A model to account for the consequences of host nutrition on the outcome of gastrointestinal parasitism in sheep: logic and concepts

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SUMMARY

A deterministic, dynamic simulation model is developed to account for the interactions between gastrointestinal parasitism and host nutrition, and predict their consequences on performance and level of parasitism of sheep. Larval intake and established adult worms are assumed to result in nutrient loss for the host. In order to reduce this loss the host will mount an immune response, which will affect the establishment rate of incoming larvae, mortality rate of adult worms, and fecundity of female worms, as well as nutrient loss caused by larval intake *per se*. Host anorexia is modelled as a function of worm mass. Parasitism is also assumed to affect the allocation of ingested nutrients to the host's bodily functions, with maintenance getting absolute priority, and protein allocated to immunity and production proportionally to their requirements. Inputs to the model include the expected growth attributes of the animal, feed quality, various parasitological parameters and daily larval intake. Outputs include feed intake, growth rate and body composition, as well as worm burden and faecal egg counts. The model allows exploration of the consequences of gastrointestinal parasitism on sheep of different growth characteristics, kept under environments that vary in the provision of nutrients and exposure to parasites.

Key words: mathematical model, sheep, parasitism, nematodes, nutrition, anorexia.

INTRODUCTION

Gastrointestinal parasitism is the most pervasive challenge to the health and well being of grazing small ruminants, as well as the costliest disease in economic terms. In a recent study, Nieuwhof and Bishop (2005) estimated that infestation with gastrointestinal parasites causes a loss of £84 million, making it the costliest disease of small ruminants in the UK. Its control through the use of chemoprophylaxis is no longer sustainable due to the development of parasitic resistance to anthelminthics, but also due to environmental and consumer concerns. For these reasons there is an urgent need to develop alternative, sustainable methods of controlling gastrointestinal parasitism.

Host nutrition and breeding for resistance to parasitism are two alternatives that represent short and long term options, respectively, for the control of parasitism. Host nutrition, in particular, has been shown to have positive effects on the ability of small ruminants to deal with parasitism (Coop and Kyriazakis, 1999, 2001). Whilst this effect seems to be consistent for reproducing animals, where protein nutrition seems to be able to overcome the periparturient breakdown in immunity (Houdijk *et al.* 2000), it has been less so with young ruminants. For example van Houtert *et al.* (1995) found that dietary supplementation of lambs with protein led to increased growth and reduced faecal egg counts, whereas Kahn *et al.* (2000) found no effect of protein on worm burden. Such inconsistencies may arise due to interaction between host nutrition and genotype, level of infection, parasite species, etc.

When addressing the consequences of nutrition on gastrointestinal parasitism, we need to have an understanding of how these interactions might arise and their effect. In principle, it is possible to design experiments to study these interactions but in practice this is extremely difficult. In this light, mathematical modelling offers a feasible alternative approach. Using our current understanding of these processes, a model can be built that could help us gain insight and study possible mechanisms through which these interactions might operate.

In the current paper we develop a model that describes the interaction between nutrition and gastrointestinal parasitism. We develop the model for a single growing, immunologically naïve animal.

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The model may be extended to include genotype differences and can also, in principle, be extended to model a population of animals.

DESCRIPTION OF THE MODEL

Firstly, the model for daily growth of an unchallenged animal is described and developed for both non-limiting and nutritionally limiting conditions in the absence of parasitic challenge. The model is then extended to accommodate parasitic challenges, host immunity and host-parasite interactions, and to predict the growth of the animal and its parasitic burden over time. Finally, the model parameterization is then described. A list of abbreviations and subscripts used in the model description is shown in Table 1.

Parasite-free animal

(*a*) *Growth model – unconstrained resources*

(*i*) *Basic model of growth and nutrient requirements*. The growth of a healthy, uninfected animal is modelled based on Wellock *et al*. (2004), in which growth is modelled using a Gompertz function. This model considers the body of the animal as the sum of 4 components: body protein, ash, water and lipid. The animal has an expected growth for each of these components, defined by its genotype and its current state. Estimated accretion of ash and water is based on predicted daily body protein growth. Wool growth is modelled based on Cronje and Smuts (1994), as a function of the current protein mass and expected growth. Thus, the driving forces of growth are assumed to be protein and lipid growth. A detailed account of body growth and the associated nutrient requirements is given in Appendix 1.

As in the model of Wellock *et al*. (2004), only protein and energy requirements are considered. All other nutrients are assumed to be satisfied by the diet and therefore are not limiting the growth of the animal. Furthermore, the diet is assumed to be free of substances that restrict or impair the growth of the animal, such as toxins. Energy and protein requirements are estimated separately for maintenance and growth as described in Wellock *et al*. (2004) and Appendix 1. The energy requirements for wool growth are estimated assuming that wool has the same energy requirement per unit as body protein. The total energy and protein requirements are estimated as the sum of the requirements for maintenance, growth (both protein and lipid) and wool.

(*ii*) *Estimation of food intake*. It is assumed that the animal will attempt to ingest sufficient nutrients to meet its expected requirements for growth, which depend on its genotype and current state. Furthermore, the voluntary feed intake of a healthy animal is assumed to be constrained only by its gut capacity and feed free of toxins is available in non-limiting quantity.

Table 1. Main acronyms used throughout the paper

Variable	Description
BW	Body weight
B	Growth parameter
B	Density dependence effects constant
C	Constants
CAP	Capacity for food intake
CFI	Constraint food intake
DM	Dry matter
EEC	Effective energy content of feed
ERQ	Energy requirement
F	Fecundity
Fi	Constant in fecundity equation
FI	Food intake
IOM	Indigestible organic matter
K	Exponent
LI	Larval intake
Mi	Constant in mortality equation
MP	Metabolizable protein
PAC	Protein allocated to a function
P	Protein
PLOSS	Protein loss
PRQ	Protein requirement for a function
RED	Reduction of growth parameter
WB	Worm burden
E	Establishment
M	Mortality
Subscript	**Description**
Avail	Available
Eq	Equivalent
Imm	Immunity
Infl	Inflection
Labile	Labile
Maint	Maintainance
Max	Maximum
Min	Minimum
Pot	Potential
Prod	Production
Tot	Total
E	Establishment

Desired daily feed intakes for meeting, separately, the energetic (FI_E) and protein (FI_P) needs for the expected growth of the animal are estimated as:

$$FI_E = \frac{ERQ}{EEC} \quad (\text{kg DM/day}) \tag{1}$$

$$FI_P = \frac{PRQ}{MP} \quad (\text{kg DM/day}) \tag{2}$$

where ERQ = energy requirements of the animal for expected growth, EEC = effective energy content (Emmans, 1994), PRQ = feed metabolizable protein content that is required for the animal to achieve its expected growth, MP = feed metabolizable protein content, DM = dry matter. (N.B. Throughout the

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text, numbered equations are those that appear in the final model).

The actual food intake will be the higher of FI_E and FI_P.

(*b*) *Growth model – constrained resources*

Under many circumstances resources may be constrained and insufficient to meet requirements. The procedure described above would result in a food intake which would increase continuously as the quality (protein and energy content) of the food decreased. However, in reality it is observed that the rate of increase in daily food intake declines as food quality declines, and daily food intake may actually decrease with poor quality food (Kyriazakis and Emmans, 1995) due to an assumed maximum capacity for bulk. To achieve this, a quantity called constrained food intake (CFI) is defined as:

$$CFI = \frac{CAP}{IOM} \quad (kg/day) \tag{3}$$

where CAP = capacity of the animal for daily indigestible organic matter (kg), IOM = indigestible organic matter (kg/kg DM).

Using data from Lewis *et al*. (2004), CAP in young lambs was found to increase linearly and to be equal to proportionally 0·0223 of the current body weight up to 0·51 of mature body weight, remaining constant thereafter. Thus, using this result, and defining BW as the current body weight (kg) and BW_{Mature} as BW at maturity, CAP is estimated as the smaller of:

$$CAP = 0{\cdot}0223 \cdot BW \quad (kg/day) \tag{4}$$

$$\text{or: } CAP = 0{\cdot}0223 \cdot 0{\cdot}51 \cdot BW_{Mature} \quad (kg/day) \tag{5}$$

Actual food intake is then the lower of desired food intake and CFI.

The metabolizable protein system (AFRC, 1993) is used to calculate the protein requirements and the effective energy (EE) system (Emmans, 1994) to estimate energy requirements. If intake of protein is limiting then the animal will partition scarce protein amongst its various functions. In this model we assume that the animal will first try to satisfy its maintenance needs, then a basic wool growth, and then wool (above basic wool) and body growth.

Basic wool growth is defined as the minimum amount of wool that an animal will grow after it has satisfied its maintenance needs and before allocating resources to growth. The basic wool production is assumed to be fixed at 3 g/day in accordance with AFRC (1993) for growing animals. This is supported by the findings of Butler-Hogg (1984) who observed that animals that were given submaintenance dietary protein would still grow on average 2·5 g/day of wool.

Any metabolizable protein available after satisfying maintenance and basic wool requirements is assumed to be allocated proportionally to wool and body growth. Actual tissue accretions for wool and protein are simply the product of the protein allocated to these tissues and the respective efficiencies of MP utilization for protein and wool growth, e_G (0·59) and e_W (0·26), respectively (AFRC, 1993).

If the animal has an intake of MP which is below its maintenance requirements, it is assumed to use its body reserves to cover its maintenance functions. If this protein inadequacy is prolonged the animal will catabolize body protein, eventually leading to death. Based on the reports of Houdijk *et al*. (2001) and Sykes (2000) the amount of protein the animal can mobilize from its body, i.e. labile protein, is defined as:

$$P_{Labile} = 0{\cdot}2 \cdot P_{max} \quad (kg) \tag{6}$$

where P_{max} = maximum achieved body protein content (kg).

Energy may also be limited, in which case the animal will use lipid as an energy source. As in Wellock *et al*. (2004), if the animal's lipid content reaches a certain minimum value the animal is assumed to die (see Appendix 1).

Parasitized animal

A diagram of the assumed host-parasite interactions in a growing animal is given in Fig. 1. The model aims to describe the processes in this figure. Ingested larvae have a cost to the host manifested by protein loss, e.g. tissue loss or plasma loss (Houdijk *et al*. 2001). A proportion of these larvae will be established in the host gastrointestinal tract and develop to adult worms. These adult worms will also cause protein loss to the host, for example, via damaged tissue or reduced absorption. For this purpose, a term called protein loss (PLoss) is defined as the dietary and/or body protein which is not available or is lost from the diet and/or the body due to the effect of parasitism, excluding protein allocated to immunity. Furthermore, the host will have reduced appetite, i.e. parasite-induced anorexia. The host will try to combat the infection by mounting an immune response, which also requires protein. Three host controlled immunity traits may be defined (Bishop and Stear, 1997): establishment rate of ingested larvae, mortality rate of adult parasites and fecundity of adult female parasites. A successful immune response will limit the protein loss from the host, thus making more nutrients available for growth and wool production. Details of these processes and how they are modelled are now described.

(*a*) *Effect of ingested larvae on protein metabolism*

When the animal is challenged with infective larvae, it is assumed that there will be a protein loss

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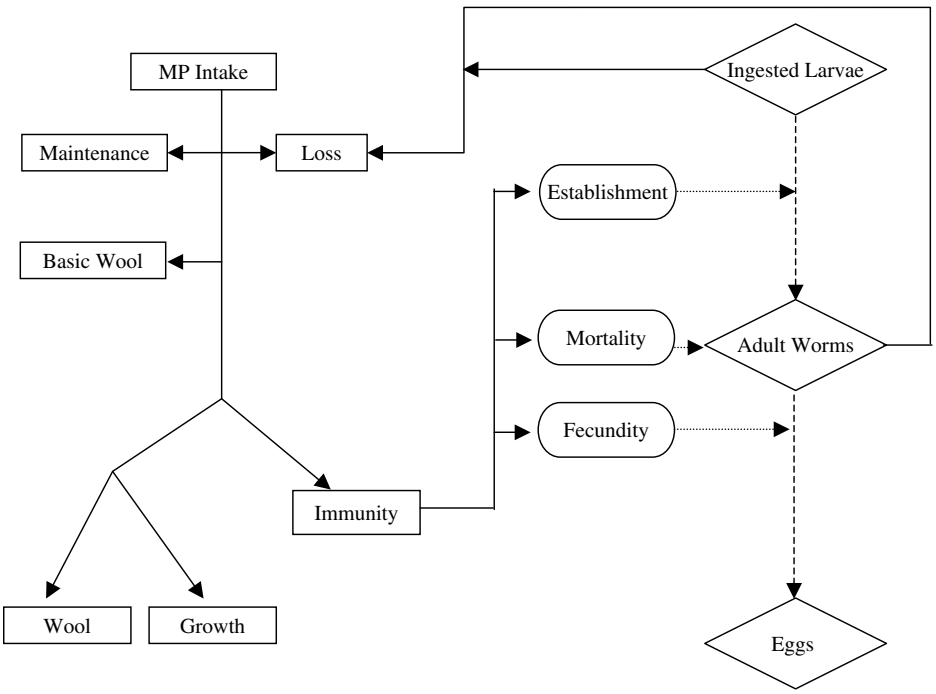

Fig. 1. A schematic description of the host-parasite interactions in relation to host nutrition. Rectangular boxes indicate the fate of ingested protein, rounded boxes indicated host-parasite interactions and diamond boxes indicate key quantifiable parasite life-cycle stages.

associated with the larval intake *per se* in accordance with previous models (Leathwick *et al*. 1992, Bishop and Stear, 1997). In the absence of immunity, the loss caused by the larval challenge is assumed to increase with increasing larval intake, reaching an asymptote or plateau. We are not aware of published literature for the form of the function of loss caused by pathogens with respect to pathogen challenge. An appropriate function should be as flexible as possible with respect to the inflexion point, on both axes, and it should be possible to reach the same asymptote irrespective of the form of the curve. A function with these characteristics is given by Yin *et al*. (2003):

$$PLI_{Pot} = PLoss_{max} \cdot \left(1 + \frac{LI_{max} - LI}{LI_{max} - LI_{infl}}\right) \times \left(\frac{LI}{LI_{max}}\right)^{\left(\frac{LI_{max}}{LI_{max} - LI_{infl}}\right)} \quad (kg/day) \qquad (7)$$

where PLI_{Pot} = potential daily protein loss when there is no immune response, $PLoss_{max}$ = daily protein loss when LI equals LI_{max} (kg/day), LI = daily larval intake, LI_{infl} = inflection point of the LI curve, LI_{max} = daily LI beyond which the immune response does not increase.

(*b*) *Effect of adult worms on protein metabolism*

The established larvae will mature to adult worms after a period of time, creating a worm burden (WB). The female adult worms will produce eggs which will be excreted onto the pasture. It is assumed that it is the total mass of worms (WM), rather than worm numbers *per se*, that is associated with protein loss. The method for estimating WM is described in equations 23 and 24, below. We assume that the protein loss caused by a given WM can be scaled to that caused by an equivalent LI. Thus, a quantity called larval intake equivalent is estimated, which is the larval intake which would cause the same damage as the given worm mass:

$$LI_{Eq} = c_1 \cdot WM \qquad (8)$$

where c_1 = assumed constant.

The daily protein loss due to worm mass is estimated using the same relationship as for the daily protein loss (equation 7) due to larval intake, but substituting LI by LI_{eq}.

$$PWM_{Pot} = PLoss_{max} \cdot \left(1 + \frac{LI_{max} - LI_{Eq}}{LI_{max} - LI_{infl}}\right) \times \left(\frac{LI_{Eq}}{LI_{max}}\right)^{\left(\frac{LI_{max}}{LI_{max} - LI_{infl}}\right)} \quad (kg/day) \qquad (9)$$

The total potential daily protein loss in the absence of immunity is the sum of the components due to larval intake and worm mass:

$$PLoss_{Pot} = PLI_{Pot} + PWM_{Pot} \quad (kg/day) \qquad (10)$$

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(*c*) *Estimation of immunity requirements and worm population dynamics*

Immune requirements due to larval intake. In response to infection the animal will mount an immune response. This should result in a profit, in protein terms, for the animal as protein loss due to larval intake will decrease. This reduction in protein loss is assumed to follow the law of diminishing returns as explained by Behnke *et al.* (1992), and is achieved by modelling the effect of immunity on the potential daily protein loss due to larval intake (PLI) as a decreasing exponential:

$$PLI = PLI_{Pot} \cdot e^{-K_{Imm} \cdot PAC_{Imm}} \quad (kg/day) \tag{11}$$

where PAC_{Imm} = protein allocated daily to immunity (kg/day) and K_{Imm} = exponent associated with protein PAC_{Imm}.

It will be very expensive and not profitable for the animal to reduce the protein loss to zero, even if there is an abundance of protein. This is in agreement with experimental observations where immune animals usually have small worm burdens, without any apparent detrimental effect on their well-being or production (Houdijk *et al.* 2001). The maximum protein the animal can allocate to immunity is assumed to be a function of maintenance protein requirements. Following the study of Houdijk *et al.* (2001), the maximum protein an animal can allocate daily to immunity is:

$$(PAC_{Imm})_{max} = c_2 \cdot P_{Maint} \quad (kg/day) \tag{12}$$

where c_2 = assumed constant.

We assume that $(PAC_{Imm})_{max}$ will be the requirement for protein allocated to immunity when $LI = LI_{max}$. Therefore, when $LI = LI_{max}$, (and as a consequence $PLI_{Pot} = PLoss_{max}$) and $PAC_{Imm} = (PAC_{Imm})_{max}$, then $PLI = PLoss_{min}$, where $PLoss_{min}$ is the value at which the animal will stop allocating protein to immunity. Substituting the above values in the equation for PLI and solving for K_{Imm} we have, when $LI = LI_{max}$:

$$PLoss_{min} = PLoss_{max} \cdot e^{-K_{Imm} \cdot (PAC_{Imm})_{max}} \quad (kg/day)$$

$$\text{Therefore, } K_{Imm} = -\frac{\ln\left(\frac{PLoss_{min}}{PLoss_{max}}\right)}{(PAC_{Imm})_{max}} \tag{13}$$

After some algebra and by substituting PLI_{Pot} the formula for PLI becomes:

$$PLI = PLI_{Pot} \cdot \left(\frac{PLoss_{min}}{PLoss_{max}}\right)^{\left(\frac{PAC_{Imm}}{(PAC_{Imm})_{max}}\right)} \quad (kg/day) \tag{14}$$

In equation (14) the protein allocated to immunity for a given LI remains to be estimated. First we estimate the protein requirements for immunity. For any given larval intake it is assumed that the animal attempts to reduce the PLI to a minimum value. Using the same methodology we used for estimating K_{Imm}, we have an alternative but equivalent formulation for $PLoss_{min}$:

$$PLoss_{min} = PLI_{Pot} \cdot e^{-K_{Imm} \cdot PRQ_{Imm}}$$

$$\text{Therefore, } PRQ_{Imm} = -\frac{\ln\left(\frac{PLoss_{min}}{PLI_{Pot}}\right)}{K_{Imm}} \quad (kg/day)$$

and by substituting K_{Imm} we have:

$$PRQ_{Imm} = (PAC_{Imm})_{max} \cdot \frac{\ln\left(\frac{PLoss_{min}}{PLI_{Pot}}\right)}{\ln\left(\frac{PLoss_{min}}{PLoss_{max}}\right)} \quad (kg/day) \tag{15}$$

Establishment of incoming larvae. The ability of the animal to affect the establishment rate of parasites is assumed to increase, towards a plateau, as the animal acquires immunity. Based on the report by Louie *et al.* (2005) the acquisition of immunity, in terms of establishment, is modelled as a function of cumulative larval intake:

$$\varepsilon_0 = \varepsilon_{max} \cdot e^{-K_\varepsilon \cdot \sum_t LI^*}$$

where K_ε = assumed constant, ε_{max} = establishment when PAC_{Imm} is 0, $\sum_t LI^*$ = scaled cumulative larval intake.

Further, it is assumed that the expression of immunity increases with larval intake as indicated in the above equation for ε_0, but again towards an asymptote, reflecting the finite capacity of the immune system to respond to increasing challenge levels. Thus, the scaled cumulative larval intake is estimated as:

$$\sum_t LI^* = \sum_{t-1} LI + \left(LI_{max} \cdot \frac{LI}{LI + c_3}\right) \tag{16}$$

where c_3 = assumed constant.

Establishment is also assumed to be affected by protein availability, through a decreasing exponential relationship, following the laws of diminishing returns:

$$\varepsilon_1 = \varepsilon_{max} \cdot e^{-K_\varepsilon \cdot \left(\frac{PAC_{Imm}}{PRQ_{Imm}}\right) \cdot \sum_t LI^*}$$

When $PAC_{Imm} = PRQ_{Imm}$ the above relationship reduces to the relationship of Louie *et al.* (2005). However, when protein allocated to immunity is less than the protein requirements of immunity,

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establishment has a higher value, i.e. more larvae become established.

The limit of the above equation for establishment is zero. However, it has been observed in experimental data that there is always a small number of worms, even in immune adult animals with no apparent sign of infection (Houdijk *et al*. 2001). Thus there should be a minimum establishment and the equation used in the model for establishment is:

$$\varepsilon = \left(\varepsilon_{\max} \cdot \mathrm{e}^{-\mathrm{K}_{\varepsilon} \cdot \left(\frac{\mathrm{PAC}_{\mathrm{Imm}}}{\mathrm{PRQ}_{\mathrm{mm}}} \right) \cdot \sum_{\mathrm{t}} \mathrm{LI}^{*}} \right) + \varepsilon_{\min} \qquad (17)$$

The number of larvae establishing is simply the product of ingested larvae and establishment rate.

Immune requirements due to adult worms. To estimate the daily protein requirements for immune response due to adult worms we use the concept of the equivalent larval intake explained above. The protein loss caused by WM is estimated using the equation for LI, substituting LI by $\mathrm{LI}_{\mathrm{eq}}$:

$$\mathrm{PWM} = \mathrm{PLoss}_{\max} \cdot \left(1 + \frac{\mathrm{LI}_{\max} - \mathrm{LI}_{\mathrm{eq}}}{\mathrm{LI}_{\max} - \mathrm{LI}_{\mathrm{infl}}} \right) \times \left(\frac{\mathrm{LI}_{\mathrm{eq}}}{\mathrm{LI}_{\max}} \right)^{\left(\frac{\mathrm{LI}_{\max}}{\mathrm{LI}_{\max} - \mathrm{LI}_{\mathrm{infl}}} \right)} \quad (\mathrm{kg/day}) \qquad (18)$$

In a similar manner to the requirements of immunity due to LI, the daily requirements for immunity due to WM are estimated as:

$$\mathrm{PREQ}_{\mathrm{Imm}} = -\frac{\ln\left(\frac{\mathrm{PLoss}_{\min}}{\mathrm{PWM}_{\mathrm{Pot}}} \right)}{\mathrm{K}_{\mathrm{Imm}}} \quad (\mathrm{kg/day}) \qquad (19)$$

Having estimated an immunity protein requirement for LI and for WM, the higher of the two is used as the overall protein requirement for immunity.

Mortality of adult worms. The mortality rate of adult worms will also affect worm burden. Based on the study of Louie *et al*. (2005) we estimate host expression of mortality as a function of scaled cumulative larval intake:

$$\mu_0 = \frac{\mu_{\max} \cdot \left(\sum_{\mathrm{t}} \mathrm{LI}^{*} \right)^2}{\mathrm{mi}^2 + \left(\sum_{\mathrm{t}} \mathrm{LI}^{*} \right)^2}$$

(proportion of adult worms/day)

This general form of this relationship is shown in Fig. 2.

Using the same methodology as for establishment (equation (19)), actual mortality is expressed as a function of protein allocated to immunity and immunity requirements. Furthermore, adult worms may die due to causes unrelated to host immunity and this is taken into account by adding a minimum mortality. Thus, mortality is estimated as shown in equation 23. When the immune requirements are satisfied this formula reduces to that given by Louie *et al*. (2005), whereas if they are not satisfied mortality rate is lower.

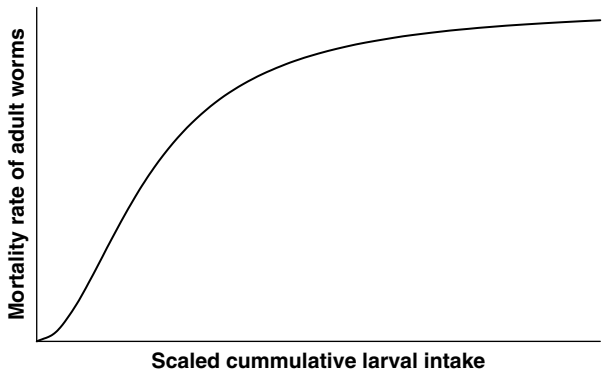

Fig. 2. The relationship between (scaled) cumulative larval intake and mortality rate of adult worms.

$$\mu = \left(\frac{\mu_{\max} \cdot \left(\mathrm{PAC}_{\mathrm{Imm}} \cdot \sum_{\mathrm{t}} \mathrm{LI}^{*} \right)^2}{(\mathrm{PRQ}_{\mathrm{Imm}} \cdot \mathrm{mi})^2 + \left(\mathrm{PAC}_{\mathrm{Imm}} \cdot \sum_{\mathrm{t}} \mathrm{LI}^{*} \right)^2} \right) + \mu_{\min} \quad (\text{proportion of adult worms/day}) \qquad (20)$$

where $\mu_{\min}$ = minimum value of mortality when $\mathrm{PAC}_{\mathrm{Imm}}$ is 0, $\mu_{\max}$ = maximum value of mortality when $\mathrm{PAC}_{\mathrm{Imm}}$ is $\mathrm{PRQ}_{\mathrm{Imm}}$, mi = constant related to the inflection point.

Worm burden (WB) at time t is a function of the WB of the previous day, the mortality rate and the number of the newly matured larvae:

$$\mathrm{WB}_{\mathrm{t}} = (\mathrm{WB}_{\mathrm{t}-1} \cdot \mu) + \mathrm{WB}_{\mathrm{New}} \qquad (21)$$

where $\mathrm{WB}_{\mathrm{New}}$ = newly matured larvae to worms.

Fecundity of adult female worms. The trait fecundity is used for 2 purposes, to estimate the number of eggs produced per worm, and also to assist in the estimation of worm mass, using the observation that individual worm length is strongly correlated with the number of eggs *in utero* in the worm, hence fecundity (Stear *et al*. 1995). For fecundity, the function of Louie *et al*. (2005) is used:

$$\mathrm{F}_0 = \frac{\mathrm{F}_{\max} \cdot \mathrm{fi}^2}{\mathrm{fi}^2 + \left(\sum_{\mathrm{t}} \mathrm{LI}^{*} \right)^2} \quad (\mathrm{eggs/worm/day})$$

where $\mathrm{F}_{\max}$ = assumed maximum value of fecundity when $\mathrm{PAC}_{\mathrm{Imm}}$ is equal to 0, fi = constant related to the inflection point. The general form of this relationship is given in Fig. 3.

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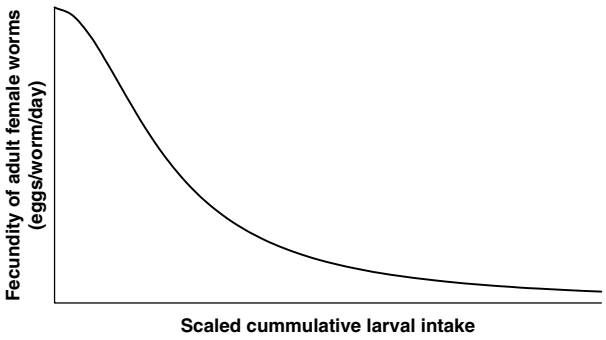

Fig. 3. The relationship between (scaled) cumulative larval intake and fecundity of adult female worms.

Modifying the above relationship so as to add protein dependency and a minimum fecundity, we have:

$$F = \left(\frac{F_{max} \cdot (fi \cdot PRQ_{Imm})^2}{(fi \cdot PRQ_{Imm})^2 + \left(PAC_{Imm} \cdot \sum_t LI^*\right)^2} \right) + F_{min} \quad (eggs/worm/day) \tag{22}$$

For gastrointestinal worms density dependence effects, i.e. decreasing worm size and fecundity with increasing worm burden resulting in a non-linear increase of faecal egg counts with worm burden, have been observed (Bishop and Stear, 2000). Following this study (Bishop and Stear, 1997), the density dependence effects are modelled as a scaling of fecundity:

$$F_{Scaled} = F \cdot \left(\frac{WB}{WB_F}\right)^b \tag{23}$$

where $b = \text{constant}\ (-1 \leqslant b \leqslant 0)$, WB_F = assumed WB at which $F_{Scaled} = F$.

Worm mass is estimated as the product of fecundity and by worm burden:

$$WM = WB \cdot F_{Scaled} \tag{24}$$

(*d*) *Effect of parasitism on protein partitioning*

As in the case of no parasitic challenge, it is assumed that the maintenance needs of the animal will be satisfied first and then the basic wool needs. If the available protein is less than the requirements for the basic protein turn-over then the animal must catabolize protein. In this case no protein is allocated to immunity or wool and body growth. However, there will be loss due to LI and/or WM and this will be equal to the estimated $PLoss_{Pot}$.

For simplicity we have assumed that available protein, in excess of maintenance and basic wool growth requirements, will be allocated to immunity and production traits in proportion to their requirements. Metabolized protein allocated to immunity will be used with an efficiency (e_{Imm}) less than 1, and thus the quantity of immune proteins produced per day is:

$$P_{Imm} = e_{Imm} \cdot PAC_{Imm} \quad (kg/day) \tag{25}$$

Since there has been protein allocated to immunity there will be a reduction of the protein loss due to larval intake, as previously estimated, i.e. $PLI = PLI_{Pot} \cdot e^{-K_{Imm} \cdot PAC_{Imm}}$.

The actual protein loss due to worm mass is estimated after reducing fecundity (equation (22)) and recalculating worm mass. In this way the effect of immunity on protein loss is accounted for. The overall loss due to parasitism is, once again, the sum of the loss caused by larval intake and worm mass, and it will be lower than the losses due to parasitism in the absence of immunity. This difference is the 'profit' the animal makes from allocating protein to immunity.

The sum of protein for immunity, production and loss ideally should be less than or equal to the dietary protein available for these processes. If not, there will be a deficit. This deficit cannot be accounted for by retracting protein from either immunity or protein loss, because retraction of protein from immunity would lead to increased protein loss. But, it can be accounted for by reducing the protein available to production purposes (body and wool growth). Thus:

$$PREQ_{Loss} = (PAC_{Imm} + PAC_{Prod} + PLoss_{Tot}) - P_{Avail} \quad (kg/day) \tag{26}$$

If $PREQ_{Loss}$ is greater than 0, then the final protein allocated to production is $PAC^F_{Prod} = PAC_{Prod} - PREQ_{Loss}$.

(*e*) *Effect of parasitism on food intake*

A well-established effect of parasitism on immunologically naïve animals is the reduction of food intake, i.e. anorexia (Coop and Kyriazakis, 1999). Anorexia becomes apparent 2–3 weeks after the initial challenge (Kyriazakis *et al*. 1998), which coincides with the development of larvae to adult worms. In our model, anorexia is assumed to be a function of worm mass. Worm mass is assumed to affect the potential of the animals to grow in the current environment by reducing the growth rate parameter; this approach has also been used in other models where the impact of environmental stressors have been considered (Wellock *et al*. 2005). The reduced potential for growth leads to reduced nutrient requirements and thus reduced desired food intake.

Anorexia is adequately modelled by a sigmoid reduction in food intake followed by a period where the food intake remains constant before it recovers to levels similar to those of control uninfected animals (Sandberg *et al*. 2006). For modelling such a pattern

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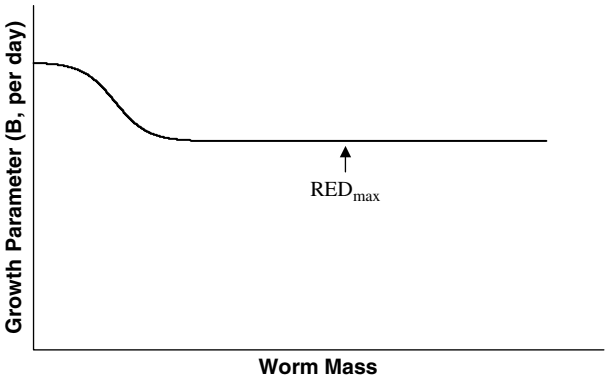

Fig. 4. The relationship between the worm mass and the Gompertz growth rate parameter (B, per day), which allows for the prediction of expected growth. RED_{max} is the maximum reduction in the growth parameter for subclinical infections.

an equation based on the logistic regression was derived, which was bound between zero and 1, and had the property that when the independent variable is zero the value of the dependent variable is 1. This equation (see Appendix 2 for derivation) is:

$$RED = RED_{max} + (1 - RED_{max}) \cdot \left(\frac{1 + e^{c_4}}{1 + e^{(c_4 + c_5 \cdot WM)}} \right) \quad (27)$$

where RED = reduction of growth parameter, RED_{max} = maximum reduction of growth parameter c_4, c_5 = assumed constants.

The new Gompertz curve growth parameter, used for estimating body protein growth, is then estimated as:

$$B_{New} = B \cdot RED \quad (28)$$

The form of the resulting relationship between food intake and worm mass, for a subclinically infected animal, is shown in Fig. 4. The recovery of food intake is a function of the developing immunity of the host and its impact on worm mass. Thus it does not have to be modelled explicitly.

Dynamic model

The above model predicts events in 1 day of the life of the animal. It is straightforward to extend it to model a period of the animal's life. An initial fleece-free empty body weight (defined as body weight minus the gut fill and wool), expected mature fleece-free empty body weight, protein and lipid body content at maturity are required as inputs. The animal is given access to food of a particular composition in terms of MP and effective energy. The daily larval intake can be either assumed to be constant, as in trickle infections, or a function of food intake, as in natural challenges.

Briefly, a naive animal ingests food, i.e. energy and protein, and infective larvae. The impacts of the ingested larvae, and eventually the adult worm mass, on protein utilization and immunity are estimated as described above, as is the quantitative impact of the host on the parasite population. The model is updated on a daily basis. As a result, the above model is extended from being static to dynamic. Currently, this model describes only the growth of an animal and not other nutrient demanding phases, such as gestation and lactation.

Parameterization

For the parameterization of the model, published values were used whenever possible. Some quantities like the protein loss due to larval intake are very difficult to measure. For these quantities reasonable values were assumed, and the impact of large variations in input parameters on output variables was investigated, as described below. The values used and their source are given in Table 2 below.

As some of the parameters in Table 2 are assumed rather than estimates, it was necessary to perform a sensitivity analysis. This analysis is described in the companion paper (Vagenas *et al*. 2007).

RESULTS

Outputs from the model are illustrated for a single lamb, given a single feed, with various levels of daily larval intake. The food offered contained 12·6 MJ/ kg DM metabolizable energy and 190 g/kg DM crude protein, corresponding to a good quality grass (AFRC, 1993). The initial fleece-free empty body weight of the lamb was assumed to be 21 kg, which corresponds approximately to weaning. The lamb's genotype is characterized by expected mature body protein and lipid contents of 12·5 and 68·8 kg, respectively. The model was run for 3 *in silico* months. The animal was assumed to be challenged with 0, 1000, 3000 or 6000 infective larvae per day, from day zero, corresponding to challenge levels that normally lead to subclinical *Teladorsagia circumcincta* infections (e.g. Coop *et al*. 1985).

The effect of cumulative larval intake on the establishment rate of the incoming larvae is given in Fig. 5. Increasing larval intake from 1000 to 3000 has a greater impact on the establishment rate than increasing larval intake from 3000 to 6000. Mortality and fecundity show similar patterns to those for establishment, across time and with increasing larval intake (not shown).

The worm burdens for different larval intakes are given in Fig. 6A. As expected, the lower the larval challenge the lower the worm burden. A consequence of immunity developing, as modelled, is that when the animal faces a high larval intake, it can control the worm burden sooner than with lower

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Table 2. Parameters used in the parasite-host model

Description	Symbol	Value	Source
Maximum daily protein loss	$PLoss_{max}$	0·01	Based on Steel *et al.* (1980)
Maximum daily LI for which there is immune response	LI_{max}	10 000	Based on Steel *et al.* (1980)
Inflection point for LI	LI_{infl}	5000	Assumed
Minimum damage for which there is no immune response	$PLoss_{min}$	0·0001	Assumed
Maximum establishment rate	ε_{max}	0·70	Jackson *et al.* (2004)
Maximum *per capita* fecundity of adult female worms	F_{max}	20	Bishop and Stear (1997)
Maximum mortality rate of adult worms	μ_{max}	0·11	Kao *et al.* (2000)
Minimum establishment rate	ε_{min}	0·06	Jackson *et al.* (2004)
Minimum *per capita* fecundity	F_{min}	5	Assumed
Minimum mortality rate	μ_{min}	0·01	Kao *et al.* (2000)
Constant of relationship ε and PRQ_{Imm}	K_{ε}	0·00001	Assumed
Constant of relationship F and PRQ_{Imm}	fi	100 000	Assumed
Constant of relationship μ and PRQ_{Imm}	mi	100 000	Assumed
Constant of relationship LI_{eq} and WM	c_1	0·80	Assumed
Constant of relationship $PLI_{max}$and P_{maint}	c_2	0·20	Houdijk *et al.* (2001)
Constant of relationship $\sum_t$ LI and $\sum_{t-1}$ LI	c_3	2000	Assumed
Constant of relationship RED and WM	c_4	−5	Assumed
Constant of relationship RED and WM	c_5	0·000014	Assumed

larval challenges. Thus, the peak worm burdens for the 1000, 3000 and 6000 scenarios are observed at days 42, 37 and 35 respectively. Even though there is a rapid development of immunity when the animal is challenged with high larval intake, in the initial stages of the challenge substantial numbers of larvae become established, and high challenge levels are reflected by high worm burdens. The combined effect is that the lower the larval intake the lower the peak and the flatter the distribution of worm burden across time.

Faecal egg counts (eggs/g DM faeces) are estimated as the daily egg output of female worms divided by the daily faecal output of the animal (i.e. daily food DM intake multiplied by the indigestibility of the food). Faecal egg counts follow a similar pattern to worm burden and are shown in Fig. 6B. Compared to the case when larval intake is 1000, the worm burdens when larval intakes are 3000 and 6000 are, respectively, 2·25 and 3·95 times higher. The equivalent numbers for faecal egg counts are 1·99 and 3·75, respectively. Density dependence effects partly account for the smaller relative difference among faecal egg counts compared to the differences among worm burdens.

In both figures it can be seen that animals with high larval intakes have slightly lower worm burdens and faecal egg counts than animals with lower larval intakes, after 75–80 days. This is a consequence of faster development of immunity for animals with higher larval intakes.

The food intake for the various challenge levels are shown in Fig. 7. When the animal is challenged, food intake is the outcome of 2 factors: the desire to increase food intake so as to cover its additional requirements and the anorexia caused by the presence of worms. Net changes in food intake depend on the relative magnitudes of these two forces. For example

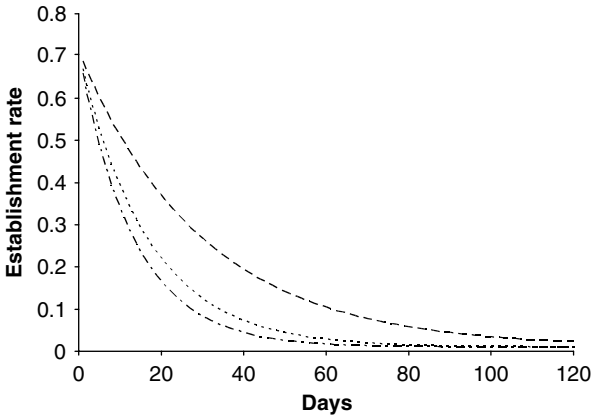

Fig. 5. The establishment rate of incoming larvae over time, in sheep given different levels of larval intake (– – – 1000, ····· 3000, – · – 6000).

in the case of 1000 larval intake, as modelled here, the desire to eat to cover the increased immunity requirements outweighs the anorexia effect. Thus the animals have a higher predicted food intake than uninfected controls. On the other hand, when the larval intake is 6000, the anorexia initially outweighs the desire to eat to cover the immunity requirements, and there is a decrease in food intake. However, as the animal acquires immunity and the worm mass decreases, the anorexia effect wanes and food intake increases again. Thus, as it can be seen in Fig. 7, after approximately 80 days, the food intake of the animals challenged by 6000 larvae per day is higher than the control and eventually higher than that for animals facing a challenge of 1000 larvae per day.

The reduction in food intake has, as expected, an effect on body growth. This can be seen in Fig. 8 where fleece-free empty body weight is given for different larval intakes. The major cause of growth reduction is anorexia. Before anorexia sets in, larval

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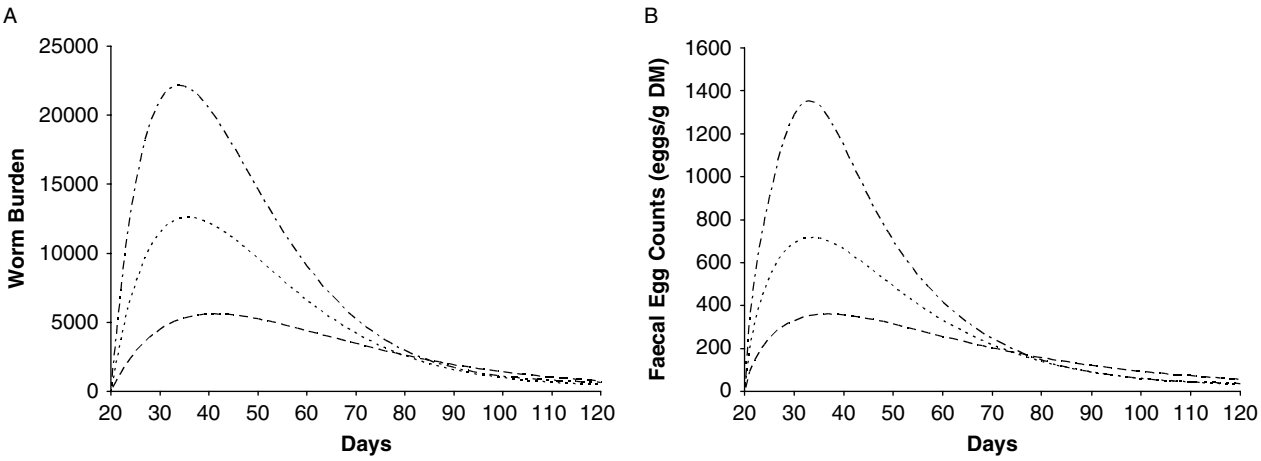

Fig. 6. The worm burdens (A) and faecal egg counts (B) over time, in sheep given different levels of larval intake (– – – 1000, ····· 3000, – · – 6000).

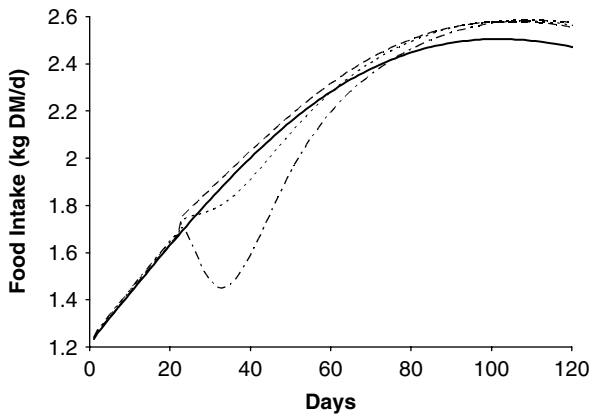

Fig. 7. The daily food intake of sheep given one of three levels of larval intake (—— Control, – – – 1000, ····· 3000, – · – 6000), from weaning (day 0) to 6 months of age (day 120). The daily food intake of uninfected sheep is also shown.

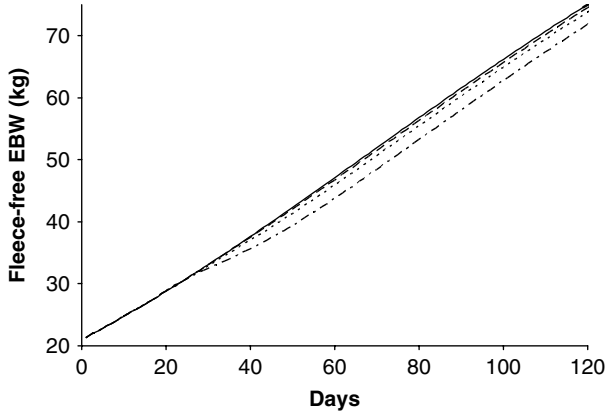

Fig. 8. The fleece-free empty body weight of sheep given one of three levels of larval intake (—— Control, – – – 1000, ····· 3000, – · – 6000), from weaning (day 0) to 6 months of age (day 120). The daily food intake of uninfected sheep is also shown.

intake has almost no effect on growth rate, under the scenario modelled. Small larval doses have an insignificant effect on growth rate and hence fleece-free empty body weight. The maximum reductions in daily growth rate, as a proportion of the control, are 0·02, 0·07 and 0·23 for the 1000, 3000 and 6000 larvae per day challenges respectively.

DISCUSSION

A model has been developed to account for the interactions between host nutrition and parasitism in the growing lambs. The growth of the animal is described in terms of its body content in protein and lipid, with these tissue growths driving protein and energy requirements. When the animal is challenged with larvae of gastrointestinal parasites, both larval intake and established adult worms are assumed to have an effect on the requirements and partitioning of nutrients. As a consequence, nutrient requirements are increased, but desired food intake decreases (i.e. pathogen induced anorexia). The net outcome of the 2 processes is that the animal has to partition scarce nutrient resources between the functions of maintenance and growth on one hand, and functions arising from parasitism on the other.

During the challenge there is an initial increase of worm burden and as a consequence a reduction in food intake and growth rate is observed, which may be quite severe. However, as the animal grows, food intake and live-weight recover and become similar to the uninfected control. As a result subclinical gastrointestinal parasitism can have an important, temporary, effect on the productivity of lambs. However, since this effect coincides with the first few months after weaning, it can impose a considerable cost in the expected life of a lamb raised for meat production.

This model has attempted to describe many of the known consequences of parasite infection on the host, and it is useful to explore the concepts that underpin this model. The very notion of parasitism

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implies a (nutritional) cost to the host. This cost has been quantified in the current model by the term damage. The relationship between damage and larval intake or worm burden is unknown and very difficult to infer experimentally. What can be safely assumed is that damage will be an increasing function of larval intake or worm burden. The 3 simplest shapes of the above relationship that could be assumed are the following: (1) a simple linear; (2) an increasing exponential relationship (Behnke *et al*. 1992), where increments of parasitic challenge result in an exponential increase in damage (equivalent to saying that an already 'weakened' host suffers more from the effects of additional parasitism); (3) damage decreases proportionally as parasitic burden increases. This is the converse of the previous relationship (2) and implies that there is a decreasing amount of host tissue that is available for damage as parasite burden increases. There is no strong evidence in favour of any of these functions in the literature (Casadeval and Pirofski, 1999). It was therefore decided to use a flexible function which can be applied to explore different scenarios (Yin *et al*. 2003). The exploration of the consequences of the above function is given in a companion paper (Vagenas *et al*. 2007).

In order to restrict the damage incurred by parasites the animal will mount an immune response. Before being able to mount an immune response the animal has to develop the appropriate apparatus to do so, i.e. acquire immunity. Whilst the phases of acquisition and expression of immunity to parasites may be conceptually defined, in reality these 2 phases constitute a continuum (Coop and Kyriazakis, 1999). In the current model, the 2 phases have been modelled for their effects on parasite establishment, fecundity and mortality by using single equations (equations (17), (20) and (22) respectively). Using establishment as an example, equation (17) is an elaboration of the equation for ε_0, which is derived from Louie *et al*. (2005) and makes the phase of acquisition of immunity dependent only on a function of cumulative larval intake. This is consistent with observations in the literature (Coop *et al*. 1995; van Houtert and Sykes, 1996; Kahn *et al*. 2000) and with the theoretical suggestions of Coop and Kyriazakis (1999) that acquisition of immunity is independent of nutrient supply. As immunity is acquired, its degree of expression is proposed to depend on the degree of protein scarcity, i.e. ratio of the protein allocated to immunity to the protein required for immunity. The mechanisms describing the acquisition and expression of immunity for mortality and fecundity follow a similar logic.

Having in place mechanisms describing body growth and the effects of parasitism on the host in terms of nutrient demands, a mechanism for allocating scarce nutrients between the various functions was required. Maintenance is given priority over all other functions since this would lead to the long-term survival of the animal. In the classical approach immunity is considered to be part of maintenance and hence is prioritized in terms of nutrient allocation above the production functions. Thus, breakdown of immunity will occur only with sub-maintenance intakes. However, this is not observed experimentally and restriction of nutrient intake penalises both immunity and production (e.g. van Houtert *et al*. 1995; Bown *et al*. 1991; Kambara *et al*. 1993; Coop *et al*. 1995; Wallace *et al*. 1995). Thus, a reasonable allocation rule should be able to account for the effects of scarce nutrient allocation on both immunity and production traits. Here, we chose to model the allocation of resources to production and immunity proportionally to their requirements. This is a simple rule, requiring no extra parameters and not giving absolute priority to either immunity or production traits. A consequence of this rule is that if animals with different expected growth rates are given access to the same quantity of feed (less than total requirements) and the same level of challenge and assuming equal efficiency of utilization of nutrients, the genotype with the lower expected productivity will be relatively more resistant than that with the higher expected productivity. This issue is explored further in our companion paper (Vagenas *et al*. 2007), and is expected to result in genotype by nutrition interactions for resistance. The proposed rule is consistent with the finding that breeds which have higher maintenance and production outputs tend to be less resistant and suffer greater productivity losses compared to less productive ones, when compared under challenging and nutritionally limiting conditions (Abbot *et al*. 1985; Miller *et al*. 1998; Gruner *et al*. 2003; Amarante *et al*. 2004; Bricarello *et al*. 2005). Although other factors such as grazing behaviour could also account for the above observations, different allocation of resources would contribute to these results.

One well-established effect of gastrointestinal parasites on the host is the induction of anorexia. Anorexia is thought to be a major cause of reduction in production during parasitic challenge (Coop and Holmes, 1996; van Houtert and Sykes, 1996). Anorexia becomes apparent usually after 2 weeks or more of the challenge (Kyriazakis *et al*. 1998). Thus, it was modelled as a function of adult worms rather than larval intake or established larvae. Furthermore, Kyriazakis *et al*. (1996) found that anthelminthic treatment led to immediate recovery of food intake. The food intake of the treated animals was similar to the food intake of the control despite continuous larval challenge, suggesting that anorexia was related to adult worms rather than larval intake. In assuming that it is the adult worms which are causing the reduction of food intake rather than larval intake, we indirectly assume that anorexia will decline as immunity increases (Greer *et al*. 2005; Langhans *et al*. 2000). Worm mass (which is essentially worm

burden scaled by worm size) is a function of all the immunological variables, i.e. the ability of the host to control both worm burden and worm development, and therefore has been used preferentially over worm burden.

In the current model, anorexia is created through a reduction of the expected growth of the animal, which leads to a reduction of requirements. The idea that 'stressed' animals have reduced ability to grow rather than a direct reduction of food intake has been proposed by Chapple (1993) and used in models of responses to nutrients such as that of Black *et al*. (1999) and Wellock *et al*. (2003). The alternative suggestion to account for parasite-induced anorexia is to assume that a pathogen directly affects food intake and consequently growth (Sandberg *et al*. 2006). Although we have opted for a mechanism of creating anorexia *via* reduction of the growth requirements, our model is flexible enough to be modified to incorporate direct impact on desired food intake.

In summary, we have developed a framework that describes the utilization of nutrients, their partitioning to growth or immunity, and the impact of parasitism on these processes. Outputs of the model include the host food intake, growth rate, worm burden and faecal egg counts. Thus, this model gives us the opportunity to explore the impact of nutrition and genotype on the performance of parasitized lambs kept in different environments. Furthermore, the model allows us to explore host genotype at several levels, i.e. for performance traits, for parasite resistance traits, and for varying degrees of interactions between these traits.

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APPENDIX 1

Body growth

The expected daily body protein growth is estimated based on the Gompertz function as:

$$\Delta\text{PGrowth}_{max} = P \cdot B \cdot \ln\left(\frac{P_m}{P}\right) \quad \text{(kg/day)} \qquad \text{(A1.1)}$$

where B = Gompertz growth rate parameter, P_m = body protein content at maturity (kg) and P = current body protein content (kg).

It is assumed that the animal aims to achieve its expected growth for protein, which depends only on its genotype and current state. The ash and water content are functions of body protein content. The daily rates of change of ash and water in the body are estimated as:

$$\Delta\text{Ash} = 0{\cdot}211 \cdot \Delta\text{PGrowth} \quad \text{(kg/day)} \qquad \text{(A1.2)}$$

$$\Delta\text{Water} = \Delta\text{PGrowth} \cdot w \cdot (W_m/P_m) \cdot (P/P_m)^{(w-1)} \quad \text{(kg/day)} \qquad \text{(A1.3)}$$

where W_m = body water content at maturity (kg) and w = 0·815. Since ash is a simple linear function of body protein and it is not easily mobilized, it can be used as a marker for the maximum body protein content achieved by the animal. This is useful for the estimation of how much protein the animal can lose.

For modelling wool growth, a function based on Cronje and Smuts (1994) was derived. The expected daily wool growth is modelled as a function of both size and expected body protein growth:

$$\Delta\text{PWool}_{max} = \left(\frac{c_6 \cdot P}{P_m^{0{\cdot}27}}\right) + (\cdot c_7 \cdot \Delta\text{PGrowth}_{max}) \quad \text{(kg/day)} \qquad \text{(A1.4)}$$

where $\Delta\text{PGrowth}_{max}$ = maximum body protein growth (kg/day), P_{Maint} = protein turnover at maintenance (kg/day), $c_6 = 0{\cdot}00085$, $c_7 = 0{\cdot}16$.

Thus, the daily metabolizable protein requirements for wool growth are estimated as:

$$\text{PRQ}_{Wool} = \frac{\Delta\text{PWool}_{max}}{e_{Wool}} \quad \text{(kg/day)} \qquad \text{(A1.5)}$$

The daily lipid growth the animal seeks to achieve (ΔLipid_{des}) is essentially a function of the state of the animal and its lipid to protein ratio content at maturity:

$$\Delta\text{Lipid}_{des} = \Delta\text{PGrowth}_{max} \cdot \left(\frac{L_m}{P_m}\right) \cdot d \cdot \left(\frac{P}{P_m}\right)^{(d-1)} \quad \text{(kg/day)} \qquad \text{(A1.6)}$$

Lipid will be deposited if there is feed energy left after accounting for maintenance, wool and protein retention, immunity and the loss caused by parasitism, as they all have an energetic cost. The energy partitioning is based on protein partitioning. The energetic cost of one unit of protein for wool, immunity and damage inflicted by parasites is assumed to have the same energetic cost as 1 unit of protein deposited as muscle (body growth).

For the daily energetic cost of the total protein metabolism we have:

$$E_{Protein} = (\Delta\text{PWool} + \Delta\text{PGrowth} + P_{Loss} + P_{Imm}) \cdot bp \quad \text{(MJ EE/day)} \qquad \text{(A1.7)}$$

where bp = 50 MJ/kg, i.e. the energetic cost per kg of protein retained.

The daily lipid deposited is then the difference between the energy intake and the energy for maintenance and protein transactions.

$$\Delta\text{Lipid} = \frac{((FI \cdot EEC) - E_{Maint} - E_{Protein})}{bl} \quad \text{(kg/day)} \qquad \text{(A1.8)}$$

where E_{maint} = energy for maintenance (MJ/day), bl = 56 (energetic cost of kg lipid retained) (MJ/kg).

If ΔLipid is negative, then lipid will be catabolized to satisfy the animal's energetic needs:

$$\Delta\text{Lipid} = \frac{((FI \cdot EEC) - E_{Maint} - E_{Protein})}{bl_C} \quad \text{(kg/day)} \qquad \text{(A1.9)}$$

where heat combustion of lipid, $bl_C = 39$ MJ/kg.

The minimum body lipid level, L_{min}, below which the animal is assumed to die, is estimated as a proportion of its body protein content:

$$L_{min} = 0{\cdot}2 \cdot P \quad \text{(kg)} \qquad \text{(A1.10)}$$

The daily change in fleece-free empty body weight is simply the sum of the daily increases in the protein, ash, water and lipid components. Total body weight is then the sum of fleece-free empty body weight,

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wool and gut fill. Gut fill is estimated according to Coffey *et al*. (2001) as:

$$GF = FI \cdot \left(11 - \left(\frac{7 \cdot ME}{15}\right)\right) \quad (kg) \qquad (A1.11)$$

where FI = food intake (kg DM) and ME = metabolized energy of the feed (MJ/kg DM).

Daily protein requirements for maintenance are estimated as a function of the state of the animal:

$$P_{maint} = 0{\cdot}004 \cdot \left(\frac{P}{P_m^{0{\cdot}27}}\right) \quad (kg/day) \qquad (A1.12)$$

APPENDIX 2

Equation (27) was derived from the equation for logistic regression. In its simplest form the logistic regression is modelled as:

$$Y = \frac{1}{1 + e^{-(a+bx)}} \qquad (A2.1)$$

This function asymptotes at zero and 1. Furthermore when $x = 0$, $Y = \frac{1}{1+e^{-a}} \neq 0$.

For modelling the reduction of food intake in the manner described in this paper we require a function which is bound between C ($0 \leqslant C \leqslant 1$) and 1. Furthermore, when x is equal to zero (which in this case is WM) then Y should be equal to 1 (which in this case is RED, the reduction in the Gompertz growth parameter). By modifying the numerator so that:

$$Y = \frac{1 + e^{-a}}{1 + e^{-(a+b \cdot x)}} \qquad (A2.2)$$

we have $Y = 1$ when $x = 0$.

To restrict the value of Y in [C, 1] we can linearly transform the equation as follows:

$$Y = C + \left[(1 - C) \cdot \left(\frac{1 + e^{-a}}{1 + e^{-(a+b \cdot x)}}\right)\right] \qquad (A2.3)$$

which gives us for the reduction of the Gompertz parameter (equation 27):

$$RED = RED_{max} + (1 - RED_{max}) \cdot \left(\frac{1 + e^{c_4}}{1 + e^{(c_4 + c_5 \cdot WM_t)}}\right) \qquad (A2.4)$$

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