Electronic Supplementary Material

For: Parasite resource manipulation drives bimodal variation in infection duration

ESM: Additional analyses

We model the growth of the mouse host according to a standard demand-driven dynamic energy budget (DEB) model, parameterized for *Mus musculus* [1, 2, 3]. The baseline settings of the model (host-only) result in growth curves that correspond closely to the results from a previously published dynamic energy budget model for mouse growth. The effect of varying food availability also results in realistic variation of the growth curves [Fig. ESM3; cf. Fig. 3 in reference 1]). We use these baseline dynamics as model validation and use the full-grown mouse as initial state for parasite infection. This assumption facilitates equilibrium analyses and is consistent with the mature mice used in the rewilding field experiments (Fig. ESM1).

In addition to time series and equilibrium analyses, we analysed two bifurcation points that characterize specific regions in parameter space (Fig. ESM7) [4, 5]. These bifurcation points represent the persistence and invasion thresholds of the parasite. The invasion threshold (mathematically, a branching point bifurcation) occurs for the parameter value that discriminates whether the parasite can invade the system from low biomass and establish ('invasion' is here used to mean that the parasite can successfully infect the host). The persistence threshold (mathematically, a limit point bifurcation) occurs for the parameter value that discriminates whether the parasite can persist in the system. Persistence, however, does not guarantee the potential for invasion (Fig. ESM7) this is explained below.

It is often the case that the invasion and persistence boundaries are identical. In this case, only chronic or acute outcomes will occur, since the parasite can either invade and persist, or not (for example, the invasion and persistence boundaries are identical when $\epsilon_{Amin} = 0$ in Fig. ESM7a). In contrast, when these boundaries occur at different parameter values, system bistability occurs if there is a region where persistence is possible, but invasion is not (region II in Fig. ESM7a, b). In this case, the system is bistable, and both the equilibrium where the parasite is extinct (acute infection) and the equilibrium where the parasite persists (chronic infection) are stable attractors. These two stable attractors are separated in variable space by an unstable equilibrium. For example, if the parasite's initial biomass is above the unstable equilibrium, it will persist and establish a chronic infection; if the initial biomass is below the unstable equilibrium, it will be driven extinct by the immune response (an acute infection, see also Fig. ESM4).

Table ESM1. Definition of DEB model parameters and values

Parameter	Value	Unit	Description	Source
Host energy budget parameters				
F	$1.2, 1.5, 3.0$	g	Food availability	
ι_{max}	0.5	$\mathrm{g} \cdot \mathrm{g}^{-2/3} \cdot \mathrm{t}^{-1}$	Scaling constant in maximum ingestion rate	
η	20	-	Steepness in condition scaling of intake rate	[6]
m_w	0.09	$\mathrm{g}^{-1} \cdot \mathrm{g}^{-1} \cdot \mathrm{t}^{-1}$	Maintenance costs per unit total mass	[7]
ϵ_a	0.75	$\mathrm{g} \cdot \mathrm{g}^{-1}$	Assimilation efficiency	[8]
ϵ_r	1.0	$\mathrm{g} \cdot \mathrm{g}^{-1}$	Conversion efficiency reserve biomass	
γ	0.02	t^{-1}	von Bertalanffy growth rate	[2]
s_{max}	25	g	Maximum structural mass	[2]
θ_r	0.25	-	Target body condition (R as fraction of W)	[1]
ρ	2.0	t^{-1}	Turn-over rate egesta (colon)	
Host immune system parameters				
c	0.0005	–	Body mass fraction in constituent immune system	[9]
m_c	0.3	$\mathrm{g}^{-1} \cdot \mathrm{g}^{-1} \cdot \mathrm{t}^{-1}$	Metabolic cost per unit mass of constituent immune response	[9]
m_i	0.3	$\mathrm{g}^{-1} \cdot \mathrm{g}^{-1} \cdot \mathrm{t}^{-1}$	Metabolic cost per unit mass of induced immune response	[9]
b	1.0	$\mathrm{g}^{-1} \cdot \mathrm{t}^{-1}$	Rate of reserve biomass allocation to immunity per gram of parasite biomass	
ϵ_i	0.8	$\mathrm{g} \cdot \mathrm{g}^{-1}$	Conversion efficiency reserves to induced immune response	
μ_i	0.3	t^{-1}	Biomass turn-over rate induced immune response	
Parasite parameters				
ϵ_p	0.2	–	Conversion efficiency host tissue to parasite biomass	
h_c	0.9	g	Parasite uptake half-saturation biomass	
σ_c	varied	t^{-1}	Parasite attack rate (energy uptake rate)	
h_ϵ	0.0001	g	Half-saturation level in parasite modulation function, $E_a(P)$	
ϵ_{Amin}	$0 - 0.5$	–	Fractional reduction in digestive efficiency (modulation)	
μ_p	0.05	t^{-1}	Parasite background mortality rate	
ν_c	0.6	$\mathrm{g}^{-1} \cdot \mathrm{t}^{-1}$	Parasite mortality rate due to constituent immune response	
ν_i	0.3	$\mathrm{g}^{-1} \cdot \mathrm{t}^{-1}$	Parasite mortality rate due to induced immune response	

Table ESM2. Definition of model parameters used in the simplified model

Parameter	Unit	Description
ω	$R \cdot \mathrm{t}^{-1}$	Resource inflow
ϕ	$P^{-1} \cdot \mathrm{t}^{-1}$	Resource uptake rate of the parasite
ξ	t^{-1}	Resource decay rate
β	$P \cdot R^{-1}$	Conversion factor resource to parasite
δ	t^{-1}	Parasite death rate

Simplified model definition and validation of bistability

To analytically validate the conclusions of the more biologically detailed DEB model, we formulated a simplified version of the model where many details of the energy budget were omitted. To validate the conclusions from the DEB model results, we focus in this simplification on the aspect of resource modulation and include only parasites (P) and their resources (R):

$$\frac{dR}{dt} = \omega + f(P) - \phi RP - \xi R \tag{1}$$

$$\frac{dP}{dt} = \beta\phi RP - \delta P \tag{2}$$

Here, $f(P)$ is the positive feedback of the parasite on resource availability, analogous to the positive effect of parasites on the rate of energy flow to egesta in the DEB model, and all other flows are linear. The simplicity of this model allows us to draw general conclusions about how parasite modulation (embodied in the shape of $f(P)$) affects the dynamics and stability properties of the system. Note that we have not included an immune response here. We focus on the parasite-resource interaction because it illustrates the general conditions necessary for bistability; in particular, adding an immune response complicates the expression of bistability conditions, but does not affect the that resource modulation is sufficient to produce bistability. Results of the model analysis can be found in the online SI.

Analysis of simplified model

We use the simplified model (Equations 1 – 2) to corroborate the finding that the saturating parasite modulation function permits bistability between acute and chronic infections, and to connect the invasion and persistence boundaries to stability conditions for system equilibria. For the simplified model (Equations 1 - 2), there are two possible resource equilibria: an extinction equilibrium, corresponding to an acute infection where the parasite is absent: $\hat{R}_0 = \xi/\omega$; and an endemic equilibrium, corresponding to a chronic infection where the parasite is present: $\hat{R}_P = \delta/(\beta\phi)$. Bistability requires that both of these equilibria are stable simultaneously.

The invasion boundary is equivalent to the stability boundary for the acute infection equilibrium. The acute infection equilibrium will be stable if $R_P > R_0$, that is, if the resource level in the chronic infection equilibrium is larger than the resource level in the acute infection equilibrium. In the absence of parasite modulation, the only effect of parasites on resources is depletion, making it biologically impossible for the chronic resource equilibrium to be larger than the acute equilibrium. This gives a strong sense that, in the absence of modulation, bistability will be impossible. Expressed in terms of the parasite's resource intake rate, ϕ (analogous to σ_C in the DEB model), the invasion boundary is $\phi = \frac{\delta\xi}{\beta\omega}$. Note that this boundary is independent of $f(P)$, the function governing parasite modulation.

The persistence boundary is equivalent to the stability boundary for the chronic infection equilibrium. Stability of the chronic infection equilibrium requires $\phi\hat{P}\left(\delta - \beta f'(\hat{P})\right) > 0$. Whether the chronic equilibrium will be stable or not depends critically on the shape of the modulation function, $f(P)$. If the modulation function is accelerating ($f''(P) > 0$), then stability is likely only if $\hat{P}$ is sufficiently small (because as $\hat{P}$ increases, so will $f'(\hat{P})$, making it increasingly likely that $\delta - \beta f'(\hat{P}) < 0$). (A linear modulation function does not work either, because stability of the acute infection equilibrium guarantees instability of the chronic equilibrium, and vice versa.) If, on the other hand, the modulation function is saturating ($f''(P) < 0$), then stability is likely for a much wider range of $\hat{P}$ values (because as $\hat{P}$ increases, $f'(P)$ decreases, making it increasingly likely that $\delta - \beta f'(\hat{P}) > 0$). Saturating modulation is also the only functional form that makes biological sense, given that host resource acquisition cannot increase indefinitely. An accelerating modulation function would create unconstrained positive feedback between parasite growth and modulation, leading to uncontrolled growth in both resources and parasites.

Assuming that $f(P) = \alpha P/(1 + P)$, where α is the maximum resource modulation rate, then the persistence boundary is $\phi = \frac{\delta\xi}{\beta\omega + (\sqrt{\alpha\beta} - \sqrt{\delta})^2}$; the invasion boundary is unchanged from above ($\phi = \frac{\delta\xi}{\beta\omega}$). Thus, when there is modulation, the persistence boundary will always be less than the invasion boundary, implying bistability. In the absence of modulation ($\alpha = 0$), the persistence and invasion boundaries are identical. As the parasite's capacity for resource modulation (α) increases, the region of bistability enclosed between the persistence and invasion boundaries increases, confirming the findings for the more biologically realistic DEB model.

Field system with rewilding experiment

Experimental design

To examine tradeoffs between infection, immunity, and within-host resources, 40 female C57Bl/6 mice aged 5-6 weeks were obtained from Jackson Laboratories. The data reported here is available on Dryad Digital Repository [10]. For 7 days, mice were housed in groups of 5 in the laboratory while temperature

and light cycles were gradually increased to mimic outdoor conditions (September in New Jersey, USA: $26\,^{\circ}\mathrm{C} \pm 1\,^{\circ}\mathrm{C}$ with a 15 hour light – 9 hour dark cycle). Ear tags and RFID tags were used to identify individuals. On day 8, cages were randomly assigned to four outdoor enclosures, and before release, half of the cages were randomly assigned to receive infection with 200 embryonated *Trichuris muris* eggs (strain E) via oral gavage. Thus, each outdoor enclosure received 5 infected and 5 control mice.

The outdoor enclosures are ~ 180 m^2 areas fenced in by 1.5 m-high zinced iron walls that extend 80 cm deep [11]. Predators are excluded by electric fencing and reflective plates strung up above the enclosures. In addition to natural vegetation, straw-filled sheds provided shelter. Mice were provided two watering stations and standard rodent chow ad libitum (PicoLab Rodent Diet 20) and organic peanut butter.

Three-weeks post-infection, mice were trapped with chow-baited Longworth traps, weighed to the nearest 0.5 g with a spring scale, and humanely euthanized with CO2 inhalation followed by cervical dislocation. A blood sample was drawn from the heart of each mouse, spun in a heparinized tube to separate plasma, and stored at $-80\,^{\circ}\mathrm{C}$ for subsequent leptin analysis. To measure carcass weight (i.e. irreversible mass), mice were necropsied and all organs (excluding brains) were removed before weighing on a balance to the nearest 0.001 g.

Interleukin-13 (i.e. induced immunity) measurement

Following established protocols [12, 11], mesenteric lymph node (MLN) tissue was excised during necropsy, prepared into single cell suspensions at a density of 5×10^6 cells $\cdot$ ml^{-1}, stimulated with *T. muris* antigen at 5 μm $\cdot$ ml^{-1}, and cultured for 48 hours. Supernatants were collected then analysed for interleukin 13 (IL13) using half-reactions of Beckton Dickinson Cyometric Bead Array Mouse/Rat Soluble Protein Flex Set system (BD Biosciences, Oxford, UK) and a LSRII flow cytometer [BD Biosciences, 11]. Concentrations were analysed with the FCAP Array software (version 3.0.1, BD Biosciences).

Parasite biomass assessment

Caecums were removed at necropsy, cut open longitudinally, and examined under a dissecting microscope. Worms were isolated by scraping the gut mucosa into clean petri dish of water. After enumeration, worms were stored in 70% ethanol for subsequent biomass measurements. Each worm was photographed under a dissecting scope ($2-4\times$ power) and ImageJ (Version 1.49, NIH, USA) was used to measure total length and width (mean of 3 measurements). Worm biomass was estimated by calculating the cylindrical volume of the worm, multiplied by the approximate density of parasitic helminths (1.1 g $\cdot$ ml^{-1}, [13, 14, 15]. To estimate total worm biomass, up to 25 worms were measured per mouse and the average biomass per worm was multiplied by total worm count. Infected mice with no worms (n = 3) were denoted as having cleared their infections.

Serum leptin (i.e. reversible biomass) measurement

Serum leptin concentrations were analysed in duplicate using a RayBio® Mouse Leptin ELISA kit following manufacturer‘s instructions (RayBiotech, Norcross, Georgia, USA). Briefly, samples were diluted 1:10, incubated on a 96-well plate coated with mouse leptin antibody. After washing, a biotinylated anti-mouse leptin antibody was added. Next, the plate was washed, horseradish peroxidase-conjugated strepavidin was added. Following another washing step, a buffered 3,3,5,5‘ -tetramethylbenzidine solution produces a color change reaction that is stopped with 0.2M sulfuric acid. Color intensity was read with a Multiscan™ GO spectrophotometer (Thermo Scientific) at 450 nm. Concentrations were calculated using a standard curve (standards run in duplicate, $R^2 = 0.998$).

Code to reproduce parasite burden distribution figures

We provide the C code needed to simulate the dynamic energy budget model specified by equations (3-9) in the main text and the R code needed to generate Fig. 2 and Fig. ESM6.

```c
#include <R.h>
#include <stdio.h>

static double parms[26];

#define imax parms[0]
#define eta parms[1]
#define mw parms[2]
#define epsA parms[3]
#define epsG parms[4]
#define epsR parms[5]
#define gamma parms[6]
#define Smax parms[7]
#define thetar parms[8]
#define rho parms[9]
#define c parms[10]
#define mc parms[11]
#define mi parms[12]
#define b parms[13]
#define epsI parms[14]
#define ui parms[15]
#define epsP parms[16]
#define hc parms[17]
#define sigmac parms[18]
#define heps parms[19]
#define epsAmin parms[20]
#define up parms[21]
#define uc parms[22]
#define ui parms[23]
#define InfDose parms[24]
#define Food parms[25]
#define MAX(a,b) (((a)>(b))?(a):(b))

/* initializer */
void initmod(void (* odeparms)(int *, double *)) {
  int N=26;
  odeparms(&N, parms);
}

/* derivatives */
void derivs (int *neq, double *t, double *y, double *ydot) {

  // state variables
  double C = y[0];
  double R = y[1];
  double Ii = y[2];
  double P2 = y[3];

  // condition-dependent ingestion rate
  double In = imax * pow(Smax, 0.66666667) * Food / (1 + exp(eta * (R/Smax - thetar)));
  // parasite-dependent assimilation efficiency
  double eA = epsA * (1 - epsAmin * P2 / (heps + P2));
  // constitutive defense
  double Ic = c * (Smax + R);
```

```
  // maintenance rate
  double M = mw * (Smax + R)  + mc * Ic + mi * Ii;

  // rate equations
  ydot[0] = (1-eA) * In - rho * C - sigmac * P2 * C/(hc + C);
  ydot[1] = epsR * (eA * In - M - b * R * P2);
  ydot[2] = epsI * b * R * P2 - ui * Ii;
  ydot[3] = epsP * sigmac*P2*C/(hc+C) - up * P2 - vc * Ic * P2 - vi * Ii * P2;
}

/* At some point the parasite invades and the parasite abundance goes from 0 */
/* to  something positive */
void event(int *n, double *t, double *y) {
  y[3] = InfDose;
}
```

```
library(deSolve)
library(magrittr)
library(MASS)
## C code for fast solution of the system
system("R CMD SHLIB macro_deb.c")
## if working on a Mac/Linux/Unix-based system
dyn.load("macro_deb.so")
## if working on a PC
#dyn.load("macro_deb.dll")

pars <- c(## host energy budget parameters
    imax=0.5, eta=20, mw=0.09, epsA=0.75, epsG=1, epsR=1,
    gamma=0.02, smax=25, thetar=0.25, rho=2,
    ## immune parameters
    c=5e-4, mc=0.3, mi=0.3, b=1, epsI=0.8, ui=0.3,
    ## parasite parameters
    epsP=0.2, hc=0.9, sigmac=0.52, heps=1e-4, epsAmin=0.4,
    up=0.05, vc=0.6, vi=0.3,
    InfDose=0.0004, Food=1.5)
## set the random number generator seed
set.seed(101234098)
## generate variation in the initial parasite dose
doses <- rnorm(1000, mean=3e-4, sd=8e-5)
## simulate the system. Initial colon and reversible biomass
## are at the parasite-free equilibrium
lapply(doses, function(d) {
    y0 <- c(C=0.4635946, R=5.854884, Ii=0, P2=d)
    times <- seq(0, 1100)
    ode(y=y0,
        times=times,
        func="derivs",
        parms=pars,
        dllname="macro_deb",
        initfunc="initmod",
        method="lsoda")
}) -> out

## grab parasite biomass at different points
data.frame(time=rep(seq(100,500,200),1000),
           ind=rep(1:1000, each=3),
           parasites=unlist(lapply(out,
               function(o) o[seq(101,501,200),"P2"]))) -> np

## Now simulate at a different sigamC value that produces only acute infections
pars["sigmac"] <- 0.45
set.seed(101234098)
doses <- rnorm(1000, mean=3e-4, sd=8e-5)
lapply(doses, function(d) {
    y0 <- c(C=0.4635946, R=5.854884, Ii=0, P2=d)
    times <- seq(0, 1100)
    ode(y=y0,
        times=times,
        func="derivs",
        parms=pars,
        dllname="macro_deb",
        initfunc="initmod",
        method="lsoda")
}) -> out2
data.frame(time=rep(seq(100,500,200),1000),
           ind=rep(1:1000, each=3),
           parasites=unlist(lapply(out2,
               function(o) o[seq(101,501,200),"P2"]))) -> np2

## Now simulate at a different sigamC value that produces only chronic infections
pars["sigmac"] <- 0.9
set.seed(101234098)
doses <- rnorm(1000, mean=3e-4, sd=8e-5)
lapply(doses, function(d) {
    y0 <- c(C=0.4635946, R=5.854884, Ii=0, P2=d)
    times <- seq(0, 1100)
    ode(y=y0,
        times=times,
        func="derivs",
        parms=pars,
        dllname="macro_deb",
        initfunc="initmod",
        method="lsoda")
}) -> out3
data.frame(time=rep(seq(100,500,200),1000),
```

```
          ind=rep(1:1000, each=3),
          parasites=unlist(lapply(out3,
              function(o) o[seq(101,501,200),"P2"]))) -> np3

## plot the results
par(mfrow=c(4,3), mar=c(1,1,1,1), oma=c(4,4,0,0))
## plot the burden distribution at fixed time points
for (t in c(100,300,500)) {
    ## fit different distributions to these data

    ## convert parasite biomass to number of parasites
    parasites <- abs(round(subset(np, time==t)$parasites/5e-5))

    ## fit different statistical distributions to the data
    legtxt <- c(fitdistr(parasites, 'negative binomial') %>% AIC %>% round,
                fitdistr(parasites, 'normal') %>% AIC  %>% round,
                fitdistr(parasites, 'Poisson') %>% AIC  %>% round)
    ## bin the parasite burdens
    yvals <- sapply(seq(2, 38, 2),
                    function(i)
                        sum(parasites >= (i-2) & parasites < i)/length(parasites))
    yvals <- c(yvals, sum(parasites > 38)/length(parasites))

    ## plot
    plot.new()
    plot.window(xlim=c(0,40), ylim=c(0,0.5))
    for (i in 1:20)
    rect(seq(0,40,2)[i], 0, seq(0,40,2)[i+1], yvals[i])
    axis(1, tick=TRUE, labels=FALSE)
    if (t==100) axis(2) else axis(2, tick=TRUE, labels=FALSE)
    mtext(side=3, line=-1.5, paste0("Time = ", t), cex=0.75)
    box('plot')
    legend(x=40, y=0.45, xjust=1, legend=legtxt, text.col=c(1,2,4), bty='n')
}
## plot the burden at randomly chosen time points
for (t in 1:3) {
    parasites <- lapply(out, function(o) o[sample(1:501, 1),"P2"] %>% unname) %>% unlist
    parasites <- abs(round(parasites/5e-5))
    legtxt <- c(fitdistr(parasites, 'negative binomial') %>% AIC %>% round,
                fitdistr(parasites, 'normal') %>% AIC %>% round,
                fitdistr(parasites, 'Poisson') %>% AIC %>% round)
    yvals <- sapply(seq(2, 38, 2),
                    function(i)
                        sum(parasites >= (i-2) & parasites < i)/length(parasites))
    yvals <- c(yvals, sum(parasites > 38)/length(parasites))
    plot.new()
    plot.window(xlim=c(0,40), ylim=c(0,0.5))
    for (i in 1:20)
    rect(seq(0,40,2)[i], 0, seq(0,40,2)[i+1], yvals[i])
    axis(1, tick=TRUE, labels=FALSE)
    if (t < 1.5) axis(2) else axis(2, tick=TRUE, labels=FALSE)
    mtext(side=3, line=-1.5, paste0("Population = ", t), cex=0.75)
    legend(x=40, y=0.45, xjust=1, legend=legtxt, text.col=c(1,2,4), bty='n')
    box('plot')
}
for (t in c(100, 300,500)) {
    ## fit different distributions to these data
    parasites <- abs(round(subset(np2, time==t)$parasites/5e-5))
    if (sum(parasites > 0) > 10)
        legtxt <- c(ifelse(inherits(try(fitdistr(parasites, 'negative binomial') %>%
                                            AIC %>%
                                            round),
                                    'try-error'),
                           '',
                           fitdistr(parasites, 'negative binomial') %>% AIC %>% round),
                    fitdistr(parasites, 'normal') %>% AIC %>% round,
                    fitdistr(parasites, 'Poisson') %>% AIC %>% round)
    else {
        legtxt=c('','','')
    }
    ## bin the burdens
    yvals <- sapply(seq(2, 38, 2),
                    function(i)
                        sum(parasites >= (i-2) & parasites < i)/length(parasites))
    yvals <- c(yvals, sum(parasites > 38)/length(parasites))
    ## plot
    plot.new()
    plot.window(xlim=c(0,40), ylim=c(0,1))
    for (i in 1:20)
    rect(seq(0,40,2)[i], 0, seq(0,40,2)[i+1], yvals[i])
    axis(1, tick=TRUE, labels=FALSE)
    if (t==100) axis(2) else axis(2, tick=TRUE, labels=FALSE)
    mtext(side=3, line=-1.5, paste0("Time = ", t), cex=0.75)
    box('plot')
    legend(x=40, y=0.9, xjust=1, legend=legtxt, text.col=c(1,2,4), bty='n')
}
for (t in c(100, 300,500)) {
    ## fit different distributions to these data
    parasites <- abs(round(subset(np3, time==t)$parasites/5e-5))
    if (sum(parasites > 0) > 10)
        legtxt <- c(fitdistr(parasites+1, 'negative binomial') %>% AIC %>% round,
                    fitdistr(parasites+1, 'normal') %>% AIC %>% round,
                    fitdistr(parasites+1, 'Poisson') %>% AIC %>% round)
    else legtxt=c('','','')
    yvals <- sapply(seq(2, 38, 2),
                    function(i)
                        sum(parasites >= (i-2) & parasites < i)/length(parasites))
```

```
    yvals <- c(yvals, sum(parasites > 38)/length(parasites))
    plot.new()
    plot.window(xlim=c(0,40), ylim=c(0,1))
    for (i in 1:20)
    rect(seq(0,40,2)[i], 0, seq(0,40,2)[i+1], yvals[i])
    axis(1, at=seq(0,40,10), labels=c("0","10","20","30",">40"))
    if (t==100) axis(2) else axis(2, tick=TRUE, labels=FALSE)
    mtext(side=3, line=-1.5, paste0("Time = ", t), cex=0.75)
    box('plot')
    legend(x=0, y=0.9, xjust=0, legend=legtxt, text.col=c(1,2,4), bty='n')
}
mtext(side=1, "Number of parasites", outer=T, line=2)
mtext(side=2, "Fraction of hosts", outer=T, line=2)
```

```
pars <- c(## host energy budget parameters
    imax=0.5, eta=20, mw=0.09, epsA=0.75, epsG=1, epsR=1,
    gamma=0.02, smax=25, thetar=0.25, rho=2,
    ## immune parameters
    c=5e-4, mc=0.3, mi=0.3, b=1, epsI=0.8, ui=0.3,
    ## parasite parameters
    epsP=0.2, hc=0.9, sigmac=0.52, heps=1e-4, epsAmin=0.4,
    up=0.05, vc=0.6, vi=0.3,
    InfDose=0.0004, Food=1.5)

## set the random number generator seed
set.seed(10001)

## generate variation in parasite "strain" by generating
## 10 parasite strains that vary in their attack rate
## generate variation in parasite dose
strain_by_dose <- data.frame(strain=rnorm(10,mean=0.52,sd=0.05)%>%rep(.,each=100),
                             dose=rnorm(1000,mean=3e-4,sd=8e-5))
apply(strain_by_dose, 1, as.list) %>% lapply(., unlist) -> strain_by_dose

## simulate the dynamics
lapply(strain_by_dose, function(s) {
    pars["sigmac"] <- unname(s["strain"])
    y0 <- c(C=0.4635946, R=5.854884, Ii=0, P2=unname(s["dose"]))
    times <- seq(0, 1100)
    ode(y=y0,
        times=times,
        func="derivs",
        parms=pars,
        dllname="macro_deb",
        initfunc="initmod",
        method="lsoda")
}) -> out

## grab parasite biomass at different points
data.frame(time=rep(c(100,300,500), 1000),
           ind=rep(1:1000, each=3),
           parasites=unlist(lapply(out, function(o) o[seq(101,501,200),"P2"]))) -> np

par(mfrow=c(5,3), mar=c(1,1,1,1), oma=c(4,4,0,0))
layout(matrix(c(rep(rep(1:3,each=4),4),
                rep(rep(4:6,each=4),4),
                rep(7:9,each=4),
                rep(rep(10:12,each=4),4),
                rep(rep(13:15,each=4),4)),
              nrow=17,
              ncol=12,
              byrow=T))
for (t in c(100,300,500)) {
    ## fit different distributions to these data
    parasites <- abs(round(subset(np, time==t)$parasites/5e-5))
    legtxt <- c(fitdistr(parasites, 'negative binomial') %>% AIC %>% round,
                fitdistr(parasites, 'normal') %>% AIC %>% round,
                fitdistr(parasites, 'Poisson') %>% AIC %>% round)
    yvals <- sapply(seq(10, 130, 10),
                    function(i)
                        sum(parasites >= (i-10) & parasites < i)/length(parasites))
    yvals <- c(yvals, sum(parasites > 130)/length(parasites))
    plot.new()
    plot.window(xlim=c(0,150), ylim=c(0,0.8))
    for (i in 1:length(yvals))
    rect(seq(0,150,10)[i], 0, seq(0,150,10)[i+1], yvals[i])
    axis(1, at=c(seq(0,125,25),150), tick=TRUE, labels=FALSE)
    if (t==100) axis(2) else axis(2, tick=TRUE, labels=FALSE)
    mtext(side=3, line=-1.5, paste0("Time = ", t), cex=0.75)
    box('plot')
    legend(x=150, y=0.7, xjust=1, legend=legtxt, text.col=c(1,2,4), bty='n')
}
for (t in 1:3) {
    parasites <- lapply(out, function(o) o[sample(1:501, 1),"P2"] %>% unname) %>% unlist
    parasites <- abs(round(parasites/5e-5))
    legtxt <- c(fitdistr(parasites, 'negative binomial') %>% AIC %>% round,
                fitdistr(parasites, 'normal') %>% AIC %>% round,
                fitdistr(parasites, 'Poisson') %>% AIC %>% round)
    yvals <- sapply(seq(10, 130, 10),
                    function(i)
                        sum(parasites >= (i-10) & parasites < i)/length(parasites))
    yvals <- c(yvals, sum(parasites > 130)/length(parasites))
    plot.new()
    plot.window(xlim=c(0,150), ylim=c(0,0.8))
    for (i in 1:length(yvals))
```

```
    rect(seq(0,150,10)[i], 0, seq(0,150,10)[i+1], yvals[i])
    axis(1, at=c(seq(0,125,25),150), labels=c(as.character(seq(0,125,25)), ">150"))
    if (t < 1.5) axis(2) else axis(2, tick=TRUE, labels=FALSE)
    mtext(side=3, line=-1.5, paste0("Population = ", t), cex=0.75)
    legend(x=150, y=0.7, xjust=1, legend=legtxt, text.col=c(1,2,4), bty='n')
    box('plot')
}

plot.new()
plot.new()
plot.new()

## now allow both hosts and parasites to vary.
## Parasites vary in attack rate, and hosts vary in immune mobilization
set.seed(123401)
strain_by_dose <- data.frame(host=rep(rnorm(10, mean=5, sd=1.2), each=100),
                             strain=rep(rnorm(100, mean=0.55, sd=0.1),10),
                             dose=rnorm(1000, mean=3e-4, sd=8e-5))
apply(strain_by_dose, 1, as.list) %>% lapply(., unlist) -> strain_by_dose2

simmodel <- function(s) {
    pars <- c(## host energy budget parameters
        imax=0.5, eta=20, mw=0.09, epsA=0.75, epsG=1, epsR=1,
        gamma=0.02, smax=25, thetar=0.25, rho=2,
        ## immune parameters
        c=5e-4, mc=0.3, mi=0.3, b=1, epsI=0.8, ui=0.3,
        ## parasite parameters
        epsP=0.2, hc=0.9, sigmac=0.52, heps=1e-4, epsAmin=0.4,
        up=0.05, vc=0.6, vi=0.3,
        InfDose=0.0004, Food=1.5)
    pars["sigmac"] <- unname(s["strain"])
    pars["b"] <- unname(s["host"])
    y0 <- c(C=0.4635946, R=5.854884, Ii=0, P2=unname(s["dose"]))
    times <- seq(0, 1100)
    ode(y=y0,
        times=times,
        func="derivs",
        parms=pars,
        dllname="macro_deb",
        initfunc="initmod",
        method="lsoda")
}

out <- vector(mode='list', length=length(strain_by_dose2))
for (i in 1:length(strain_by_dose2)) {
  #  print(i)
    out[[i]] <- simmodel(strain_by_dose2[[i]])
}

## grab parasite biomass at different points
data.frame(time=rep(c(100,300,500),10000),
           ind=rep(1:10000, each=3),
           parasites=unlist(lapply(out, function(o) o[seq(101,501,200),"P2"]))) -> np

for (t in c(100,300,500)) {
    ## fit different distributions to these data
    parasites <- abs(round(subset(np, time==t)$parasites/5e-5))
    legtxt <- c(fitdistr(parasites, 'negative binomial') %>% AIC %>% round,
                fitdistr(parasites, 'normal') %>% AIC %>% round,
                fitdistr(parasites, 'Poisson') %>% AIC %>% round)
    yvals <- sapply(seq(5, 75, 5),
                    function(i)
                        sum(parasites >= (i-5) & parasites < i)/length(parasites))
    yvals <- c(yvals, sum(parasites > 75)/length(parasites))
    plot.new()
    plot.window(xlim=c(0,75), ylim=c(0,0.8))
    for (i in 1:length(yvals))
    rect(seq(0,75,5)[i], 0, seq(0,75,5)[i+1], yvals[i])
    axis(1, tick=TRUE, labels=FALSE)
    if (t==100) axis(2) else axis(2, tick=TRUE, labels=FALSE)
    mtext(side=3, line=-1.5, paste0("Time = ", t), cex=0.75)
    box('plot')
    legend(x=75, y=0.7, xjust=1, legend=legtxt, text.col=c(1,2,4), bty='n')
}
for (t in 1:3) {
    parasites <- lapply(out, function(o) o[sample(1:501, 1),"P2"] %>% unname) %>% unlist
    parasites <- abs(round(parasites/5e-5))
    legtxt <- c(fitdistr(parasites, 'negative binomial') %>% AIC %>% round,
                fitdistr(parasites, 'normal') %>% AIC %>% round,
                fitdistr(parasites, 'Poisson') %>% AIC %>% round)
    yvals <- sapply(seq(5, 75, 5),
                    function(i)
                        sum(parasites >= (i-5) & parasites < i)/length(parasites))
    yvals <- c(yvals, sum(parasites > 75)/length(parasites))
    plot.new()
    plot.window(xlim=c(0,75), ylim=c(0,0.8))
    for (i in 1:length(yvals))
    rect(seq(0,75,5)[i], 0, seq(0,75,5)[i+1], yvals[i])
    axis(1)
    if (t < 1.5) axis(2) else axis(2, tick=TRUE, labels=FALSE)
    mtext(side=3, line=-1.5, paste0("Population = ", t), cex=0.75)
    legend(x=75, y=0.7, legend=legtxt, text.col=c(1,2,4), bty='n')
    box('plot')
}
mtext(side=1, "Number of parasites", outer=T, line=2)
mtext(side=2, "Fraction of hosts", outer=T, line=2)
```

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ESM Figures

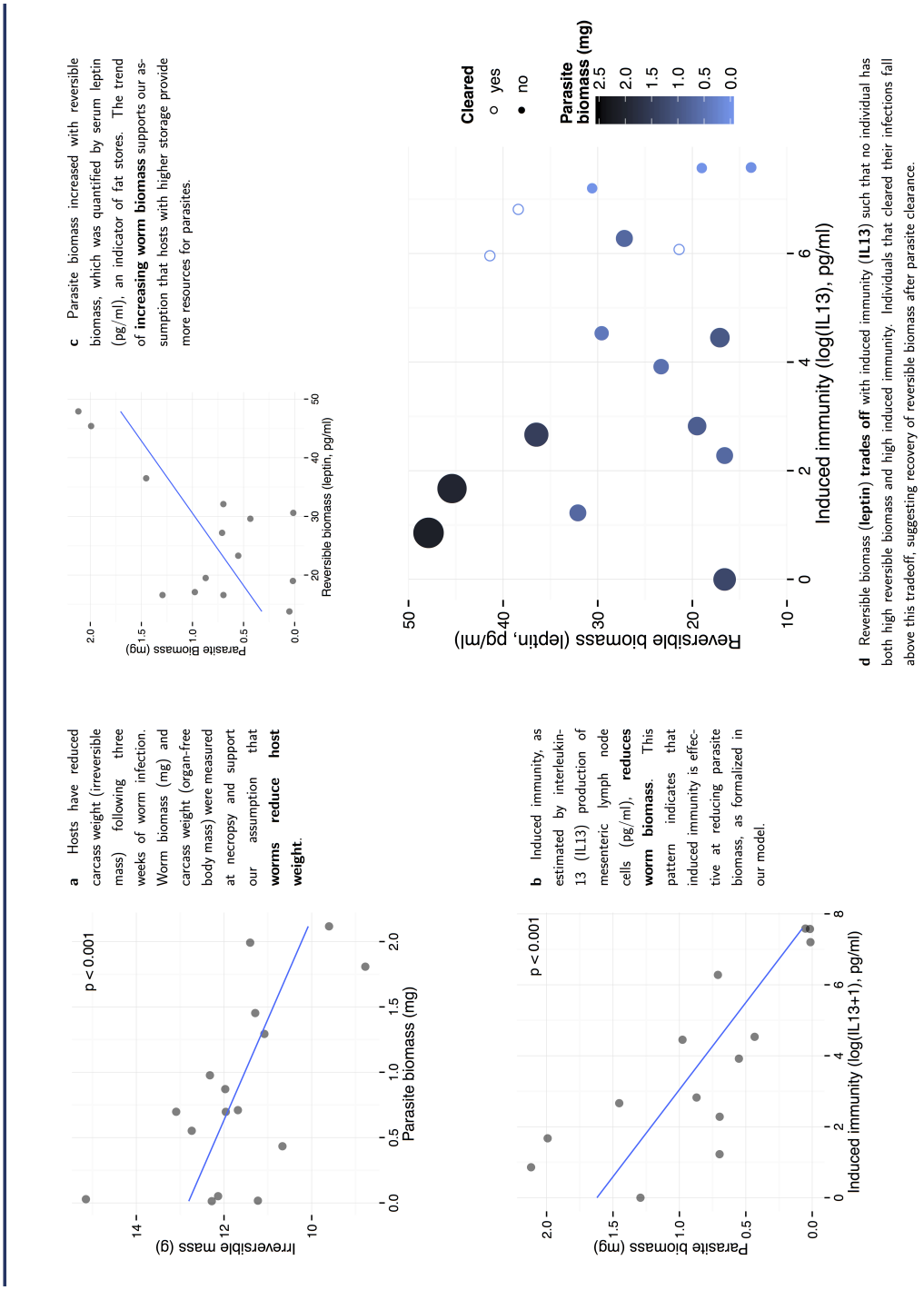

Figure ESM1. Empirical patterns as found in the field rewilding study. Mice (*Mus musculus*, C57Bl/6) were infected with 200 eggs of the gastrointestinal worm *Trichuris muris* and housed in outdoor enclosures for 3 weeks [16, 11], also see Dryad Digital Repository [10] for the data and ESM text for a more detailed description of protocol and methods.

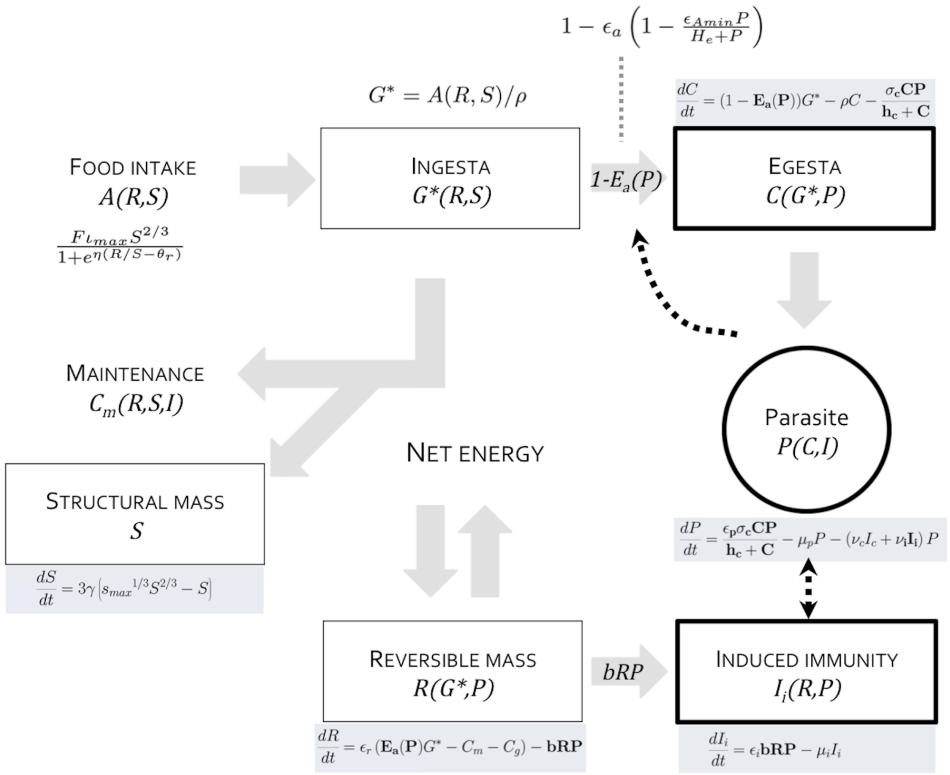

Figure ESM2. Biomass compartments and resource flows in the within-host model. Our conceptual framework and modelling setup account for the energetic basis of host-parasite interactions. Baseline processes and variables (thin solid shapes) follow standard Dynamic Energy Budget (DEB) formulations. Novel elements (in bold shapes, right column) are formulated on the basis of first principles in ecology and immunology and included to account for the energetics of parasite and the hosts immune response. Block arrows represent directions of biomass flows. Compartments in solid lines correspond to dynamic variables; implicit variables (maintenance and net resources) and food intake are labelled only. Parasite biomass (P) triggers an induced immune response (I_i), which itself represses parasite biomass (double-sided dotted arrow). The flow of biomass to egesta increases due to parasite biomass (dotted arrow, following $(1 - E_a(P))$, see Methods), which represents resource modulation. The system equations are included with the variable they pertain to.

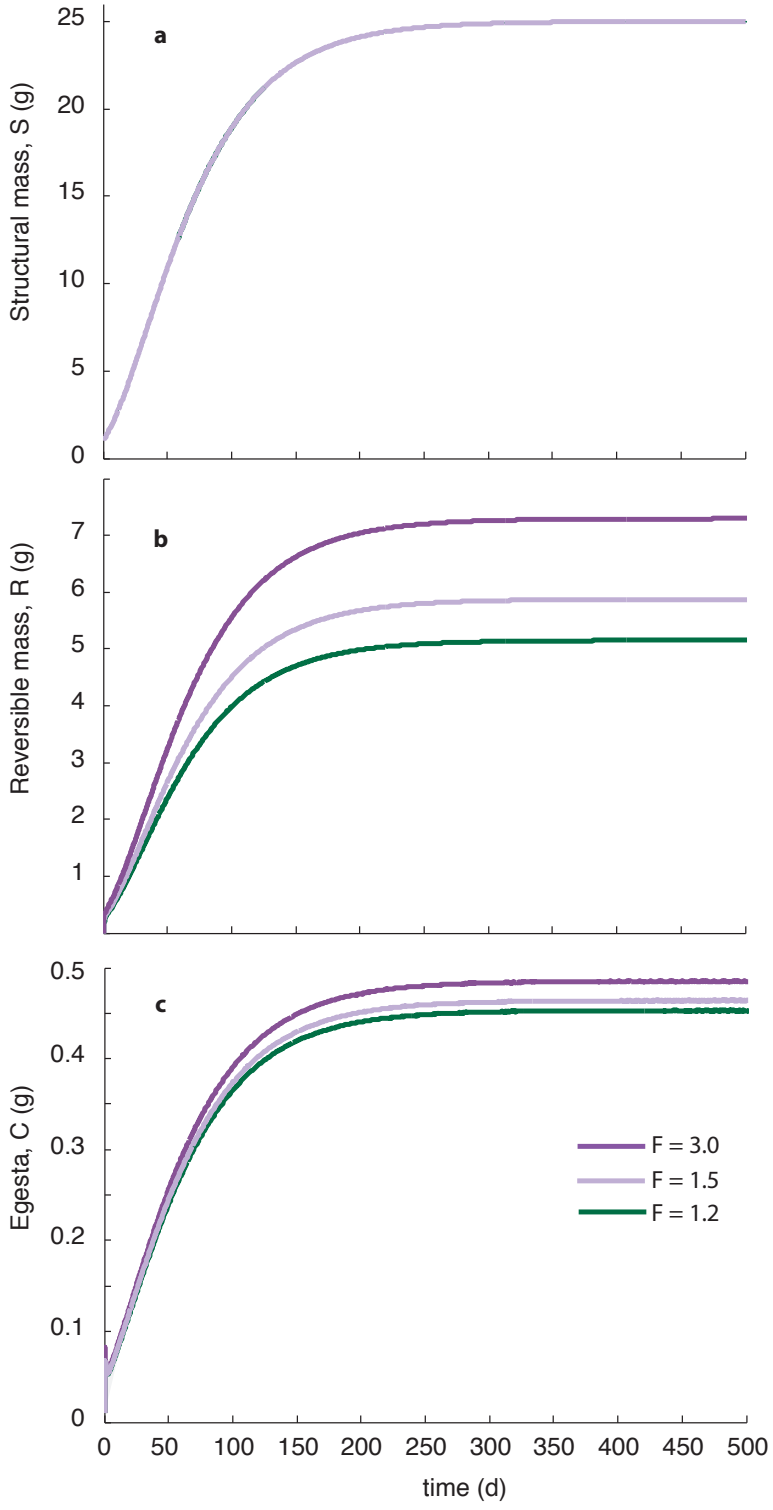

Figure ESM3. Mouse development over time. Growth and development of the host compartments during a period of 500 days. **a**, Structural biomass; **b**, reserve biomass; **c**, biomass in the colon. The three different curves reflect different food levels (see legend), which correspond to the consecutive larger asymptotic sizes reached by the mouse. Because growth in structural mass is independent of food availability (and follows a prescribed curve), the three curves are identical for S (**a**). Parameters have default values, see Table ESM1.

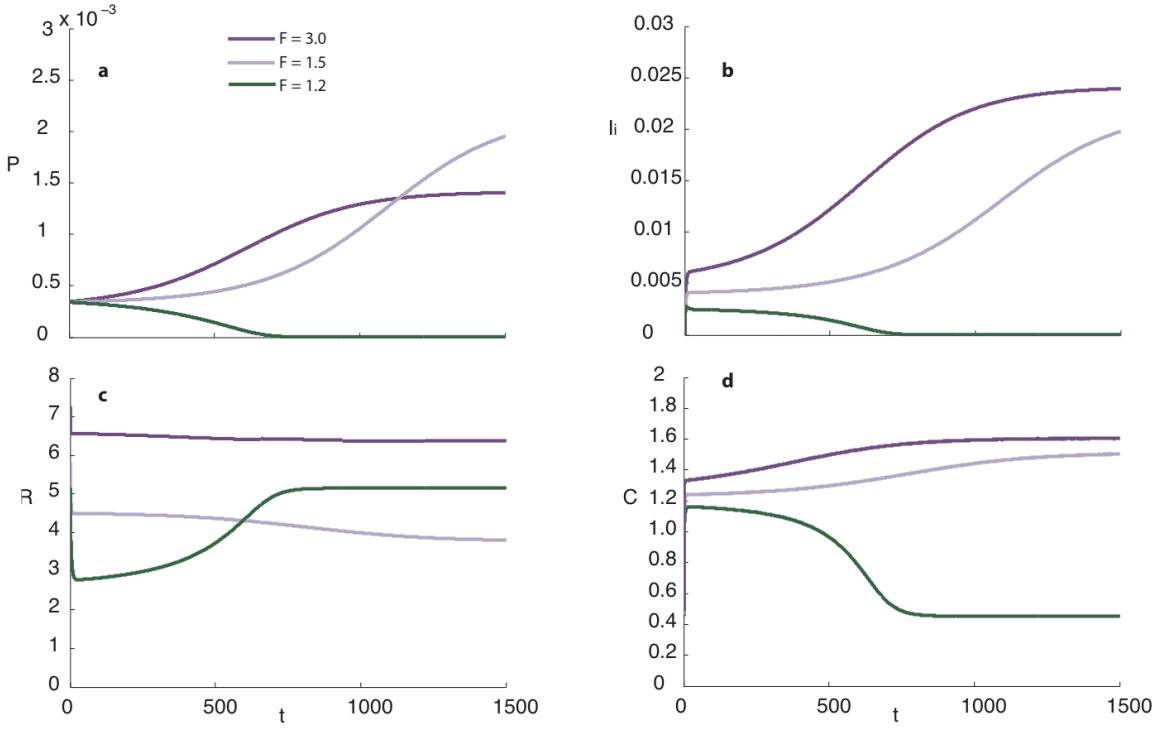

Figure ESM4. Time series of dynamic simulation for different food levels. Additional variables for main text figure 1b. Simulation of infection starting at three host condition states that result from varying host food availability levels. Differently colored lines indicate model simulations with varying food level (see legend). The simulations are all done with identical initial parasite biomass, infecting a host that has developed under three different food availability levels. $\sigma_C = 0.52$ and other parameters have default values. Please note that here only the first 1500 time steps are shown, the transient dynamics extending main text figure 1b, here also showing the other system variables, **a**, parasite biomass (P);**b**, induced immune response (Ii); **c**, reversible biomass (R); **d** egesta (C).

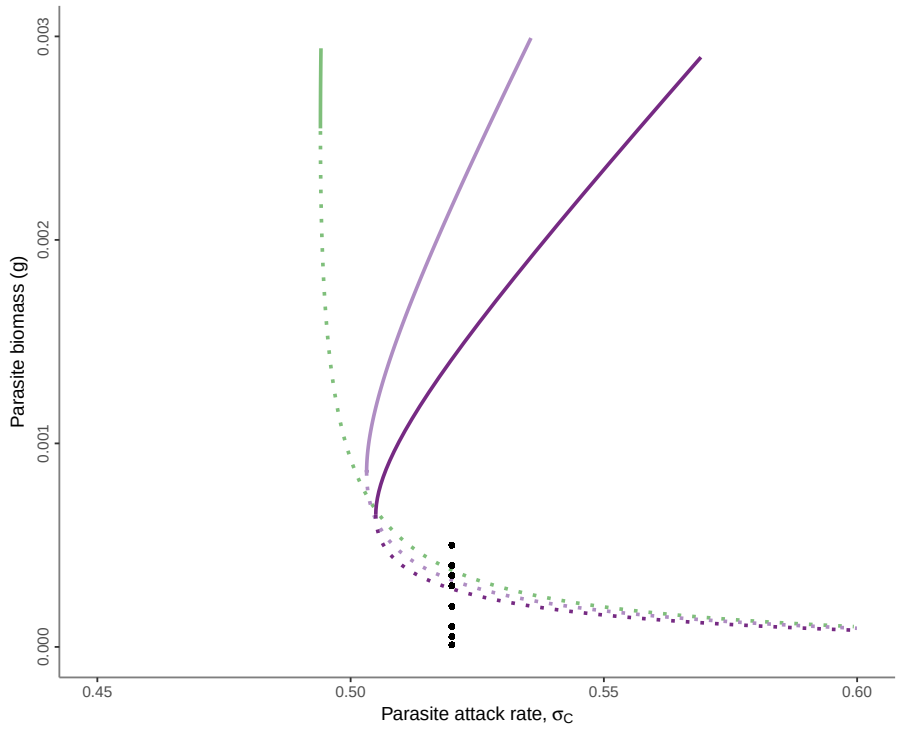

Figure ESM5. Equilibrium analysis for three different food levels. Parasite equilibrium biomass as function of parasite attack rate for three different food intake levels: $F = 1.2$ (green);$F = 1.5$ (lilac, default); and $F = 3.0$ (purple). The configuration of the stable (solid) and unstable (dashed) equilibria changes for different food levels. This means that the separatrix distinguishing acute and chronic trajectories is located at different positions in parameter space. In black dots the initial parasite dose for main text Fig. 1 are indicated. The graph was zoomed in to show how initial dose and food level impact the eventual outcome of the time series. Note the linear y-axis, as opposed to the logarithmic representation in main text Fig. 3.

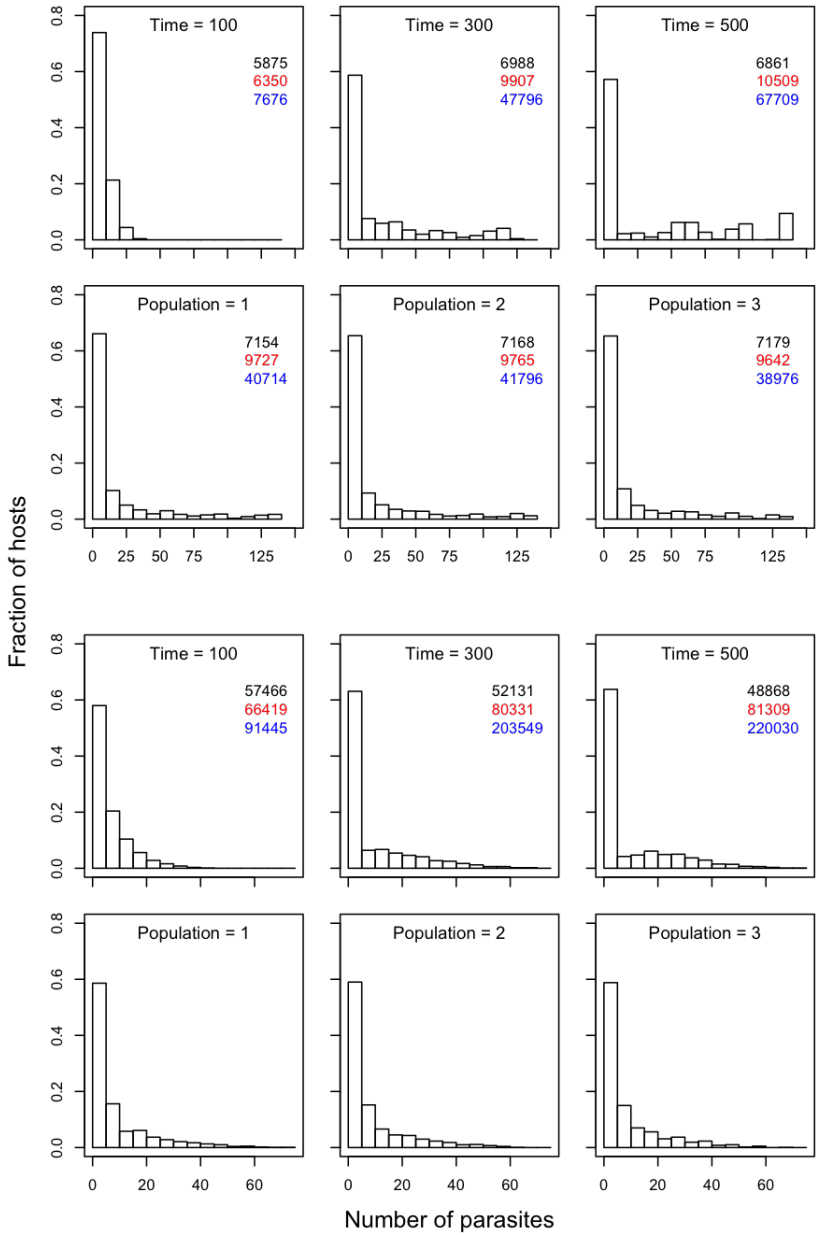

Figure ESM6. Parasite distributions when parasites and hosts are not identical. For the first two rows, all hosts are genetically identical, in terms of the rate of reserve allocation to immunity in the presence of parasites ($b = 1$) but there are 10 different parasite strains that vary in attack rate (σ_C was drawn from a normal distribution with mean of 0.52 and a standard deviation of 0.05. Each strain infects 100 hosts, with an infectious dose (in biomass units) drawn from a normal distribution with a mean of $3.0 \cdot 10^{-4}$g and a standard deviation of $8.0 \cdot 10^{-5}$g. Row 1 shows the distribution of parasite burden through time, assuming that all 1000 hosts were infected at the same time and infections were tracked, as in a controlled infection experiment. Biomass was converted to adult parasite numbers assuming an adult biomass of $5.0 \cdot 10^{-5}$g. Row 2 shows distributions of parasite burden assuming that 1000 hosts were sampled at different infection ages, as would be the case when a wild population is sampled. Across the row are three different populations of 1000 hosts. For the bottom two rows, we assume there are 10 host genotypes that vary in immune energy mobilization b (each host's mobilization was drawn from a normal distribution with a mean of 5 and standard deviation of 1.2). There were 100 individuals of each host genotype. Each of these 100 hosts is infected with a unique parasite strain whose attack rate was drawn from a normal distribution with mean of 0.52 and a standard deviation of 0.05. Infectious dose was drawn from a normal distribution with a mean of 10 and a standard deviation of 2. Row 3 shows the distribution of parasite burden through time, assuming that all 1000 hosts were infected at the same time and infections were tracked, as in a controlled infection experiment. Row 4 shows distributions of parasite burden assuming that 1000 hosts were sampled at different infection ages, as would be the case when a wild population is sampled. Across the row are three different populations of 1000 hosts. The legend gives the AIC scores from fitting different statistical distributions to the distribution data (Black - Negative binomial, Red - Normal, Blue - Poisson).

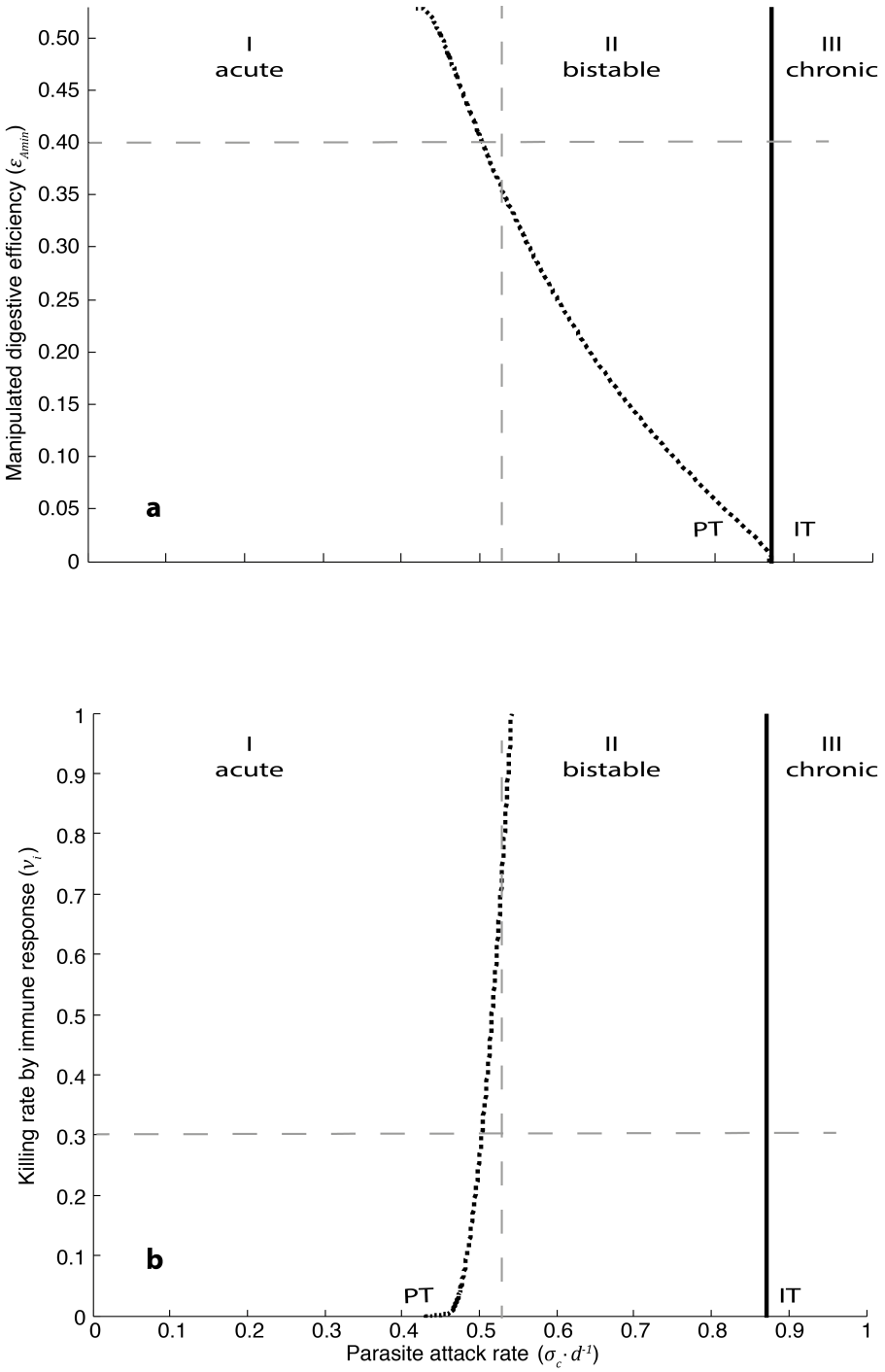

Figure ESM7. Bistability region in parameter space. The region of system bistability as function of parasite attack rate, σ_C, in combination with ϵ_{Amin}, **a** and ν_i, **b**. The bistable parameter range (region II) is enclosed by the persistence threshold (representing a fold bifurcation, dotted line, PT) and by the invasion threshold (representing a branching point bifurcation, solid line, IT, occurring for $\sigma_C = 0.89$). Parameter combinations in region I result in acute infections only. Parameter combinations in region III result in chronic infections only (the only stable equilibrium has positive parasite biomass). The persistence and invasion thresholds enclose region II, where bistability is found between chronic and acute infection equilibria. The parameter values as used in other figures are indicated by thin, dashed lines. **a**, Increasing values of ϵ_{Amin} result in an increasing region of bistability. **b**, Increasing values of ν_i result in a decreasing region of bistability. Compare the region of bistability with main text Fig. 3, which represents a slice in these two-parameter plots. $F = 1.5$ and other parameters have default values.