RESULTS FROM PRIOR FUNDING

Ecology of Infectious Disease Award DEB-0091961, 2000-2006, Spatial & Temporal Dynamics of Prion Disease in Wildlife: Responses to Changing Land Use. $2,166,690

Intellectual Merit: Hobbs, Miller, Williams (deceased), Hoeting, and Tavener received support to study dynamics of chronic wasting disease (CWD) in populations of mule deer, and, in particular, to identify effects of land-use on disease prevalence. We produced 13 refereed publications in core journals and one in review. We developed the first live animal diagnostic for CWD (Wolfe et al. 2004). We discovered that CWD can be transmitted from excreta (Miller et al. 2004) and that infectious residues persist in the environment for years (Miller et al. 2004, Miller et al. 2006). We provided the first evidence of a genetic basis for susceptibility (Jewell et al. 2005, Fox et al. 2006). We showed that prevalence is shaped by human land use (Farsnworth et al. 2005, 2006) and host demographics (Farnsworth et al. 2005, Miller and Conner 2005, Farnsworth et al. 2006). We revealed an exponential increase in prevalence within the male segment of deer populations within epidemic areas of Colorado (Miller and Conner 2005). We were the first to estimate the net reproductive rate of the disease, R_0 (Miller et al. 2006). We were the first to apply multi-model inference to the estimation of R_0 in a model of infectious disease (Miller et. al. 2006). Although papers acknowledging this award and its supplement (below) have been recently published, they have nonetheless motivated 337 citations, demonstrating the high impact of our work.

Broader Impacts: We trained four post-doctoral fellows, one Ph.D. student, two Master's students, and two undergraduates. We presented findings to the Panel on Prions in the Nation's Food Supply, Institute of Medicine, National Academy of Sciences. We testified to the Subcommittee on Forests and Forest Health and the Subcommittee on Fisheries Conservation, Wildlife, and Oceans of the Committee on Resources, United States House of Representatives. We served on the Yellowstone National Park Wildlife Health Working Group. We advised the US National Park Service, the Canadian Food Inspection Agency, the Canadian Cooperative Wildlife Health Centre, numerous state agencies, and non-governmental environmental groups. We gave interviews to NBC Evening News, the Wall Street Journal, the New York Times, the Denver Post, the Rocky Mountain News and other media. Our work was characterized by a close partnership with the Colorado Division of Wildlife and our findings have been directly incorporated into their routine management practices.

Supplement to Ecology of Infectious Disease Award DEB-0091961, 2003-2004. $65,000.

Applying novel statistical analyses to data collected during our investigations was crucial to several insights described above. Motivated by the need for such approaches, Hobbs and Hoeting proposed a workshop composed of statisticians and ecologists to communicate emerging statistical methods to the research community in ecology. The workshop, supported by a supplemental award to our original grant, produced a Special Feature in *Ecological Applications* including eight papers acknowledging support from DEB-0091961. See Hobbs et al. (2006) and accompanying papers.

RESPSONSES TO PREVIOUS REVIEWS

This is a resubmission of a renewal proposal that has received helpful, encouraging reviews. It was rated competitive in 2007 (1E, 3V, 1V/G, 1G) and highly competitive in 2008 (1E, 4V). The panel summary from 2008 expressed a single concern, that our sample size might not be adequate to estimate states and parameters in our model. In response, we have simulated data under plausible assumptions for process and observation uncertainty and used the simulated data to examine the sensitivity of our proposed sampling regime (see *Adequacy of Sample Size,* page 11).

SIGNIFICANCE

Chronic wasting disease (CWD) of the deer family (collectively known as "cervids") is a transmissible spongiform encephalopathy, a member of a group of infectious diseases affecting

animals and people caused by an accumulation of a proteinase-resistant prion protein (*PrP*) in the brain of affected individuals. Similar diseases include scrapie in sheep and goats, bovine spongiform encephalopathy in cattle and Creutzfeldt-Jacob disease in humans, all of which cause neural degeneration and, inevitably, death (Prusiner 1999).

When we received our Ecology of Infectious Disease award in August of 2000, the known distribution of CWD was limited to a single cluster of populations of mule deer (*Odocoileus hemionus*), white-tailed deer (*O. virginianus*) and elk (*Cervus* elaphus) arrayed along the eastern slope of the Front Range and the Medicine Bow Mountains in northeastern Colorado and Southeastern Wyoming (Miller et al. 2000). Today, the spatial distribution of CWD is far more extensive. As of December 2008, CWD has been found in free-ranging cervid populations in 13 states and provinces in North America and as well as in over 80 captive herds. Discovery of an infection in South Korea exposes Asia to the disease (Kim et al. 2005) and discovery of CWD in moose (*Alces alces*) (Baeten et al. 2007) means that it could spread to boreal regions.

It is well known that CWD can be transmitted freely among some cervid species (Williams 2005, Tamguney et al. 2006), but interspecific differences in susceptibility to infection by mule deer prions have not been studied comprehensively. Beyond species in the family *Cervidae*, however, the natural host range of the CWD prion appears limited, and there currently is no evidence that the disease can be transmitted naturally to people (Belay et al. 2004, Novakofski et al. 2005, Tamguney et al. 2006, Xie et al. 2006) or domestic livestock (Williams 2005), and thus the emergence of CWD does not appear to pose a particularly significant direct threat to health of humans or domestic animals.

By contrast, CWD poses far more serious risks to human economies and to natural ecosystems of North America and, in the fullness of time, to the ecosystems of the world. A recent field study at Table Mesa in north central Colorado revealed that prion infection dramatically lowered mule deer survival and increased their vulnerability to predation; moreover, emergence of prion disease in that population coincided with a 45% decline in estimated mule deer abundance over about two decades (Miller et al. 2008). In light of these data, and because there are no clear biological mechanisms for affected cervid populations to resist or recover from prion disease (Williams 2005, Miller et al. 2008), unchecked epidemics appear capable of substantially disrupting affected native ecosystems with far-reaching consequences. Members of the deer family play fundamentally important roles in ecosystem processes across the globe, linking large predators to food webs, influencing disturbance regimes, mediating nutrient cycling, and shaping the composition of landscapes (reviewed by Hobbs 1996, 2006, Pastor et al. 2006). These species also provide basic subsistence to indigenous people throughout the Northern Hemisphere. Rural, recreation-based economies in North America could be severely harmed by the continued emergence of CWD (Bishop 2002, Seidl and Koontz 2004, Miller et al. 2008). Thus, the potential for spread of CWD represents a global threat to the integrity of ecosystems and to the welfare of people who depend on them.

PREVIOUS FINDINGS MOTIVATING PROPOSED WORK

Transmission

Much progress has been made in understanding mechanisms of transmission of CWD. Unlike bovine spongiform encephalopathy but similar to scrapie, CWD is transmitted horizontally (Miller and Williams 2003), likely via oral exposure to saliva, blood (Mathiason et al. 2006) or to residual excreta or carcass remains (Miller et al. 2004). Oral infection via urine or feces cannot be ruled out (Miller et al. 2004, Mathiason et al. 2006). Evidence suggests that infectious materials can persist in the environment for years (Miller et al. 2004, Miller et al. 2006) and soil particles appear to represent a plausible environmental reservoir for prion infectivity (Pedersen et al. 2006, Schramm et al. 2006, Cooke and Shaw 2007). Recent, experimental findings show remarkable amplifying effects of clay soils on infectivity. Binding infectious prions to montmorillonite (clay) soils increased their infectious titer by a factor of 680 relative to an unbound agent (Johnson et al. 2007). Oral exposure to

clay-associated prions led to TSE development in experimental animals even at doses insufficient to cause clinical symptoms when prions were not bound to clay particles (Johnson et al. 2007). However, evidence for indirect, environmental transmission does not exclude a major role for transmission via direct contact between susceptible and infected individuals. The relative importance of these two routes has not been established. Models of disease dynamics in captive populations found substantial support in data for both direct and indirect transmission (Miller et al. 2006).

Influence of genetics on CWD prevalence

Prion proteins (*PrP*) are found in all mammals, and probably all vertebrates. A specific function of *PrP* has not yet been discovered, although *PrP* is highly conserved and under purifying selection in mammals (Wopfner et al. 1999, Seabury et al. 2004). We characterized the prion protein (*PrP*) gene in 1,482 free-ranging mule deer from Wyoming and Colorado (Jewell et al. 2005), finding dimorphisms at codons 20 (aspartate/glycine) and 225 [serine (S)/phenylalanine (F)]. Polymorphism at codon 225 correlated with CWD status: the odds that deer of the *SS* genotype were CWD-infected were 30 times greater (95% confidence interval = 4–213) than for *SF* deer. These results suggest that the *SF* genotype conveys resistance to CWD, a result that resembles findings on genetic controls on susceptibility in other cervids (Johnson et al. 2006). In laboratory studies (Fox et al. 2006) oral challenge of *SF* mule deer caused infection, but with slower progression to disease, showing that the genotype does not convey absolute resistance. The *F* allele varies in frequency from 0 to as high as 11% in populations sampled in Colorado and Wyoming (Jewell et al. 2005), with higher frequencies in Colorado than in Wyoming. In Colorado, as many as 20% of deer have the SF genotype, based on hunter samples from northeastern Colorado (Jewell et al. 2005) and random sampling (N = 212) in Rocky Mountain National Park (M.K. Watry 2007, unpublished MS thesis, CSU).

Modeling disease dynamics

Simple, compartment models based on systems of differential equations explained trajectories in observations of CWD-induced mortality in captive populations (Miller et al. 2006), but our ability to portray dynamics of free-ranging populations infected with CWD remains rudimentary. Parameter estimation has been hampered by relatively brief time series of data on prevalence in infected populations and by the absence of studies of individually marked animals. Modeling efforts to date (Gross and Miller 2001) predicted local extinction of mule deer populations, but these results were criticized as being excessively reliant on untested assumptions about modes of transmission (Schauber and Woolf 2003). Although we have gained substantial knowledge of the factors that influence prevalence (Farnsworth et al. 2005, Miller and Conner 2005, Farnsworth et al. 2006), controls on the probability of transmission remain unknown. It is clear for example that there are very important differences in prevalence among sexes and ages (Miller and Conner 2005, Farnsworth et al. 2006). Thus, future modeling efforts must be able to incorporate demographic heterogeneity in transmission.

Our experience in trying to model dynamics of an emerging infectious disease is not unusual. Efforts to evaluate models of diseases with data, to estimate their parameters, and to assess uncertainties in model predictions[1] have had the greatest success using long time series of observations (e.g., Bjornstad et al. 2002, Clark and Bjornstad 2004, Koelle and Pascual 2004, Morton and Finkenstadt 2005) or where broad scale, detailed case reporting was feasible over short time spans (e.g., Ferguson et al. 2001a, Ferguson et al. 2001b, Keeling et al. 2001, Lipsitch et al. 2003, Riley et al. 2003, Keeling 2005). In all of these instances, the underlying form of the process model was well established (or was assumed false with confidence) before parameters were estimated. In contrast, current approaches to assimilating data with models of disease processes have not been

[1] We will refer to parameter estimation, model selection, and assessing uncertainty in model projections as *data assimilation.*

widely successful when the structure of the process model is uncertain, when the duration of data collection is relatively brief, and when disease incidence must be observed in nature rather than reported by people. Many infectious diseases, particularly emerging diseases in wildlife, zootonic and otherwise, are characterized by precisely these limitations.

Moreover, until recently (Clark and Bjornstad 2004, Morton and Finkenstadt 2005), multiple sources of stochasticity influencing disease dynamics were often lumped into a single "error" term, glossing over differences in uncertainties arising from process variance, observation error, and random effects created by differences among individuals. The failure to properly partition sources of stochasticity can lead to erroneous conclusions about population dynamics (De Valpine and Hastings 2002, Calder et al. 2003, Clark and Bjornstad 2004) and can produce excessively optimistic confidence envelopes on model predictions (Clark and Bjornstad 2004).

We identify three needs in a new approach to data-assimilation for models of emerging infectious diseases. The approach must 1) exploit multiple sources of data that may have been collected at different scales of time and space, 2) quantify key sources of uncertainty, including process variance, errors in observations, random effects among individuals, and uncertainty about underlying models of transmission, and 3) provide confidence envelopes on all quantities of interest that incorporate these multiple sources of uncertainty.

PROPOSED WORK

Aims

We propose research to meet the following aims:

Aim 1: Provide a case example of a novel, general approach for assimilating data with models of emerging infectious diseases that meets the three needs outlined above.

Aim 2: Evaluate support in data for competing models of transmission of CWD and estimate the basic reproductive rate of the disease.

Aim 3: Reveal demographic, genetic, and environmental sources of heterogeneity in disease transmission.

Aim 4: Use the models developed under Aim 1 and 2 to evaluate the consequences of disease for the trajectories of populations infected with proteinase resistant prions. Examine potential for transient behaviors in population growth rates (λ), examine sensitivities of λ to variation in model parameters, and evaluate opportunities for disease control, particularly the consequences of increases in frequency of disease resistant genotypes.

Overview

We will conduct a field study using multi-state, mark-capture-recapture methods to estimate survival probabilities ($\boldsymbol{\varphi}$) and probabilities of infection ($\mathbf{g}$) in populations of mule deer infected with CWD. These estimates will be used in three ways. First, they will allow estimation of transition matrix elements in a process model of disease dynamics. This model will be used to meet Aims 1 and 2. In a separate analysis, the $\mathbf{g}$ will be estimated using a series of covariates to examine sources of individual variation in probability of transmission (Aim 3). This analysis will address how differences in genotype, relatedness, age, sex, local population density, and exposure to clay soils shape probabilities of survival and infection. Finally, we will use our understanding of these sources of variation in transmission probabilities and our process model to explore potential, future trajectories of the disease (Aim 4).

The remainder of this proposal will be organized as follows. We begin by describing a statistical approach to integrating field data with process models of disease dynamics. Next, we sketch a field study designed to provide data to parameterize and evaluate these models and to examine sources of heterogeneity in disease transmission. We then outline mathematical analyses aimed at understanding

the consequences of variation in model parameters for dynamics of the disease and for the potential for control. Finally, we discuss potential problems that are likely to arise. We close the proposal by discussing the broader impacts of our work.

Process model

Proposals like this one customarily place descriptions of experiments and sampling ahead of descriptions of modeling and analysis. We depart from that custom by describing our process model and model-data assimilation first, thereby providing a rationale and framework for the observations needed to estimate model parameters and to evaluate competing ideas about disease transmission. We then describe the details of those observations, returning later to describe how we will use the parameterized model to gain general insight about CWD and prion diseases.

Stage structured, discrete time models of population dynamics provide widely used methods for representing and analyzing dynamics of populations (Caswell 2001), but these models have rarely been applied to infectious disease (but see Morton and Finkenstadt 2005, Oli et al. 2006). The historic absence of discrete time formulations from models of infectious disease is better attributed to culture than to mathematical necessity; Van Boven and Weissing (2004) provide a rationale for using discrete time formulations for disease models and offer a detailed treatment of the relationships between discrete and continuous forms. Using a model similar to the one used in Oli et al. (2006), we will represent a population of mule deer infected with chronic wasting disease using two sexes, two ages, and two disease states:

$$\mathbf{N_{t+1}} = \mathbf{M}\mathbf{N_t} \tag{1}$$

$$\mathbf{M} = \begin{bmatrix} 0 & \alpha F_2 & \alpha F_3 & 0 & 0 & 0 \\ \varphi_1 g_{2,1} & \varphi_2 g_{2,2} & 0 & 0 & 0 & 0 \\ \varphi_1 g_{3,1} & \varphi_2 g_{3,2} & \varphi_3 & 0 & 0 & 0 \\ 0 & (1-\alpha)F_2 & (1-\alpha)F_3 & 0 & 0 & 0 \\ 0 & 0 & 0 & \varphi_5 g_{5,4} & \varphi_5 g_{5,5} & 0 \\ 0 & 0 & 0 & \varphi_4 g_{6,4} & \varphi_5 g_{6,5} & \varphi_6 \end{bmatrix}, \quad \mathbf{N}\begin{bmatrix} 1 \\ 2 \\ 3 \\ 4 \\ 5 \\ 6 \end{bmatrix} = \begin{bmatrix} \text{juvenile female susceptibles} \\ \text{adult female susceptibles} \\ \text{adult female infecteds} \\ \text{juvenile male susceptibles} \\ \text{adult male susceptibles} \\ \text{adult male infecteds} \end{bmatrix}$$

where $\mathbf{N_t}$ is a vector of numbers of individuals in six possible states characterized by age, sex, and disease status. The *F's* are state specific fertilities, α is the sex ratio of offspring, the φ_i 's give survival probabilities for state *i* during time *t* to *t + 1* and the g_{jk}'s give the probability of transition from state *k* to state *j*. The values of the g_{ik} within a column sum to 1 because within any interval of time, each stage must reach one of two states: susceptible or infected. We will refer to these parameters collectively as the vectors **F,.** It is important to note that while equation 1 might appear to be a purely linear formulation with time invariant parameters, we do not assume linear dynamics because the $\boldsymbol{\varphi}$, and $\mathbf{g}$ can be themselves be functions of the abundance of individuals in different states. So, for example, we might represent the probability of transmission from adult female infecteds to adult female suspectibles as $g_{t3,2} = 1 - e^{-\beta(N_{t3}+N_{t6})\Delta t}$ where β is the continuous time transmission rate (t^{-1}) and Δt = 1 year.

Equation 1 represents the basic elements of our understanding of the disease, for example there is no vertical transmission (Miller and Williams 2003) and the disease is uniformly fatal (Williams 2005). Aspects that are not understood will be treated as hypotheses and will be evaluated by selecting among competing models as described subsequently (see *Evaluating competing models of transmission*, below). To economize space, we have shown only six state variables here, but others could be added as needed to reflect additional structure in the population resulting, for example, from differences in genotype or location[2]. Moreover, different functional forms can be used to describe the parameter vectors as described below (see below, *Evaluating competing models of transmission*).

Model-data assimilation

Parameter estimation

Hierarchial Bayesian models (Wilke 2003, Clark 2007, Cressie et al. 2008) allow us to embed equation 1 in a composite likelihood that also includes a data model for capture-mark-recapture estimating **φ** and **g**. We can also incorporate historic, landscape level data on disease prevalence (supporting estimates of **g)**, observations of sex and age structure (supporting estimates of **F** and **φ**) and estimates of total population size into the model (Figure 1) (Buckland et al. 2007, Clark 2007). It is possible to include prior information from lab and paddock studies on disease death rates. Here, we briefly outline how this assimilation of multiple data sources will be achieved. Our approach is novel because it is the first to combine data from multi-state mark recapture studies with time-series observations on population states to estimate parameters in a discrete time, stage-structured model of disease dynamics.

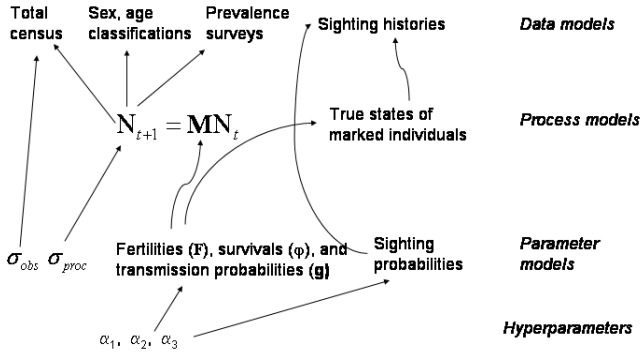

Figure 1. Schematic of relationships among data, models, and parameters in proposed studies of chronic wasting disease. Process models represent hypotheses on disease dynamics. Data models represent the probability that observations would be obtained conditional on being generated by the hypothesized process models. Hyperparameters represent variation among individuals.

Mark-capture-recapture methods provide a well-developed approach to estimating survival of organisms (reviewed by Sandercock 2006). These methods have recently been extended from the two state case (alive or dead) to >2 states, thereby providing a basis for parameter estimation for a rich variety of stage-structured models (reviewed by Clark et al. 2005). Because infection status can be viewed as a state and disease transmission as a transition between states, mark-recapture methods offer a novel way to estimate disease transmission rates (e.g., Faustino et al. 2004, Lachish et al. 2007) and associated statistics like the net reproductive rate of the disease (Oli et al. 2006).

Brief capture histories or low encounter rates in mark-recapture studies can reduce precision of estimates of parameters in multi-state models (Faustino et al. 2004). To enhance precision, it is critical to use all sources of data relevant to state transitions. This can be done as follows. The estimates of **φ** and **g** derived from mark-recapture are also included within the process model (equation 1, matrix **M**). The process model predicts observable population characteristics over time – total population size, the proportion of infected and susceptible animals, and the proportions of the population in different sex and age classes. Within the Bayesian framework, each of these predictions is influenced by process uncertainties because our model, by definition, is not a perfect representation of the processes it portrays. Data models link predictions to observations; each (Wilke

[2] As described later, some of these structural differences can also be represented as random effects in a Bayesian hierarchy.

2003, Clark 2007, Cressie et al. 2008) data model has its own observation error structure. The overall likelihoods are the product of the individual likelihoods, including the likelihoods of the model predictions given the population data and the likelihoods of the mark-recapture estimates of $\boldsymbol{\varphi}$ and **g**. The Bayesian approach to merging observation likelihoods from capture-recapture data and other population observations using a stage-structured process model is described by Brooks et al. (2004). The hierarchical structure of process variance and observation error is discussed in Clark (2007) and Cressie et al. (2008).

Evaluating competing models of transmission

Emerging infectious diseases will virtually always include some uncertainty about how the disease is transmitted, which is to say that the *form* of the underlying transmission model is uncertain. Failure to incorporate this uncertainty will produce unwarranted confidence in estimates of quantities of interest. In earlier work, we offered a new approach to incorporating model selection uncertainty in estimates of parameters of systems of differential equations representing transmission of infectious disease (Miller et al. 2006). We now describe how we will extend this general approach to stage structured models.

The vector **g,** which is composed of probabilities of transition from susceptible to infectious stages, will form a basis for evaluating alternative models of disease transmission representing effects of demographics, nonlinear feedbacks, and environmental transmission. For example, a single, constant value for probability of transmission (i.e., all values of **g** specifying infection probability are the same) will represent the hypothesis that disease transmission does not depend on demographic composition or disease prevalence in the population. Effects of sex and / or age can be represented by allowing elements of **g** to differ according to stage. Non-linear feedbacks can be added by treating elements of **g** as a function of the predicted number of susceptibles and infected individuals in the population (representing density dependent transmission), or their predicted proportion in the population (representing frequency dependence). These feedbacks can also be given demographic structure — for example making nonlinear feedbacks functions of infected males, but not females, or young. A latent variable representing an environmental pool of infectious material can be included in the function for **g** as was done by Miller et al. (2006). In the most detailed models, non-linear feedbacks (density or frequency dependence) can be stage-specific to represent the interplay of demographic and disease states.

Including alternative transmission terms within a matrix population model as a way to evaluate competing models of transmission and estimate model selection uncertainty has not been accomplished previously. We will use Bayesian methods, including Bayesian model averaging (Hoeting et al. 1999) to estimate parameter values incorporating model-selection uncertainty and, for the functional forms that are supported by the data, we will examine sensitivity of the model to variation in parameters as described in a later section (see **Mathematical modeling**).

Explaining individual variation using covariates

The multi-state mark recapture model we describe above can be extracted from the data-model hierarchy (Figure 1) so that it stands alone, without using historic, time series data. Doing so allows the use of covariates to explain variation among individuals. We will use covariates to address the following questions: 1) How do sex, age, and genotype modify the probability that an animal becomes infected? 2) Is transmission probability modified by membership in family groups, that is, does relatedness to infected individuals change transmission probability? 3) Does spatial variation in soil types change transmission probabilities? Do animals that live in areas with predominantly clay soils run a greater risk of infection than animals that live in areas with other soil types?

Random effects

The traditional approach to modeling heterogeneity in stage structured models is to simply add new stages or strata to account for variation among individuals due, for example, to differences in

their spatial location. This approach rapidly expands the number of parameters that must be estimated. An alternative to simply adding more stages to matrix models is to assume that individuals are drawn randomly from a population that has its own defining parameters (i.e., hyperparameters). For example, to accommodate spatial heterogeneity, we could add stages to the model for subpopulations or groups. This can drastically increase the number of parameters while decreasing the number of observations used to estimate each parameter. Alternatively, hierarchical Bayes allows for this variability by adding a level to the hierarchy of data and process models. Instead of being fixed, prior parameter values are random, having priors of their own (hyperpriors) (Gelman et al. 2004). We will explore the use of random effects to account for variation that is not included in the stages of our process model or in covariates.

Estimating the net reproductive rate of the disease

One advantage of the Bayesian approach is that estimates of uncertainty for all model parameters and quantities derived from them are a natural output of the modeling effort. We will estimate the net reproductive rate of the disease (R_0) following the approach of Oli (1996). In the absence of disease processes, the matrix **M (**equation 1), can be specified in terms of the transition matrix **T** (where element t_{ij} is the probability that an individual in stage j at the time t is alive and in stage i at time $t + 1$), and the fertility matrix **F** that specifies recruitment (where the element f is the expected number of i-type recruits produced by an individual in stage j), i.e., **M = T + F.** In this case, we define the fundamental matrix **N** as $\mathbf{N} = (\mathbf{I} - \mathbf{T})^{-1}$. We add the CWD disease process to the model by modifying the entries in the recruitment matrix **F** to represent the addition of new infections rather than the recruitment of susceptibles, allowing us to define the next generation matrix of the disease as **R = FN**. The dominant eigenvalue of **R** provides an estimate of R_0. Bayesian estimates of the net reproductive rate are also available (e.g., Elderd et al. 2006).

Statistical modeling in detail

Thus far, we have described the statistical model in general terms; we now provide additional detail (Box 1). The proposed model integrates two sources of data, a longer time series of population-level data collected by the Colorado Division of Wildlife (CDOW) on population size, age and sex ratios, and CWD prevalence, as well as individual capture history data collected using the proposed mark-recapture study. We broadly follow the approach of Brooks et al. (2004), which similarly combines animal abundance and demographic data, but we incorporate the disease model of Oli et al. (2006), the model for recapture data used in Clark et al. (2005), and the model selection approach of Miller et al. (2006). Many enhancements and simplifications to the proposed model are possible, such as a model that assumes that the stage structure parameters in the projection ***M*** matrix in equation (1) change over time. With multi-state capture-recapture models, special care must be taken to develop biologically meaningful models and to avoid parameter redundancy (Gimenez et al. 2003). During the study period we will consider and develop a number of appropriate models.

Field studies

Study areas

Data needed to parameterize and evaluate the process models described above will be obtained as follows. We will study three sub-populations in northeast Colorado, chosen from undeveloped, public land. There are several candidates for study identified as distinct units using cluster analysis based on radiotelemetry location data (Conner and Miller 2004). Each of these candidate sub-populations offers 11 years of data on CWD prevalence from ongoing surveillance. CWD prevalence among males averages 15-35% and is increasing exponentially; female prevalence is < 10% and appears static (Miller and Conner 2005). Final choices of study areas will be based on pilot surveys of genetic composition, availability and duration of time series of data on sex and age composition and total census, and our ability to control access and hunting.

Box 1: **Statistical models**

Individual model: Using the mark-recapture (MR) data, we assume that each animal is in one of six states (1) as well as an additional, seventh state, dead. We observe $i = 1\ldots n$ marked individuals at $t=1\ldots T$ intervals. Two state vectors provide the capture history of the ith individual, $\mathbf{x}_i = (x_{it},\ldots x_{iT})'$ is the observed state and $\mathbf{z}_i = (\mathbf{z}_{it},\ldots z_{iT})'$ is the true state. For example, for animal 8 at time 2, $x_{82}=3$ denotes state 3 (adult female infected). If we fail to observe the animal at any given time, then its state is unknown at that time. The Bayesian paradigm allows us to estimate the unknown states. We construct a function which relates the parameters in (1) to data,

$$p(\mathbf{x},\mathbf{z}\,|\,\mathbf{n},\mathbf{g},\mathbf{p}) = \underbrace{\prod_{i=1}^{n}\prod_{t=1}^{T} p(x_{i,t}\,|\,z_{i,t},\mathbf{p})}_{A}\underbrace{\prod_{i=1}^{n}\prod_{t=1}^{T-1} p(z_{i,t+1}\,|\,z_{i,t},\mathbf{n},\mathbf{g})}_{B},$$

where $\mathbf{x}$ and $\mathbf{z}$ denote the capture histories and true states for all animals, Ω and $\mathbf{g}$ are described in equation (1), and $\mathbf{p}$ denotes capture probabilities which are assumed to vary with disease state (Jennelle et al. 2007). The likelihood in A is a problem-specific multi-state MR model likelihood equation (Newman and Lindley 2006). Component B is based on an appropriate function of the parameters that describes the transitions between states.

Population and individual covariates can be used to improve model parameter estimates. Consider the probability of a transition from a susceptible adult female to an infected adult female (from state 2 at time t to state 3 at time t+1), g_{32t}. We could adopt the model $\text{logit}(g_{32t}) = \beta_0 + \beta_1 w_{1t} + \alpha$, where w_{1t} is a measure of percent CWD positive for closely related deer observed at time t and α is a random effect accounting for multiple sites. A simpler model allows for one transition parameter for all time periods, g_{32}. Individual covariates can be used for any parameters that are not in the process model in equation (1) such as models for individual capture probabilities. p_i..

Combining the individual and population models: We have historical CDOW data which include estimates of total population size, sex and age ratios, and CWD prevalence. These are estimates for large areas, but provide information about the parameters of interest and can be used to enhance the MR model. Considering only the population estimates here, the CDOW large-area population estimates $\mathbf{u}_t$ are informative about the state vector $\mathbf{N_t}$. We can define a likelihood equation which links these data to the state vector as well as the parameters for survival and state transitions, $p(\mathbf{u}\,|\,\mathbf{N},\boldsymbol{\varphi},\mathbf{g})$.

Various approaches are available to combine the individual and population models. If we assume that the data sources are independent, then the joint probability distribution is simply the product of the two likelihoods. If needed, we can model the relationship between the data sources, by using the population-level data to calibrate the prior distributions for the parameters in the individual model or by using methods to combine multiple sources of evidence (Spiegelhatler and Best 2003). We can thus define the joint distribution between the observed data $\mathbf{x},\mathbf{u}$ and covariates $\mathbf{w}$. The posterior for all parameters is given by

$$p(\boldsymbol{\varphi},\mathbf{g},\mathbf{p},\mathbf{N},\mathbf{z}\,|\,\mathbf{x},\mathbf{w},\mathbf{u}) \propto p(\mathbf{x},\mathbf{w},\mathbf{u}\,|\,\boldsymbol{\varphi},\mathbf{g},\mathbf{p},\mathbf{N},\mathbf{z})\,p(\boldsymbol{\varphi},\mathbf{g},\mathbf{p},\mathbf{N},\mathbf{z}).$$

Note that $\mathbf{z}$ contains both known and unknown components so the nomenclature here reflects that the Bayesian model can produce estimates for unobserved states in $\mathbf{z}$. MCMC methods are used for estimation (Givens and Hoeting 2005).

Mark-recapture data

During November-December of year one, we will capture 80 animals from each study population (total captures = 210) using aerial net gunning from a helicopter, a procedure widely used for capturing large mammals in open habitats (Scotton and Pletscher 1998, Merrill and Mech 2003, Bleich et al. 2005, McClintock and White 2007). We will initiate searches from random starting points within each study area; thereafter deer will be captured as encountered. All captured animals will be tested for CWD using rectal mucosa biopsy (Wolfe et al. 2007), marked with a visible ear tag, fitted with a VHF radio collar equipped with a mortality sensor / transmitter. Tissue samples also will be collected for genetic analysis. During November-December of years 2-5, we will recapture 40-55 animals from each subpopulation and add 15-20 new marks (total captures = 150). Aerial telemetry from a fixed wing aircraft will be used to direct the helicopter to marked animals to facilitate recapture, a technique that has been shown to cut time to recapture by half (Bleich et al. 2005).

Location data

Fifteen animals in each population, captured as described above, will also be fitted with global positioning system collars programmed to release from the animal approximately one year after deployment. These will be annually retrieved, GPS data will be downloaded, units will be refurbished with fresh batteries and redeployed on new animals. In so doing we will accumulate a sample of 225 individual-years of observation by the end of the study. The locations of all instrumented animals will be imported into spatial analysis software (ArcGIS 9, ESRI, Redlands, CA) and mapped to check for spatial consistency. Location data from GPS collars will be filtered to reduce bias due to land cover (Frair et al. 2004) and serial correlation (Swihart and Slade 1985). We will overlay GPS locations on the soils maps and integrate through time the habitats used by each animal. For example, we will characterize the clay content of the soil inhabited by a given animal each day. The mean of that measure through a year (and standard deviation) will be used to reflect an animal's exposure to clay soils as a covariate in the analyses described above.

Sex and age composition, census, and estimates of CWD prevalence

Time series of estimates of total population density, age and sex composition, and CWD prevalence are available from the Colorado Division of Wildlife (CDOW) for the population from which our sub-populations are drawn. These data will continue to be accumulated during our studies.

Genetic measurements

We will examine the role of genetics in creating heterogeneity in transmission by incorporating genotypic information as covariates in the analysis described above. First, we will determine *PrP* genotypes of all captured deer, using a simple restriction fragment analysis (Jewell et al. 2005). The *PrP* gene is variable in at least seven cervid species (Wopfner et al. 1999, Heaton et al. 2003, van Rheede et al. 2003, O'Rourke et al. 2004, Seabury et al. 2004, Happ et al. 2007), and variation in the *PrP* gene in mule deer relative to other cervids is well established (Brayton et al. 2004, Jewell et al. 2005). Genotypic information (*SS, SF, FF*) will be used in population genetic analyses and as covariates in the analysis of sources of heterogeneity in transmission. Second, all deer will be genotyped for a series of microsatellite markers and the control region of the mitochondrial DNA (mtDNA), to: 1) calculate relatedness among deer; and 2) assess movement of males relative to females. Here, we describe methods for genotyping *PrP*, microsatellites, and mtDNA. Genetic analyses will have high statistical power because hundreds of deer will be sampled. DNA will be extracted from tissue or blood using standard protocols; PCR protocols and scoring of alleles have been standardized (Jewell et al. 2005, Watry 2007).

Microsatellite markers will be used to estimate relatedness of individuals within maternal groups. Tetranucleotide (CATC, TAGA) microsatellites, developed by the California Department of Fish and Game (GenBank AF102240–AF102260) are sufficiently diverse to allow accurate estimation of relatedness (Jones et al. 2000, 2002, Merideth et al. 2005, Watry 2007). Each deer will be genotyped

for at least ten markers, which will provide adequate power for both estimating relatedness between deer and determining population assignment (see below). The ten markers should yield >99% probability of identity, calculated as the probability of (not) sampling the same multilocus genotypes within maternal groups, given the total probability of sampling any possible genotype twice (Hedrick 2004). Because of maternal inheritance, mtDNA analysis will allow us to further distinguish between gene flow by male dispersal (deduced from microsatellite markers), and genetic structure and stability of local female groups (in the cases where microsatellites show no differentiation, but mtDNA does). We will sample the mtDNA control region, which is highly variable in mammal populations (Polziehn and Strobeck 1998, GenBank U12865, AF016952).

We will test whether populations are mixed within and between social groups, to assess both the likelihood of transmission and gene flow of the *F* allele between populations. It is unlikely that mule deer populations are isolated into distinct clusters beyond local social groups: previous studies in Colorado indicated high gene flow among subpopulations (Scribner et al. 2001, Watry 2007). We will use Bayesian assignment techniques (e.g., program STRUCTURE, University of Chicago) to determine the proportion of migrants within each population (Pritchard et al. 2000, Roach et al. 2001, Manel et al. 2005, Waples and Gaggiotti 2006). These methods calculate probabilities that microsatellite genotypes match others found in the same site (low gene flow) or that every genotype is equally likely to be collected in all places (high gene flow). Similarly, mtDNA variation will be analyzed in program STRUCTURE by coding each haplotype as a unique allele.

Finally, our most informative analysis will be within female groups, via estimates of relatedness among deer within locations to infer group membership, and thus the probability of contact between individuals (c.f. Root et al. 2004, Blanchong et al. 2007). A recent analysis of deer in Rocky Mountain National Park, CO revealed that infection status was correlated with relatedness (Watry 2007), suggesting that group membership predicts CWD transmission. Relatedness between individual deer will be estimated using standard methods (Peakall and Smouse 2006). Adding relatedness as a covariate to the model above will allow us to compare the relative influence of environmental characteristics like soil type with the effect of social structure. We are particularly interested in the interaction between these two sources of variation to address the question "Does the effect of relatedness depend on the environmental context where it occurs?"

Adequacy of sample size

To evaluate the adequacy of our proposed sampling regime, we simulated data under plausible assumptions for process and observation uncertainty and then used a fully Bayesian model to estimate the known, generating parameters. We simulated dynamics of a population of 1000 animals with infection introduced to the population in year 1 of a 25 year simulation. We assumed that no data were taken until year 10 of the epidemic. We simulated the "true" process using equation 1 with each state subject to lognormally distributed process variance. We used the process equation to generate four sources of data relevant to the parameters in the model as described above (**Field Studies**): five years of capture histories and three, 15 year time-series[3] of observations of prevalence, population sex and age composition, and total census. Observation errors on count data were assumed to be negative binomial with a standard deviation of 40. Data models for prevalence were binomial and for sex and age data were multinomial. Bernouli models were used for mark-recapture data. We modeled the probability of transmission as $g_{t,j,k} = 1 - e^{-\beta_k (N_{t3} + N_{t6})\Delta t}$ where β_k is the continuous time transmission rate and $N_{t,3} + N_{t,4}$ is the number of infected animals. We modeled transmission for males and females separately and consistent with our earlier findings, assumed that the transmission rate for males was 3.5 time higher than the rate for females. Juvenile recruitment

[3] This assumes 10 years of legacy data and five years of new data.

was a logit function of total population size. We were able to accurately estimate states and parameters with reasonable precision (Table 1), but only when we combined all four sources of data.

We also explored our ability to estimate covariates controlling transmission probabilities. Although power analyses are not typically considered under the Bayesian paradigm, an examination of power in the frequentist paradigm may be useful. If we assume independent observations over time and space, only one observation of CWD status per deer instead of the multiple observations planned for in the proposal, and one covariate, we can undertake a power analysis. Using methodology developed by Demidenko (2007), we examined power under a several reasonable scenarios and found high power to detect significant covariate effects for the proposed study. For example, under a simplistic one-covariate logistic regression model and based on models of CWD prevalence for our study area reported in Miller and Conner (Figure 2, 2005), we found the following. Assuming a sample of 300 deer with probability that the deer is a male equal to 0.3 and probability of infected given male equal to 0.12, the power to detect an odds ratio of 3.2 due to sex with a significance level of 0.05 is 0.90. Considering the relationship between genotype and CWD prevalence, we assume that the probability of deer in Colorado are SF equals 0.2 (Jewell et al. 2005, M.K. Watry 2007, unpublished MS thesis, CSU) and that probability of infected given SF equals 0.004 (Jewell et al. 2005). It follows that the power to detect an odds ratio of 30 due to having the SS genotype (Jewell et al. 2005) with a significance level of 0.05 is 100%. Even if we observe the lower limit of the CI for the odds-ratio of 4 for the SS genotype /CWD positive that was reported in Jewell et al. (2005), we still have power of 0.99.

Table 1. Estimates of states and parameters.

Parameter or State	Generating value	Estimated mean	95% Credible Interval
Transmission rates			
Males, $\beta 1$	.007	.008	.006, .009
Females, $\beta 2$	.002	.0017	.00028, .004
Survival probabilities			
Juveniles	.45	.47	.36, .59
Susceptible females	.90	.92	.88, .96
Susceptible males	.60	.60	.51, .68
Infecteds	.50	.50	.37, .61
Logit parameters for density dependence			
Intercept	3.0	2.79	2.0, 3.6
Slope	-.008	-.0076	-.009, -.004
States during year 25			
Total population size	NA	253	168, 364
Juveniles	NA	83	55, 124
Susceptible females	NA	116	72, 173
Infected females	NA	10	5, 17
Susceptible males	NA	30	19, 44
Infected males	NA	11	6, 22

Mathematical modeling

The process model, statistical framework, and observations proposed above will allow us to evaluate competing representations of disease transmission and will estimate posterior distributions on all parameters of interest. The covariate analysis will allow us to estimate how survival and transmission probability are shaped by individual variation. Taken together, these results will form a basis for model projections that can be used to address several questions of interest. In this projection modeling, we can expand equation 1 to include more stages, for example, genotype as well as sex, age, and infections status. The proper expansion of our model will be guided by our studies of individual variation in survival and probability of infection.

Questions specific to CWD that can be addressed with standard model projections and analysis include: 1) What is the long-term future of populations infected with CWD? 2) What is the probability that such populations will face local extinction? 3) Are resistant alleles likely to increase in frequency in infected populations? 4) How rapidly will this occur and what are the consequences for disease dynamics? 5) Are there optimal control strategies that exploit demographic differences in survival and probability of infection? Additionally, our model can expand understanding of prion

diseases in general by focusing on the implications of environmental transmission, which appears to be likely for other diseases, notably scrapie (Brown and Gajdusek 1991).

To this point, we have focused on projecting equilibrium behavior of the disease, which coupled with analysis of stability properties, has become conventional in mathematical modeling of infectious diseases. We also propose to break new ground by developing mathematical approaches that have not been applied to disease systems. Traditionally, mathematicians and ecologists have studied populations by analyzing their equilibria. That is, they have examined the long term (asymptotic) behavior of continuous or discrete time models, and by applying bifurcation theoretic ideas, have investigated how this asymptotic behavior changes qualitatively as the parameters in their models vary. This approach is undoubtedly valuable and has led to important insights. However, it can become cumbersome to determine bifurcation behavior when there are large numbers of parameters. Because this approach is based on eigenvalues, it provides no information regarding transient behavior.

Recently there has been increased interest in the short-term (transient) behavior of population models (see e.g., Hastings 2001, 2004, Wysham and Hastings 2008) because initial, transient dynamics can have important consequences for population management. If a manager is attempting to accomplish a certain goal within decades, it is important for him or her to take into account short-term phenomena that may not be apparent in the long term (asymptotic) analysis. In this case, the bifurcation theoretic approach may not be the correct paradigm for management decisions. We will develop mathematical approaches to the study of transient behavior in specific disease systems, beginning with classical differential equation models that we used earlier (Miller et al. 2006), and then extend the approach to discrete time models of the type we describe here. We describe our approach to linear discrete time systems in Box 2. As an example of the value of this approach, the study of transient behavior under non-equilibrium conditions will allow us to examine the dynamics of spread of rare resistance alleles into mostly susceptible populations, including transient amplification of alleles early in the process.

BROADER IMPACTS

Our project has an opportunity to offer exemplary broader impacts. This opportunity arises because we will study a charismatic species infected with an unusual agent of disease that has a highly publicized analogue in humans. People care about the species we will study It is actively managed throughout the region. The project is rich in science and mathematics that align well with K-12 state science and mathematics content standards. Thus, we are unusually well positioned to attract broad interest from the general public, from K-12 educators, and from decisions makers. *Graduate education:* We will train four graduate students, two in ecology, one in mathematics, and one in statistics. In additional to traditional, disciplinary training, we will strive to assure that our students are well prepared to contribute to interdisciplinary projects and to couple research with broader impacts. All of the PI's on this project have extensive interdisciplinary experience, and Hobbs, Hoeting, Tavener, and Antolin were leaders of a recently completed, highly successful Integrated Graduate Education and Research Traineeship, the Program in Interdisciplinary Mathematics, Ecology, and Statistics (http://www.primes.colostate.edu/). We will apply lessons learned from this traineeship to our mentoring in this project. We will hold semi-weekly meetings of the PI's and students. Subsets of PI's will be members of the graduate committee of all of the students. We will encourage joint publication and dissertation chapters. We will require students to take coursework outside of their core disciplines to assure their ability to communicate across disciplines and to share disciplinary tools. In addition to their academic and research training, graduate students will participate in all aspects of the broader impacts, described below.

Box 2. Modeling transient behavior: Instead of using bifurcation techniques to partition parameter space into regions with qualitatively similar *asymptotic* behavior we wish to understand the transient behavior and the robustness of that transient behavior with respect to the parameters in the model. Given the parametrized transition matrix $\mathbf{M}(\vec{\lambda}_1) \in R^{n\times n}$ we consider the map,

$$\vec{x}_{t+1} = \mathbf{M}(\vec{\lambda}_1)\vec{x}_t, \quad t = 0,\ldots,T-1, \quad \vec{x}_0 = \vec{\lambda}_0, \tag{1}$$

where we treat the initial conditions $\vec{\lambda}_0 \in R^n$ as a set of parameters as well the vector. The stability analysis suggested by Caswell (2007) differentiates (1) and evolves the matrix of partial derivatives

$$\frac{d\vec{x}_{t+1}}{d\lambda_k} = \frac{d\mathbf{M}}{d\lambda_k}\vec{x}_t + \mathbf{M}\frac{d\vec{x}_t}{d\lambda_k}, \ k = 1,..., p. \tag{2}$$

We may well be interested in some linear functional of the solution (such as the fraction of the population expressing a resistant allele), which we may write as

$$q(\vec{\lambda}) = \sum_{t=0}^{T} \langle \vec{\psi}_t, \vec{x}_t \rangle . \tag{3}$$

Sensitivities of such a quantity of interest with respect to the parameters may then be computed as

$$\frac{dq}{d\lambda_k} = \sum_{t=0}^{T} \left\langle \vec{\psi}_t, \frac{d\vec{x}_t}{d\lambda_k} \right\rangle. \tag{4}$$

Alternatively extending ideas of *a posteriori* error analysis from differential equations, where they have been used with considerable effect, to iterated maps, we solve an *adjoint* problem and compute a linear functional of the solution as the inner product of the adjoint solution and the initial conditions (Buzby et al. 2007). The analysis for maps has been performed by W. Newton in his recent M.S. thesis, Newton (2007). We solve the adjoint problem: $\vec{\phi}_{t-1} = \mathbf{M}^{\bullet}\,\vec{\phi}_t + \vec{\psi}_{t-1},\ t = T,\ldots,1, \quad \vec{\phi}_T = \vec{\psi}_T,$

and then compute the quantity of interest as: $q(\vec{\lambda}) = \langle \vec{\phi}_0, \vec{\lambda}_0 \rangle,$

and sensitivities to parameters as: $$\frac{d\vec{x}_{t+1}}{d\lambda_k} = \frac{d\mathbf{M}}{d\lambda_k}\vec{x}_t + \mathbf{M}\frac{d\vec{x}_t}{d\lambda_k}, \ k = 1,..., p \tag{5}$$

A simple calculation shows the differences of efficiency between two approaches. By observing that we may write

$$\frac{dq}{d\lambda_k} = \sum_{t=0}^{T} \left\langle \vec{\psi}_t, \left(\sum_{j=1}^{t} \mathbf{M}^{t-j}\,\frac{d\mathbf{M}}{d\lambda_k}\,\mathbf{M}^{j-1}\vec{\lambda}_0 + \mathbf{M}^j\,\frac{d\vec{x}_0}{d\lambda_k} \right) \right\rangle, \quad k = 1,..., p, \tag{6}$$

we see that the approach proposed by Caswell requires $O\left(Tn^3\right)$ operations compared to $O\left(Tn^2\right)$ operations for the adjoint based approach, where *n* is the number of unknowns. This is not an issue for single realizations of small systems, but may become so for larger systems (such as those arising when spatial models are considered and the number of classes increases dramatically), or where the parameters are provided in distributional quantities and the corresponding distributions of the linear functionals and their sensitivities are required. Equation (3) is particularly efficient for changes in initial conditions. We therefore suggest that this approach is superior as a general tool. Our methods can be extended to include nonlinear systems $\mathbf{M}(\vec{\lambda}_1, \vec{x}, t)$, for example, by changing the forms of transmission to include density-dependence or frequency dependence. However, just as in the differential equation context, these nonlinearities gives rise to implementation problems associated with storage of the solution and the matrix. There are of course considerably more complicated stability issues connected with nonlinear models (see e.g., Cushing 1998, Kot 2001).

K-12 and teacher education: Increasing teacher competency and student content knowledge is a critical step towards improving environmental literacy. We believe that tradition coursework and workshops complemented by immersion into research with scientists and their students is an effective tool to achieve these goals. Each year, two high school teachers will be invited to work on the project, provided a stipend of up to $7,000, and offered graduate credit through existing professional development programs supported by the Natural Resource Ecology Laboratory (NREL) at CSU. Specific examples that embrace these ideals and practice include the NSF and CDE funded Mathematics and Science Partnership programs, and the NSF funded GK-12 and Teacher Professional Continuum. Teachers will be directly involved in some aspect of the field, laboratory, and modeling portions of the project. Following the NSF GK-12 model, each graduate student will work directly with a teacher to develop and deliver materials based on their research and experiences aligned with the state content standards. Additionally, teachers will meet monthly with teachers, scientists, and graduate students working on other research projects as part of the broader professional development activities coordinated by the NREL. We have participated in several planning meetings with teachers, district science coordinators, and administrators from our two largest school districts - Poudre School District and Greeley-Evans School District 6 - to shape and coordinate our plan (letters in supplementary documents).

Citizen education: Hobbs has a 30 year history of research and outreach with Rocky Mountain National Park. The park is visited annually by more that 3 million people, presenting a rich opportunity for education of citizens in a location close to Colorado State University. Hobbs will lead a collaboration with Park staff, graduate students, and participating high school teachers to develop interpretive programs on CWD and disease ecology. There is a natural entry point for this citizen education because many of the native ungulates are marked as part of other, ongoing CWD research. These marks stimulate curiosity by park visitors creating natural teaching moments for interpretive staff. See letter of participation by park staff in supplementary documents.

Outreach to management. Miller is the Head of the Wildlife Health program for the Colorado Division of Wildlife and has frequent and direct opportunity to influence management and policy decisions in Colorado. He will continue to serve as the liaison between the project and wildlife managers in the state. We will expand the reach of our influence by convening two regional workshops with managers and stakeholders. In the first workshop, to be held in year two of the study, we will seek advice from participants on key questions that need to be resolved to support wise management of the disease, particularly questions that could be addressed with our parameterized model. We will annually update the workshop participants on project findings using an electronically delivered report prepared specifically for this audience. In year 5 of the study, we will report back to this community in a second workshop. The Colorado Division of Wildlife will co-sponsor these workshops. See participation letter in supplementary documents.

Outreach to researchers: Our analytical approach is novel because we combine well established methods of population modeling and parameter estimation in a framework that has been rarely applied to the study of infectious disease. Hobbs and Hoeting will teach our approach in the annual NSF-funded (PI - Antolin) Ecology of Infectious Diseases Workshops, which are geared toward upper-level graduate students and post-docs, with a focus on statistical and analytical modeling of disease dynamics. They will also hold a special workshop on data assimilation for disease models at the annual meeting of the Ecological Society of America. They will write a synthetic paper on the approach for a journal targeting a broad range of biological researchers (e.g., Hoeting et al. 1999, Hobbs and Hilborn 2006, Hoeting et al. 2006, Hoeting 2008).