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Parasite resource manipulation drives bimodal variation in infection duration

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Abstract

Over a billion people on earth are infected with helminth parasites and show remarkable variation in parasite burden and chronicity. These parasite distributions are captured well by classic statistics, such as the negative binomial distribution. But the within-host processes underlying this variation are not well understood. In this study, we explain variation in macroparasite infection outcomes on the basis of resource flows within hosts. Resource flows realize the interactions between parasites and host immunity and metabolism. When host metabolism is modulated by parasites, we find a positive feedback of parasites on their own resources. While this positive feedback results in parasites improving their resource availability at high burdens, giving rise to chronic infections, it also results in a threshold biomass required for parasites to establish in the host, giving rise to acute infections when biomass fails to clear the threshold. Our finding of chronic and acute outcomes in bistability contrasts with classic theory, yet is congruent with the variation in helminth burdens observed in human and wildlife populations.

Keywords

parasite, within-host, resource manipulation, acute, chronic, immunity

Background

Over one billion people are infected with parasitic worms and suffer the health costs of hosting helminths [1, 2]. Yet hosts vary tremendously in their duration of infection, parasite burden [3], and subsequent morbidity outcomes [1, 4]. Because of this variation, host populations typically have a few individuals with many parasites while most individuals have few or no parasites [3]. Variation in parasite burden has been classically formalized by the overdispersed negative binomial distribution [5, 3], but the biology underlying this pattern remains unclear [6]. Many of the hypotheses to explain variation in parasite burden relate to host heterogeneity in susceptibility, recovery, or exposure [7, 8]. In this study we focus on infection duration, the inverse of recovery, and show that variation in infection

duration can generate realistic variation in parasite burden. We then identify key within-host processes that lead to divergence in duration. Because parasite burden and infection duration drive many health costs of infection [1, 2], it is crucial to understand the within-host processes that lead some hosts to expel parasites quickly in acute infections while others suffer persistent infections.

To elucidate these critical within-host processes, we integrate the two dynamic perspectives that have dominated within-host theory: resource competition between host and parasite [9], and immunity-driven top-down control of parasite growth by the host [10]. Since ultimately parasite growth as well as the host immune response relies on resources [11, 12], we focus on within-host resource flows and the impact of the parasite on host metabolism.

Parasite modulation of the immune system is well-studied [13, 14, 15], but parasites are also capable of modulating host energy dynamics through altered resource uptake or reduced digestive transit time [16]. However, the implications of these manipulations are poorly understood, despite the fact that resource modulation by parasites is widespread [e.g. 17] and is likely decisive for infection outcome [12], especially under food-limited conditions [18, 19, 20, 21].

Here we represent host resource dynamics using Dynamic Energy Budget theory [22, 23], and build a novel framework to analyse the within-host interaction between parasite and host. Our model accounts for within-organism resource flows by integrating the dynamics of food intake, metabolism, and growth for hosts, and by including the resource-dependent immune response and parasite growth. We formulate the model on the basis of the outcomes from mouse rewilding studies that have examined the relationships between resources, immunity, and infection in a realistic setting, yet with controlled parasite exposure [24, 25].

In this framework, parasites modulate within-host resources, which results in a positive feedback of the parasite population on its own resource availability (i.e. an Allee effect). This positive feedback gives rise to outcomes that vary in infection duration, parasite burden, and host health. Because these outcomes are emergent results of the within-host interactions, we avoid making any *a priori* assumption of an acute or chronic outcome, which is the norm in theoretical epidemiology [10]. In this study we will use the terms acute and chronic to indicate infections of short and (life-) long duration. In the

biomedical literature, descriptions of infections as acute or chronic often also carry connotations about both the nature of the immune response (e.g. acute implies inflammatory) and the severity of infection. Here we use these words only as a shorthand to describe the duration of infection, although we note that our modelling approach could be extended to consider the health costs of infections of short- versus long-duration.

Crucially, we find that when parasites modulate host resource flow, both acute and chronic infections are possible for identical model settings. Acute and chronic infections encompass the most extreme variation in infection outcomes, while this variation emerges from the resource-driven interaction between parasite and host. In population settings, the bistability underlying these outcomes moreover drives parasite burdens that follow negative binomial distributions, as so frequently observed in nature.

Methods

Model formulation

To analyse how host metabolism, immunity and parasite growth interact with parasite modulation of resources, we formulate and analyse a mathematical model of these within-host processes. Using Dynamic Energy Budget (DEB) theory [22, 23] to account for resource-driven processes (where all processes and flows are translated into units of biomass), we extend the baseline DEB model to include parasite and immune processes.

As a case study for model formulation, we use a mouse-gastrointestinal nematode system (the *Mus musculus* – *Trichuris muris* interaction). A widely studied system, murine growth and immunity to infection (reviewed in [27]), allow for empirically grounded model assumptions. The host organism is modelled using biomass 'pools', including structural mass (S), reversible mass (R), and ingesta (G). We explicitly account for the biomass in the colon, referred to as 'egesta' (C), and for induced immunity (I_i, Fig. ESM2). Structural mass and reversible mass form the two major components of total body mass. Structural mass represents essential body components, such as bone, muscle, and organs, whereas

reversible mass can be metabolized when food supply is low, such as fat tissue, liver glycogen stores, and non-essential muscular tissue.

We use a standard demand-driven, net-production DEB model [28, 29]. This model structure is representative for mammal hosts and deviates (here and elsewhere) from the model defined in [30]. The model is parameterized for M. musculus [31, 23, 32] and its baseline settings (host-only) result in realistic growth curves [31], as does varying food availability (Fig. ESM3, [cf. Fig. 3 in ref. 31]). With this validation, use the full-grown mouse as the initial state for parasite infection. This assumption facilitates equilibrium analyses and is consistent with mature mice being used in the rewilding field experiments (Fig. ESM1). All model flows and processes are discussed below, full model equations and variables are given in Fig. ESM2, and parameter definitions and values are given in Table ESM1.

The host has a constant food availability, F [31], and intake is defined by size and body condition, according to $A(R,S) = \frac{F\iota_{max}S^{2/3}}{1+e^{\eta\left(\frac{R}{S}-\theta_r\right)}}$ [29]. Intake is then scaled with maximum ingestion rate, ι_{max}, and with structural mass to the power 2/3, following [29]. Intake is limited according to a target body condition, θr, the ideal ratio between reversible and structural mass (Fig. ESM2, Table ESM1). The parameter η controls the steepness of the intake rate as it compensates for low body condition (Table ESM1).

We distinguish external 'food' from within-host 'resources', where 'resources' are used as the energy source for growth in either host or parasite biomass. Incoming resources (from food intake) flow into the pool of ingesta at the rate $A(R,S)$, and flow out at rate ρ, with outflow subdivided between assimilated resources and egesta (Fig. ESM2). The dynamics of ingesta are then:

$$\frac{dG}{dt} = A(R,S) - \rho G, \quad (1)$$

We assume that the flow processes in this compartment are fast, relative to other processes and in particular to the host-parasite interaction, such that:

$$G^* = \frac{A(R,S)}{\rho}, \quad (2)$$

From the resources in the ingesta, a fraction $Ea(P)$ is assimilated (dependent on parasite biomass, *P*), with the remainder flowing to the egesta, *C*. Both the inflow (from ingesta) to and outflow from egesta occur at rate ρ, such that:

$$\frac{dC}{dt} = \rho\big((1 - E_a(P))G^* - C\big), (3)$$

Assimilated resources first cover maintenance demands, following $M = mw\,(S + R)$. *M* is here a 'field' metabolic rate, which is an average of active, resting, and moving maintenance levels. Surplus resources first go to structural mass according to the solved von Bertalanffy equation [23]:

$$g(S) = 3\gamma\big(s_{max}^{1/3}S^{2/3} - S\big), (4)$$

where γ is the growth rate, and $smax$ the asymptotic size. Further surplus resources are allocated to reversible mass, R:

$$\frac{dR}{dt} = \epsilon_r\big(\rho E_a(P)G^* - M(S,R) - g(S)\big), (5)$$ where εr is the conversion efficiency. Reversible mass decreases whenever the assimilate flow is insufficient for maintenance or structural growth costs. Equations (2), (3), and (5) define a balance between costs for metabolism and growth and energetic gains through feeding (Fig. ESM2).

Immune response dynamics

Host immunity consists of constitutive (baseline) immunity I_c, which equals a small fraction (c) of total mass, $I_c = c(S + R)$ [33], and induced immunity I_i, which responds dynamically to parasite infection. Because the capacity to mount an induced immune response depends on host body condition and reserves, the resource input to induced immunity is taken directly from reversible biomass [33]. This assumption is supported by the observed correlation between measures of reversible mass (e.g. the fat- associated hormone leptin) and induced immunity (e.g. the cytokine interleukin (IL)-13, a promotor of helminth clearance) in our rewilded mouse experiment (Fig. ESM1,

[26] [24]), as well as by previous laboratory experiments (reviewed in [34]) and wildlife experiments [35].

The rate of resource flow to induced immunity is a function of response-fuelling reversible mass and response-provoking parasite biomass, defined as bRP, with b as the biomass flow rate per gram parasite [10]. Reversible biomass is converted to induced immunity with efficiency ϵ_i. Induced immunity decays at a constant rate, μ_i, so that:

$$\frac{dI_i}{dt} = \epsilon_i bRP - \mu_i I_i, \quad (6)$$

Because constituent and induced immunity impose additional maintenance costs to the host (captured by the parameters m_c and m_i), total maintenance cost $M = m_w(S + R) + m_c I_c + m_i I_i$ (Table ESM1, [33]) such that equation (5) becomes:

$$\frac{dR}{dt} = \epsilon_r\left(\rho E_a(P)G^* - M(S,R,I_c,I_i) - g(S)\right) - bRP, \quad (7)$$

Parasite dynamics

Parasites exploit the biomass in the egesta (C) as resource, reflecting the biology of *Trichuris spp.* and other helminths that live in the colon [36]. Parasite resource intake rate follows a type II functional response, $\frac{\sigma_c C}{h_c + C}$, with uptake rate σc and half-saturation constant hc. Resources are converted into parasite biomass through the conversion factor ϵ_P. Parasite biomass decreases at background mortality rate, μ_p, reflecting mortality and metabolic losses, and at the immune-imposed rates, $v_c I_c + v_i I_i$, reflecting mortality or stunting of parasite growth by the immune response (Table ESM1). The parasite dynamics are then determined by growth from resources and mortality through top-down imposed immune responses:

$$\frac{dP}{dt} = \epsilon_p \frac{\sigma_c C}{h_c + C} P - \mu_p P - (v_c I_c + v_i I_i)P, \quad (8)$$

We explicitly account for modulation of resources by the parasite. Gastrointestinal worms can cause a decrease in the digestive efficiency of their host, either by directly stealing resources from the intestines

158 [17], or by decreasing the assimilation efficiency [37]. To include this effect we use a saturating function
159 of parasite biomass to reduce the proportion of ingested food that is assimilated by the host:

160 $$E_a(P) = \epsilon_a\left(1 - \frac{\epsilon_{Amin}P}{h_e + P}\right), \quad (9)$$

161 This function simplifies to the default value of assimilation efficiency, ϵ_a, in absence of the parasite.
162 The un-assimilated resources that flow to the egesta are useless for the host, but exploitable by the
163 parasite. As such, gastrointestinal parasites create a positive feedback on their own resource availability,
164 controlled via the parameter ϵ_{Amin}, which is the fractional reduction in assimilation efficiency by the
165 parasite (for example, $\epsilon_{Amin} = 0.05$ translates into a 5% reduction in assimilation efficiency when the
166 parasite burden is very high, and $\epsilon_{Amin} = 0.5$ means that assimilation efficiency is reduced by 50%).
167 Parameter h_e is the half-saturation level in the resource modulation by the parasite (Fig. ESM2).

168

169 *Model analysis*

170 We analysed transient (Fig. 1, 2) and equilibrium (Fig. 3) dynamics of the system defined by equations
171 (2), (3), and (6 – 8) with MatCont [38] (6p10), in MATLAB (version 2018b). In addition, we analysed
172 two bifurcation points that characterize specific regions in parameter space (Fig. ESM7) [39], which
173 represent the persistence and invasion thresholds of the parasite. The interpretation and explanation of
174 these techniques can be found in the ESM.

175 To examine the consequences of bistability for parasite burden distributions, we projected the within-
176 host model outcomes to the population-level. We simulated infection dynamics for 1000 hosts, where
177 the initial parasite dose (biomass) for each host was drawn from a normal distribution. Hosts were then
178 sampled at the same or at different timepoints, to explore how the distribution of burden varied across
179 hosts (Fig. 2). To fit statistical distributions to these data, including the negative binomial distribution,
180 we used the mass of an adult *T. muris* parasite to convert the continuous parasite biomass measurement
181 into a discrete number of parasites.

In addition to the extensive analysis of the DEB model (equations (2), (3), (6 – 8), Fig. ESM2), we also analysed a simplified model that considers only parasite and resource dynamics. This simplified system is mathematically tractable and allowed us to corroborate our bistability findings analytically (ESM).

Results

Acute and chronic infections emerge from different initial conditions

Our model analysis shows both acute and chronic parasite infections as emerging outcomes of the within-host interactions among resource allocation, parasites, and immunity (Fig. 1). These divergent outcomes were observed by changing the initial conditions of the model in terms of parasite dose and by changing the equilibrium configuration by adjusting the food level (see Fig. ESM5). We do not change any assumptions about the mechanistic basis of the model, unlike standard theory in which infection duration is determined by the model's structural assumptions [14].

Parasite dose and food availability together determine infection outcome. Low parasite dose results in acute infections where the parasite is expelled, and high parasite dose results in chronic infections with parasite persistence (Fig. 1a). This divergence is caused by the potential for a positive feedback of the parasite on its own resource availability. Biologically, this positive feedback generates an Allee effect: if initial parasite biomass is too low, the host's immune response keeps parasite biomass low, preventing it from effectively modulating host resources and leading to acute infections, because parasites are rapidly expelled. If initial parasite biomass is high enough, the positive feedback allows the parasite to increase the resource flow towards egesta sufficiently to establish in the host, leading to chronic infections (Fig. 1, ESM4).

We also simulated parasite infections using a constant initial parasite dose for three food levels. Higher food level resulted in chronic infections, whereas low food availability allowed the host to expel the parasite (Fig. 1c, d, and ESM4). This is somewhat counterintuitive, because higher food level improves host body condition, and therefore the strength of the immune response. Immunity was, however, counterbalanced by the fact that hosts with better body condition at the onset of infection (due to higher

208 food levels) initially had higher resource availability for parasites (Fig. 1c). Parasites therefore
209 expanded in biomass and strengthened the positive feedback on their own resources (through resource
210 modulation), leading to a chronic infection. Low food levels provided a less profitable resource
211 environment to the parasite. Parasites could not grow as fast and did not effectively enforce the positive
212 feedback loop between parasite biomass and resource availability. Suppressed by the immune response,
213 parasites were expelled and hosts experienced an acute infection (Fig. 1c, d, and ESM4).

214 The time series show diverging results and eventually stable system attractors that represent either acute
215 or chronic outcomes for the within-host dynamics (Fig. 1, ESM4). We hypothesized that such diverging
216 outcomes for host individuals may contribute to the well-known pattern of overdispersed parasite
217 distributions in host populations [3]. Assuming a population of hosts, each exposed to a unique parasite
218 dose and sampled either at the same (Fig. 2, top row) or different (Fig. 2, second row) timepoints in
219 infection, we find that the parasite burden distributions conform to a negative binomial distribution if
220 the system state is bistable. Moreover, when parameter values are outside of the bistable region, parasite
221 burden distributions approach entirely acute (Fig. 2, third row) or entirely chronic distributions (Fig. 2,
222 bottom row). This final negative result confirms that a negative binomial distribution is unlikely to arise
223 due to variation in exposure alone [3], but rather requires underlying dynamical variation. This negative
224 binomial burden distribution also occurs when we include variation in the parameterization of host and
225 parasite processes (ESM6). Including this variation is more representative of natural systems, where
226 genetic and phenotypic variation exists among both hosts and parasites.

227

228 *Stability analyses of acute and chronic equilibrium states*

229 The two stable states we found in time simulations (Fig. 1) represent the core dynamics of our system.
230 We studied these dynamics further through stability analysis of the stable states, using parameter
231 bifurcations, which illustrate how the system stability changes as a function of parameters.

232 For this analysis we studied the equilibrium outcomes as a function of the parasite attack rate, σ_c,
233 because this parameter quantifies a key process for the parasite (resource uptake) and is an important

234 determinant of the interaction strength between host and parasite. We found three regions with
235 qualitatively different dynamics (Fig. 3 and ESM7). Low attack rates (below the persistence threshold)
236 only allow for acute infections (Fig. 3a), since the extinct-parasite equilibrium is the only stable
237 attractor. Parasites were expelled upon infection by the host's immune response, and the final system
238 state (equilibrium) did not contain the parasite. High attack rates (above the invasion threshold) only
239 allow for chronic infections (Fig. 3b), since the positive-parasite biomass equilibrium is the only stable
240 attractor. Here, parasites are able to invade even from very low biomass, resulting in a chronic infection.
241 Intermediate attack rate values allow for both acute and chronic infections (Fig. 3 and ESM7), with the
242 outcome being dependent on initial conditions (Fig. 1, 3a,b). The acute and chronic equilibria are
243 characterized by parasite biomass being zero or positive (Fig. 3c, ESM), but these states also differed
244 with respect to host body condition.

245 In the acute infection equilibrium, the parasite was absent, and because of this all host variables, S, R,
246 C, and I_i, were constant and independent of the parasite attack rate. The induced immune response was
247 absent (Fig. 3d), reversible biomass was high (Fig. 3e), and biomass in egesta was low (Fig. 3f). Note
248 that host irreversible mass is constant across the entire parameter range because we initiate simulations
249 in adult-sized hosts.

250 In the chronic infection equilibrium, the host had an elevated induced immune response, triggered by
251 the presence of the parasite (Fig. 3d). The induced immune response intensity increased with increasing
252 parasite attack rate, in response to increasing parasite biomass (Fig. 3c). Because of the resource
253 demands of the immune response and the reduction in assimilation efficiency due to the parasite,
254 reversible biomass was reduced with respect to the acute infection state (Fig. 3e). In the chronic
255 infection equilibrium, the parasite exerted a positive feedback on the biomass in the egesta, keeping the
256 resource level high, and maintaining a profitable environment for itself (Fig. 3f).

257 We verified that bistability depends on resource modulation using a simplified model that only
258 accounted for resources and parasites (ESM). The analysis of this simple model revealed the importance
259 of a non-linear functional form for the resource modulation function, $E_a(P)$ (equation (9)). We also
260 carried out two-parameter bifurcation analysis to quantify the importance of the parameters ϵ_{Amin},

which determines how much parasites are able to modulate assimilation efficiency, and v_i, which determines the killing rate of the induced immune response. These analyses showed that the larger the impact a given parasite biomass has, the stronger the potential for positive feedback and for bistability (Fig. ESM7a). Increasing the immune killing rate did not qualitatively affect the occurrence of bistability (Fig. ESM7b).

Discussion

We show that the positive feedback of parasites on their own resources can produce both acute and chronic infections in a single within-host model. This positive feedback is comparable to an Allee effect in free-living consumer species [40], where per capita increase is positively correlated to population density at low densities. Accounting for bottom-up, resource driven processes is essential to capture this possibility of acute and chronic infections emerging simultaneously in the same model.

Our results contrast with previous within-host theory that must define *a priori* whether a model represents an acute or chronic infection. In these classic models, one makes separate assumptions about the parasite-host interaction to produce differences in infection outcomes (acute vs chronic [9, 41, 10]). Even previous approaches where both resource-competition and immunity are explicitly accounted for were restricted to chronic infections [11]. In contrast, we only assume that all within-host processes rely on available resources (or energy). And we consequently find acute and chronic infections as emergent model outcomes, depending on the initial conditions in parasite dose or different food-availability. These results fill a knowledge gap in within-host theory, by showing that acute and chronic infections can both be the outcome of infection in a single (general) within-host model [10, 11].

Our assumption that parasites can reduce their host's assimilation efficiency is based on various mechanisms found in empirical systems. Helminths commonly reduce the host's ability to assimilate nutrients. For example, many species feed on intestinal cells [37], alter intestinal lining structure [42], and increase intestinal permeability [43]. While some immune defences ameliorate these effects [43], other defences reduce nutrient acquisition, thereby indirectly reducing assimilation [44, 45]. Reduced

digestive efficiency has substantial consequences [46, 47, 48]: calves infected with GI nematodes had nearly 40% lower conversion efficiency of feed to liveweight gain [49]. We capture all these sources of reduced assimilation efficiency in the term $E_a(P)$ in our system.

The immune response was represented using a minimal form, where we did not do justice to many known aspects of immunology, such as the specific cell types involved in responses against nematodes [50] or the many positive and negative feedbacks inherent to the dynamics of the immune system [51]. Moreover, (genetic) variation in immune function is expected to alter host susceptibility and parasite infection outcome and may explain some discrepancies between our model predictions and empirical results [52]. For example, in our model, higher parasite doses are more likely to lead to chronic infections, whereas dose-response experiments suggest that lower parasite doses can produce chronic infections in otherwise resistant host strains [53, 54, 55]. In laboratory settings, this outcome is attributed to low-dose infections leading to a response biased towards immune activity that is ineffective against nematodes (instead of an effective response that follows high-level exposure [52]). In our model, effective or ineffective immune responses would bear the same resource costs, but we do not capture the parasite-dose dependence in the immune response type that is being triggered (effective or ineffective). Accounting for a more sophisticated representation of the parasite-dose dependence in the immune response could reveal the interplay with resource modulation, and how these processes in concert explain variability in infection duration.

Additionally, previous studies showed that immune modulation by parasites is a decisive factor of parasite-host interactions [13, 14, 15]. But the theoretical models accounting for this effect have not shown bistable outcomes [41], such as we present here. We included the resource-dependence of the immune response, providing an indirect route for immune modulation by parasites [12]. It is, however, likely that immune modulation by parasites can also directly produce bistability through a similar Allee effect. It would be a valuable extension to investigate the interplay of immune and resource modulation combined, and the relative potential of these processes in determining infection outcomes.

An important challenge to testing our model predictions against experimental data is that in laboratory environments high-dose exposure is usually performed in hosts fed to excess (see [18, 19, 20] for

exceptions). To avoid confounding effects, we need direct, experimental manipulation to pair dose variation with diet variation in factorial designs. And quality matters also, as in a study where hosts fed on low-protein diets more rapidly expelled helminth parasites [20]. In line with our finding that the immune response to parasites strongly depends on available resources, [56] showed that lactating mice experimentally infected with *T. muris* had a suppressed immune response compared to non-lactating individuals. Our finding of bifurcating infection outcomes resonates with recent empirical studies in *Drosophila* and *Tribolium*, both of which showed that experimental infections could produce either short-duration, fatal infections or long duration, persistent infections [57, 58]. Importantly, these divergent outcomes were observed even when host and pathogen genetic variation, dose, and host environment were tightly controlled. In the light of all these laboratory observations, note that field systems and real-world parasite infections are likely to be more resource-limited than laboratory conditions, and unravelling where and why differences occur between controlled and real-world systems is crucial for progress towards solving real-world parasite infection patterns.

The results we present may help explain the ubiquitous pattern of burden variation amongst individuals in field systems [3]. Our population level projection of the bistability between acute and chronic infections in individual hosts generated aggregated burden distributions starting with only stochastic variation in dose. But dose variation by itself is insufficient to generate heterogeneity in burden; at the same time, without a source of host heterogeneity, bistability alone does not produce burden variation. It is the combination of the two that drives burden variation.

For the population projection, we assumed that parasite biomass represents a fixed number of parasites of the same size, discounting the effects of different numbers of differently-sized parasites. This is an important simplifying assumption, since a few large parasites may have very different energetic requirements (both in terms of host resource ingestion rates and metabolic rates) than many small parasites of equal biomass, given the difference in surface area-to-volume relationship.

Future work should incorporate knowledge of these heterogeneities into the DEB framework to tighten predictions for how parasite biomass and burden are related, and how these traits combine to affect host health and parasite transmission. This would also allow a more mechanistic analysis of processes like

(biomass-dependent) parasite-induced host mortality [59], or biomass-driven infection by free-living parasite stages. Such a mechanistic model would build towards a nested approach including the energetic dependencies between parasites and their hosts, integrating from the within-host to the population level [60].

Previous adaptations of Dynamic Energy Budgets for parasite-host interactions revealed the importance of host metabolism for parasite virulence [30], parasite production [11, 21], and parasitic castration [61], but none of these systems accounted for bistability. Here we highlight the variability of infection duration and parasite burdens, which have wide-ranging implications for parasite transmission, infectivity, and host mortality [21].

The dynamics we present here take place in an ecological dimension, where the interaction between host and parasite, as well as the functioning of the immune response, are all dependent on bottom-up resource availability. There is evidence that parasite modulation is dependent on parasite density or parasite biomass [62], but further studies should explore how this relationship differs between (resource-limited) field versus laboratory systems. The energy-dependence of all processes in our modelling framework ensures that the outcomes we find emerge from low-level assumptions and calls for extensions from the within-host scale to considering the between-host dynamics of infectious disease.

Competing interest

We have no competing interests.

Author contributions

All authors conceived of the project and developed the DEB model. AvL analysed the DEB model, with input from CEC, SB, and ALG. AvL, CEC, and SB developed the simplified model and CEC analysed this model. ALG and SB designed the rewilding study and performed the empirical work. AvL wrote the first draft of the manuscript and all authors contributed substantially to revisions and gave final approval for publication.

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Data accessibility

Data available from the Dryad Digital Repository: https://doi.org/10.5061/dryad.b2g21j1 [26].

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631

632 **Figure captions**

633 **Figure 1. Parasite biomass and induced immune response in time series starting from various**
634 **initial conditions.** Simulation of infections starting at eight different doses (**a** and **c**), and starting at
635 different host food availability levels (**b** and **d**). $\sigma_C = 0.52$, other parameters have default values (Table
636 ESM1). Only the first 500 time steps of the integration are shown, see Fig. ESM4 for the extended time
637 series with full transient dynamics up to the attractor states and for the dynamics of other system
638 variables.

639

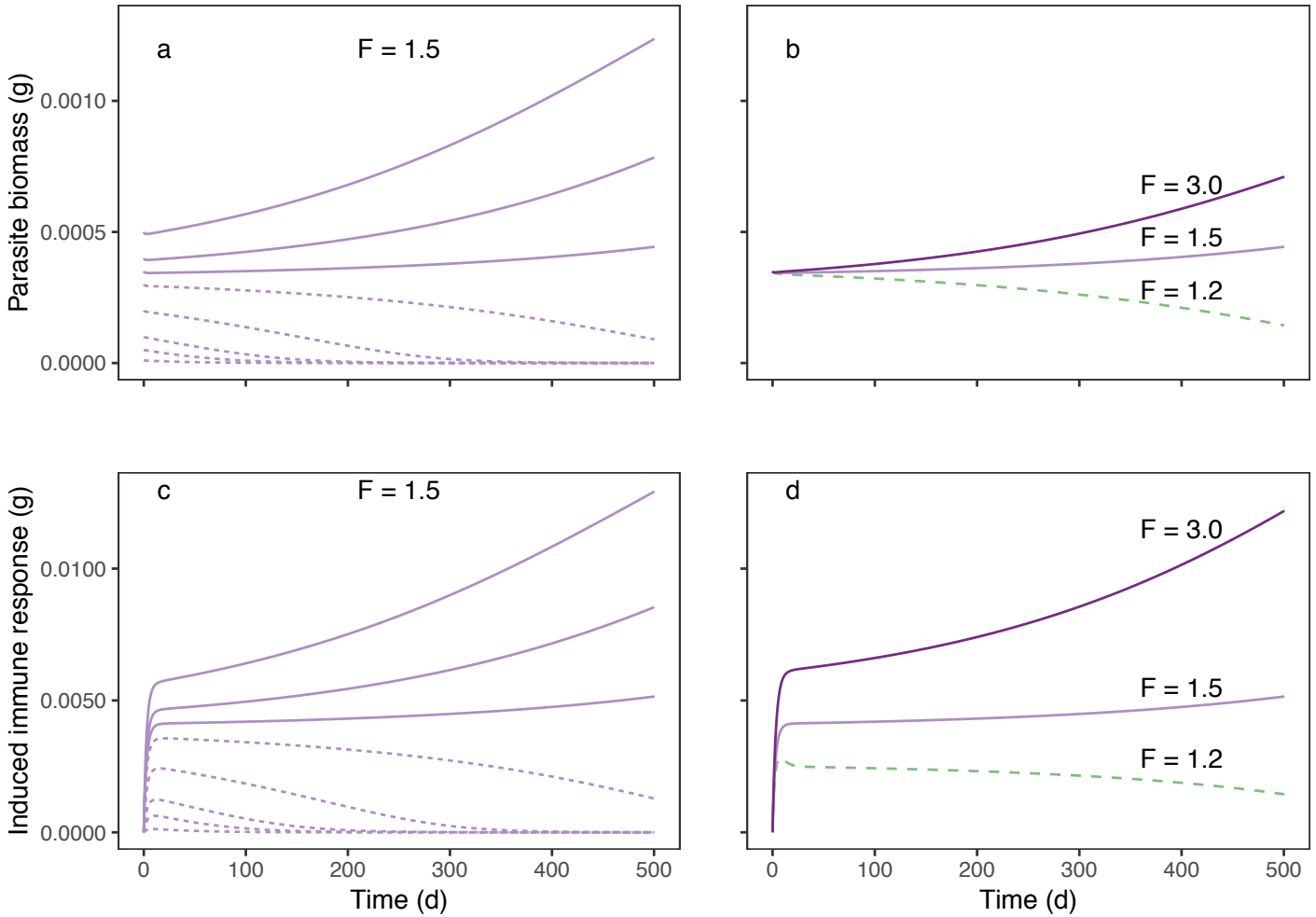
640 **Figure 2. Distribution of parasite burdens under different scenarios.** For each scenario, 1000 hosts
641 were infected with a parasite dose randomly drawn from a normal distribution with mean of 3×10^{-4}
642 g and standard deviation of 8×10^{-5} g. With the default value $\sigma_C = 0.52$, this distribution centers
643 around the unstable equilibrium in Figure 3c. All parameters have default values (Table ESM1); to
644 convert biomass into parasite numbers, we used the mass of an adult worm of 5×10^{-5} g. First
645 scenario: every host is sampled at the same infection age (top row). Second scenario: each host is
646 sampled at a different infection age, as in sampling a natural population (second row), which was
647 repeated three times to simulate sampling three different populations. Third scenario: $\sigma_C = 0.45$, only
648 acute infections are possible (third row). Last scenario: $\sigma_C = 0.9$, only chronic infections are possible
649 (bottom row). Legend in panels: AIC scores from fitting different statistical distributions to distribution
650 data using the 'fitdistr' function (MASS package in R; black - Negative Binomial, red - Normal, blue -
651 Poisson).

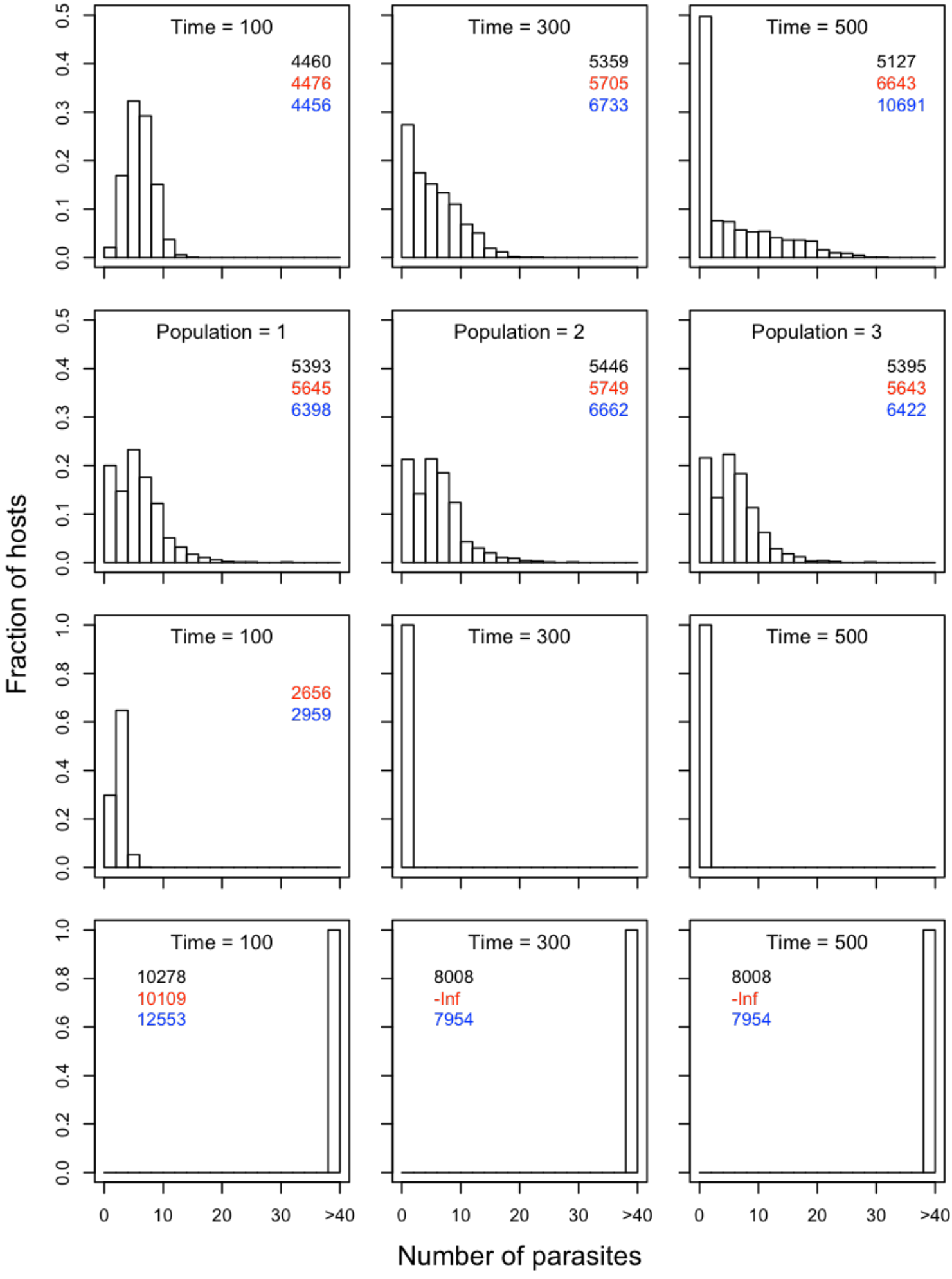
652

653 **Figure 3. Bistability with acute and chronic infections.** Within-host biomass dynamics as a function
654 of parasite attack rate (resource uptake rate). Low attack rate values $(0 < \sigma_C < 0.5)$ exclusively allow
655 for acute infections (no equilibrium with positive parasite biomass, **a**, **c** left of PT). High attack rate
656 values $(\sigma_C > 0.89)$ exclusively allow for chronic infections (only an equilibrium with high parasite
657 biomass, **b**, **c**, right of IT). Intermediate attack rate values result in bistability between acute and chronic

658 infection states, meaning that both the state with extinct parasite (acute) and high parasite biomass
659 (chronic) are stable equilibria. The relationship between time-series (**a** and **b**) and equilibrium solutions
660 (**c** – **f**) is shown. Time series (**a** and **b**) illustrate the induction and waning of immune response in an
661 acute infection (**a**) and the elevated end point in a chronic infection (**b**). Grey shaded area: bistable
662 region, enclosed between the persistence threshold (PT) and invasion threshold (IT), see ESM. Bold,
663 grey arrows (**c**) indicate dynamics in time as approaching equilibria. $F = 1.5,\ \epsilon_{Amin} = 0.4$ (compare to
664 Fig. ESM7); other parameters have default values.

665


a
F = 1.5
b
F = 3.0
F = 1.5
F = 1.2
c
F = 1.5
d
F = 3.0
F = 1.5
F = 1.2
Parasite biomass (g)
0.0010
0.0005
0.0000
Induced immune response (g)
0.0100
0.0050
0.0000
0
100
200
300
400
500
Time (d)


Time = 100
4460
4476
4456
Time = 300
5359
5705
6733
Time = 500
5127
6643
10691
Population = 1
5393
5645
6398
Population = 2
5446
5749
6662
Population = 3
5395
5643
6422
Time = 100
2656
2959
Time = 300
Time = 500
Time = 100
10278
10109
12553
Time = 300
8008
-Inf
7954
Time = 500
8008
-Inf
7954
Fraction of hosts
0.0
0.1
0.2
0.3
0.4
0.5
0.0
0.2
0.4
0.6
0.8
1.0
0
10
20
30
>40
Number of parasites

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