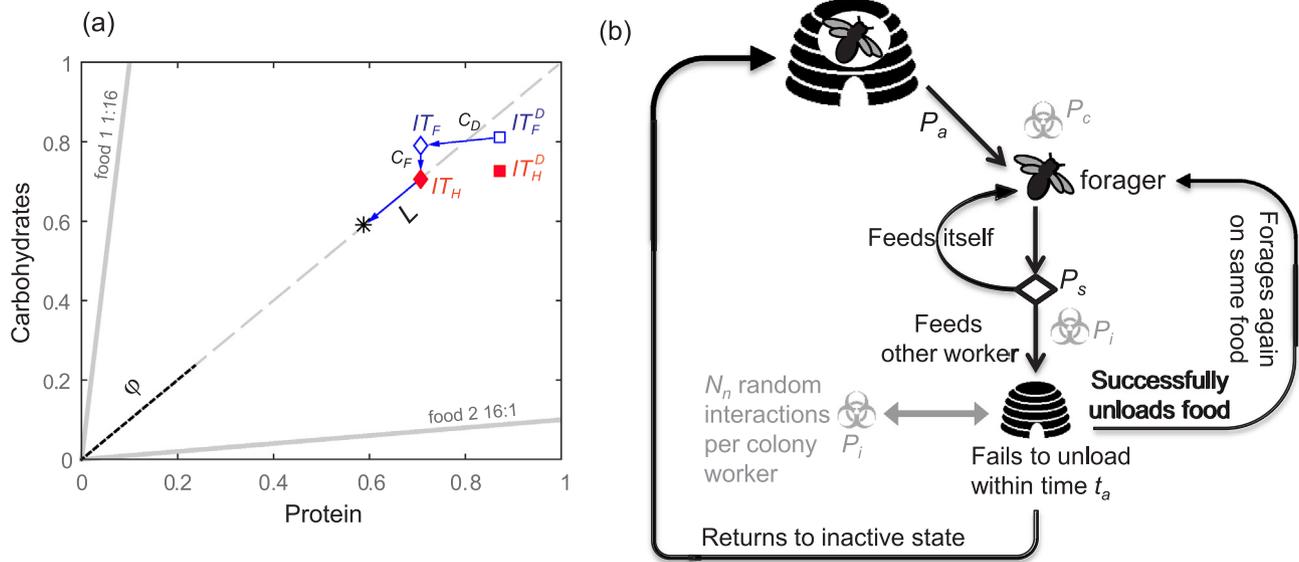


Fig. 1. Schematic overview of the model. All model parameters and variables are defined in Table 1. (a) Nutritional rules. Individual workers are defined by their nutritional state (NS, black star) and intake target (IT) in a two-dimensional nutrient space containing two foods. Non foragers have a P:C 1:1 intake target IT_H of magnitude 1. Foragers have an intake target IT_F composed of IT_H with an extra amount of carbohydrates C_F is added. Workers can adopt a defence intake target, IT_H^D for non foragers or IT_F^D for foragers, by adding $\overline{C_D}$, a protein rich component (P:C 8:1, magnitude m_D) to their respective IT. A forager brings back an amount of food φ per time step. At each time step, the NS of a worker is decreased by an amount that depends on its role and whether it has activated its immune response. The blue arrows illustrate the hypothetical path of a NS of a forager with activated immune response who managed to have its NS exactly on its IT_F^D . At the end of the step, this worker would see its NS decreased by C_D , C_F and L . (b) Foraging rules. Any mature worker has a probability P_a to start foraging in response to the nutritional demands of the colony. Foragers have a probability P_s of collecting foods for themselves, otherwise they will offer the collected food to other colony members first. Only foragers that have been able to completely unload their crop after a set time t_a continue to forage, otherwise they return to the status of non-foragers. If the forager was foraging for itself and continues to do so, it has a probability P_i to change food. Parasite transmission can occur in three different ways: foragers have a probability P_c of getting contaminated during the first simulation step in the initial infection regime or every time they successfully forage on a food source in the continuous infection regime; when food is unloaded from a forager to a non-forager, there is a probability P_i that a state 0 worker will be contaminated by a state 2 worker; at the end of every time step, each non-forager randomly interacts with N_n other non-foragers and there is a probability P_i that a state 0 worker will be contaminated by a state 2 worker during this interaction. All parameters and variables are defined in Table 1.

their own nutritional needs in various social contexts, as evidenced by self-selection diet experiments (Dussutour and Simpson, 2009; Hendriksma and Shafir, 2016) and simulations of individual-based models (Lihoreau et al., 2014, Senior et al., 2015; 2016a). However, whether social animals can respond to the infection states of their social partners by adjusting their nutrient intake in order to feed conspecifics and combat pathogen invasion has not been established.

The question of dietary collective medication is especially relevant in social insects, such as bees and ants, that exhibit high levels of social complexity (Hollnagel and Wilson, 2009). In these animal groups, individuals specialised in food collection (foragers) must regulate a nutrient intake target to a colony level comprising the needs of all the workers (e.g. nurses, guards), the breeders (e.g. queens, drones) and the brood (larvae), without a global knowledge of the intake targets of their nestmates, nor of the food stores in the colony (Behmer, 2009; Feldhaar, 2014). Disease transmission has been mainly explored in bees due to the fact that parasites and pathogens are major causes of population declines (Goulson et al., 2015; Klein et al., 2017). Social bees are infected by a wide range of viruses, protozoans, bacteria, mites, fungi and parasitoid insects, against which they have evolved behavioural strategies to prevent infection and limit contamination (Schmid-Hempel, 1998). At the individual level, foragers can adjust food collection, for instance by prioritising flowers with nectar rich in secondary metabolites to combat gut parasites (Baracchi et al., 2015) or collecting resins containing antimicrobial substances to limit the spread of fungus within colonies (Simone-Fintrom et al., 2012). At the collective level, bees also display a range of social immunity responses (Cremer et al., 2007) that include grooming (Büchler et al., 1992), social exclusion of infected nestmates (Waddington and Rothenbuhler, 1976, Baracchi et al., 2012), spatial segregation (Naug and Smith, 2007) and thermo-modulation to heat-kill pathogens (Starks et al., 2000). Although there is no direct evidence for a change of nutrient

intake target in infected bees (de Grandi-Hoffman and Chen, 2015), honey bees and bumblebees are able to accurately balance their intake of multiple nutrients (i.e. carbohydrates and free amino acids in nectar, protein and lipids in pollen) (Altaye et al., 2010; Hendriksma and Shafir 2016; Vaudo et al., 2016a; Stabler et al., 2015) and protein intake modifies baseline immune-competence levels in adults (honey bees: Alaux et al., 2010), thus setting the stage for dietary collective medication in these social insects. Recently, it was shown that honey bees infected with microsporidians *Nosema* spp. increase their intake of sugar syrup containing amino-acids, presumably to support their immune responses (Martín-Hernández et al., 2011; Lach et al., 2015).

Here we developed an individual-based model of nutritional geometry to explore the impact of dietary collective medication on a pathogen spread in a social insect colony. The model simulates a hypothetical social insect colony infected by a hypothetical horizontally transmitted parasite, inspired from the well-described interactions between honey bee (*Apis mellifera*) and *Nosema ceranae* (Higes et al., 2013). In this host parasite system, infected workers start foraging earlier in life (Goblirsch et al., 2013; Natsopoulos and McMahon, 2014), increase their number of daily foraging trips (Alaux et al., 2014; Wells et al., 2016) and spend more time outside the colony (Alaux et al., 2014; Wolf et al., 2014; Kralj and Fuchs, 2010). The reduced foraging workforce is compensated with the premature onset of foraging by young workers that have cognitive deficits (Vance et al., 2009; Ushitani et al., 2016), potentially leading to colony collapse (Russel et al., 2013). Using our model, we examined the influence of the immune response duration on the efficiency of collective dietary medication. Next, we described the impact of foraging failure related to pathogen virulence on parasite spread. Our aim was not to provide a quantitative model of bee-parasite interactions but rather to propose a new theoretical approach for social insect nutritional immunology that could guide future experimental research.

Table 1
Model parameters, variables, their notations and values.

variable/parameter	notation	description	Value
Total number of steps in a simulation	T_s	Duration of a simulation in steps	$T_s = 2000$
Number of mature workers	n_m	Number of mature workers, which can either be foragers or remain in the nest	$n_m = 400$
Number of foragers	n_f	Number of mature workers which are foraging	Variable
Number of immature workers	n_j	Number of workers in the nest which can never engage in foraging activity	$n_j = 100$
Nutritional state	NS	An agent's nutritional state, as tracked by its (p, c) position in the nutrient space, and denoting total intake of the two nutrients.	Variable (p, c) and initialised at the value of the individual's intake target
Intake target	IT	An agent's IT is the (p, c) coordinate in the nutrient space that maximizes fitness	$IT_H = (0.707, 0.707)$ $IT_F = (0.707, 0.715)$ $IT_H^D = (0.724, 0.709)$ $IT_F^D = (0.724, 0.717)$
Nutritional performance	D	The Euclidean distance between an agent's NS and the IT.	Variable
Food rail slope	V	The nutritional composition of a food in terms of the amount of carbohydrate (c) in a given food relative to single equivalent unit of protein (p) .	Food 1: $V = 16$ Food 2: $V = 1/16$
Appetite	A	The amount of a given food that an agent would consume to minimize D .	Variable
Current/ideal food rail angle	α_f, α_{ideal}	α_{ideal} and α_f are the angles associated with the ideal rail joining the NS and the IT of the individual and with the food rail f respectively	Variable
Food ingested	φ	The maximum amount of food that an agent is able to consume at a given time.	$\varphi = 0.2$
Cost of life	L	Amount by which the NS are decreased at each time step along a food rail of P:C 1:1	$L = \varphi/12 = 0.0167$
Cost of foraging	C_F	Additional carbohydrate cost for foraging	$C_F = L/2 = 0.0083$
Cost of immune response	C_D, m_D	C_D represents the cost of the immune response and is a vector along a food rail of P:C 8:1 and of magnitude m_D	$m_D = L = 0.0167$
Probability to start foraging and associated constant	P_a, K_a	P_a is the probability to start foraging	$P_a = e^{< D > \times K_a - 1}$ $K_a = 2$
Probability for a forager of collecting foods for itself	P_s, K_s	P_s is the of collecting foods to address a forager's own requirements	$P_s = e^{D \times K_s - 1}$ $K_s = 4.5$
Foraging giving up time	T_a	Time after which a worker will give up foraging and return to the status of worker in the nest if it did not unload the food it brought back to the nest	$T_a = 6$
Probability for a forager to leave a food while foraging for itself	P_L	Probability P_L to change food according to the difference between the current food rail it exploits and the ideal angle linking its NS and IT	$P_L = \frac{ \alpha_{ideal} - \alpha_f }{\pi/2}$
Probability of forager's contamination	P_c	Probability for a forager to be contaminated with the pathogen when it successfully brings food back to the nest	Initial contamination: $P_c = 0.2$ Continuous contamination: $P_c = 0.001$
Probability of becoming contaminated during interactions	P_i	Probability of becoming contaminated (state 1) by an interaction with an infected worker (state 2)	$P_i = 0.0025$ (default), 0.01 (fast pathogen spread simulations)
Probability for the infection to worsen	P_w, K_w	Probability that an individual's state worsen from state 1 to 2	$P_w = e^{D \times K_w - 1}$ $K_w = 6$
Probability for the infection to ease	P_R	Probability that an individual in state 2 returns to state 1	$P_R = e^{-D \times K_R}$ $K_R = 25$
Immune response time	T_d	Time during which an individual engages its immune response (workers cannot recover or die)	$T_d = 2, 5, 20, 200, 500$
Probability of engaging in a social immune response	P_D	Probability that an individual in state 0 or 1 activates its immune response when interacting with a state 2 individual	$P_D = 0.0, 0.01, 0.05, 0.25, 0.5, 0.75, 1$
Probability of failing to forage	P_f	The probability that an infected (state 2) bee will fail to forage for a simulation step	$P_f = 0.25$ (default), 0.0, 0.1, 0.35, 0.5 0.75

2. Model

2.1. Model overview

We developed an individual-based model of nutritional geometry to explore dietary collective medication in a social insect colony infected with a horizontally transmitted parasite (Fig. 1). In the model, the pathogen is transferred by passive contacts between individuals inside the colony. Each individual can be in a pathogen free state (state 0), contaminated at low level (state 1) or seriously infected (state 2). State 2 individuals are contagious and can fail foraging. All individuals have a normal intake target for protein and carbohydrates. Once infected, however, individuals adopt a defence intake target that is higher in protein. This defence target provides individuals with a better resistance to the pathogen. Uninfected foragers can detect infected nestmates and also adopt a defence intake target to engage in social immunity (Fouks and Lattorf, 2011). In what follows we describe the rules

for nutritional decisions, foraging choices, pathogen spread and defence response. All parameters and variables are defined in Table 1.

2.2. Nutritional decisions

Individual workers are defined by their nutritional state (NS, the amount and ratio of nutrients ingested and available to the worker at a certain time, which changes every step) and nutrient intake target (IT, the amount and ratio of nutrients that the worker must reach to maximize fitness, according to its activity and infectious status) in a two-dimensional nutrient space defined by protein P (x-axis) and carbohydrates C (y-axis; Fig. 1a). Note that while we focused on two nutrients for which social insect regulatory behaviour have been best characterised (Dussutour and Simpson, 2009; Altaye et al., 2010; Hendriksma and Shafir, 2016), a similar approach could be readily extended to different nutrients or more nutrients simultaneously (Simpson and Raubenheimer, 2012). The nutritional environment is

composed of two foods each represented by a nutritional rail V with a specific ratio of P to C (P:C). Instead of simulating natural food resources (Nicolson, 2011; Vanderplanck et al., 2017), in this theoretical exploration we used a C-rich food (P:C 1:16) and P-rich food (P:C 16:1) with extreme P:C ratios in order to cover a broad nutrient space.

The colony is composed of 500 individuals. To account for the aged-based division of labour of many social insects (Hollnagel and Wilson, 2009), we simulated two types of individuals. The immature workers (N_j) stay in the nest and never undertake foraging. The mature workers (N_m) can dynamically shift between staying in the nest and foraging, in accordance with the nutritional demands of the colony. Workers have different ITs depending on their foraging activity and whether they defend themselves against the pathogen (Fig. 1a). Non-foraging workers (mature and immature workers) have a P:C 1:1 intake target IT_H of magnitude 1. Foragers (mature workers) have an intake target IT_F composed of IT_H to which an extra amount of carbohydrates C_F is added, to account for their increased need of energy to travel and collect resources. When insects defend themselves against the pathogen they adopt a defence intake target, IT_H^D for non-foraging workers or IT_F^D for foragers, by adding \vec{C}_D , a protein rich component (P:C 8:1, magnitude m_D) to their respective IT. This increase of protein replicates the observed behavioural response of many insects following an infection (Lee et al., 2006; Povey et al., 2009; Povey et al., 2014; Mason et al., 2014). Note that similar simulations could have been run with an increase of carbohydrate as some parasites can also induce an energetic stress to the host (Mayack and Naug, 2010). At the beginning of a simulation all workers have their NS initialised at their respective IT. Their NS can then increase (the bees acquire food) or decrease (the bees used part of their resources) at each time step. Again these values were chosen for the sake of simplicity and do not necessarily reflect the intake target of real workers.

When foraging, insects carry an amount φ of food which is a fraction of the initial IT magnitude $|IT_H|$ ($\varphi = |IT_H|/5$ in our simulations) (Fig. 1a). The amount L by which the NS are decreased at each time step is itself set as a fraction of φ ($L = \varphi/12$ in our simulations). In effect, this means that a fully loaded forager could provide food for itself and for another nestmate for six time steps before being empty if these individuals were at a distance L from their IT (i.e. they were previously on their IT and had their NS decreased by L for one step before being fed). Alternatively, the forager could provide enough food for one nestmate to return to its IT if it had not received food for 12 steps (provided that the food itself would point directly to the IT). The magnitude of the extra-costs for foraging and the immune defence were also set in relation to L with $C_F = L/2$ and $m_D = L/k_D$ (with $k_D = 1$) in all simulations.

D , is the Euclidian distance between the NS and IT of an individual. D is a proxy of the nutritional performance of the individual (i.e. ability to track its IT). In the context of nutritional geometry, the lower D the higher the fitness of the individual (Senior et al. 2015, 2016b). In our model, insects use a ‘closest distance’ rule of compromise (ROC), meaning that foods are consumed to minimize D , to decide when to stop eating or receiving a meal. This parsimonious rule, in which individuals can over eat one nutrient while under eating the other up to a certain point, has been observed in many animals and has the advantage of making the same assumption for both nutrients (Simpson and Raubenheimer, 2012). The amount of food that an individual ideally needs to consume from a given food, its appetite A , is calculated as follows:

$$A = \min\{\varphi, D|\alpha_{ideal} - \tan^{-1}V|\}$$

where φ is the maximum amount of food an individual can eat on one time step, α_{ideal} is the angle of a hypothetical ‘ideal’ food rail connecting an individual’s NS to its IT, and V is the food rail of the food being consumed.

2.3. Foraging decisions

Any mature worker has a probability P_a to start foraging in response to the global nutritional demands of the colony (Fig. 1b). P_a increases with average D as follows:

$$P_a = e^{<D> \times K_a - 1}$$

where K_a is a constant.

Foragers have a probability P_S of collecting foods for themselves. Otherwise they will offer the collected food to other colony members first (Fig. 1b). P_S increases with the forager’s D as follows:

$$P_S = e^{D \times K_S - 1}$$

When an individual forages for others, it first attempts to unload its crop to a randomly chosen worker in the nest. This individual accepts as much food as allowed by its ROC. If the individual does not accept the whole meal, the forager can consume part of the load according to its own ROC. If its crop is still not empty the forager waits until the next step to unload any remaining food using the same procedure, to another randomly chosen worker in the nest and then potentially consuming part of the remaining food for itself again. The outcome of these interactions between foragers and non-foraging workers in the nest is what provides a social feedback for the foragers to choose whether to continue the task. Only foragers that have been able to completely unload their crop after a set time t_a continue to forage, otherwise they return to the status of workers in the nest (Fig. 1b). If the forager was foraging for itself and continues to do so, it has a probability P_L to change food according to the difference between the current food rail it exploits and the ideal angle linking its NS and IT:

$$P_L = \frac{|\alpha_{ideal} - \alpha_f|}{\pi/2}$$

where α_{ideal} and α_f are the angles (in radians) associated with the ideal rail joining the NS and the IT of the individual and with the food rail f respectively.

2.4. Pathogen spread

Each worker can be in a pathogen free state (state 0), contaminated but with low levels of infection (state 1), or seriously infected (state 2). In the model, no individual can die or definitely leave the colony. Pathogen spread was simulated in three different ways.

Infection initially occurs through direct contacts between foragers and food. Contamination could be either initial or continuous. In the ‘initial contamination’ regime, foragers have a probability P_c ($P_c = 0.2$) to become contaminated only during the first simulation step. In the ‘continuous contamination’ regime, foragers have a probability P_c ($P_c = 0.001$) to become contaminated at each simulation step.

Infection can also happen through interactions between foragers and workers in the nest during food exchanges. When state 0 workers interact with state 2 workers (see below), state 0 workers have a probability P_i of getting infected.

Finally, infection can occur via passive contacts between workers in the nest. On each time step, each worker in the nest randomly draws a number Nn of other nestmates to interact with, with a constant probability P_i to infect or to be infected by their partner following the same rules as with interactions between foragers and non-foraging workers.

2.5. Defence rules

On each time step, state 1 workers have a probability P_w of seeing their infection state worsen to state 2.

$$P_w = e^{D \times K_W - 1}$$

Individuals that turn into state 2 then immediately adopt their defence intake target IT_D . State 2 workers have a probability P_R to

decrease their pathogen load and revert to state 1, and this probability is inversely proportional to D .

$$P_R = e^{-D \times K_R}$$

When this happens, the recovering worker continues to engage its immune response for T_d time steps. During this time T_d the infection state of workers cannot worsen to state 2. However workers can revert from state 2 to state 1. The higher T_d the longer the immune response duration. Using different values of T_d is analogous to triggering different components of the insect immune system. A low T_d replicates an innate immune response whereas a high T_d is more similar to an adaptive immune response (Schmid-Hempel, 1998).

State 2 workers also potentially suffer from a decreased foraging efficiency due to their heavy infection rates. On each time step, foragers have a probability P_f of failing to bring back food to the nest. In this case, workers must wait for the next step until they attempt foraging again. This simulates the impaired foraging performances of insects infected with parasites (Gómez-Moracho et al., 2017).

At the collective level, workers that are not yet infected (state 0) or just contaminated (state 1) have a probability P_D to engage in a social immune response by adopting their defence intake target IT^D whenever they interact with a seriously infected worker (state 2). Through social immunity, foragers can adjust their nutrient intake to prepare themselves to fight a potential contamination and to address the needs of infected nestmates and help them recover.

2.6. Simulations and analyses

All simulations and statistical analyses were conducted in Matlab. We ran simulations with either an initial contamination regime (contamination during the first simulation step only) or a continuous contamination regime (contamination at each simulation steps).

Each simulation ran for 2000 steps and was replicated 250 times (26250 simulations in total). We used populations of 500 insects (100 immature workers, 400 mature workers) with 40% of foragers at the beginning of the simulation (200 workers in the nest + 200 foragers). For each simulation, we measured variables related to pathogen spread (number of infected individuals in state 1, state 2 and state 1 + 2), colony nutritional performance (average D) and colony foraging effort (final number of foragers n_f , total number of foraging trips accomplished by all foragers n_T).

We conducted two-way analyses of variances (ANOVAs) on these results to test the effects of the immune response duration (T_d), the probability to engage in a social immune response (P_D) and their interaction on state 1, state 2, state 1 + 2, contamination latency L (i.e., the time elapsed until half of the colony was in state 1 or 2), D , n_f and n_T . For the initial infection regime, some simulations never reached a state where half of the bees were contaminated or infected. In this case we used one-way ANOVAs to test the effect of P_D on contamination latency L for each value of T_d (Table S1).

3. Results

3.1. Effect of immune response duration

We explored the effect of the immune response duration ($T_d = 2, 5, 20, 200, 500$) and the probability to engage in a social immune response ($P_D = 0.0, 0.01, 0.05, 0.25, 0.5, 0.75, 1$) on pathogen spread (state 1, state 2, state 1 + 2, contamination latency L), colony nutritional performance (the lower D the higher the performance) and colony foraging effort (n_f , n_T). Here we focussed on the initial contamination regime only (Table 2) and a relatively slow pathogen spread ($P_s = 0.0025$), where a majority of the workers is contaminated or infected within the simulated time (Fig. 2). Simulations with the continuous infection regime yielded similar results (Fig. S1, Table S2).

The immune response duration (T_d), the probability to engage in a

social immunity (P_D) and their interaction had a significant effect on pathogen spread (Table 2; for the effect of P_D on contamination latency L see Table S1). Long immune responses ($T_d = 200, 500$) resulted in the lowest level of pathogen spread (Fig. 2) and the lowest colony foraging effort (Fig. 3). In these conditions, there was no clear effect of engaging in social immune response.

By contrast, short immune responses ($T_d = 2, 5, 20$) resulted in a much stronger pathogen spread, with larger numbers of contaminated workers (state 1 + state 2 individuals) due to the higher proportions of infected workers (state 2 individuals) and the shorter contamination latencies (L) than for long immune responses (Table S1). The colony foraging effort (n_f and n_T) was also higher (Fig. 3). In these conditions, increasing the probability to engage in a social immune response (P_D) led to a significant reduction of pathogen spread and foraging effort, down to similar values to those obtained for long immune responses (Fig. 3). The average nutritional performance of insects (D) was always higher (lower D) in the presence of social immunity ($P_D > 0$) than without social immunity ($P_D = 0$). Therefore, social immunity, by which foragers adjust their nutrient intake to address the needs of their infected nestmates, is an efficient mechanism to reduce pathogen spread when immune responses are short.

3.2. Effects of pathogen virulence

Social insect infected by parasites often show impaired foraging behaviours (Gómez-Moracho et al., 2017), which suggests a reduced food intake at the colony level. Here we explored the consequences of foraging impairment on pathogen spread by varying the probability for infected foragers (state 2 workers) to fail foraging ($P_f = 0.0, 0.1, 0.35, 0.5, 0.75$) for slow pathogen transmission ($P_s = 0.0025$, i.e. same value as in the previous section), and fast pathogen transmission ($P_s = 0.01$).

At a slow pathogen transmission rate ($P_s = 0.0025$), increasing the probability of failing foraging (P_f) was generally beneficial to the colony. Colonies experienced reduced numbers of contaminated individuals (state 1 and 2 workers; Fig. 4a) and longer contamination latencies (L ; Fig. 4c). Here, the impaired activities of foragers only induced a slight decrease of the colony nutritional performance (D ; Fig. 5a) and an increase of the foraging effort (n_f and n_T ; Fig. 5b and c).

Interestingly the results were markedly different at a fast pathogen transmission rate ($P_s = 0.01$). In these conditions, the pathogen almost always contaminated the entire colony (average number of state 1 + 2 workers: 498.64 ± 2.95 (mean \pm SD)) within the simulated time. Increasing the probability of failing foraging (P_f) led to an increased number of infected workers (state 2 workers; Fig. 4b), up to nearly the whole population (average number of state 2 workers: 489.32 ± 7.35 (mean \pm SD)) being infected for frequent foraging failure of contaminated individuals ($P_f = 0.75$). The contamination latency (L) was generally low and increased with P_f (Fig. 4c), indicating that while the final spread of the pathogen reached catastrophic levels, the early stages of the contamination were still partly delayed when infected foragers often failed to bring food back to the colony. Frequent foraging failure ($P_f = 0.75$) led to a very marked decrease in colony nutritional performance (higher D) up to an average level that was approximately five times lower than for other values of P_f (Fig. 5a). The effect of P_f on the foraging effort was also very pronounced. Increasing P_f led to a recruitment of much higher numbers of foragers (n_f ; Fig. 5b) and an exponentially growing number of cumulated foraging trips throughout the simulations (n_T , Fig. 5c). Therefore, while high probabilities of failing foraging were beneficial to colonies at low transmission rates, by removing infected individuals and limiting pathogen spread, high probabilities of failing foraging were highly detrimental at fast transmission rates, by reducing social immunity and accelerating colony declines.

Table 2

Results of two-way ANOVAs testing the effect of P_D and T_d on the number of contaminated individuals (state 1 + state 2), contaminated individuals (state 1), infected individuals (state 2), number of foragers n_f and total number of foraging trips n_T , for an initial contamination regime. Parameters and variables are defined in Table 1.

Source	SS	df	MS	F	p
Variable: number of contaminated and infected individuals (state 1 + 2)					
P_D	237699.9	6	39616.6	77.08	3.391E-94
T_d	627124.9	4	156781.2	305.05	5.56E-246
Interaction	174465	24	7269.4	14.14	2.921E-56
Error	4479056	8715	513.9		
Total	5518346	8749			
Variable: number of state 1 individuals					
P_D	427.9	6	71.317	1.08	0.3689
T_d	2738.4	4	684.588	10.41	0
Interaction	3024.9	24	126.039	1.92	0.0045
Error	573019.9	8715	65.751		
Total	579211.1	8749			
Variable: number of state 2 individuals					
P_D	230031.5	6	38338.6	106.25	1.11E-129
T_d	547890.9	4	136972.7	379.6	7.33E-302
Interaction	182613.1	24	7608.9	21.09	5.856E-89
Error	3144675	8715	360.8		
Total	4105211	8749			
Variable: D					
P_D	0.00176	6	0.00029	14.68	0
T_d	0.00051	4	0.00013	6.32	0
Interaction	0.00047	24	0.00002	0.97	0.5018
Error	0.17433	8715	0.00002		
Total	0.17706	8749			
Variable: n_f					
P_D	4265.1	6	710.85	17.86	1.099E-20
T_d	9059.4	4	2264.86	56.89	1.858E-47
Interaction	4065.2	24	169.38	4.25	1.572E-11
Error	346955.7	8715	39.81		
Total	364345.4	8749			
Variable: n_T					
P_D	5.10E+09	6	8.51E+08	39.45	1.297E-47
T_d	1.69E+10	4	4.23E+09	196	3.46E-161
Interaction	3.94E+09	24	1.64E+08	7.61	4.611E-26
Error	1.88E+11	8715	2.16E+07		
Total	2.14E+11	8749			

4. Discussion

Many insects adjust their nutrient intake to combat pathogens and parasites (Lee et al., 2006; Povey et al., 2009; Povey et al., 2014). Here we explored how such self-medication behaviour could scale up to a social insect colony, where individuals forage for their nestmates and dynamically balance their collection of multiple nutrients to reach a colony-level intake target. Based on recent advances in nutritional

geometry modelling (Lihoreau et al., 2014, 2015), we developed an individual-based model to explore the consequences of dietary collective medication in hypothetical social insect colonies infected by a horizontally transmitted parasite that impairs the foraging behaviour of workers.

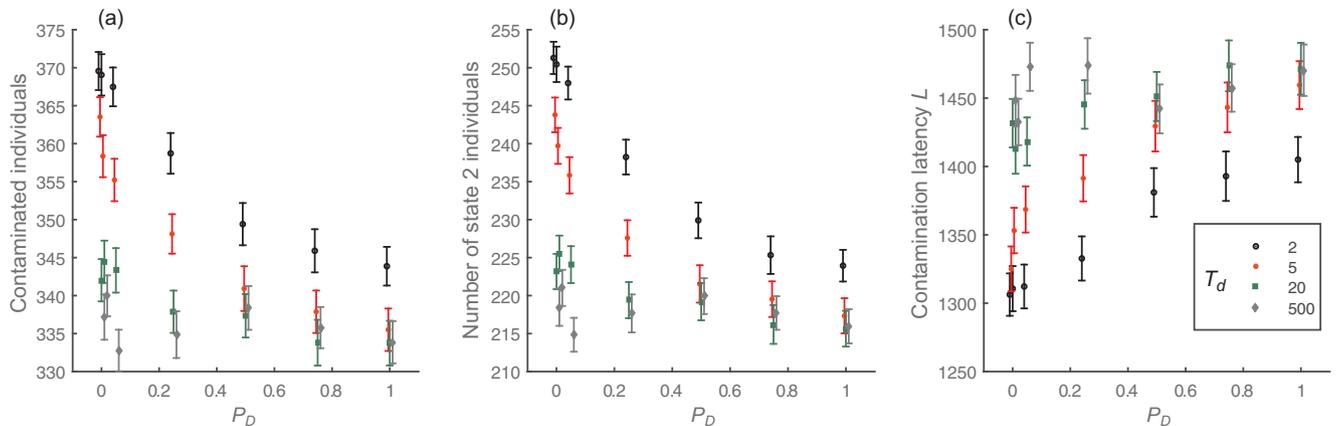


Fig. 2. Effect of the immune response duration (T_d , colour coded series) and the probability to engage in a social immune response (P_D) on (a) the total number of contaminated workers (state 1 + 2), (b) the number of infected workers (state 2), and (c) the contamination latency (L). All means are shown with their standard deviation. Parameters and variables are defined in Table 1.

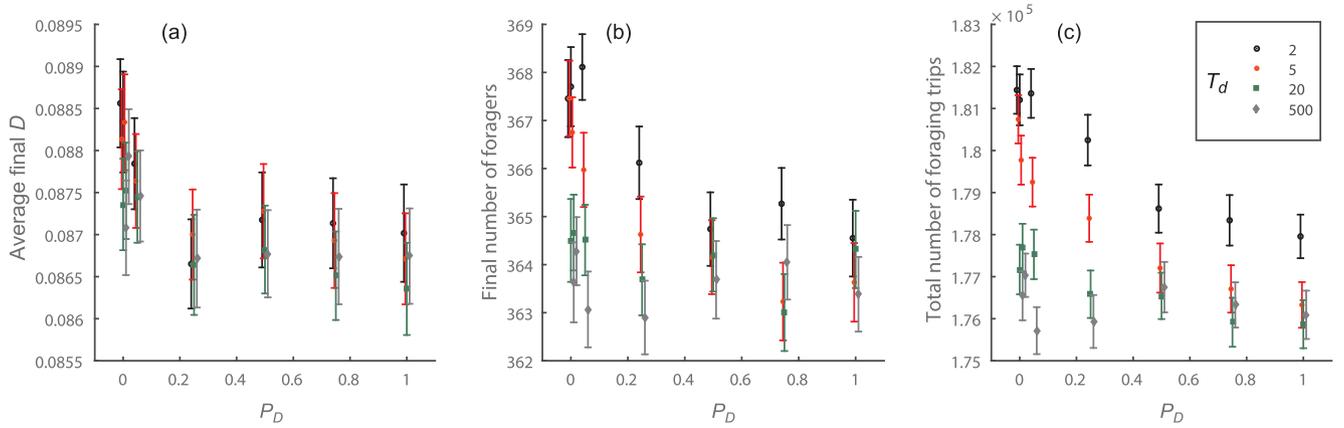


Fig. 3. Effect of the immune response time (T_d , colour coded series) and the probability to engage in a social immune response (P_D) on (a) the average nutritional performance of the colony (D), (b) the final number of foragers (n_f), (c) and the total number of foraging trips during a simulation (n_T). All means are shown with their standard deviation. Parameters and variables are defined in Table 1.

4.1. Collective nutrition can efficiently limit pathogen spread

Several recent models have considered the effects of pathogens and parasites on colony dynamics (Becher et al., 2014; Horn et al., 2016). Social insects are known to prophylactically collect anti-pathogen non-food materials such as resins to prevent contaminations of parasites and pathogens (Christe et al., 2003; Chapuisat et al., 2007; Simone et al., 2009; Simone-Finstrom et al., 2012). However, none of these studies have considered the potential role of nutrition, and in particular the interacting effects of specific nutrients, in mitigating these effects. Our theoretical exploration of dietary medication based on nutritional geometry suggests that collective nutrition is a potentially efficient social immunity mechanism to limit pathogen spread in a colony. This is true especially when immune responses are short, which is typically the case for innate immune responses in insects (Schmid-Hempel, 1998). Through social immunity, foragers can adjust their nutrient intake to address the needs of infected nestmates and prepare themselves to fight a potential contamination.

Although the basic assumption that social insects make dietary medication decisions remains to be empirically validated, several recent studies suggest that all the ingredients are met. In bees for instance, mounting evidence show that workers accurately balance their intake of macronutrients to address their nutritional needs at the individual (Altaye et al., 2010; Stabler et al., 2015) and collective (Hendriksma and Shafir, 2016; Vaudo et al., 2016b) levels. Additionally, foragers are known to exploit secondary metabolites in plant products with anti-microbial properties in order to combat pathogens (Erler et al., 2014; Manson et al., 2010; Baracchi et al., 2015). Similar observations have been made in ants (Christe et al., 2003; Chapuisat et al., 2007; Dussoutour and Simpson, 2009; Cook et al., 2010).

Importantly, individual-based models such ours are a powerful mean to generate well-defined predictions for empirical testing using experiments with nutritional geometry designs (Lihoreau et al., 2015).

4.2. Foraging impairment limits pathogen spread at slow transmission rates

Our theoretical exploration of dietary collective medication also suggests interesting consequences of behavioural changes in infected foragers for the colony health. For instance, infected honey bees often spend more time outside the colony and sometimes even never come back (e.g. Kralj and Fuchs, 2010; Dussaubat et al., 2013). Such behaviour may reflect impaired cognitive capacities that reduce the orientation performances of honey bee foragers or a host manipulation by the pathogen to favour its own spread (Schmid-Hempel, 2011). Reduced homing rates have also been interpreted as an altruistic ‘self-removal’ strategy by which infected honey bees remove themselves from the colony to prevent disease transmission (Rueppell et al., 2010). Interestingly, our model suggests contrasted influences of impaired foraging on pathogen spread depending on its transmission rate. Inefficient infected foragers can benefit the colony provided that the pathogen does not spread fast enough, because their inability to feed nestmates or to return to the colony can act as a de facto quarantine mechanism. But if that quarantine effect of failing foragers is insufficient to stop the initial spread of the pathogen, there is a risk of failing to provide the colony with the adequate intake requirements necessary to engage its immune defence response. Therefore, affecting the foraging activity can either hinder or help its progression, depending on the specific effects of a pathogen, suggesting that different selection pressures may lead to similar behaviour depending on the host-pathogen system under consideration.

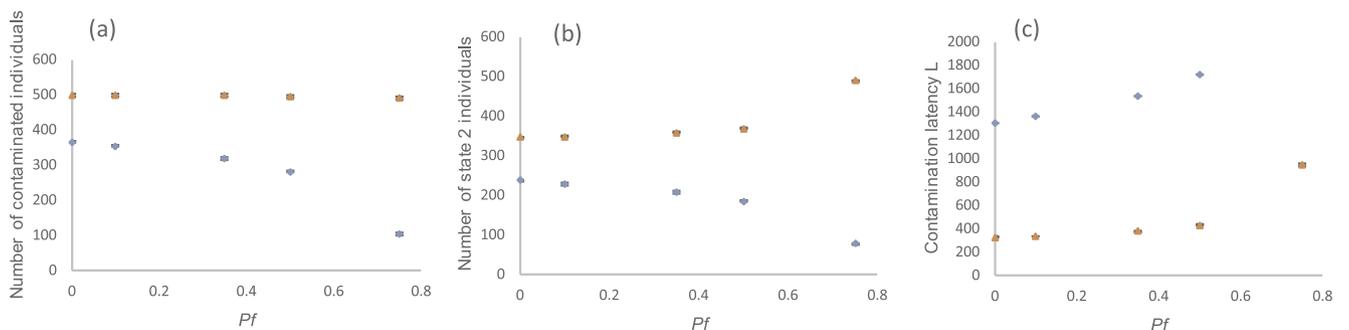


Fig. 4. Effect of the probability of infected individuals to fail foraging (P_f) for slow (blue: $P_s = 0.0025$) and fast (red: $P_s = 0.01$) transmission rates on (a) the total number of contaminated individuals in state 1 or 2, (b) the number of infected individuals (state 2), (c) and the contamination latency (L). All means are shown with their standard deviation. Parameters and variables are defined in Table 1.

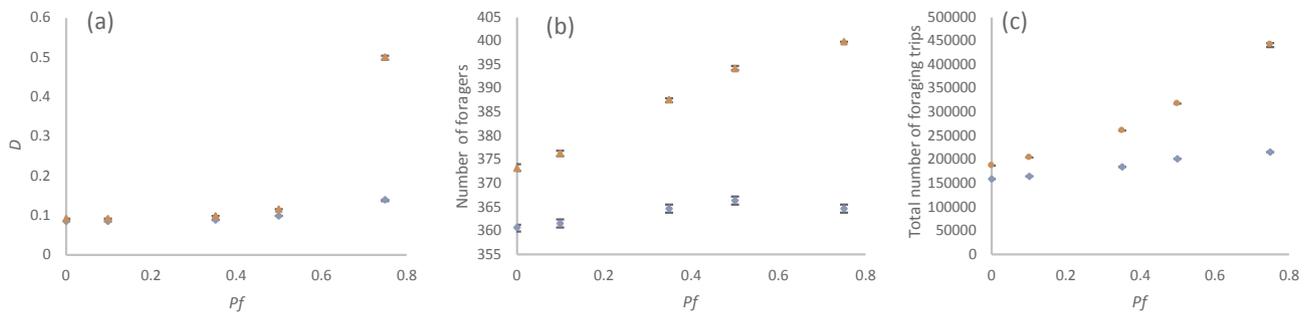


Fig. 5. Effect of the probability of infected individuals to fail foraging (P_f) at two different pathogen transmission probabilities (blue: $P_s = 0.0025$; red: $P_s = 0.01$) on (a) the average nutritional performance of the colony (D), (b) the final number of foragers (n_r), (c) and the total number of foraging trips during a simulation (n_T). All means are shown with their standard deviation. Parameters and variables are defined in Table 1.

4.3. Implications for colony health

An imbalanced nutrition is known to induce high mortality rates and colony collapse in social insects (Dussutour and Simpson, 2012). Over recent years, malnutrition has become particularly concerning in bees and is now considered a major cause of population declines, due to the lack of key nutrients for development, cognition or survival (Goulson et al., 2015; Klein et al., 2017). For instance, honey bees fed omega-3 poor pollen have reduced learning abilities, potentially incurring important foraging costs to colonies (Arien et al., 2016). Under natural conditions, when foragers fail in their collect food or disappear, more hive bees tend to become foragers and cease their hive-related activity, potentially translating into reduced brood care, defence and hygiene, as well as less efficient foraging efficiencies by the inexperienced foragers. Above a certain rate of forager disappearance, colony population may decrease dramatically and lead to an inevitable colony collapse (Khoury et al., 2011, 2013; Russell et al., 2013; Perry et al., 2015). Although purely theoretical, our study suggests that a failure in addressing the different nutritional needs of nestmates with various infection levels can have similar consequences.

Ultimately, accurate mapping of nutrient intake by infected bees and its consequences on colony functions, using our models, may allow for designing constructive interventions to limit these dynamics, for instance by providing infected colonies with appropriate plant resources that produce nectars and pollens that enable bees to self-medicate. Of course this would require some more development and precise parameterisation of our exploratory model, based on observations and experimental work. For instance, honey bee workers may use an “asymmetrical quadratic” rule of compromise when balancing carbohydrates and essential amino acids instead of the parsimonious nearest distance rule of compromise used here (Paoli et al., 2014). Bees also appear to balance their intake of lipids in pollen (Vaudo et al., 2016a,b) and mineral salt in water (Lau and Nieh, 2016) in addition to carbohydrates and protein. Importantly, all these adjustments are readily available in classical state-space models of nutritional geometry (Simpson and Raubenheimer, 2012) and can be implemented in our individual-based platform.

4.4. Nutritional immunology of social animals

Beyond identifying novel predictions about social insect-pathogen interactions, our model introduces a new framework for studying the nutritional immunology of social animals, by integrating models of epidemiology (Fefferman et al., 2007) and social nutrition (Lihoreau et al., 2014, 2015). This approach, here developed for a superorganism, could be expanded to a wider range of social species in which individuals make nutritional decisions for others, for instance when adults provision their brood or choose nesting environments that will provide nutrition for offspring. In principle, nutritional geometry models can be applied to many host-pathogen interactions in order to

derive new empirically testable predictions, with only minimal fine tuning of the nutritional rules (number of nutritional dimensions, intake targets, rule of compromises, non-dietary foods), social rules (nature and frequency of interactions), and fitness consequences (impaired development and behaviour) for the hosts and the pathogens (Simpson et al., 2015a). A major challenge for host-pathogen research is to study these interactions from both perspectives (Schmid-Hempel, 2011). In the present case, the potential overlap of the nutritional changes required by the defence of the hosts and the nutritional requirements of the pathogens themselves may be critical. In honey bees, for instance, diets with higher pollen quantities increase *N. ceranae* intensity but also enhance the survival of honey bees (Jack et al., 2016). Models of nutritional geometry have already begun to explore these aspects by integrating the nutrient intake and fitness responses of multiple actors (hosts, pathogens, symbionts) and how they influence each other (Ponton et al., 2011; Wong et al., 2015). How these complex interactions scale up at the level of animal groups, where hosts interact with each other, remains an open question.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.jinsphys.2017.08.005>.

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