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Modeling of bovine spongiform encephalopathy in a two-species feedback loop☆

Richard Barnes[a,*], Clarence Lehman[b,**]

[a] Ecology, Evolution, & Behavior, University of Minnesota, USA
[b] College of Biological Sciences, University of Minnesota, USA

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ABSTRACT

Bovine spongiform encephalopathy, otherwise known as mad cow disease, can spread when an individual cow consumes feed containing the infected tissues of another individual, forming a one-species feedback loop. Such feedback is the primary means of transmission for BSE during epidemic conditions. Following outbreaks in the European Union and elsewhere, many governments enacted legislation designed to limit the spread of such diseases via elimination or reduction of one-species feedback loops in agricultural systems. However, two-species feedback loops—those in which infectious material from one-species is consumed by a secondary species whose tissue is then consumed by the first species—were not universally prohibited and have not been studied before. Here we present a basic ecological disease model which examines the rôle feedback loops may play in the spread of BSE and related diseases. Our model shows that there are critical thresholds between the infection's expansion and decrease related to the lifespan of the hosts, the growth rate of the prions, and the amount of prions circulating between hosts. The ecological disease dynamics can be intrinsically oscillatory, having outbreaks as well as refractory periods which can make it appear that the disease is under control while it is still increasing. We show that non-susceptible species that have been intentionally inserted into a feedback loop to stop the spread of disease do not, strictly by themselves, guarantee its control, though they may give that appearance by increasing the refractory period of an epidemic's oscillations. We suggest ways in which age-related dynamics and cross-species coupling should be considered in continuing evaluations aimed at maintaining a safe food supply.

1. Introduction

Bovine spongiform encephalopathy (BSE) is a disease in which a molecule of a specific protein misfolds into a pathogenic state; this misfolded protein then amplifies by inducing similar pathogenic misfoldings in other molecules of that protein (Prusiner, 1997). For short-hand in this paper, we use the term "prion" to refer only to the misfolded form of the protein. The disease leads to neurodegeneration and death. It can be transmitted when a non-infected individual consumes prion-containing tissues from an infected individual (Cummins et al., 2001; Wilesmith et al., 1992). In the late stages of the incubation period, the brain and spinal cord are known to have especially high levels of prions; prions are also known to be present in the peripheral nervous system and ileum, but to a lesser extent (Arnold et al., 2009; Masujin et al., 2007; Wells et al., 1998).

Consider a hypothetical disease limited to vertebrates and transmitted when a susceptible individual consumes tissues from an infected one. The spread of the disease is normally self-limiting. Prey are consumed by predators, predators become prey, and the disease propagates along the food chain until non-susceptible invertebrate decomposers take charge.

Suppose, however, that the trophic structure is not a simple food chain, but rather a food web containing a feedback loop connecting two or more vertebrate species. For example, if a scavenger and predator species are trophically linked such that individual scavengers consume some dead predators, and living predators occasionally kill and consume the scavengers, then the dynamics are wholly different. The spread of the disease can progress cyclically around the feedback loop, limited not by the number of links in the chain but only by the size of the vertebrate populations.

Feedback loops can occur not just in nature, but also in agriculture. Livestock fed restricted diets often need food supplements, such as additional protein. Soybean meal can be used for this, but

* Corresponding author.
** Principal corresponding author.
E-mail addresses: rbarnes@umn.edu (R. Barnes), lehman@umn.edu (C. Lehman).

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animal-derived protein is another source. Because large numbers of animals are slaughtered daily, and because not all of the slaughter is marketable to humans, a fraction remains. This fraction represents a prodigious quantity of material—up to 24 million tons or more per year in the US alone (Kirstein, 1999)—that can be rendered into a diet supplement for livestock called meat-and-bone meal, among other names. Livestock may also be fed animal byproducts such as poultry litter. For example, in 2003, the state of Florida produced one million tons of poultry litter, 350,000 of which were available for use in feed (Sapkota et al., 2007).

TSEs are known to spread among livestock such as cows (Prusiner, 1997; Nathanson et al., 1997; Wilesmith et al., 1988; Wells et al., 2007) and sheep (Detweiler and Baylis, 2003) when their feed is contaminated with infected tissues. To combat such spread, many countries have enacted legislation restricting what may be fed to susceptible species by either eliminating feedback loops altogether or prohibiting one-species feedback loops. Two-species loops are not, however, universally prohibited.

Our model considers a form of feedback in which prions are amplified in one species and then fed to a secondary species in which they may or may not be decreased before being fed back to the first species. Although the disease is also thought to propagate via direct maternal transmission (Donnelly et al., 1997; Wilesmith et al., 1997) and via cross-contamination of feed (Abrial et al., 2005; Wilesmith, 1996a,b), the former, if it occurs, does so only at levels insufficient to maintain an epidemic (Donnelly et al., 2002; Wilesmith et al., 2010) whereas the latter has been heavily regulated. Feedback through consumption of infected tissues is the primary means of BSE transmission during epidemic conditions (Cummins et al., 2001), so it seems worthwhile to consider this in the context of a two-species loop. This is especially so given that regulations prohibiting single-species cattle loops have created interest in making up the difference by sourcing protein from other species (Jenkins, 2006).

In the two-species feedback loops we consider, infectious material passes through a secondary species. In the worst-case scenario, the secondary species becomes infected and actively contributes to the growth of the disease, but it is not necessary that infection occur. There is also the possibility that the secondary species harbours infectious material for either long or short periods without ever developing symptoms.

Although it is not known whether the disease has transmitted in this way, it represents a possible means which has not been universally prohibited nor, to the best of our knowledge, considered by prior studies.

2. Methods of analysis

The aim of our model is to examine population dynamics and feedback loops under the most basic conditions, applying the simplest feasible model in order to expose underlying theoretical patterns and the relative importance of parameters in one- and two-species loops. Previous models have focused on different questions such as quantifying the real world risk of human and cattle exposure during and following the UK epidemic (Ferguson et al., 1999; Cohen et al., 2004), the dynamics of the UK epidemic (Ferguson et al., 1997; Thornley and France, 2008), or the spread of BSE in the cells of a single individual (Nowak et al., 1998; Kellershohn and Laurent, 2001).

Instead of tracking the number of hosts that are infected, susceptible, and resistant, as is common in ecological disease models, this model simplifies that structure by tracking the total quantity of disease agents (prions in this case) resident within each host species, treating the hosts merely as an environment in which the disease exists.

Because the conditions which could lead to an epidemic are of primary interest, the model focuses on the early growth phase of the potential epidemic, when the disease would still be spreading undetected and mitigation measures would not be in effect. Individuals are not clearly symptomatic and, therefore, are neither being culled nor dying. Although individual animals' susceptibility may vary, the model focuses on a subpopulation wherein all members are susceptible, and equally so. For simplicity, the model also assumes—as may be the case in an agricultural setting—that the lifespan of all hosts is artificially limited to a fixed number of years, that the size of the population is held constant, and that all individuals in an age-class are treated equally.

3. One-species model

The tightest possible feedback loop occurs when individual animals ingest tissues or byproducts of their own species, a practice which led to the spread of BSE in the United Kingdom and elsewhere (Wilesmith et al., 1988, 1992). We show that for such a loop, there are critical combinations of lifespan, infectivity, and feedback below which the number of infections in a population will decrease with time and eventually vanish, and above which the infection will expand epidemically.

The model uses three parameters per species, x_i, c_i, and R. The net total prion level of all animals in the herd in their ith year of life, at the beginning of that year, is represented by x_i. The prions are amplified in infected tissue by a factor of R in each time unit. Upon slaughter, some fraction c_i of the tissues from the oldest age class is fed back and incorporated into the tissues of the younger age class i. This term also incorporates the probability of infection, which relates to the infectivity of the prions, dose size, and heterogeneity of consumption.

In the model, the lifespan of the species is n years. In the United States and the United Kingdom, the lifespan of most beef cattle is held close to 2–3 years, with breeding and dairy cattle living an average of 5–7 years, but with a minority of cattle living up to 16 years (Donnelly et al., 2002; USDA, 2006).

The model could also be arranged to include the effects of slaughtering younger age-classes and feeding them back. However, this would mean that fewer prions would make it to older age-classes leading to slower growth of the disease. The more conservative formulation of the system we examine here assumes that all members of a species make it to the same (old) age. This maximizes amplification resulting in stronger conclusions concerning the efficacy of control measures.

For cattle, the consumption of even very small amounts of infectious tissue is sufficient to spread the disease: Wells et al. (2007) experimentally determined that 50% of cattle would be clinically affected by a dose of 0.20 g, with no evidence for a minimum dose. Here we arbitrarily seed our model with a "prion level" of 1. Despite the disease's infectivity, clinical signs take an extended period to present themselves: the incubation period in cattle is approximately 3–5 years (Wells et al., 2007). Nowak et al. (1998) suggest on theoretical grounds that within an individual the disease's amplification is a trade-off between the linear growth of prion aggregates and exponential growth caused by the fracturing of these aggregates, while Arnold et al. (2009) experimentally determined that the disease had a doubling time of 1.2 months in the central nervous system. This implies an exponential growth rate of $R = 3$ per year, which we adopt here.