Resource Ecology of Virulence in a Planktonic Host-Parasite System: An Explanation Using Dynamic Energy Budgets

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abstract: Parasites steal resources that a host would otherwise direct toward its own growth and reproduction. We use this fundamental notion to explain resource-dependent virulence in a fungal parasite (*Metschnikowia*)–zooplankton host (*Daphnia*) system and in a variety of other disease systems with invertebrate hosts. In an experiment, well-fed hosts died faster and produced more parasites than did austerely fed ones. This resource-dependent variation in virulence and other experimental results (involving growth and reproduction rate/timing of hosts) readily emerged from a model based on dynamic energy budgets. This model follows energy flow through the host, from ingestion of food, to internal energy storage, to allocation toward growth and reproduction or to a parasite that consumes these reserves. Acting as a consumer, the parasite catalyzes its own extinction, persistence with an energetically compromised host, or death of the host. In this last case, more resources for the host inadvertently fuels faster parasite growth, thereby accelerating the demise of the host (although the opposite result arises with different resource kinetics of the parasite). Thus, this model can explain how resource supply drives variation in virulence. This ecological dependence of virulence likely rivals and/or interacts with genetic mechanisms that often garner more attention in the literature on disease.

Keywords: consumer-resource interactions, *Daphnia-Metschnikowia*, dynamic energy budget, ecology of virulence, within-host dynamics.

Introduction

Studies of disease ecology and evolution often focus on factors that drive variation in the virulent effects of parasites on host survival and fecundity. Many parasites reduce the fitness of their hosts by decreasing reproduction, survivorship, and/or growth. To explain these effects, much theoretical and empirical work has focused on three major, interrelated drivers of virulence. First, we often think of virulence as a genetic trait of hosts and parasites (Flor 1956; Henter and Via 1995; Schmid-Hempel and Ebert 2003) that is elegantly captured by models ranging from "gene-for-gene" to "allele matching" (Agrawal and Lively 2002). Certain genotypes of parasites are better at infecting all hosts (gene-for-gene) or particular host genotypes (matching alleles). Second, when hosts become infected, virulence of parasites can depend on trade-offs between strategies of host species (e.g., resistance vs. tolerance; Antonovics and Thrall 1994; Bowers et al. 1994; Boots and Haraguchi 1999; Hoyle et al. 2008) or between traits of a parasite species (such as transmission rate vs. virulent effects on survivorship). In the latter case, evolution of virulence theory typically predicts that parasites should evolve toward an intermediate, prudent level of virulence (Frank 1996; Day and Proulx 2004; Jensen et al. 2006). Third, competition among strains of coinfecting parasites can upend this "prudent" prediction. Such competition can ultimately increase virulent effects of infection in certain situations, but the net outcome of interstrain interactions can depend on underlying assumptions of the biology modeled (Nowak and May 1994; Frank 1996; Brown et al. 2002). Pursuit of all three processes (involving genetic identities, life-history trade-offs among hosts or parasites, and coinfection) can provide powerful insights into variation in virulence.

Recently, a growing amount of empirical evidence has indicated that host environment, particularly resource ecology, can also strongly influence virulence and production of parasites. In general, the theory cited above was not designed with this source of variation in mind (although it can intersect with genetic mechanisms via gene × environment interactions; Lazzaro and Little 2009). For infected hosts, food quantity and/or quality can influence survivorship of (e.g., snails-trematodes: Jokela et al. 1999; Seppälä et al. 2008; bumblebees-trypanosomes: Brown et al. 2000; mosquitoes-protozoans: Tseng 2004; mosquitoes-

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microsporidians: Agnew and Koella 1999; *Daphnia*-microparasites: Frost et al. 2008; Hall et al. 2009*b*; moths-viruses: Hodgson et al. 2002, 2004) and production of parasites from (mosquitoes-parasites: Bedhomme et al. 2004; Tseng 2004, 2006; *Daphnia*-parasites: Ebert et al. 2000, 2004; Bittner et al. 2002; Pulkkinen and Ebert 2004; Hall et al. 2009*b*; ladybirds-mites: Ryder et al. 2007; monarch butterflies–protozoans: de Roode et al. 2008; snails-trematodes: Johnson et al. 2007) infected hosts. Both of these traits (virulence on survivorship and parasite production) can determine parasite fitness, depending on the details of the system, and therefore could shape prevalence of infection in host populations. Despite its prominence in a diverse array of systems and its potential importance for disease dynamics, this environmental driver of virulence has undergone considerably less theoretical development than have the factors summarized above. This theoretical gap is unfortunate, because frequently occurring variation in resources of hosts, driven by either external factors or host grazing, could substantially influence disease dynamics, host evolution, and maintenance of host diversity through direct resource-virulence links (Hall et al. 2009*b*; Lazzaro and Little 2009). Therefore, a lack of theory integrating resource-host-parasite interactions could compromise the predictive power of eco-evoepidemiological models in many natural systems.

Our study aims squarely at this conceptual hole by developing a resource-dependent, within-host model of parasite dynamics. This model can later form a building block of models designed to track population dynamics of hosts. From a theoretical point of view, environmental dependence of virulence by invertebrates might not seem surprising. Parasites build new parasites by consuming resources (energy and materials), thereby steering them away from the host's growth, reproduction, and maintenance demands (Read 1994; Frank 1996; Bonds 2006). Virulence, then, emerges as a natural consequence of this theft of resources within hosts; resource-dependent virulence arises because resource consumption by hosts alters the availability of resources within hosts for parasites to steal. Here we operationalize this intuitive notion, using empirical evidence and the development of a model. In an experiment with a fungal parasite (*Metschnikowia bicuspidata*), we exposed infected and uninfected individuals from one clone (genotype) of a crustacean zooplankton host (*Daphnia dentifera*) to a gradient of algal food supply. Thus, the design isolated resource supply as a driver of virulence and held the genetic backgrounds of host and parasite constant. Results from this experiment and others readily emerged from a model based on dynamic energy budgets (DEBs). Kooijman's (1993) DEB model follows energy flow through a host from initial consumption to internal storage to later utilization for growth, reproduction, and associated metabolic costs. To this DEB model we added a parasite that steals from the energy reserve of the host, following standard consumer-resource dynamics (Grover 1997; Hall et al. 2007*b*). By explicitly considering parasites as consumers of resources stored within hosts, this physiology-based model ultimately mechanistically offers a minimal explanation for resource-dependent virulence.

Experiment: Methods

Host-Parasite System

The focal host-parasite system involved the freshwater crustacean *Daphnia dentifera* (Cladocera) and its ascomycetous fungal parasite *Metschnikowia bicuspidata*. *Daphnia dentifera* (hereafter referred to as *Daphnia*) is a large-bodied grazer zooplankter that is common in the deep lakes of the midwestern and northeastern United States (Tessier and Woodruff 2002). Reproduction of *Daphnia* depends on food intake and is cyclically parthenogenetic. In natural communities, multiple microparasites, including *Metschnikowia*, infect *Daphnia* (Ebert 2005; Hall et al. 2005*b*; Cáceres et al. 2006). Transmission of *Metschnikowia* occurs horizontally as the host ingests waterborne asci that propel needlelike ascospores through the gut wall and into the host's body cavity (Codreanu and Codreanu-Balcescu 1981; Hall et al. 2007*a*). When it has passed through the gut of its host, this parasite proliferates in the hemolymph, filling the host's body cavity with spores that are eventually released from the dead hosts (Ebert and Weisser 1997). Infection by the fungus reduces the fecundity and life span of *Daphnia*, and infected hosts cannot recover (Ebert et al. 2000; Hall et al. 2006). To perform the life-table experiment detailed below, we used a single clone of *Daphnia dentifera* and a strain of *Metschnikowia* collected in 2003 from Baker Lake (Barry County, MI). Parasites were farmed in vivo using this *Daphnia* clone, fed algal food (*Ankistrodesmus falcatus*) to excess, and raised in filtered (1 μm) lake water.

Life-Table Experiment

In the life-table experiment, we compared the fecundity and survivorship of individual animals infected with *Metschnikowia* with that of healthy ones. We exposed randomly selected, 9–10-day-old juvenile *Daphnia* (75 animals L^{-1}; fed 1.0 mg carbon [C] L^{-1} of *Ankistrodesmus* daily) to fungal spores (750 spores mL^{-1}; hosts fed 0.75 mg C L^{-1} of food during exposure). After a 24-hour exposure period, we randomly assigned infected and uninfected hosts to plastic tubes containing 30 mL of filtered lake water and one of four food treatments: 0.125, 0.250, 0.5, or 1.0 mg C L^{-1} (levels determined using absorbance–

dry weight regressions). The number of replicates differed among treatments: 20 (10 infected, 10 control) at 0.125 mg C L^{-1}; 24 (15 infected, 9 control) at 0.25 mg C L^{-1}; 23 (13 infected, 10 control) at 0.5 mg C L^{-1}; and 16 (8 infected, 8 control) at 1.0 mg L^{-1}. Animals were transferred to containers, provided with fresh food daily, and maintained in a 16L : 8D regime at 20°C. Animals were checked daily for survival, and offspring were counted and removed. Dead adults were visually scanned for infection and measured (top of head to base of the spine). To estimate spore load, we ground each animal in 50 μL of water and estimated spore density of the slurry using a hemocytometer. The experiment ended with death of all infected individuals (37 days).

Survivorship of infected hosts in each food treatment was analyzed using the LIFETEST procedure in SAS (SAS Institute 1999). Spore production and host length at death were tested using one-way ANOVA, while reproductive rates between infected and uninfected hosts were compared using two-way ANOVA (type III SS, GLM procedure; SAS Institute 1999).

Experiment: Results

The food treatments strongly influenced virulence in this host-parasite system. Infected animals died more quickly when fed more food (Wilcoxon $\chi^2 = 34.3$, df = 3, $P < .0001$). Infected hosts subjected to the highest food treatment lived 58% (on average) as long postinfection as those receiving the lowest food treatment, and time until death decreased monotonically with food supply (fig. 1*A*). Meanwhile, almost all uninfected hosts survived the duration of the experiment (see app. A in the online edition of the *American Naturalist* for survivorship curves). Reproduction rate was always higher for healthy hosts than for infected hosts (infection effect: $F_{1,73} = 225.0$, $P < .0001$; fig. 1*D*), and it increased with food levels for both infected and uninfected hosts (ANOVA, food effect: $F_{3,73} = 260.2$, $P < .0001$; fig. 1*B*). However, the birth rate increased more steeply with food for uninfected hosts than for infected hosts (ANOVA, food × infection interaction: $F_{3,73} = 36.4$, $P < .0001$; fig. 1*B*). In appendix A, we partition this food-dependent, compromised-fecundity effect into reproductive turnover and clutch size for the two host classes. The average infected host in the lowest food treatment group (0.125 mg C L^{-1}) stopped reproducing twice as many days before death than did those that were fed more food (ANOVA, food effect: $F_{3,41} = 13.3$, $P < .0001$; fig. 1*C*). As shown below, this "nutritional castration" result suggests periods of energetic stress experienced by these parasitized hosts in low-food environments. When survivorship and reproduction are combined, we see instantaneous rate of increase declining with infection but increasing with food supply (fig. 1*D*). Even though hosts in the highest food treatments died more quickly, they achieved larger body sizes (ANOVA: $F_{3,41} = 4.31$, $P = .0099$; fig. 1*E*) and produced (on average) >60% more spores of the parasite than did animals in the lowest treatments (ANOVA: $F_{3,41} = 6.75$, $P = .0008$; fig. 1*F*).

Model: Development

To understand these empirical results, we make the assumption that the fungal parasite steals energy from its host. To capture this biology, we use an existing DEB model to track energy flow through an ectothermic host (Kooijman 1993; Nisbet et al. 1996, 2000; see also table 1; fig. 2) as functions of its structural mass (W) and reserve energy (E). The kappa (κ) rule governs allocation of this reserve energy, with a fixed portion (κ) going to growth (dW/dt) and the remaining portion ($1 - \kappa$) going to reproduction (dR/dt, where R represents number of offspring produced daily) of the host. We then add a parasite (with population mass denoted by N) that steals energy reserves from the host and therefore exacts virulent effects on host growth, reproduction, and survival.

Here we present the core equations of the DEB-parasite model. Readers can review its derivation in appendix B in the online edition of the *American Naturalist* (also see Hall et al. 2007*b*). When parasitized hosts are in a relatively good energetic state (fig. 2*A*, "normal"), the model is

$$\frac{dW}{dt} = W\left[\frac{\kappa\left(aL^2/e_{\mathrm{M}}\right)(E/W) - mW}{\kappa E + gW}\right], \tag{1a}$$

$$\frac{dE}{dt} = aL^2\left(\frac{F/c}{h + F/c} - \frac{E}{e_{\mathrm{M}}W}\right) + E\left(\frac{dW}{dt}\right) - \frac{a_{\mathrm{N}}}{\varepsilon_{\mathrm{N}}}\left(\frac{E}{h_{\mathrm{N}} + E}\right)N, \tag{1b}$$

$$\frac{dR}{dt} = \left(\frac{q}{E_0}\right)\left[(1 - \kappa)\left(\frac{E}{W}\right)\left(\frac{aL^2}{e_{\mathrm{M}}} - \frac{dW}{dt}\right) - \left(\frac{1 - \kappa}{\kappa}\right)m\min\left(W, W_{\mathrm{P}}\right)\right], \tag{1c}$$

$$\frac{dN}{dt} = a_{\mathrm{N}}\left(\frac{E}{h_{\mathrm{N}} + E}\right)N - m_{\mathrm{N}}N. \tag{1d}$$

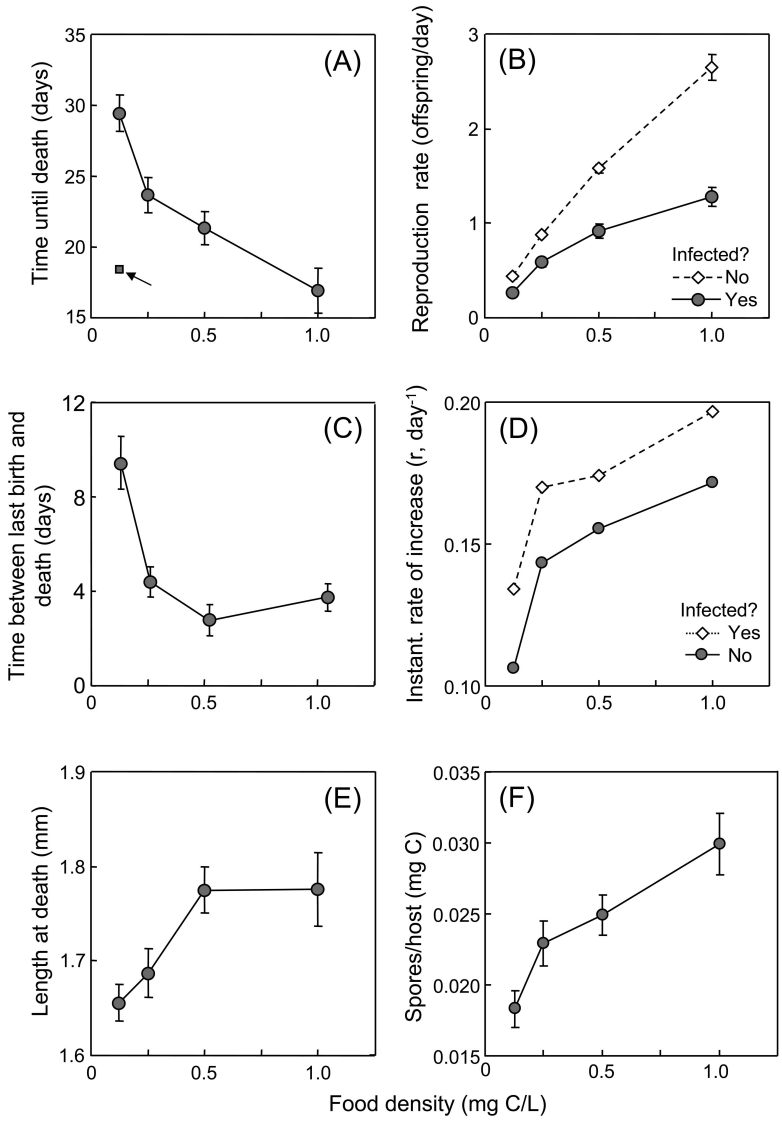

Figure 1: Response of infected hosts (a zooplankton, *Daphnia dentifera*) and parasites (a fungus, *Metschnikowia bicuspidata*) to a gradient of food density in a life-table experiment. With increasing algal food density, we see that time until death of infected hosts dropped (with an outlier denoted by an arrow), while almost all uninfected *Daphnia* survived for the duration of the experiment (see app. A in the online edition of the *American Naturalist*; *A*); reproduction increased, but at a lower rate for infected hosts than for uninfected hosts (*B*); the time span between last reproduction event and death of infected hosts decreased (*C*); per capita instantaneous growth rate of the host, *r*, increased with resource supply but was lower for uninfected hosts (*D*); and infected hosts who ate more food died at a larger size (*E*) but yielded fewer spores (*F*). Points are mean ± 1 SE.

Structural mass of the host (dW/dt; eq. [1a]) increases as a fixed proportion (κ) of reserve energy (E) is used (governed by maximal surface area–specific assimilation rate, a [which equals feeding rate, f, times maximal conversion efficiency, ε]; surface area L^2, where L is length; and maximal energy reserve per unit mass, e_M) and maintenance costs are paid for maintaining existing mass (at per mass rate m) and growing new structural mass (at cost g). Reserve energy E increases as food (F) is assimilated (where c is container size and h is a half-saturation parameter of the host's saturating, Type II functional response; leftmost term of eq. [1b]). However, it decreases as energy is utilized for growth and reproduction (central term of eq. [1b]) and is stolen by the parasite, N (right-hand term of eq. [1b], where a_N is the assimilation rate, ε_N is the conversion efficiency, and h_N is the half-saturation constant of the parasite's own Type II function response).

Reproduction rate (dR/dt; eq. [1c]) involves conversion

Table 1: State variables, fluxes, and parameters used in the dynamic energy budget (DEB) model with parasites

Term	Units	Definition	Value or range
State variables:			
e	…	Reserve energy density; equal to E/W	…
E	mg C	Reserve energy mass; equal to eW	…
F	mg C	Food (algae)	…
N	mg C	Mass of the parasite	…
R	Offspring	Reproduction	…
t	day	Time	…
W	mg C	Structural mass (weight) of the host	…
Fluxes:			
A	mg C day^{-1}	Assimilation rate	…
C	mg C day^{-1}	Energy utilization rate	…
Parameters:			
a	mg C mm^{-2} day^{-1}	Surface area–specific maximal assimilation rate	.00455
a_N	day^{-1}	Maximal assimilation rate of the parasite	.4
c	L	Volume of food container	.1
d	day^{-1}	Combined loss rate of the parasite	.08
E_0	mg C	Carbon investment per offspring	.0021
e_M	…	Maximal energy density	1.0
F_0	mg C	Initial food mass, replenished at interval T	.015–.1
g	…	Mass-specific cost of growth	.8
h	mg C L^{-1}	Half-saturation constant of the host	.1
h_N	mg C	Half-saturation constant of the parasite	.005
L	mm	Size of host; relates to W ($W = \alpha L^3$)	
L_0	mm	Initial size of hosts when exposed to parasite	1.3
m	day^{-1}	W-specific maintenance rate of the host	.2
m_N	day^{-1}	Loss rate of the parasite	.08
N_0	mg C	Initial spore mass consumed by the animal	4×10^{-5} to 5×10^{-3}
q	…	Metabolic cost of production of an offspring	.9
T	days	Interval of food replenishment	1.0
W_P	mg C	Mass at puberty	.002
α	mg C mm^{-3}	Conversion for structural mass–length regression	1.8×10^{-3}
ε	…	Maximal conversion efficiency of the host	.75
ε_N	…	Maximal conversion efficiency of the parasite	.8
κ	…	Fraction of energy spent on growth	.2
ρ	…	Mechanical threshold of the infected host	1.68

Note: Parameter values here were chosen to produce growth dynamics that resemble those of our host species (*Daphnia dentifera*) on the basis of data from the work of Nisbet et al. (2004) with *Daphnia pulex* and from disease dynamics echoing our findings from the experiment. Future empirical work could strive to actually parameterize this DEB-parasite model using data. C = carbon.

of a fixed-proportion $(1 - \kappa)$ energy reserve allocated to reproduction (first term in brackets in eq. [1c], as governed by the κ rule) minus a metabolic cost of development (for juveniles, who are smaller than a threshold size at maturity, $W < W_P$) or "maturity maintenance" (for adults, $W \geq W_P$; see Kooijman 1993 for justification). Reserves allocated to reproduction are converted into offspring with efficiency q, assuming that each neonate contains a fixed quantity E_0 of reserves. (Note that Kooijman [1993] proposed a relationship between reserve densities in mother and offspring; this detail adds greatly to model complexity and typically has a small impact on results.) Finally, parasite dynamics (dN/dt; eq. [1d]) follow gains (from feeding on energy reserves E) and losses (from death, maintenance costs, etc., at per capita rate m_N). Dynamics of food abundance can be found in appendix B.

One debatable assumption in our model is that the parasite growth rate is determined by the total amount of reserves E rather than by reserve density ($e = E/W$). Which form is more appropriate will depend on the spatial distribution of energy reserves and parasites within the organism (see de Koeijer et al. 1998 for a discussion of this point in an epidemiological context). While we have not conducted an exhaustive study of a model based on consumption of reserve density e, we found results that were essentially comparable with many of those presented here.

This energy budget for the infected host changes as theft of reserves by parasites induces energetic stress on the host.

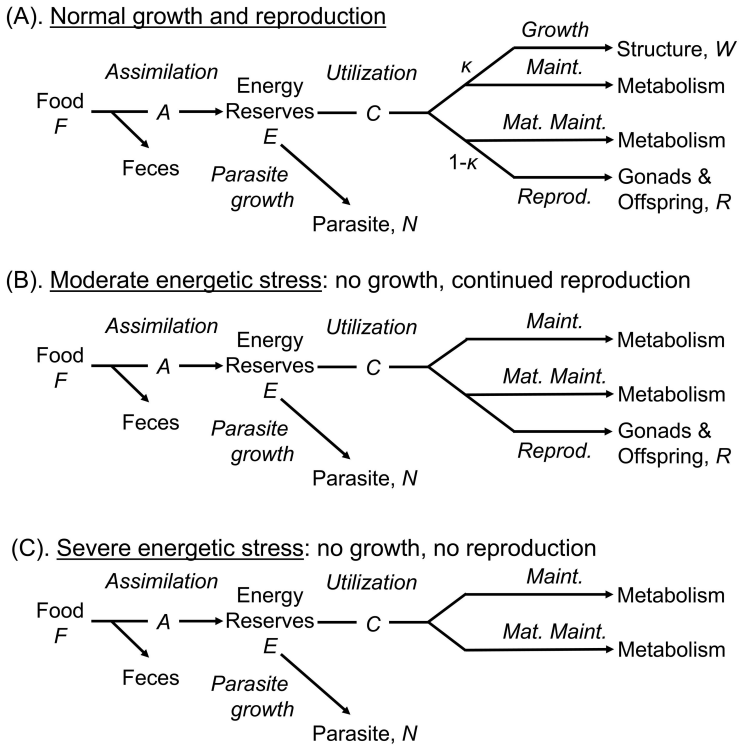

Figure 2: Conceptual diagram of the flow of energy in the dynamic energy budget (DEB) of an infected host (after Kooijman 1993; Muller and Nisbet 2000), moving through three energetic stages. *A*, When food is plentiful and parasites are not abundant, a fixed proportion (κ) of energy that is assimilated from food and not eaten by parasites is utilized and allocated for growth and somatic maintenance ("maint."); the rest ($1 - \kappa$) is allocated for reproduction and maintenance of reproductive ability (maturity maintenance ["mat. maint."]). *B*, As parasites begin to starve the host by depleting internal energy reserves, the host stops growing but reproduces and pays maintenance costs, entering a state of "moderate energetic stress." *C*, In the state of "severe energetic stress," parasites deplete stored energy to the point that the host neither grows nor reproduces (i.e., the host becomes nutritionally castrated) but still meets maintenance requirements.

Therefore, it becomes necessary to explicitly model dynamics of energetically compromised hosts. We present the key details in appendix B, and thus we rely on verbal/graphical explanations here. We follow previous variations of the DEB model for starving hosts (Muller and Nisbet 2000; Fujiwara et al. 2004; Hall et al. 2007*b*). Here, a host experiencing moderate energetic stress stops growing (i.e., $dW/dt = 0$) but continues reproducing after paying maintenance costs (fig. 2*B*). As energetic conditions worsen (fig. 2*C*, severe stress), the host stops reproducing altogether and only pays maintenance costs. The host dies after these maintenance costs cannot be met; at this point, energy reserves E drop to 0. The equations for hosts experiencing these three energetic states (fig. 2) connect smoothly and depend on internal energetic conditions of the host (reserve energy E and its flux C). Those conditions, in turn, depend on food supply and energy theft by parasites.

The parasite equation (eq. [1d]) reveals a key feature. This parasite will grow until it has depleted the energy reserve of the host E to the parasite's minimal energy requirement, E^*_{N}:

$$E^*_{\mathrm{N}} = \frac{h_{\mathrm{N}} m_{\mathrm{N}}}{a_{\mathrm{N}} - m_{\mathrm{N}}}. \tag{2}$$

This represents the minimal amount of energy reserve that the parasite needs to just offset its metabolic losses (similar to R^* in analogous resource-competition models; Grover 1997). Parasites with lower E^*_{N} values are more efficient than those with higher E^*_{N} values. Because this energetic requirement must exceed 0, the parasite cannot directly kill its host by starving it (because death from starvation occurs when $E = 0$ but $E^*_{\mathrm{N}} > 0$). Instead, the parasite should draw reserve energy down to its minimal requirement, perhaps by shutting down first growth and then reproduction, but then it should persist with the (compromised) host. However, a problem emerges: efficient parasites may achieve unreasonably high masses within the

host (e.g., an order of magnitude greater than host structural mass W). As a first approximation, to avoid this unrealistic result, we assume that the parasite N indirectly kills the host shortly after a "mechanical" threshold,

$$N = \rho W, \tag{3}$$

is crossed, where the parameter ρ is a proportional mechanical limit of the host to support the parasite (see app. A). At this threshold, the sheer bulk of the parasite burden physically interferes with the feeding of the host (at least, in the way we have modeled it). Therefore, when $N = \rho W$, the animal stops eating (J. L. Simonis and S. R. Hall, personal observation). When food intake stops, E drops to 0 as the host struggles to meet its metabolic demands (given energy uptake by parasites). Then, when its energy reserve is depleted, the host dies. Note, however, that this mechanical mechanism could also represent other means that scale with parasite mass (besides physical interference) by which a parasite could kill its host (through build-up of toxins, hormonal disruption, etc.). Regardless, within-host dynamics become a race between two key thresholds for the parasite; if the minimal resource-requirement/parasite equilibrium (eq. [2]) is achieved before the size-dependent mechanical threshold (eq. [3]), the compromised host will live with persistent infection. Otherwise, the parasite will kill the host.

Model: Results

This DEB-parasite model, complete with starvation dynamics, can capture the essence of the life-table experiment, but it also produces two other results that are not observed experimentally. Indeed, along a food gradient, we see three types of behaviors: coexistence, killing, and parasite extinction. To illustrate, we first examine three representative simulations of the model, at very low, low, and high food supplies to the host (fig. 3). At very low food supplies, the parasite does not kill the host but instead reaches a within-host equilibrium (fig. 3*A*). Stated in terms of the thresholds here, the parasite reaches its minimal resource requirement (E^*_N) before the mechanical threshold is crossed. Therefore, the parasite persists, but only after shutting down the growth (at threshold $\hat{W}$) and then the reproduction ($\hat{R}$) of its severely compromised host. These thresholds arise as parasites induce moderate and then severe energetic stress on the host (fig. 2). At low food supply, host animals grow slowly. Because food intake in turn depends on body size, parasites grow slowly within the host. When it reaches moderate population size, the parasite indirectly stops growth (at $\hat{W}$) and then reproduction (at $\hat{R}$) of the host. However, it takes some time after this nutritional castration to kill the host, because the parasite begins to experience reduction of its own growth rate via depletion of the internal energy reserve of the host, which is the parasite's food supply. This effect arises as energy reserve E of the host drops and approaches the minimal resource requirement of the parasite, E^*_N. However, the mechanical limit $N = \rho W$ ultimately prevails in the race of thresholds (at threshold $\hat{N}$ of fig. 3*B*) before E drops to E^*_N. Thus, the animal stops eating but continues to live until the parasite exhausts the remaining energy reserve. The host then dies (at the threshold in fig. 3*B*). Contrast these results with those observed with a high food supply (fig. 3*C*). In this latter scenario, the rapidly growing host fuels fast growth of its parasite by providing high levels of internal energy reserve. Shortly after it stops growth of the host, the parasite continues to grow rapidly; that is, resource depletion within the host is not hampering its own population growth rate. Therefore, the parasite quickly reaches the mechanical limit well before the declining energy reserve approaches the parasite's minimal requirement E^*_N, even while the host still reproduces. When the mechanical limit is crossed, the parasite rapidly depletes the remaining energy reserve of the host, quickly killing it (fig. 3*C*).

Over a gradient of food supply to hosts, the model qualitatively (and potentially even quantitatively) predicts the results observed in the experiment. As food supply increases from low levels, time until death initially diminishes quickly, and then it drops more slowly with an intermediate-to-high supply of food over most spore doses shown (moving along the X-axis of fig. 4*A*). At high spore doses, the increase in time until death levels out as food levels increase from moderately low to high. However, as we show elsewhere, parasites with different resource kinetics (especially lower half-saturation constants) can elicit the opposite response: hosts in higher-resource environments might live longer with infection than would those in lower-food environments (app. B). This difference can be understood simply. When half-saturation constants are higher, per capita feeding of parasites slows more as internal energy reserves are depleted; this depletion is more likely when food supply (and, hence, incoming energy supply) is lower. When half-saturation constants are low, per capita feeding of parasites slows only just before death of the host (i.e., when E is quite low). In this case, the mechanical threshold is reached faster at low levels of external resources. Furthermore, regardless of uptake kinetics of the parasite, daily reproduction rates of both healthy and infected hosts increase with food supply; however, infected hosts produced fewer offspring on average (fig. 4*B*). A large gap in time between last reproduction and death can emerge at low food supplies (figs. 3*A*, 3*B*, 4*C*). Instantaneous rate of increase of the population (r) rises over the food gradient, but it diminishes overall as a result

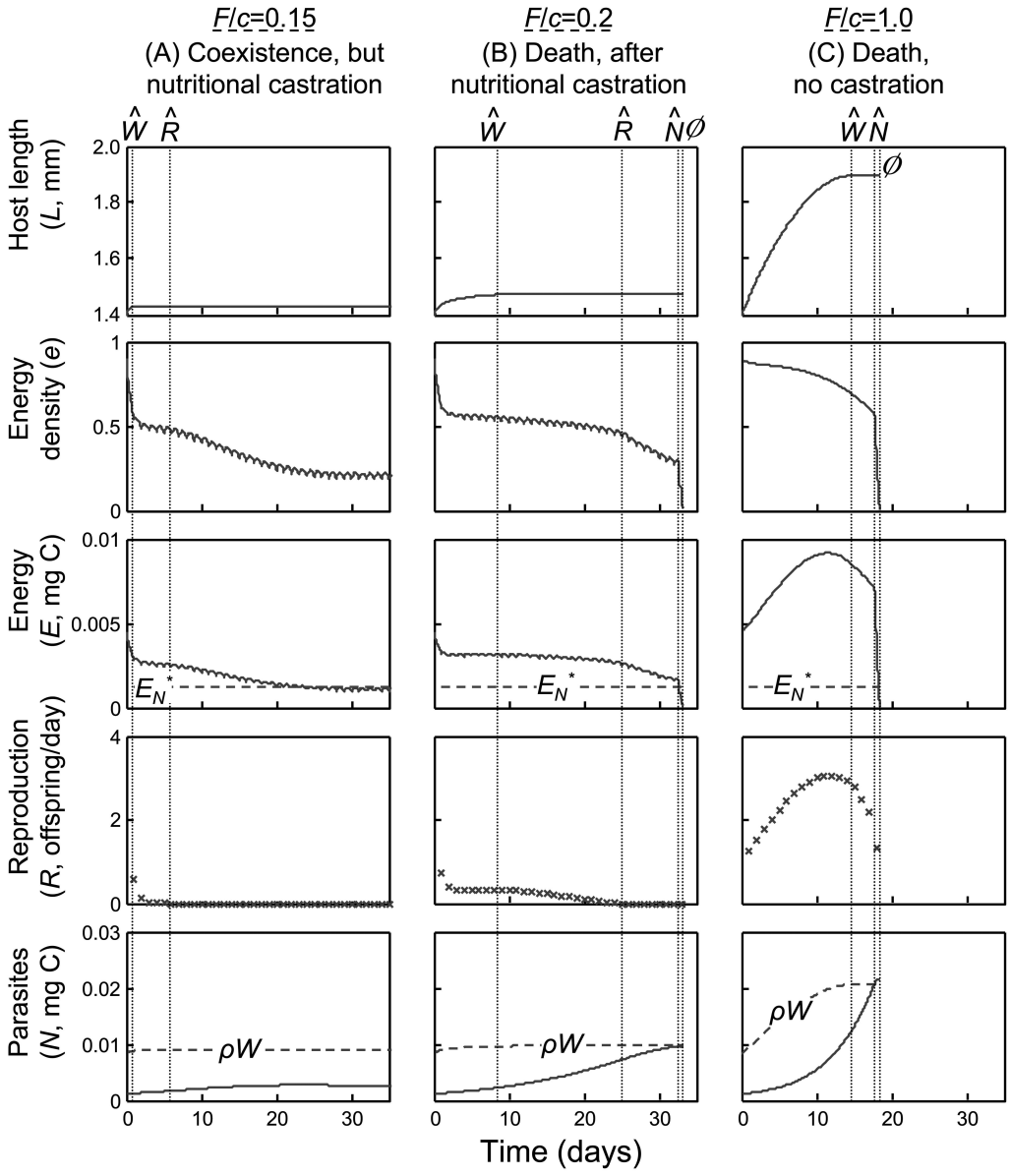

Figure 3: Simulations of the dynamic energy budget (DEB) model with parasites at very low (F_0/c = 0.15 mg L^{-1}), low (0.2 mg C L^{-1}), and high (1.0 mg C L^{-1}) levels of food supply. Three scenarios emerge. At very low food levels, coexistence of an individual host with its parasite becomes possible. The host first stops growing (at threshold $\hat{W}$, entering moderate energetic stress in fig. 2), and then it stops reproducing (at threshold $\hat{R}$, a state of severe energetic stress). However, the parasite drops internal energy reserve, E, to the parasite's minimal energy requirement, E_N^*, before the critical mechanical threshold is crossed (eq. [3]). Thus, in theory the host can persist in a severely compromised energetic state with chronic infection. At slightly higher food levels, the parasite first shuts down growth (again at $\hat{W}$), and then it shuts down reproduction (at $\hat{R}$). However, this time the parasite reaches the mechanical threshold (at $\hat{N}$); at this point, the host stops feeding, and the scant internal energy reserves that do remain rapidly plummet to 0 (at $\varnothing$). At high food levels, the parasite kills its host after first shutting down growth but not reproduction. Actually, in this case, when the parasite reaches the mechanical threshold, the host is still in a decent energetic status; after feeding stops, the internal energy reserve rapidly falls to 0 and the host then dies. Initial conditions: L_0 = 1.4 mm; e_0 = 0.9; N_0 = 0.0001 mg C; all other parameters follow those listed in table 1.

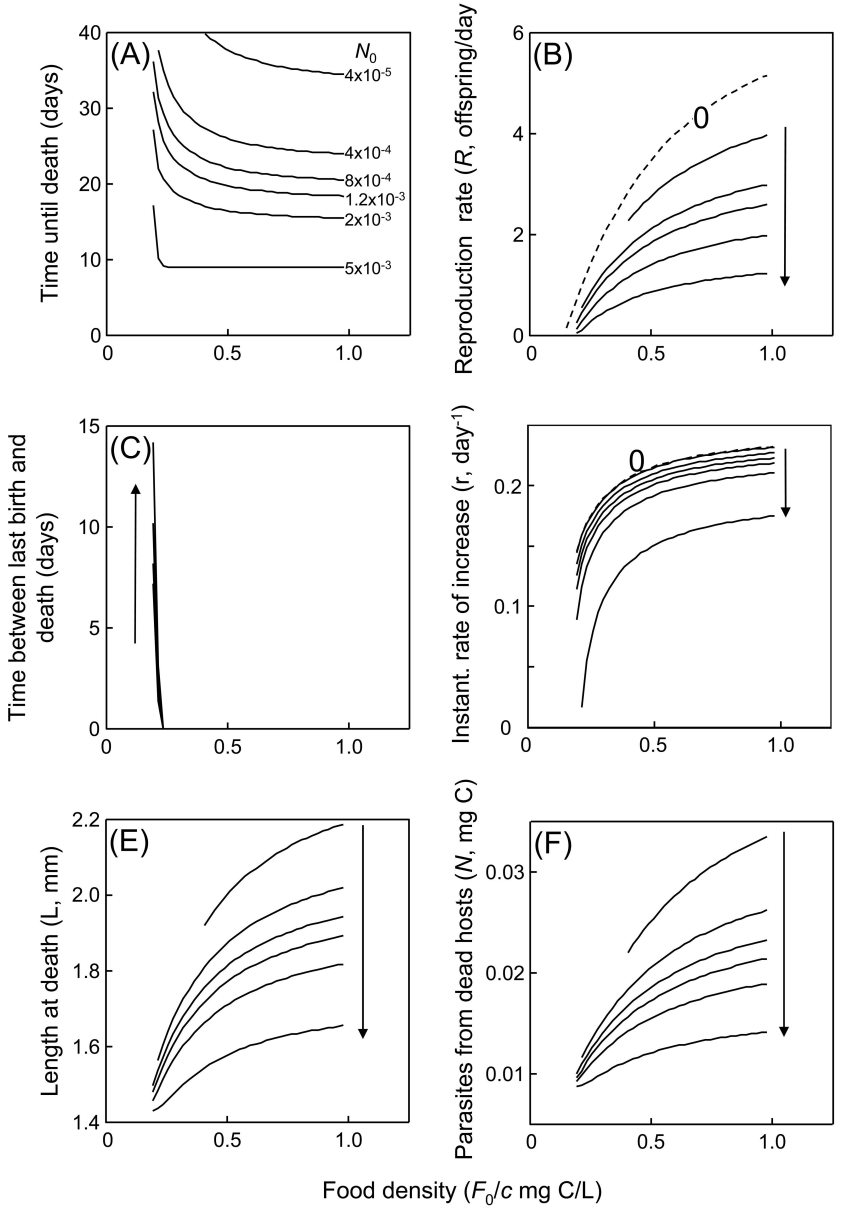

Figure 4: Results from the dynamic energy budget (DEB) model with parasitism readily capture the qualitative signal observed in the life-table experiment (fig. 1). That is, with increasing food supply, time until death decreases (particularly in the low range of food; *A*); reproduction rate increases but at a slower rate with parasites than observed without parasites ($N_0 = 0$; *B*); time drops between last date of reproduction and death (assuming that offspring are produced daily, not with each molt, as in fig. 1; *C*); instantaneous rate of increase, *r*, rises for both host classes, but infected hosts have lower *r* (*D*); length of the infected animal at death increases (*E*); and the number of parasites produced at death of the host increases (*F*). Also, as initial density of parasite spores (N_0) increases (along the gradient illustrated, where the arrows point to higher N_0), we see that infected animals live for a shorter time, produce fewer parasites, die at smaller sizes, reproduce at a lower rate, and live for a longer period between end of reproduction ("nutritional castration") and death. Other initial conditions: $L_0 = 1.4$ mm; $e_0 = 0.9$; all other parameters follow those listed in table 1.

of infection (fig. 4*D*). Dead infected hosts achieved larger sizes (fig. 4*E*) and produced more parasites (fig. 4*F*) at higher food levels. These latter two results are robust to resource kinetics of the parasite (app. B).

Additionally, a higher initial dose of parasites (N_0) exacts more virulent effects on reproduction and survival, regardless of food supply (fig. 4*A*, 4*B*, 4*D*). We did not manipulate initial spore dosage in our experiment here,

but Ebert et al. (2000) describe empirical results resembling our theoretical ones. Indeed, this spore-dosage result is closely related to the resource-dependent DEB-parasite framework. Large initial populations of parasites (i.e., higher N_0) more quickly reach the mechanical threshold that kills the host. Consequently, higher doses of parasites kill faster (fig. 4*A*), reduce fecundity to a greater degree (fig. 4*B*), terminate reproduction (via nutritional castration) more quickly at low food levels (fig. 4*C*), and further depress instantaneous rate of increase (r; fig. 4*D*), but they ultimately yield fewer parasites from smaller hosts (fig. 4*E*, 4*F*). Similar results arise for parasites that grow more efficiently within hosts (i.e., higher assimilation rate a_N, lower half-saturation constant h_N, lower loss rates m_N): more efficient parasites deplete internal energy reserves of the host more rapidly, ultimately killing the host faster but producing fewer parasites when hosts die (app. B). On the other hand, parasites that infect hosts with an initially higher energy reserve (e_0) or a larger size (L_0) more quickly kill their host (because parasites enjoy higher resource density or flux, respectively, fueling faster growth). Yet parasites infecting hosts that are initially more energy rich or larger also ultimately produce more parasites from larger, more fecund hosts (app. B).

This model offers another major prediction (not illustrated): the parasite can fail to establish within the host. Consider a parasite that is relatively inefficient (high E^*_N via low assimilation rate, high half-saturation constant) or has high loss rates (perhaps due to "immune" response), that is, it is more inefficient than those already discussed. If this parasite infects a host inhabiting a low-food environment and internal energy reserves of the host (E) fall below E^*_N, then the host may never provide sufficient resources for the parasite to establish itself. Therefore, infection fails and the parasite has little effect on host growth and reproduction. The parasite fails to infect as a result of a purely resource-based, energetic mechanism. If food levels in the host's environment were elevated, growth of the host—with subsequent increases in E due to higher assimilation rates—could inadvertently "save" the parasite from extinction within the host. The end result is either a host-parasite coexistence or obligate killing, as seen previously (fig. 3).

Discussion

Our goal here centers on building some theoretical muscle around an environmentally dependent source of variation in virulence of parasites on hosts (Thomas et al. 2002; Lazzaro and Little 2009), the resource ecology of the host. The host's resource supply influences virulence because parasites use these resources, when they are converted into energy and materials within hosts, to build more parasites. Because of this energy theft, parasites exact virulent effects on host survivorship, growth, and reproduction (Bonds 2006; Hall et al. 2007*b*). Furthermore, resources of hosts vary through time and space. If resource consumption by hosts directly influences virulence, integration of resources into disease models should yield a more predictive theory for epidemiologists and ecologists alike.

Our model linking resources of hosts to virulence of parasites was inspired by the many examples of resource-dependent virulence in disease systems with invertebrate hosts, especially by the life-table experiment with *Daphnia* and its fungal parasite *Metschnikowia* we presented here. This lab experiment revealed that key factors of the relationship of an "obligate killer" (Ebert and Weisser 1997) to its host can depend sensitively on external resource supply to the host. Along a broad but ecologically reasonable gradient, *Daphnia* with higher food supply levels died more quickly. This finding conflicts with several examples in which elevated food levels enhance survivorship of invertebrate hosts (Jokela et al. 1999; Bedhomme et al. 2004; Tseng 2004; Ryder et al. 2007). Meanwhile, well-fed hosts produced more spores of the fungus. This result strongly resonates with those observed for other parasites of *Daphnia* (Ebert et al. 2000; Bittner et al. 2002; Pulkkinen and Ebert 2004) and other invertebrates (Bedhomme et al. 2004; Tseng 2004, 2006; Ryder et al. 2007). Well-fed hosts achieved larger sizes at death and enjoyed higher fecundity, but parasitized hosts reproduced less than healthy ones. Finally, a gap arose between reproductive bouts and death in infected hosts feeding on meager diets. This nutritional castration reflects parasite-induced energetic stress (Baudoin 1975; Schultz et al. 2006; Hall et al. 2007*b*). In contrast, well-fed parasitized animals continued to reproduce close to their deaths.

All of these experimental results—involving production of parasites and their virulent effects on survivorship, average rate and timing of reproduction, and growth of the host—were readily forecast by a simple model. This model, based on DEB models, incorporates a minimal set of key physiological details centered on energetics of the host, tracking energy flow from initial ingestion of food through internal energy storage to later utilization for growth, reproduction, and payment of maintenance costs (Kooijman 1993). To add parasitism to Kooijman's (1993) framework, we assumed that parasites steal from energy stored as reserves before it is irreversibly used by the host for growth, reproduction, and maintenance. Dynamics of this theft by parasites were captured using a classic equation borrowed directly from resource competition theory (Grover 1997). In a sense, parasites in this model act as consumers of a resource within a biologically dynamic "chemostat": parasites influence resource supply rates in their chemostat by reducing host growth (because smaller hosts eat less).

Virulence then emerges naturally as the result of energy flow through hosts to consuming parasites.

The DEB-parasite model developed here predicts that the end result of resource-dependent virulence is determined by two key thresholds: a minimal resource requirement of the parasite and a mechanical limit of the host's ability to tolerate infection load. The parasite's minimal resource requirement (here called E_N^*) represents a basic level of reserve energy contained in the host that is needed by the parasite to maintain itself. This concept is analogous to the R^* parameter of consumer-resource theory (Grover 1997), and it influences resource-dependent growth of parasites (Ebert et al. 2000). Parasites, then, can have resource requirements within hosts (E_N^*) and among hosts (threshold community sizes; Anderson and May 1991). Here, our model predicts that the host will not die from parasitism if the internal energetic threshold (E_N^*) is reached before the mechanical one, assuming that parasites have no negative effects on their hosts besides the energy drain. In this case, the chronically infected host likely grows and reproduces at compromised rates. Furthermore, if the host provides too few resources for the parasite, that is, if energy reserves always fall below E_N^*, infection may even fail as the parasite itself starves. In this instance, the host provided an energetically depauperate environment for the parasite. Notably, failure of infection arises as a result of energetic, resource-based rather than explicit, immunological mechanisms (although immune function could raise the E_N^* of the parasite by enhancing its loss rates and also reducing energy E that is available for parasite growth).

Outcomes such as indefinite persistence within hosts or extinction of parasites are interesting; however, we mainly focused here on scenarios in which parasites kill their hosts, as in our fungus-*Daphnia* example. For this "obligate killer" fungus, the second key threshold is reached first in the model. At this mechanical threshold, intense parasite burdens physically interfere with resource acquisition of hosts, and feeding terminates altogether. Without input of food, of course, the host starves and eventually dies. Furthermore, this mechanical threshold could arrive after cessation of growth and even reproduction of the host, especially at lower food supplies (via nutritional castration; Baudoin 1975; Hall et al. 2007*b*). This mechanical-limit hypothesis invoked to explain the death of infected hosts remains empirically untested, however, and other mechanisms might catalyze host death (e.g., gradual decreases in feeding rates and/or conversion efficiency, increases in maintenance costs, costs of immune activation, and/or build-up of toxins as parasite burdens grow). Still, through a joint starvation–mechanical-limit mechanism, the model predicts (and *Daphnia* demonstrates) that ample food should fuel rapid parasite growth, high production of parasites (spores), and likely a faster death of the host. Yet at higher spore doses, the model predicts that survivorship might not vary with resources at all (see Hall et al. 2009*b* for an empirical example from this *Daphnia*-fungus system). Furthermore, a parasite with different uptake kinetics altogether (e.g., a lower half-saturation constant) might kill its host faster at a lower resource supply. The emergence of these three mortality relationships along resource gradients from the model helps to unify, under a single umbrella, the discrepancies displayed by this system versus by other systems. It also suggests that the life span of an infected host depends on parasite kinetics and growth within the host rather than/in addition to other factors determining life span (e.g., caloric-restriction mechanisms: Koubova and Guarente 2003; altered allocation to survivorship vs. reproduction in infected hosts: Hurd 2001).

Our model also captures the intensity dependence of infection observed in this and other systems. It predicts that higher initial infective doses should result in faster death but lower spore production from infected hosts, an effect that has been documented previously in other *Daphnia*-parasite systems (Ebert et al. 2000). The effect arises in the model because larger within-host parasite populations start closer to the hypothesized mechanical limit. Therefore, they more quickly kill the host. Similarly, parasites that use resources more efficiently (higher assimilation rate, lower half-saturation constant, lower loss rates) more rapidly kill their smaller host, yielding less parasite when the host dies. In contrast, parasites infecting hosts with higher internal energy reserves or larger hosts (i.e., with higher flux of energy entering them) also kill their hosts more quickly (because of faster parasite growth) but ultimately produce more parasites when hosts die. In short, more energy-rich or larger hosts offer more fertile ground for the parasite.

So what does food-dependent virulence ultimately mean for dynamics of an integrated, plant-grazer/host-parasite system? This question seems to be especially pertinent when grazing by hosts can induce fluctuations in resource levels, as in algae-*Daphnia* systems (McCauley et al. 1999; also see Wood et al. 2007). Such variation in resource supply and parasite-driven declines in host density could create interesting feedbacks that strongly influence disease dynamics (Lively 2006; Hall et al. 2009*b*). Our model couched at the individual level lays a foundation for creation of a population-level model, but we must also incorporate resource dependence of transmission rate. In this *Daphnia*-fungus system, high food supply enhances virulence and spore production, yet it depresses transmission (Hall et al. 2007*a*; see also Ebert 2005). Thus, the net outcome of variation in resources for disease dynamics will depend on the competition between these factors (Hall et al. 2009*b*). Furthermore, dynamics of plant-grazer/host-

parasite systems may depend on dead-end host competitors that consume food resources that remove parasites (Hall et al. 2009*a*) and/or predators that may feed selectively on infected hosts (Ostfeld and Holt 2004; Duffy et al. 2005; Hall et al. 2005*a*, 2006; Duffy and Hall 2008). Predators can indirectly modify producer biomass by consuming grazers but also promote oscillations in host-parasite dynamics (Hall et al. 2005*a*). Thus, much remains to be explored at this frontier of disease ecology (Hatcher et al. 2007; Hall et al. 2008).

Meanwhile, the DEB framework for within-host dynamics formed here could offer promising insights into other aspects of disease. We have already applied it to parasitic castration, a strategy in which parasites actively manipulate the allocation of energy by hosts from reproduction to growth (i.e., the κ rule; Bonds 2006; Hall et al. 2007*b*). That extension showed that a "castrator" can induce the dramatic results seen in a *Daphnia* system with a bacterial parasite (*Pasteuria*): reduced virulence on survivorship, gigantism of the host, immense production of parasites, and enhanced, early reproduction of parasitized hosts followed by virtual cessation of host reproduction (Ebert et al. 2004; Hall et al. 2007*b*). Second, the model could be converted to one characterizing a more typical parasite that continuously sheds infectious propagules from the host. Such a change might enhance generalization of the DEB framework to systems with parasites that have differing life histories. Third, addition of resource quality (digestibility, stoichiometry, etc.) to the model could be important for a variety of disease systems (e.g., moths-viruses: Hodgson et al. 2002, 2004; human diseases: Smith et al. 2005; butterflies: de Roode et al. 2008; *Daphnia*: Frost et al. 2008; Hall et al. 2009*b*).

This DEB framework might also offer an excellent platform on which to add explicit immune function. Indeed, some readers may be surprised that this current form of the model ignores immunity. After all, invertebrates such as our host *Daphnia* can exhibit a variety of cellular and molecular responses to infection (Little et al. 2005, Schmid-Hempel 2009). Furthermore, recent work shows that immune response to another parasite of *Daphnia* might be costly in terms of survivorship (Little and Killick 2007; but see Haughton and Smith 2008). If immune systems can indeed effectively remove/clear parasites, immunity might be captured by the use of an equation that associates "killing" of parasites with associated energetic costs for maintenance of innate immunity and also with the sometimes considerable energetic cost of upregulation of immune function and immunopathology (Demas et al. 1997; Kraaijeveld and Godfray 1997; Moret and Schmid-Hempel 2000; Hurd 2001; Little and Kraaijeveld 2004). Such an addition could allow a more robust integration of resistance to infection with parasite growth and with other environment-dependent physiological features of hosts (longevity, reproduction, and metabolism: Lloyd 1995; Little et al. 2005; French et al. 2007; Lazzaro and Little 2009). Furthermore, an immunity-explicit DEB model might also provide an energetically relevant description of costs underlying population genetic–centered models for variation in virulence based on genetic specificity (Agrawal and Lively 2002; Schmid-Hempel and Ebert 2003). Unfortunately, we cannot be sure at this point whether immune response is particularly costly or even effective in this *Daphnia dentifera-Metschnikowia* system. Even if it was energetically costly, the state-of-the-art technique for measuring immune response within infected *Daphnia* does not yet permit a mechanistic, energy-explicit accounting of immunity (as desired for modeling). This situation will likely change as the study of the invertebrate immunity continues (Little et al. 2005).

Until those immunity-based improvements can be made, the take-home message from our minimal (if incomplete) model focuses on the importance of ecology—specifically, resource supply to hosts—as a potentially vital driver of variation in virulence in host-parasite systems. Variation in resource supply to hosts should have predictable consequences for the fitness of both players (Bonds 2006; Hall et al. 2007*b*, 2009*b*). This conclusion stems from the combination of an experiment and the development of models that excluded other drivers of virulence (genetic specificity, trade-offs, coinfection, etc.). In the future, resource-dependent virulence should be considered with and integrated into these other drivers of virulence (Lazzaro and Little 2009).

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